cells with astrocytes alone, so that all the neurons were derived from stem cells. In these cultures, all spontaneous synaptic currents recorded must therefore have been due to transmitter release from other stem cell–derived neurons.

The neurons derived from hippocampal stem cells thus meet the criteria outlined earlier as necessary for defining neurons: they are postmitotic, morphologically polarized cells that can fire action potentials in response to synaptic input and are functionally integrated into neuronal circuits. However, although qualitatively similar to primary neurons, the stem cell–derived neurons showed some quantitative differences. For example their spontaneous synaptic currents were typically of lower amplitude than those in granule cells differentiated in primary cultures. It is possible, however, that these differences may reflect the absence of critical environmental signals in the cultures, as the addition of BDNF to the cultures caused the stem cell–derived cells to develop levels of synaptic efficacy quantitatively similar to their neonatally derived neighbors.

If the neurons added in adulthood, at least in the hippocampus, are fundamentally the same as those added during development, then why does the brain continue to add new neurons in these specific regions in adult mammals, including people[6]? Altman[7] observed that the neurogenesis of the brain proceeds in two basic phases. In the initial embryonic and fetal phase of neurogenesis, the large projection neurons (or 'macroneurons') are generated. Altman saw this as the 'hard-wired' substrate of the nervous system. In the second phase of neurogenesis, which in some rodents is largely postnatal, there is an interdigitation of granule or 'microneurons' into the framework provided by the prenatally formed macroneurons. Altman pictured this second stage of neurogenesis as a way for environmental influences to regulate the neurogenic process and produce a brain ideally suited to its environment. He summed up his hypothesis in one of the last reviews of his work: "We postulate that this hierarchic construction process endows the brain with stability and rigidity as well as plasticity and flexibility." Although it has been difficult to establish causal relationships between the presence of persistent neurogenesis in particular regions of the brain and a requirement for structural plasticity in that brain region, recent studies have come to similar conclusions. For example, in the hippocampus, changes in neurogenesis correlate with changes in behaviors related to hippocampal function[8].

A further implication of the results from these two reports, as well as other recent electrophysiological analyses of neurons derived from ES cells[9], is to raise confidence in the use of these cells for repair of the brain. Based on the present work, it is apparent that stem cell–derived neurons can integrate into the circuitry of at least some regions of the adult brain. Perhaps now we can take advantage of our renewed appreciation of the plasticity inherent in adult neurogenesis to enhance the regenerative potential of the adult brain.

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Making order from chaos: the misguided frontal lobe

Richard Ivry and Robert T. Knight

The brain continually attempts to extract patterns from environmental events. A new report suggests that this process depends on prefrontal cortex.

Memory is, in essence, a pattern-recognition process, adaptive in allowing us to detect predictive cues to guide behavior. To examine neural mechanisms of learning and memory, researchers typically present a set of stimuli repeatedly and examine how the brain's response to this information changes over time, or examine differences in neural activation to this stimulus set compared to a new stimulus set. In this issue, Scott Huettel and colleagues take a novel approach to the study of pattern recognition[1], creating a situation that could lead participants into committing the gambler's fallacy (**Fig. 1**), the belief that chance events actually form coherent patterns. Using functional MRI to track blood flow to active neural regions, the researchers demonstrate that a distributed set of regions in prefrontal cortex are exquisitely sensitive to the presence of such patterns, and as importantly, to deviations from these patterns. Whether these neural responses reflect the operation of processes involved in short-term memory, novelty detection, or the generation of explicit predictions about forthcoming events remains to be determined.

The study is elegant in its simplicity. Participants were required to respond as quickly as possible to each stimulus in a series, pressing keys to indicate whether it was a square or a circle. The experimenters explicitly instructed participants that the events were randomly determined. However, over an extended period, even random sequences of stimuli will exhibit brief periods of seemingly 'nonrandom' patterns. The authors focus on two such series: runs of the same stimulus (such as six consecutive circles) and runs in which the two stimuli alternated (circle–square–circle–square–circle–square). Reaction times were influenced by these patterns. Up to repetitions of eight, responses became faster when the same stimulus was presented on successive trials, and the reaction time to a stimulus deviating from this pattern (for instance,

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Fig. 1. We are often tempted into making predictions about upcoming events based on apparent patterns in the world around us, even when these patterns are random. For example, a gambler may feel his or her best bet is to place money on black during a game of roulette because the last several runs came up black. Huettel *et al.* report in this issue that these moment-to-moment predictions involve activation of the prefrontal cortex.

a square following a series of circles) was considerably longer. Similar results were obtained for a series of alternations, although the behavioral effects here were less pronounced. These results suggest that the participants primed their motor behavior based on belief that the brief randomly emerging 'pattern' would continue, despite explicit instructions that the stimuli were determined randomly. Their incorrect predictions were associated with a clear behavioral cost.

The authors used an event-related fMRI design, focusing on the hemodynamic response triggered by a specific stimulus breaking these randomly occurring mini-patterns. For example, the neural response to a square that follows a series of five circles can be compared to a square that does not end a run of circle repetitions or one that perturbs a series of alternations (square–circle–square–circle–square–square); thus, the comparison is between trials involving the same stimulus and response. Repetition violations were marked by increased activation in a number of prefrontal foci, including middle and inferior frontal cortex bilaterally, as well as in cingulate and insular cortex in the right hemisphere. Subcortically, neural correlates of deviation were observed in the basal ganglia. Moreover, the magnitude of the signal was a direct function of the number of repetitions. The prefrontal regions also responded to violations of alternating sequences, although those blood flow changes were restricted to the right hemisphere.

The authors emphasize that the prefrontal regions "evaluate predictive mental models for upcoming events on a moment-to-moment basis," linking short-term pattern recognition processes to working memory operations associated with prefrontal cortex. Exactly how these prefrontal regions contribute to the evaluation process remains to be specified. We can think of at least three mechanisms, none of which precludes the others, which might contribute to the observed prefrontal activations. Indeed, all three may occur in the task used by the authors.

First, prefrontal activity could reflect a short-term memory mechanism, developing and maintaining a transient representation of the current context. A series of successive circles or an alternating square–circle pattern defines a particular context, and breaking this short-term memory template constitutes a violation of that context. The increased activation could be viewed as dishabituation of short-term memory mechanisms under control of prefrontal cortex, that is, a signal corresponding to the re-engagement of the short-term memory process in response to the change in context. There is evidence supporting this role of prefrontal cortex in short-term memory. The mismatch negativity (MMN) is an auditory event-related potential with a latency of 150–200 milliseconds that provides a marker of echoic memory[2]. The MMN is generated in auditory cortices by a break in either a repetitive or an alternating pattern, and this process is modulated by prefrontal cortex[3]. Thus, the current fMRI results could represent neural activity associated with transient maintenance of short-term memory processes. Electrophysiological, neuroimaging and neuromodeling evidence support such a role of prefrontal cortex in top-down modulation of posterior association cortex[4–6]. The neural representation of short-term context could be either explicit, in a form that the participants could verbally express, or implicit, developing outside awareness. The authors seem to favor an implicit interpretation, although the report does not provide definitive supporting evidence.

A second hypothesis is that the observed activations reflect a novelty response to changes in a pattern. In this view, the prefrontal cortex is engaged by deviance from a pattern. The idea is that prefrontal cortex is recruited to examine whether the break in local context deserves further processing. There is ERP evidence that this process is reflected by a longer-latency ERP occurring at 300–400 milliseconds after occurrence of a deviant event[7]. The novelty hypothesis need not assume that prefrontal regions are involved in the actual detection of a local emerging pattern or the break in this pattern. The representation of these patterns themselves may be in other cortical or subcortical areas, as is true for the auditory MMN. There is extensive intracranial recording, lesion, electrophysiological and fMRI evidence implicating the prefrontal cortext in novelty detection[8]. One way to distinguish these two hypotheses would be to record ERPs in the task. If a long-latency novelty ERP is observed, the second hypothesis would be supported.

Third, the prefrontal activations may represent an explicit hypothesis-generation process. Consider the participants, lying in the scanner, faithfully performing this simple task over and over again. Given the low processing demands of the task, it seems reasonable that they might monitor the series of events. Indeed, given the human propensity to find pattern among randomness, they may not be able to help themselves from engaging in such monitoring. This monitoring could well lead to the development of explicit hypotheses, such as "there is now a run of squares" or "the stimuli are alternating." As noted by the authors, the ability to generate and act on predictions can also have a cost. We may know that the next event in a series is randomly determined—be it the sequence of circles and squares in the current study or the next spin of the roulette wheel. But we are easily seduced by the immediate context, inferring causation or predictability even when none exists. Hypothesis generation is an essential feature of higher-level cognition. It should not be surprising to find that we engage in such operations despite explicit instructions regarding the random determination of the events.

Although the results of Huettel *et al.*[1] provide clear evidence of prefrontal activation following pattern deviation, they do not discriminate among these three hypotheses. Moreover, it is conceivable that the distributed activations reported in this paper reflect prefrontal contributions to all

three of the operations outlined above. Short-term memory mechanisms within prefrontal cortex may automatically modulate representations of local context in other cortical regions, as has been observed in echoic memory research. This short-term memory mechanism may then signal deviations from these patterns, providing a feedback signal to prefrontal regions to view a deviance as potentially biologically significant and deserving of additional inspection. Such representations may also be accessible for systems involved in the explicit monitoring of behavior and generation of hypotheses. Evidence from neuroimaging, neuropsychology and electrophysiology supports a role of prefrontal regions in all these cognitive operations[3,8,9].

The current work can be compared to more traditional studies of pattern recognition. One approach has involved trial-and-error learning, in which participants are explicitly instructed to try to learn a response sequence[10,11]. Another has used the serial reaction-time (SRT) task, in which participants make speeded responses to successive stimuli that vary along a dimension such as spatial position or color. The SRT task is similar to that of Huettel *et al.*[1], except that the number of stimulus–response alternatives is increased, and comparisons are made between blocks of trials in which the events follow a fixed sequence or occur randomly[12,13]. This task has been used to study both explicit and implicit learning. In the former condition, participants are either taught the sequence in advance or extract it over the course of the experiment. In the latter, a distractor task is interleaved with the button-pressing task to distract the participant's attention and thus reduce awareness of the sequential nature of events.

These studies have yielded a consistent picture regarding prefrontal activation during sequence learning. When learning is explicitly guided, or when participants become aware of the sequence, prominent activation is observed in prefrontal cortex, including the areas identified by Huettel *et al.* In contrast, when learning is implicit, no changes are found in lateral prefrontal cortex, even though performance measures clearly indicate that the participants have learned the sequence of stimuli and/or responses. Under such conditions, pattern recognition occurs without hypothesis generation. Thus, the sequence-learning literature is consistent with the claims of Huettel *et al.*[1] regarding a role for prefrontal cortex in the perception (or production) of patterns, but also suggests that this role may be limited to situations in which the participants are able to explicitly express these expectations.

Future work in which the level of the participants awareness is monitored should provide a direct test of this hypothesis. We would expect a marked reduction of the prefrontal response in the current task if the participants were engaged in a distractor task that disrupted their ability to generate hypotheses. "An idle mind is the Devil's workshop," goes an old English proverb. For the gambler impressed by the run of black spots in roulette, an idle mind may result in unwarranted predictions that can lead to misguided actions.

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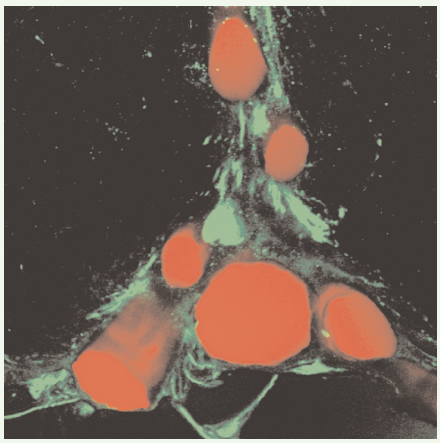
Putative chemoreceptors get close to arteries



Serotonergic raphe neurons within the medulla control respiratory and autonomic function. *In vitro*, these neurons can act as chemoreceptors, detecting small changes in CO_2 and pH in the physiological range. In support of this proposed sensing role, George Richerson and colleagues report on page 401 of this issue that the processes of these neurons are closely apposed to arterial blood vessels. Thus, these processes are in a prime location to monitor the effectiveness of lung ventilation in the blood. Because sudden infant death syndrome has been attributed to an inability to counteract rises in blood CO_2 during sleep with an appropriate respiratory response mediated by serotonergic pathways, these results support the suggestion that the syndrome may result from a developmental abnormality in serotonergic chemoreceptive neurons.

Using confocal imaging and electron microscopy, the authors examined the relationship between serotonergic neurons (green) and arterial blood vessels (red). Processes of the neurons were closely associated with the arterial vessel walls, in some cases less than one micron from the blood-containing lumen. Electrophysiological recordings confirmed that the serotonergic neurons in close proximity to arteries responded to changes in pH, an indirect measure of CO_2 concentration. The chemosensitive neurons were most common throughout the midline of the medulla, which contains large arteries and few veins. Thus the local CO_2 concentration in this region probably reflects arterial CO_2 concentration that is relatively unaffected by local tissue metabolism.

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