al. (2004) found that the level of FGF8 expression in the commissural plate was unaltered in *ne-Emx2* overexpressing mice from E9.5 to E12.5. Therefore, the authors conclude that *Emx2* is very likely to play a direct, FGF8-independent function in cortical patterning.

If EMX2 does not act through repressing FGF8 expression, then what mediates *Emx2* functions on cortical patterning? The authors propose a mechanism based on the observation that *Emx2* overexpression abolishes the high-rostral to low-caudal gradient of *Pax6* in the dorsal telencephalon. Furthermore, the phenotype observed in EMX2-overexpressing mice closely resembles the phenotype observed in *Pax6* knockout mice (Bishop et al., 2000; Mallamaci et al., 2000), and therefore, taken together, these results strongly suggest that *Emx2* acts at least partially by repressing *Pax6* expression.

Future Directions

One potential drawback of using *nestin* regulatory sequences to drive *Emx2* overexpression is obviously that *nestin* is expressed ubiquitously (unlike *Emx2*) and therefore that, in *ne-Emx2* mice, *Emx2* is now expressed ectopically at detectable levels in the ganglionic eminence (ventral telencephalon) and in the dorsal thalamus (DT) where it is not normally expressed. Despite this drawback, the authors argue that unlike *Emx2* complete knockout, which displays severe thalamocortical pathfinding defects (Lopez-Bendito et al., 2002), *ne-Emx2* mice (1) do not present obvious thalamocortical pathfinding defects and (2) do not display obvious regionalization defects in the DT using early molecular markers of thalamic nuclei. However, this is clearly where a lot of interesting work remains to be done with regard to the basic problem of how the "thalamic input" map is matched with the "transcription factor" map (Vanderhaeghen and Polleux, 2004). Rewiring experiments performed by Mriganka Sur and colleagues have demonstrated that the functional modality of a given cortical area is largely dictated by the type of input it receives, that is, by the nature of the sensory information relayed by a given thalamic nucleus onto this area. Therefore, one could imagine that despite the changes in the relative position and size of cortical areas observed in *Emx2* overexpressing mice the thalamocortical inputs might be slightly mistmatched due to aberrant innervation of V1 by VB axons, for example, as was recently shown to be the case in FGF8 hypomorph mice (Garel et al., 2003). This mismatch would also be supported by recent studies showing that the topography of thalamocortical projections is initiated by extracortical cues present in the ventral telencephalon (Vanderhaeghen and Polleux, 2004) and therefore that there is a partial uncoupling between the mechanisms patterning the size and position of cortical areas and the mechanisms that pattern the topography of thalamocortical projections.

What regulates *Emx2* expression? *Emx2* expression has been shown to be regulated by caudodorsal midline patterning cues such as BMPs and Wnts. However, much more work is needed to determine the molecular mechanisms patterning the gradient of expression of *Emx2* and *Pax6* as well as other transcription factors recently implicated in cortical patterning, such as COUP-TF1.

The results obtained in this field over the past few years, while providing some much needed answers, have opened up a number of challenging questions. What are the behavioral consequences of changing the relative size and position of cortical areas? Could some human neuropsychiatric disorders be caused by a misrepresentation of cortical areas, such as the prefrontal cortex in schizophrenia? Are these developmental mechanisms controlling the appearance of new cortical areas in a given species, the Broca "language" area in human cortex, for example? Did new patterning centers appear during evolution in the human telencephalon to underlie the appearance of a new cortical area during development, or is a subtle change in the position or size of a patterning center sufficient to induce new cortical areas? The tools and conceptual framework developed in the present and other recent studies will undoubtedly lead to answers for some of those fascinating questions.

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Selected Reading

Bishop, K.M., Goudreau, G., and O'Leary, D.D. (2000). Science *288*, 344–349.

Dehay, C., Savatier, P., Cortay, V., and Kennedy, H. (2001). J. Neurosci. *21*, 201–214.

Fukuchi-Shimogori, T., and Grove, E.A. (2001). Science *294*, 1071–1074.

Fukuchi-Shimogori, T., and Grove, E.A. (2003). Nat. Neurosci. *6*, 825–831.

Garel, S., Huffman, K.J., and Rubenstein, J.L. (2003). Development *130*, 1903–1914.

Grove, E.A., and Fukuchi-Shimogori, T. (2003). Annu. Rev. Neurosci. *26*, 355–380.

Hamasaki, T., Leingärtner, A., Ringstedt, T., and O'Leary, D.D.M. (2004). Neuron *43*, this issue, 359–372.

LaMantia, A.S., Bhasin, N., Rhodes, K., and Heemskerk, J. (2000). Neuron *28*, 411–425.

Lopez-Bendito, G., Chan, C.H., Mallamaci, A., Parnavelas, J., and Molnar, Z. (2002). J. Comp. Neurol. *451*, 153–169.

Mallamaci, A., Muzio, L., Chan, C.H., Parnavelas, J., and Boncinelli, E. (2000). Nat. Neurosci. *3*, 679–686.

O'Leary, D.D. (1989). Trends Neurosci. *12*, 400–406.

Rakic, P. (1988). Science *241*, 170–176.

Simeone, A., Acampora, D., Gulisano, M., Stornaiuolo, A., and Boncinelli, E. (1992). Nature *358*, 687–690.

Tanabe, Y., and Jessell, T.M. (1996). Science *274*, 1115–1123.

Vanderhaeghen, P., and Polleux, F. (2004). Trends Neurosci. *27*, 384–391.

Don't Go There

Response inhibition, or impulse control, is critical for normal cognitive function. In this issue of *Neuron*, Hasegawa and colleagues use a spatial nonmatch-to-sample task to reveal neurons in and around the frontal eye fields that encode where an animal should not look.

If a light flashes in the dark or if a movement occurs in an otherwise still scene, the stimulus "catches our attention," and we impulsively orient toward it (Yantis and Jonides, 1984). With an explicit instruction and a bit of practice, we can inhibit such impulses (e.g., "It's not polite to stare"). Some populations are less successful at impulse control than others, including children and patients with schizophrenia, attention deficit disorder, closed head injuries, or frontal lesions (e.g., Munoz et al., 2003). This is a serious deficit, since impulsive choices are often inappropriate. Impulse control can also be seen in many nonhuman species. For example, macaque monkeys will avoid eye contact with a dominant animal, even or precisely when it is most tempting to look in that animal's direction (Mendelson et al., 1982).

What is the neural substrate of impulse control? Both clinical and experimental lesion studies strongly implicate frontal cortex (Fuster, 2002; but also see Munoz and Wurtz, 1993; Hikosaka et al., 2000), although the mechanisms at the areal and neuronal level have not yet been fully elucidated. Many single-neuron recording studies in monkeys have used delayed go/no-go paradigms, in which a subject is instructed in advance to either execute or inhibit an eye movement (saccade) to a peripheral target (Figure 1A). Differences in neuronal activity recorded late in the delay period of go versus no-go trials are typically assumed to be candidates for inhibitory processes.

However, one caveat to this interpretation is that, in fact, impulse control is required in both go and no-go tasks, perhaps most crucially to suppress a saccade to the target when it first appears. This requirement is identical in the two tasks. Later in the delay, the need for impulse control may be greater on go than on no-go trials: on go trials, a planned movement must be actively held in check, while on no-go trials, the target can merely be ignored.

Similar objections can be raised to saccade/antisaccade tasks, another paradigm often used to study response inhibition (Figure 1B). Once again, impulse control is probably most crucial when the target first appears. Later in the delay period of the antisaccade task, there will be processes involved in suppressing the saccade to the remembered target location, planning the antisaccade, and holding that plan in check until the end of the delay. The delay period could be removed, but then impulse control signals would be confounded with movement planning and movement execution signals. Thus, although both go/no-go and antisaccade paradigms are extremely valuable tools for studying sensory to motor transformations and short-term working memory (Everling and Fischer, 1998), they may not be ideal for studying impulse control.

In this issue of *Neuron*, Hasegawa and colleagues (Hasegawa et al., 2004) take a new approach to studying impulse control by interleaving spatial match-to-sample and spatial nonmatch-to-sample tasks (Figure 1C). On each trial, an initial task cue instructs the rule: match or nonmatch. A sample is presented at a random location, and then, following a delay, two targets appear at two different locations. One target appears at the same location as the sample, while the second appears at an unpredictable nonmatching location. Animals must execute an eye movement to either the matching or the nonmatching target location, depending on the initial task cue.

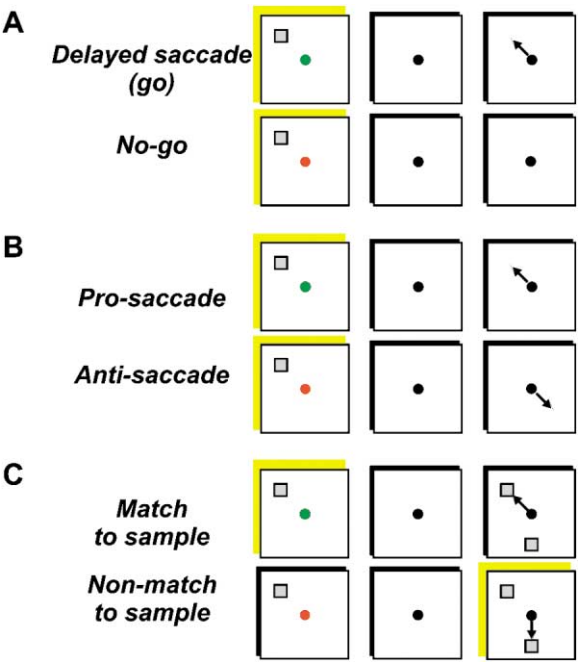

Figure 1. Three Saccade Paradigms Used to Study Impulse Control

(A) The go/no-go task begins (left panels) with the appearance of a peripheral target (gray square) while a subject fixates at the center of the visual field (colored circle). Following a brief delay period (middle panels), the subject is required to either execute ("go" condition, upper) or withhold (no-go condition, lower) a rapid eye movement, or saccade, to the remembered location of the peripheral target (right panels). The task condition for each trial is indicated by a task cue provided at the start of the trial, e.g., the color of the fixation point.

(B) The delayed saccade/antisaccade task is similar to the go/no-go task, but instead of executing or withholding a saccade, the subject must execute a saccade either directly toward or directly away from the remembered target location.

(C) The match/nonmatch-to-sample task requires that subjects perform a saccade either to the target that matches the location of the previously presented sample or to the target that does not match the previous location. In every task type except the nonmatch to sample, the correct response is fully determined in the very first frame (indicated by the yellow background). In the nonmatch task, however, the correct response cannot be determined until the two potential match targets appear ([C], bottom right).

The beauty of this paradigm is in its subtle logic. The spatial information conveyed by the sample is required for the completion of both match and nonmatch trials. In this respect, the paradigm resembles a saccade/antisaccade paradigm. And yet, while the antisaccade task allows the animal to rule out one saccade and simultaneously rule in another, the nonmatch task only allows the ruling out of a saccade. The location of the nonmatching sample cannot be predicted, and therefore the animal must wait until the end of the delay period, knowing only which saccade will *not* be made.

Hasegawa and colleagues recorded within and around the frontal eye fields (FEF) to determine whether this structure encoded information about where not to look. Previous work has indicated that the FEF contains a map of salient spatial locations as well as a movement

map for saccades (Hanes and Schall, 1996; Murthy et al., 2001). Therefore, it is not surprising that Hasegawa and colleagues found that one-quarter of spatially tuned neurons encoded only the sample location independent of task type (i.e., working memory) and an additional one-half encoded an evolving movement plan on match but not nonmatch trials. What is remarkable is that the remaining one-quarter of spatially tuned neurons carry an evolving signal on nonmatch but not match trials that encodes the sample location. They suggest that this population represents a command *not* to look at the target.

This is an appealing interpretation for the following reason. Working memory and attention are confounded to a substantial degree with saccade preparation (Kowler et al., 1995; Hoffman and Subramaniam, 1995). On both match and nonmatch trials, animals must remember or attend to the sample location. At the end of each trial, one target always appears at precisely this remembered/attended location. This abrupt target appearance is likely to be a potent stimulus for an impulsive eye movement. This movement would be task appropriate on match trials but inappropriate on nonmatch trials. Thus, on nonmatch trials, it is reasonable to imagine that a signal might arise to inhibit this impulsive and inappropriate movement. This signal cannot be a global inhibitory signal (e.g., increased activity in fixation neurons), since a visually guided saccade is required on every trial and the visually guided saccades to the unpredictable nonmatching targets have essentially the same latency as saccades to matching targets. Instead, a more selective, spatially focused strategy of impulse control must be applied. Hasegawa and colleagues' report of a spatially tuned signal, active exclusively on nonmatch trials, is consistent with such a strategy.

Of course, many interesting questions remain. For example, does the signal provide a generic impulse control signal, inhibiting any and all types of movements in the nonmatch direction, or does it specifically inhibit saccades? Consider an animal that wishes to reach out to grasp an apple that is within reach of another animal. While approaching, the animal might wish to avoid gazing at the apple, thereby giving away its intentions (Emery et al., 1997). In this circumstance, it would be useful if the inhibitory signal preventing a telltale eye movement did not also inhibit a reach and grasp to the same location. If so (and Hasegawa and colleagues support this contention), where might analogous impulse control signals for other types of movements be found? Other issues of interest include whether impulse control signals for saccades can be found within the dorsolateral prefrontal cortex, basal ganglia, and superior colliculus and whether and how multiple spatial locations might be simultaneously inhibited. Researchers should certainly not feel inhibited from addressing these and other issues!

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Selected Reading

Emery, N.J., Lorincz, E.N., Perrett, D.I., Oram, M.W., and Baker, C.I. (1997). J. Comp. Psychol. *111*, 286–293.

Everling, S., and Fischer, B. (1998). Neuropsychologia *36*, 885–899.

Fuster, J.M. (2002). J. Neurocytol. *31*, 373–385.

Hanes, D.P., and Schall, J.D. (1996). Science *274*, 427–430.

Hasegawa, R.P., Peterson, B.W., and Goldberg, M.E. (2004). Neuron *43*, this issue, 415–425.

Hikosaka, O., Takikawa, Y., and Kawagoe, R. (2000). Physiol. Rev. *80*, 953–978.

Hoffman, J.E., and Subramaniam, B. (1995). Percept. Psychophys. *57*, 787–795.

Kowler, E., Anderson, E., Dosher, B., and Blaser, E. (1995). Vision Res. *35*, 1897–1916.

Mendelson, M.J., Haith, M.M., and Goldman-Rakic, P.S. (1982). Dev. Psychol. *18*, 222–228.

Munoz, D.P., and Wurtz, R.H. (1993). J. Neurophysiol. *70*, 576–589.

Munoz, D.P., Armstrong, I.T., Hampton, K.A., and Moore, K.D. (2003). J. Neurophysiol. *90*, 503–514.

Murthy, A., Thompson, K.G., and Schall, J.D. (2001). J. Neurophysiol. *86*, 2634–2637.

Yantis, S., and Jonides, J. (1984). J. Exp. Psychol. Hum. Percept. Perform. *10*, 601–621.