forming new associations and new action patterns—the Hebbian (Hebb, 1949) "computational" processes of the brain that appear to underlie virtually all aspects of cognition.

As is the case for all significant discoveries, the new work addresses seemingly unrelated issues and raises further questions. The earliest surviving hominid fossils that could have had tongues capable of producing fully modern speech date back 50,000 years to the Upper Paleolithic (Lieberman and McCarthy, 2007). In earlier Middle Pleistocene fossils, in which the neck segment is equal to the mouth segment, neck lengths were too short to accommodate a human tongue. Tongue proportions that facilitate speech came at the cost of increasing the risk of choking—the fourth leading cause of accidental death in the U.S. Therefore, a human tongue would be worse than useless unless the hominid in question also had cortico-basal ganglia circuits capable of executing the rapid, complex motor gestures that are necessary to produce articulate speech. The presence of a human tongue in Upper Paleolithic hominids thus serves as an index for the presence of these neural circuits. But as Enard et al. (2009) show, cortico-basal ganglia circuits could have evolved before the appearance of the modern human tongue, explaining the presence of some Upper Paleolithic artifacts in Africa >50,000 years ago.

Finally, these results argue against Noam Chomsky's views concerning the neural bases of human language. In all versions of Chomskian theory, the central claim is that humans possess a species-specific, innate, neural "organ," devoted to language and language alone. Language in Chomsky's theories, moreover, is equated with syntax, the means by which distinctions in meaning are conveyed in a sentence. Cortico-basal ganglia circuits clearly are involved in sentence comprehension, but enhanced human cortico-basal ganglia circuit efficiency clearly would be expressed in cognitive acts beyond language and motor control. With the study by Enard and his colleagues, we have reached a new milestone in the journey toward understanding the evolution of human cognition.

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With Happyhour, Everyone's Under the Table

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The molecular and cellular targets that mediate alcohol intoxication are poorly understood. In this issue, Corl et al. (2009) now implicate a new Ste20 family kinase (Happyhour) and the EGFR/ERK signaling pathway it antagonizes in alcohol intoxication in flies.

The relationship between humans and alcohol is a long and complex one. It has inspired passions, both artistic and carnal, and smothered pain, both physical and mental. Worldwide, more money is spent on promoting alcohol than on promoting any other product. Often overlooked, however, is the fact that alcohol is a psychoactive drug that causes six times as many deaths as all other illicit drugs combined. Yet, despite our close relationship with alcohol, the cellular and molecular targets for alcohol's action remain as obscure as the memories of an evening after too many drinks. In this issue of *Cell*, Corl et al. (2009) provide evidence that a Ste20 family kinase called Happyhour antagonizes the epidermal growth factor receptor/extracellular signal-regulated kinase (EGFR/ERK) pathway to modulate the response of flies to alcohol.

An early theory proposed that the cellular target of alcohol is the plasma membrane lipid bilayer (Johnson et al., 1980). This theory was driven in part by three observations: (1) in all organisms tested, high concentrations of ethanol are required to elicit behavioral effects, (2) ethanol increases membrane fluidity, and (3) alcohol binds to proteins with very low affinity. The latter point has made it a heroic challenge to isolate targets of

ethanol biochemically. Forward genetic screens in flies and worms circumvent these problems. Of course, one requirement for genetic screens to be generally applicable is that alcohol must act in a similar way across species. It is therefore reassuring to observe that flies and humans go through a similar series of behaviors as the amount and time of ethanol exposure increases. Flies first show hyperactivity; this is followed by a loss of motor control and sedation, and eventually a good portion of the flies end up lying prostrate on the floor of the assay chamber (Wolf et al., 2002). Just as important as the phenotypic consequences of ethanol intoxication are the molecular targets. Fortunately, these also seem to be conserved. For instance, the most convincing ethanol target, the large conductance calcium-regulated potassium channel, plays a role in ethanol responses in organisms ranging from worms, to flies, to mice (Mulholland et al., 2009). Interestingly, these channels are not only intrinsically modulated by ethanol but also are acutely modulated by their lipid microenvironment (Mulholland et al., 2009). The results of genetic screens have shown that specific proteins, and indeed specific regions of the brain, mediate the response to ethanol (Harris et al., 2008; Scholz, 2009). Thus, the lipid bilayer model seems unlikely, or at least incomplete. So far, however, an integrated model of the molecular and cellular targets of alcohol has been lacking.

In their new study, Corl et al. (2009) took a genetic approach to look for alcohol targets in flies. In a behavioral screen, they isolated a mutant that could drink all the other flies under the table, or at least under the automated locomotor tracking device (Wolf et al., 2002). They named this mutant *happyhour* (*hppy*). Cloning of the mutant $hppy^{17-51}$ allele revealed a *P* element insertion in the promoter of the *hppy* gene, which encodes a Ste20 family kinase. A second mutant allele, $hppy^{KG5536}$, disrupted the noncoding first exon of the *hppy* gene and likewise resulted in increased resistance to the sedating effects of alcohol.

Members of the Ste20 family of kinases are diverse in both sequence and biological function (Delpire, 2009). Within the Ste20 family, Happyhour's closest relatives are the class I germinal center kinases (GCK-I) (Delpire 2009). Canonical GCK-I family members are mitogen-activated protein kinases (MAPKs) that signal via the Jun N-terminal kinase (JNK) pathway (Delpire, 2009). Interestingly, Corl and colleagues find that the JNK pathway is not involved in alcohol resistance. However, there are two other MAPK pathways (Krishna and Narang, 2008): the p38 kinase pathway and the extracellular signal-regulated kinase (ERK1,2) pathway. The investigators demonstrate that only manipulation of the ERK pathway alters resistance to alcohol.

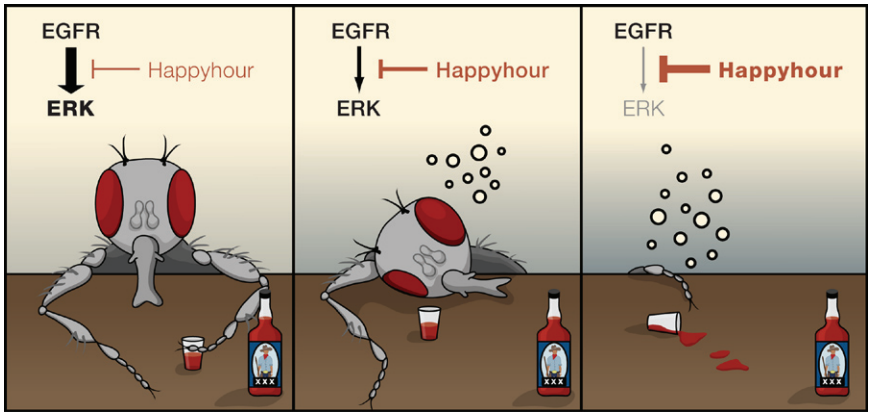

Figure 1. The Last Fly Left Standing
The *hppy* gene in flies encodes a Ste20 family kinase called Happyhour, which antagonizes the epidermal growth factor receptor/extracellular signal-regulated kinase (EGFR/ERK) pathway. Decreased Happyhour activity and increased signaling via the EGFR/ERK pathway (left) results in resistance to the sedating effects of ethanol, whereas increased Happyhour activity and decreased EGFR/ERK signaling results in hypersensitivity to ethanol (right).

They provide evidence that the product of the *hppy* gene mediates alcohol resistance by regulating the ERK pathway in the fly nervous system. Overexpression of the epidermal growth factor receptor (EGFR) or an activated form of ERK (Rolled in *Drosophila*) under a pan-neuronal promoter increases ethanol resistance, whereas inhibition of the pathway decreases ethanol resistance (Figure 1). Given that a reduction in Happyhour function increases ethanol resistance, Corl and coworkers postulated that Happyhour may be a negative regulator of the EGFR/ERK pathway (Figure 1). Several genetic interactions support this view. First, overexpression of *hppy* in the fly eye suppresses the rough eye phenotype caused by overexpression of EGFR. Second, overexpression of *hppy* in the eye enhances the rough eye phenotype caused by blocking EGFR signaling with RNA interference (RNAi). Finally, and perhaps most convincingly, the $hppy^{KG5537}$ allele fully suppresses the decrease in ethanol resistance that results from neuronal specific RNAi knockdown of the EGFR pathway.

The EGFR/ERK pathway has important roles in development. The genetic manipulations performed by Corl and colleagues all result in chronic changes in the EGFR/ERK pathway. An acute method to manipulate the EGFR/ERK pathway would demonstrate a functional rather than a developmental role for the pathway. Conveniently, it turns out that there are two well known drugs that block EGFR, erlotinib and gefitinib. This allowed the investigators to test two important questions: first, can changes in alcohol resistance be acutely elicited in otherwise wild-type flies, and second, is the role of EGFR in ethanol resistance conserved in other organisms? The answer to both of these questions is a resounding affirmative. Pharmacological inhibition of EGFR in adult wild-type flies resulted in increased ethanol sensitivity, and feeding erlotinib to mice increased the length of time necessary for them to recover from the sedative effects of ethanol. Interestingly, erlotinib also seems to play a role in the decision to ingest alcohol. Rats were given a choice of drinking water or 10% ethanol; when given erlotinib, they decreased their alcohol intake. Importantly, erlotinib did not alter their choice between water and 5% sucrose, demonstrating the specificity of erlotinib for decreasing ethanol intake.

Corl et al. provide a final piece of evidence for the specificity of the EGFR/ERK pathway in regulating ethanol resistance. They found two subsets of cells in the fly brain that are responsible for the increase in ethanol sensitivity caused by overexpression of EGFR. Overexpression of EGFR in either dopaminergic neurons or insulin-producing cells (IPCs) in the fly brain is sufficient to increase ethanol resistance. The *hppy* gene is broadly expressed, so it will be critical to demonstrate that the site of action for *hppy* is also in dopaminergic neurons and IPCs. This would demonstrate the necessity of these two neuronal foci for ethanol resistance and would corroborate the observation that expression of a dominant-negative EGFR in IPCs is sufficient to increase ethanol sensitivity. Several regions of the fly brain have been implicated in ethanol resistance (Scholz, 2009). Therefore, it will be important to determine whether ethanol has broad targets in the brain with the ERK pathway mediating a subset of the behavioral responses to ethanol, or whether several redundant pathways are at work in ethanol resistance with the observed specificity due to the expression of an ERK pathway-interacting molecule that is unique to IPCs and dopaminergic neurons.

The new study by Corl et al. boosts our understanding of alcohol resistance. Yet, potential targets still abound. Signaling pathways using cAMP are contenders for targets of ethanol (Moore et al., 1998). Ligand-gated ion channels, including the GABA, acetylcholine, glycine, and NMDA receptors, as well as various potassium channels have also been implicated as ethanol targets (Harris et al., 2008). At least 100 different knockout mice exhibit alterations in ethanol sensitivity (Crabbe et al., 2006). So far, however, remarkably few of these putative targets have been shown to bind directly to ethanol (Harris et al., 2008). Thus, it will be important to test whether Happyhour itself or a regulator of Happyhour is a direct ethanol target. Hopefully, with further genetic screens and careful validation of targets we will eventually be able to distill a cohesive model for how ethanol alters behavior.

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NPR1 in Plant Defense: It's Not over 'til It's Turned over

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NPR1 is a key transcriptional coregulator in plant defense responses. In this issue, Spoel et al. (2009) demonstrate that proteasome-mediated degradation of NPR1 in the nucleus promotes efficient expression of defense response genes following infection and prevents spurious activation of defensive responses in the absence of infection.

Systemic acquired resistance (SAR) is an inducible form of plant defense conferring broad-spectrum immunity to secondary infection of plant tissues above the initial infection site. SAR is triggered by systemic increases in salicylic acid (SA) levels following local infection by certain phytopathogens (Durrant and Dong, 2004) and results in the transcriptional activation of ~10% of the genes in the *Arabidopsis* genome. NPR1 (nonexpressor of pathogenesis-related genes 1) is a key SAR regulator. NPR1 contains a BTB/POZ (broad-complex, tramtrac, bric-à-brac/poxvirus, zinc finger) domain and an ankyrin-repeat domain. In the absence of infection, NPR1 is predominantly oligomeric and sequestered in the cytoplasm. Upon pathogen challenge, NPR1 is reduced to a monomeric state and translocates to the nucleus (Mou