cues. Muscimol injection could then be used to ask whether animals could switch between sensory representations from moment to moment, as well as from month to month.

Perhaps the most surprising thing about the results of Chowdhury and DeAngelis is that they surprise us. Visual cortex is chock-full of cells sensitive to binocular depth (Cumming and DeAngelis, 2001; Orban, 2008). Why should we expect cells in just one area to be critical for depth perception? We can perhaps trace the blame back to Lettvin et al. (1959), the famous paper whose title "What the frog's eye tells the frog's brain" implicitly asserts that signals from a neuron selective for some feature exist de facto to support behavioral responses to that feature. But this is teleology. We don't learn the purpose of a neuron—or an area full of neurons—by measuring its selectivity. For that, we must make direct measurements of the relationship between neuronal activity and behavior. Put simply, even though neuronal signals in some area may tell all we want to know about some feature, that fact alone is no reason to assume that the cells downstream are actually listening.

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The Hippocampus and Dopaminergic Midbrain: Old Couple, New Insights

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Humans have a natural ability to gain new insights by generalizing from previous experience. In this issue of *Neuron*, Shohamy and Wagner reveal how generalizations naturally emerge during associative learning through a partnership between putatively dopaminergic circuitry in the midbrain and the hippocampus.

Deriving new knowledge from past experiences can arguably be viewed as one of the most far reaching capabilities of human memory. Niels Bohr, the venerated Danish physicist, is an impressive example: his first quantum model of the atom published in 1913, is an innovative synthesis of the ideas of Planck, Einstein, and Rutherford. How, then, does the human brain accomplish such feats? In their paper in this issue of *Neuron*, Shohamy and Wagner (2008) approach an important aspect of this puzzling question, our ability to efficiently generalize past experience to new situations, based on hidden threads that cut across multiple events.

One possibility is that generalization is accomplished when it is needed: that means, when faced with a problem that requires generalization, this calls into play the effortful recall and subsequent on-line manipulation and comparison of individual exemplars or past experiences. While empirical evidence suggests that such "retrieval-based" generalizations may be important in some situations (Heckers et al., 2004), there is a more adaptive and proficient way of achieving the same goal: this is to detect and to encode generalizations as events around us unfold over time and store these generalizations as memories. The beauty of such a mechanism is that it makes generalizations available when they are needed without requiring the effortful "retrieval-based" route. The possibility of such a mechanism is exciting, but so far its identity and operating mechanisms have remained elusive. Now, Shohamy and Wagner (2008) have discovered such a mechanism and termed it "integrative encoding."

Shohamy and Wagner (2008) use functional magnetic resonance imaging (fMRI) in combination with a clever experimental design. This involved combining the acquired equivalence paradigm, a task long favored by animal learning theorists, with a conventional associative learning paradigm. University students were presented with single images of faces (out of 24 faces, from F_1–F_{24}) together with two images depicting scenes (out of 24 scenes, from S_1–S_{24}) and learned by trial-and-error which scene belonged to which face. Critically, the authors incorporated an elegant twist in their design to render pairs of faces (e.g., F_1 and F_2) that were never presented together functionally equivalent. They achieved this through partial overlap: F_1 was paired with S_1 and S_2, and F_2 was paired with S_1 (i.e., F_1–S_1, F_2–S_1, F_1–S_2). The idea, therefore, was to render F_1 and F_2 equivalent through their common association with S_1.

At the end of the learning phase participants' memory of the face-scene pairs themselves (i.e., F_1–S_1, F_2–S_1, F_1–S_2) was excellent (ca. 90% performance). During the subsequent test phase, subjects' ability to generalize was assessed by asking whether they would select S_2 when confronted with F_2. If so, this would imply faces F_1 and F_2 had acquired equivalence during training (that means they have been linked with each other in memory), allowing them to generalize information learnt about one stimulus (i.e., F_1–S_2) to the other (i.e., F_2–S_2). As it turned out, subjects were split in terms of their ability to generalize in such a fashion: whereas some performed very well (mean 96% correct), others faired rather poorly (mean 66% correct).

Interestingly, subjects who generalized successfully selected S_2 in response to F_2 very quickly, and recruited a similar pattern of brain regions as that engaged during trials involving previously seen associative pairings, arguing firmly against the use of a slower effortful "retrieval-based" reasoning strategy. Instead, participants seemed to actually have the generalizations readily stored in memory, compatible with the "integrative encoding" framework proposed by the authors.

With such a behavioral evidence for "integrative encoding" at hand, the authors turned to the learning phase of their experiment to ask which brain regions were involved. In fact, the large individual variability in the performance on generalization (38%–100%) was best captured by two brain regions whose activity increased during learning: the hippocampus and the substantia nigra/ventral tegmental area (SN/VTA) in the midbrain. Intriguingly, activity in hippocampus and SN/VTA was tightly coupled, suggesting cooperativity in their contribution to successful generalization performance.

The hippocampus and the SN/VTA are no strangers to each other when it comes to memory. The SN/VTA region harbors neurons that synthesize the neurotransmitter dopamine, and the activation of this region therefore suggests that dopamine may have influenced sites such as the hippocampus. Joint activity of hippocampus and SN/VTA has been previously observed in response to novelty for single stimuli, associations between stimuli, and when long-term memory for individual episodes is enhanced by rewards (Bunzeck and Duzel, 2006; Wittmann et al., 2005). Shohamy and Wagner's findings now indicate an exciting functional extension what this couple can accomplish.

The principle findings of this study, therefore, are that generalization relies upon encoding-related processes supported by cooperative action between the hippocampus and a putatively dopaminergic midbrain system. In the past, researchers have tended to focus on the role of the hippocampus in storing unique experiences separately from one another, in the service of episodic memory (McClelland et al., 1995). While previous work has established the role of the hippocampus in generalization (e.g., (Myers et al., 2003), primarily in the context of transitive inference tasks (Heckers et al., 2004), evidence has largely supported the operation of logical inferential processes at retrieval, that is the effortful, "retrieval-based" route. The current study, therefore, advances the field by providing convincing evidence of the importance of "integrative encoding" mechanisms in the hippocampus to future generalization. As such, these findings yield new insights into the function of the human hippocampus, favoring the idea that it supports a so-called memory space created through the linkage of multiple episodic traces through their common features (Cohen and Eichenbaum, 1993).

Thinking back to Niels Bohr, the findings raise the question as to what extent these stored generalizations would lend themselves for flexible use and decision making. Interestingly, subjects who generalized successfully informally reported that they had failed to notice that they had never previously seen the novel pairings presented in the probe trials (i.e., F_2–S_2). In future experiments, it would be illuminating to probe subjects' memory of the associative structure of the stimuli in a more explicit or challenging fashion to understand how flexible generalizations acquired through the integrative encoding mechanism actually are.

A particular highlight of the current findings is that the hippocampus and the SN/VTA were partners in "integrative encoding," suggesting that the neurotransmitter dopamine was involved. This points toward an exciting synthesis among cognitive-, molecular-, and systems-level memory research with implications for clinical conditions in which dopaminergic neuromodulation is dysfunctional, such as Parkinson's disease and schizophrenia. At the same time, this raises two acute questions regarding the specific role of dopaminergic neurotransmission in acquiring generalizations:

(1) What Is Driving the Activation of the SN/VTA and, by Inference, the Release of Dopamine?

With their "integrative encoding hypothesis" the authors provide a compelling framework that captures the putative involvement of dopamine. This framework is centered upon the assumption that each event is not merely about learning but also about detecting "what is missing" from previous events. On trials where subjects view S_1 and learn that it is associated with F_2, the memory of F_1 is also reactivated through its repeated pairing with S_1 on previous trials. This reactivation results in a mismatch, given that F_1 is not actually present on the screen. Anatomical and physiological evidence suggest that the hippocampus is ideally suited to detecting mismatches between current sensory inputs and past experience (Kumaran and Maguire, 2007) and relaying such signals to the SN/VTA, resulting in what the authors call an

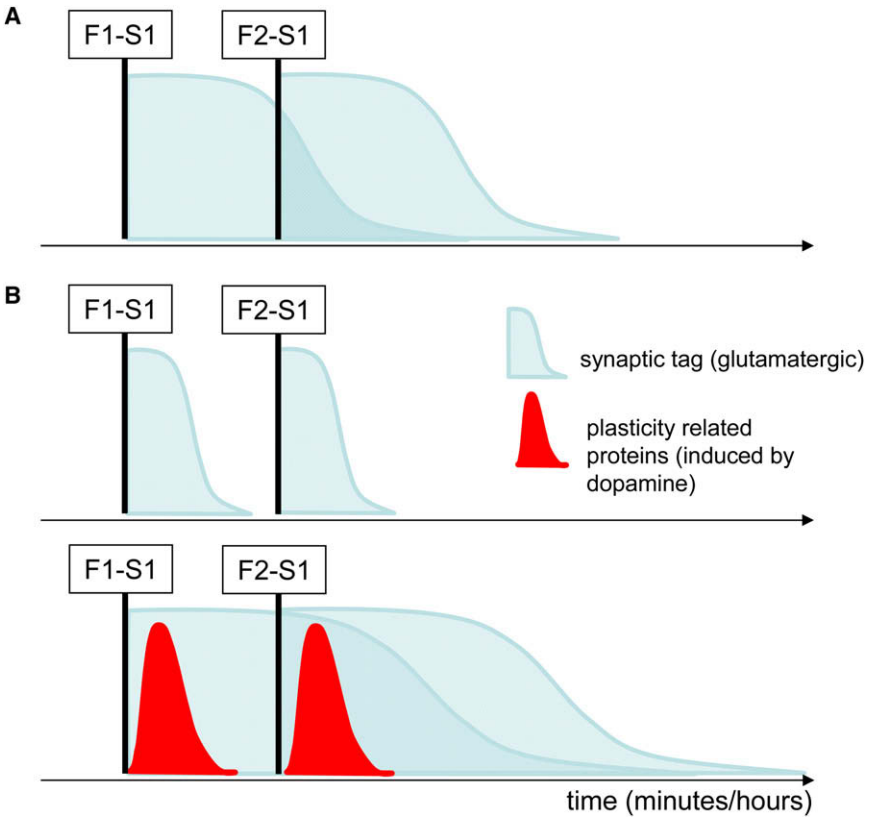

Figure 1. Temporal Relationship between the Decay of Synaptic Tags (Glutamatergic) and Experimental Trials (e.g., F_1–S_1 and F_2–S_1)

(A) If synaptic tags persist longer than the time interval between trials, associations can be acquired across trials without dopamine.

(B) If synaptic tags decay faster than the inter trial interval (upper panel), then stabilization of these tags is necessary, and dopamine release at each trial could accomplish just that by inducing plasticity related proteins (lower panel). In that case, dopamine would directly contribute to the acquisition of generalizations.

"episodic prediction error." Activation of SN/VTA areas is then viewed to trigger a release of dopamine in the hippocampus, thereby strengthening the encoding of both past (i.e., F_1) and present (i.e., F_2–S_1) features into an integrated representation.

The appealing aspect about this framework is that it captures the data very well: first, it predicts that neural activity in the hippocampus and midbrain would increase from early to late stages of learning because stronger mismatches would be generated as learning of each face-scene pair progresses. As the authors note themselves, such increase in activity in the course of learning is less than trivial: in previous studies, a decrease in hippocampal activation is typically observed as performance improves. Second, it conveniently agrees with an influential model termed the hippocampal-VTA loop model (Lisman and Grace, 2005), according to which hippocampal mismatch signals could trigger dopamine release in the hippocampus by activating VTA dopamine neurons.

The importance of Shohamy and Wagner's theoretical framework, therefore, is in proposing a new function for hippocampal mismatch signals and the hippocampal-VTA loop more generally, namely creating integrated memory representations. In contrast, previous work has emphasized the importance of mismatch signals in alerting organisms to change in the environment (Kumaran and Maguire, 2006; Kumaran and Maguire, 2007; Lisman and Grace, 2005). One uncertainty, however, regarding the mismatch-based framework is that it remains speculative as to whether or not the presentation of F_2–F_1 actually results in a mismatch for F1. In future work, it will be important to explore this issue more fully by characterizing the fit between trial-by-trial changes in neural activity and modeled prediction error/mismatch signals.

Is there an alternative account as to why dopamine may have played a role here? One interesting possibility has to do with the provision of positive and negative feedback after correct and incorrect learning trials in this experiment. As subjects improved their performance, well-learned face-scene pairs may have become predictive of positive feedback which, by virtue of being as motivating as the anticipation of a reward, may have contributed to the engagement of dopaminergic midbrain areas. As the authors note, this brain region is best known for its ability to code predictions and prediction errors for rewards. Fortunately, it should be fairly simple to test this "reinforcement-driven" hypothesis: unlike the "mismatch" hypothesis, it would predict less SN/VTA involvement in an experiment that did not involve feedback. Furthermore, according to the reinforcement-driven hypothesis, other monoaminergic modulators that also regulate hippocampal plasticity, such as noradrenaline (Frey and Frey, 2008), could be called into play if instead of rewards, emotional context were to modulate learning.

(2) What Could Be the Mechanistic Contribution of Dopamine to Learning Generalizations?

This surely is the hardest and most speculative part of the findings. As the authors point out, dopamine is well known to enhance hippocampal plasticity, and it does so by inducing plasticity-related proteins in synapses (Frey and Frey, 2008; Frey and Morris, 1998), the connection sites between neurons. However, many researchers would argue that this form of plasticity would contribute primarily to long-term forms of memory (often referred to as consolidation; e.g., O'Carroll et al., 2006) and may not necessarily contribute to the rapid type of plasticity required to acquire generalizations. To further understand the link between midbrain activation and generalization, therefore, it would be illuminating to probe participants' memory after much longer intervals, e.g., 24 hr.

This raises a pertinent question as to whether dopamine may in fact have played any role in the acquisition of generalizations in this experiment. As illustrated in Figure 1, the answer to this question may depend on the time scale over which different plasticity related mechanisms in the hippocampus interact: strengthening a link between F_1 and F_2 through synaptic plasticity will require so-called synaptic tags which are induced by the neurotransmitter glutamate and are likely to decay rapidly (Frey and Frey, 2008; Govindarajan et al., 2006; Frey and Morris, 1998). If their decay, however, is slower than the time interval between overlapping pairs (Figure 1A), they will be shared across trials and event integration may proceed without dopamine. In this case, dopamine will only contribute to long-term memory (O'Carroll et al., 2006) for the acquired generalizations. If, on the other hand, synaptic tags decay faster than overlapping events occur, acquisition may be slowed because these plasticity markers cannot be shared across different trials (Figure 1B, upper panel). In this case, dopamine released on each trial would, through plasticity-related proteins, stabilize the synaptic tags so as to make them available across different trials and thus contribute to the rapid acquisition of generalizations (Figure 1B, lower panel). It should be possible to tease apart these different scenarios by experimentally manipulating time interval between trials and the delay between acquisition and test.

Insights, discoveries, and decisions critically rely on our ability to detect hidden regularities in the world around us. The study by Shohamy and Wagner (2008) provides exciting new evidence that memory is not merely a repository of past experience but directly contributes to our natural ability to generalize. Achieving a deeper understanding of this process, at a biochemical and computational level, should keep a multidisciplinary community of neuroscientists busy for some time to come.

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