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Dating Behavior of the Retinal Ganglion Cell

There is a rather crude model of human dating behavior that can explain the tendency of people to pair up with members of the opposite sex with similar degrees of attractiveness to them. In this model, each person has a certain intrinsic degree of "attractiveness" to the opposite sex, a variable whose definition, while intriguing, will not concern us here. Thus, all members within each gender can be ordered on a scale from most to least attractive. The essential element of the model is then competition. Rather than being intrinsically drawn to members of the opposite sex with a similar degree of attractiveness to oneself, everyone wants the most attractive members. The problem is that those lucky few have already been caught by one's more attractive competitors. Assuming some kind of normalization (exclusive dating) constraint operates to ensure purely one-to-one matching, the end result is a smooth "datotopic" map where each person ends up with someone of similar attractiveness not because that's who they originally most desired, but because that's the best they were able to compete for. In principle, such a competitive mechanism could apply not just to dating behavior but also to the formation of topographic maps in other contexts. A paper in this issue of *Neuron* (Feldheim et al., 2000) provides support for the operation of such a model in the formation of the topographic map between retinal axons and their targets in the brain. In a nutshell, the authors knock out the intrinsic gradients of attractiveness (actually, repulsiveness in this case) from one gender and show that now even the most unlikely members of the other gender can end up with the previously highly desirable dates.

Two distinct stages seem to be involved in the development of topographic maps in the retinotectal system. The first is independent of neural activity and relies on molecular cues such as gradients to guide axons to roughly the right target regions. The second is activity dependent and relies on learning rules such as that proposed by Hebb to sharpen the map to a more precise topography. In Sperry's now classic formulation of the "chemospecificity hypothesis" to explain the first stage (Sperry, 1963), a process of gradient matching is proposed to occur between spatially nonuniform distributions of molecules in the input and target structures. Following Sperry, much work focused on testing this hypothesis in the retinotectal system, where normally nasal retinal axons map to the posterior tectum and temporal retinal axons map to the anterior tectum (reviewed by Goodhill and Richards, 1999). However, the actual identity of the molecules involved remained elusive. This situation changed dramatically in the mid 1990s with the discovery of gradients of Eph receptors in the retina; gradients of their ligands, the ephrins, in the tectum (or its mammalian equivalent, the superior colliculus); and evidence that the ephrins act as contact repellents for extending axons. Both in vitro and in vivo data suggest that differential levels of these molecules play a key role in guiding retinal ganglion cell (RGC) axons to their topographically appropriate targets (reviewed by Flanagan and Vanderhaegen, 1998). In mouse, the receptor EphA5 is expressed in an increasing nasal-to-temporal gradient in the retina, and its ligands ephrin-A2 and ephrin-A5 are expressed in increasing anterior-to-posterior gradients in the superior colliculus (SC). However, despite the apparent similarity of these gradients to those proposed by Sperry, several questions remain. For instance, the interactions between EphA5 and ephrin-A2/ephrin-A5 are repulsive, so why don't all RGC axons cluster at the anterior end of the tectum where ephrin levels are lowest? Do ephrin-A2 and ephrin-A5 play different roles despite their similar distributions? And how could these gradients account for the plasticity observed in some cases—for instance, the compression of the whole retina onto a half tectum after tectal ablation or the expansion of a half retina over the whole tectum after retinal ablation (reviewed by Goodhill and Richards, 1999)?

Clearly, an important piece of information to constrain hypotheses about the function of Eph and ephrin gradients in mapping is the behavior of RGC axons when the distributions of some of these molecules are disrupted. In previous work, Frisen et al. (1998) analyzed the phenotype of the single knockout for *ephrin-A5*. In this issue, Feldheim et al. (2000) describe their analysis of the *ephrin-A2* knockout and the double knockout for *ephrin-A5* and *ephrin-A2* and show that these ephrins have both overlapping and distinct roles in retinotopic targetting. The phenotype of these single and double knockouts is summarized in the table. In the *ephrin-A2* mutant and double *ephrin-A2/A5* heterozygotes, only temporal axons mistarget, while in the *ephrin-A5* mutant both nasal and temporal axons mistarget: temporal axons more posteriorly, nasal axons more anteriorly. However, the severest phenotype is seen in the double *ephrin-A2/ephrin-A5* homozygotes. In some cases, the normal projection is weak or entirely absent, with multiple ectopic arbors at apparently random positions. Together, these observations suggest that ephrin-A2 and ephrin-A5 work together to produce a normal mapping. Mistargeting was also observed along the dorsal–ventral axis, which is surprising given that most of the nonuniformity in the distribution of ephrin-A2 and ephrin-A5 is found in the anterior–posterior direction (although Feldheim et al., 2000, do find some evidence for differential distribution across the mediolateral axis of the SC). Feldheim et al. (2000) also investigated whether any other members of the ephrin-A family are expressed in the SC, which could influence targeting since there is promiscuous binding between EphA receptors and ephrin-A ligands. They found none.

One of the most interesting aspects of the retinotectal system is that the wealth of experimental data available has inspired several theoretical models, many of which have been explored computationally. Perhaps the two

Summary of Phenotypic Analysis of Retinotectal Mapping in *ephrin-A2* and *ephrin-A5* Knockout Mice

Mutant Type		Nasal Axons		Temporal Axons		DV Errors	
ephrin-A2	*ephrin-A5*	Normal	Ectopic	Normal	Ectopic	Nasal	Temporal
+/+	+/+	100%	0%	100%	0%	0%	0%
−/−	+/+	100%	0%	100%	57%	0%	0%
+/+	−/−	100%	91%	100%	50%	0%	0%
+/−	+/−	100%	0%	100%	55%	0%	0%
−/−	−/−	∼90%	92%(M)	∼75%	85%(M)	53%	27%

From Feldheim et al. (2000) (data for temporal axons in *ephrin-A5* knockout from Frisen et al., 1998). Percentages of RGC axons that target normally and ectopically are shown (even in ectopic cases, there is usually also a normal projection). "Ectopic" means more anterior for nasal axons and more posterior for temporal axons. In the double mutant (last row), the M signifies multiple ectopic arbors, rather than just one as in the single mutant cases. The percentages for normal targeting are only approximate for the double knockout; in some cases there was clearly no normal arborization, but since strength and position vary along a continuum, in other cases it is difficult to determine this conclusively. "DV errors" indicates the proportion of axons making targeting errors along the dorsal–ventral axis.

most important organizing principles for the initial activity-independent stage of map formation are gradient matching and competition. One version of gradient matching, formalized by Gierer (1983), is that two gradients each in retina and tectum serve to specify a precise, smoothly varying tectal target for each RGC axon. Gradient matching models would generally seem to predict that the removal of ephrin gradients in the tectum should cause both temporal and nasal axons to shift to more posterior termination sites. In fact, while temporal axons do shift posteriorly in the knockouts, nasal axons make an opposite, anterior shift. To account for these results, Feldheim et al. (2000) propose a qualitative model incorporating competition, related to the quantitative model of Prestige and Wilshaw (1975). According to this model, the most sensitive (temporal) axons will gravitate to the least repulsive (anterior) parts of the SC, leaving the more repulsive parts of the SC (posterior) for the less sensitive (nasal) axons. Based on this model, one would predict that when the repulsive gradients in the SC are removed, temporal axons should shift more posteriorly (since they no longer sense a repellent in the posterior half). Since this shift would fill up the territory normally taken up by the less responsive nasal axons, nasal axons would then shift anteriorly. This theory would naturally account for the "systems matching" observed after retinal and tectal ablation. Two assumptions are that the higher expression of EphA5 on temporal axons imparts them with greater competitive ability than nasal axons, and that there are normalization constraints operating in both directions (Prestige and Willshaw, 1975). That is, each region of the SC cannot receive innervation from an arbitrarily large number of RGC axons, and each RGC axon can only take over a limited amount of space in the SC.

An obvious next step is to analyze the result of knocking out various Eph receptor gradients, either alone or in conjunction with the ephrin-A2 and ephrin-A5 gradients. An interesting difference between older work, which manipulated the tissue rather than the gradients directly, and more recent molecular studies is that while the older studies often used electrophysiological means to characterize mapping, the current molecular studies have focused largely on anatomical tracing of retinal projections. One consequence of these different approaches is that while the earlier studies were able to characterize the positions and activities of axons originating from varied positions in the retina, the more recent studies often "binarize" the mapping problem into an analysis of just the behavior of axons originating at the far nasal and temporal ends of the retina. As hypotheses and models for the in vivo function of Eph and ephrin gradients become more complex, it will be advantageous to characterize the mapping function for a more continuous domain. A somewhat deeper question overshadowing all of this work is: why are topographic maps so prevalent in the brain? It seems like a good idea to preserve spatial information, but exactly what is the problem for which topography is the best solution? Formal theories have been proposed based on, for instance, information theoretic criteria (Linsker, 1989), but as yet there is no one generally accepted theory. This issue becomes yet more challenging when considering maps where other features besides spatial position are included, such as ocular dominance and orientation preference in primary visual cortex. A specific question regarding these types of maps that studies such as Feldheim et al. (2000) bear upon is how the regular periodic structure of such maps develops. Although commonly thought of as activity dependent, there is increasing evidence for some activity-independent guidance of axons to their final positions in these mosaics (e.g., Crowley and Katz, 1999). Could ephrins somehow subserve this mosaic targeting? There might well be much more to learn about the romance of the retinal ganglion cell.

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Insulation of Signaling Pathways: Odor Discrimination via Olfactosomes?

An intriguing problem in neurobiology concerns the regulation of signal integration versus signal insulation within an individual neuron. In some cases signaling pathways within a cell converge and integrate to generate a common unified output. In other cases, where a single neuron must be able to keep track of multiple independent signaling cascades, insulation to prevent "cross-talk" between the pathways becomes critically important. The mechanisms of pathway insulation are particularly interesting in cases in which the insulated pathways share many common molecular components.

An excellent system in which to address the issue of signal pathway insulation is the olfactory system of the nematode *Caenorhabditis elegans*. The worm is faced with a daunting signal-to-noise problem: it must be able to chemotax toward an odor source—a bacterial meal—through the rich odorous background of the soil in which it lives. Moreover, it must accomplish this feat with a vanishingly small number of olfactory receptor neurons. In particular, the worm uses two pairs of receptor neurons to sense a wide diversity of attractive odors. One of these pairs, AWC, expresses multiple odorant receptor genes, and all the odors it senses, including benzaldehyde, butanone, isoamyl alcohol, 2,3-pentanedione, and 2,4,5-trimethylthiazole, appear to share components of a single transduction pathway.

Despite this lean economy at both cellular and molecular levels, the worm is able to distinguish among odors, as shown in two distinct paradigms. First, prolonged exposure to one odorant decreases response to that odorant, termed odorant adaptation, but not to another odorant. Second, in the presence of a saturating background of one AWC-sensed odorant, the worm is unable to chemotax toward a point source of the same odorant but is able to migrate toward a point source of a different AWC-sensed odorant, an ability referred to as odorant discrimination. In each of these paradigms, then, two different AWC-sensed odors evoke different responses. How are two response pathways, which share many components, regulated independently within the same cell?

A fresh perspective on this problem is reported by L'Etoile and Bargmann (2000) in this issue of *Neuron*. The study concerns the *odr-1* gene, whose mutations affect chemotaxis to all AWC-sensed odors. *odr-1* is shown to encode a transmembrane guanylyl cyclase (tGC) containing a signal sequence, a large extracellular domain, a kinase-like region, and a predicted cyclase domain near the carboxyl terminus.

The identification of ODR-1 as a tGC is of special interest in that it belongs to a large family of more than 25 predicted GCs described previously (Yu et al., 1997). The expression of these receptors in chemosensory neurons, along with the large size of the family, prompted the proposal that they might represent a new family of odorant receptors. Isolation of mutants defective in one of the *C. elegans* GCs allows functional testing of this proposal. In this regard, L'Etoile and Bargmann show that a truncated version of ODR-1 lacking the extracellular domain of ODR-1 functions almost as well as the wild-type product, which supports a role for ODR-1 downstream in olfactory signaling, rather than a role as an odorant receptor. Further experiments showed that the cyclase domain is required for olfactory signaling. This result is consistent with a requirement for cGMP production and is of interest because all AWC-sensed odorants are believed to act through a cGMP-sensitive cation channel. ODR-1 was also shown, using GFP fusion constructs, to be expressed in AWC and a small number of other chemosensory neurons (although different constructs containing different extents of flanking DNA showed somewhat different expression patterns, providing a healthy reminder that such experiments require caution in interpretation).

L'Etoile and Bargmann then show a link between ODR-1 and adaptation. When ODR-1 was overexpressed by introducing high-copy transgenes of the wild-type genomic clone into *odr-1* mutant animals, a provocative result was obtained: these ODR-1(OE) animals no longer adapted normally to butanone, although adaptation to benzaldehyde or isoamyl alcohol was normal. The same results were obtained when a cyclase-defective gene was overexpressed, showing that this odor-specific effect on adaptation does not depend on excess cGMP production.

A link was also shown between ODR-1 and odor discrimination in the saturation paradigm. While wild-type animals are able to chemotax toward benzaldehyde or isoamyl alcohol in a saturating background of butanone, ODR-1(OE) animals were defective in chemotaxis toward both odorants in the presence of butanone. By contrast, ODR-1(OE) animals responded normally to butanone in a background of benzaldehyde; thus, the effect exhibits an interesting asymmetry. Interpretations of this effect are further constrained by another degree of specificity: ODR-1(OE) animals in saturating levels of butanone retain normal responses to a point source of 2,3-pentanedione, which is also sensed by AWC. The discrimination defect caused by overexpression of ODR-1 is different from the adaptation defect in that the discrimination effect requires a functional cyclase domain, as if the effect depended upon excess cGMP production. Why should butanone saturation evoke an effect not elicited by other odorants? Butanone signaling, unlike signaling by other AWC-sensed odorants, is mediated in part by the Gα protein GPA-2 (Roayaie et al., 1998). Mutation of this Gα subunit suppressed the discrimination defects of ODR-1(OE) animals, as if the effect of overexpression on odor discrimination depended on hyperactivation of the normal butanone signaling pathway.

What does this elaborate series of observations tell us about the mechanism of odor discrimination? One interpretation is that in wild type, saturating levels of one odorant cause a specific downregulation of one odorant response, such that a gradient of a second odorant can be detected. In the mutant that overexpresses ODR-1, however, high levels of butanone signaling downregulate not one but several odor responses. In other words, the normal insulation between butanone signaling and other signaling pathways is compromised. In one version of this model, the downregulation occurs locally in wild-type animals and is effected by localized production of cGMP. In mutants overexpressing ODR-1, high levels of cGMP would result in a more global effect, spreading to downregulate additional pathways. Such a model would fit especially well if olfactory signaling complexes were spatially segregated from one another, as is found, for example, in *Drosophila* phototransduction (Huber et al., 1996; Shieh and Zhu, 1996; Chevesich et al., 1997; Tsunoda et al., 1997). If odor signaling occurs in a discrete complex—an olfactosome, as it were—then cGMP concentration would be highest near stimulated receptors. Thus, L'Etoile and Bargmann speculate that such organization of olfactory transduction components might serve to physically and biochemically insulate different complexes from each other.

Olfactory adaptation is presumably affected by ODR-1 via a different mechanism, since the effect does not require cyclase activity. One possible model is that ODR-1 binds to a protein required for butanone adaptation, titrates it, and thereby blocks adaptation. Perhaps signaling complexes are heterogeneous, such that complexes responding to other odors lack the protein bound by ODR-1 and are not affected by ODR-1 overexpression.

These results invite further experimentation. It will be interesting to determine whether olfactory signaling components in various organisms do in fact cluster in discrete, spatially segregated complexes. As more is learned about the binding specificity of odorant receptors (Zhao et al., 1998; Malnic et al., 1999; Speca et al., 1999; Touhara et al., 1999), it will become more apparent whether competition for receptor binding sites plays any role in odor discrimination in various species, as has been proposed previously (Siddiqi, 1987). It should also be noted that many of the most interesting results from this work come from overexpression studies. Such studies can be enormously illuminating and incisive, but additional insight can often be gained by complementing them with studies of loss-of-function mutations.

Insulation of signaling pathways is likely to be critical not only in *C. elegans* olfactory neurons but also in a wide variety of mammalian neurons, many of which express multiple receptors that converge on common signaling pathways. Thus, our understanding of signaling in many neuronal types may benefit from further consideration of olfactosomes.

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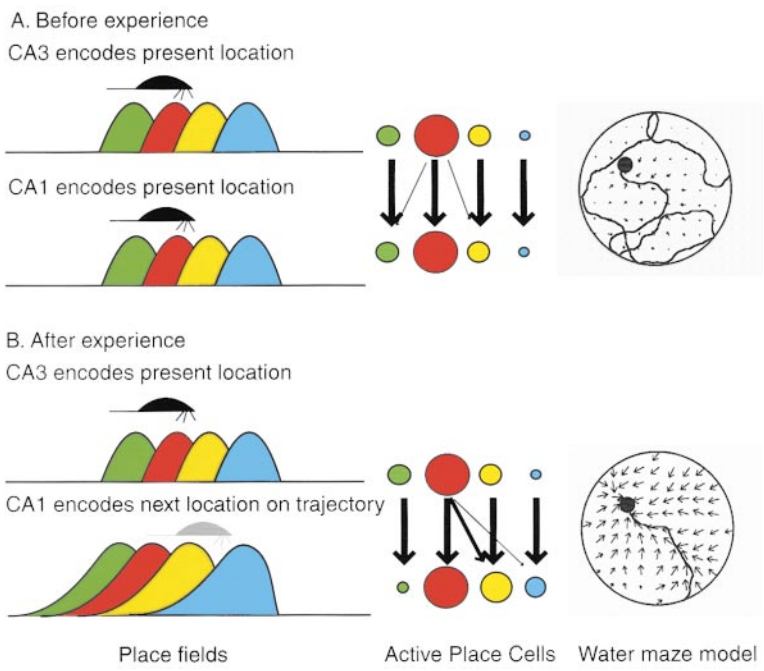
LTP Takes Route in the Hippocampus

Based on behavioral and lesion data and on the discovery of location-specific place cells in the hippocampus, O'Keefe and Nadel proposed that the hippocampus was the neural substrate of a cognitive map, used not only for navigation but as "an objective spatial framework within which the items and events of an organism's experience are located and interrelated" (O'Keefe and Nadel, 1978, p. 1). Place cells are hippocampal principal cells whose firing rate increases when the animal is at a particular location—the "place field"—in its environment (O'Keefe and Dostrovsky, 1971). The functional properties of these cells have long been a source of fascination for cognitive scientists, as they would appear to provide an important inroad into how learning and memory is encoded. Most research on place cells has focused either on the determinants of their spatial tuning (Redish, 1999) or on the extent to which they encode nonspatial information (Cohen and Eichenbaum, 1993). Although a number of theoretical models have been proposed to explain how place cells might control navigation, little experimental data exist to test these models. In this issue of *Neuron*, Mehta et al. (2000) present data that confirm the predictions of a certain subset of these models. While these results do not by themselves prove the validity of the models, they demonstrate a powerful approach to testing the predictions of models based on population analyses of neuronal ensemble data.

Mehta et al. recorded ensembles of place cells as rats made stereotyped linear trajectories. An earlier paper reported that, on average, place fields on such linear tracks became larger with experience and shifted backward, opposite to the direction of motion of the rat (Mehta et al., 1997). In the current paper, the authors



Changes to Place Fields with Experience

The size of the circles representing active place cells is proportional to the firing rate, and the line thickness is proportional to synaptic strength. The water maze model is reproduced with permission from Blum and Abbott (1996).

build on this earlier study, which examined the average behavior of populations of neurons, to track what happens on a cell-by-cell basis, and they show that the shapes of individual place fields became skewed over the first five to six laps on each day of recording. The direction of the skew was found to be opposite to the stereotyped path of the rat and thus could potentially explain both the place field expansion and the backward shift demonstrated earlier.

How might experience cause such changes in place fields? The authors reasoned that one potential explanation might involve long-term potentiation (LTP) at these hippocampal synapses. To explore this possibility, the authors modeled changes in place field shape using a network that incorporates temporally asymmetric LTP between CA3 and CA1. Since LTP is induced between two neurons if the presynaptic neuron is active before the postsynaptic neuron, but not vice versa (Levy and Steward, 1983), synapses between a given place cell and its afferent place cells that fire slightly *earlier* should be enhanced selectively over synapses between that cell and its afferent cells that fire *later*. Thus, before experience, both CA3 and CA1 encode the current location of the rat in the model (i.e., the red place cells fire strongly when the rat is centered in the red "place field") (see panel A in figure). After repetitions of the green–red–yellow–blue trajectory, however, the temporal asymmetry of LTP induction causes an asymmetric strengthening of connections between the CA3 and CA1 place cells. After experience, when the rat is at the same location as before, the newly strengthened connections between the red CA3 cell and the yellow and blue cells in CA1 cause the latter cells to also fire moderately. As a result, the CA1 place fields shift backwards, and the population activity in CA1 now encodes a location slightly ahead of the rat, corresponding to the rat's previously experienced trajectories (see panel B in figure).

In support of the idea that changes in receptive field properties may involve NMDA-dependent LTP, preliminary reports by Mehta and McNaughton (1997, Soc. Neurosci., abstract) and Ekstrom et al. (1999, Soc. Neurosci., abstract) claim that NMDA receptor blockers eliminate or reduce the place field expansion and backward shift. In addition, while only a correlation, it is interesting to note that the effects of place field expansion have been found to be reduced in aged rats, which generally have deficiencies in LTP and in spatial learning (Shen et al., 1997). If these associations between LTP and the effects reported by Mehta et al. hold true, then it adds another important clue into the functions of LTP in the hippocampus. Kentros et al. (1998) recently showed that blocking LTP does not affect place field expression per se, but blocks the maintenance of a stable representation of a novel environment over subsequent exposures to that environment. The present results suggest an additional role for LTP, but it remains to be determined where in the brain these effects really occur and it will be necessary to experimentally tie these results to LTP in different subfields of the hippocampus. For example, it could be that LTP in CA3 is responsible for one effect, whereas LTP in CA1 or dentate gyrus may be responsible for another (or even that the effects are due to LTP-dependent changes upstream from the hippocampus).

These results also have relevance to recent computational models of place cells, including models of route learning, sequence learning, and theta phase precession (for references, see Mehta et al., 2000). For instance, Blum and Abbott (1996) incorporated temporally asymmetric LTP in a goal finding/navigation model in which the rat learns the Morris water maze task. As the model rat learned the task, shifts in the locations of place fields generated a map of potential routes toward the goal. In the figure, panel A (right) shows the state of their model

at the beginning of training, when there is little information encoded in the map. At the end of training (see panel B [right]), the map now encodes the directions at each location that incrementally lead to the hidden platform. The observations made by Mehta et al. in the current paper suggest that such a representation may be encoded in the hippocampus. However, it is not yet known how such a representation would be read out and translated into the motor commands necessary for the rat to follow the route(s) laid out in this map, and there is as yet no evidence that the effect seen by Mehta et al. is actually related to goal finding. A potential means of addressing these issues would be to record multielectrode data on a navigational task similar to the Morris water maze. One predicts that place fields would be symmetric as the rat initially learns the task, but after training place fields would be skewed in a direction away from the general direction toward the learned goal location.

Mehta et al. also suggest that these results may have broad relevance to cortical receptive fields in general. Indeed, these results may offer insight into how stereotyped or repeated behaviors or perceptual experiences, such as in reading, skill learning, or enduring thousands of trials in a psychophysics experiment, are encoded and ultimately translated into the increased motor or perceptual performance associated with such tasks (Abbott and Blum, 1996). It might therefore be interesting to look for effects similar to those demonstrated by Mehta et al. in visual or motor cortex. The discovery of such general effects could elucidate a key mechanism by which neuronal populations learn sequences of neural firing patterns that underlie a multitude of perceptual and skill-learning processes.

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