

- null hypothesis. We converted this likelihood to an absolute probability value by simulating 40 experiments in which a representative number of transcripts (27,993 transcripts in each experiment) were identified and compared. We derived the distribution of transcripts used for these simulations from the average level of expression observed in the original samples. We then compared the distribution of the  $p$ -chance scores obtained in the 40 simulated experiments (false positives) with those obtained experimentally. On the basis of this comparison, a maximum value of 0.0005 was chosen for  $p$ -chance. This yielded a false-positive rate that was no higher than 0.01 for the least significant  $p$ -chance value below the cutoff.
9. Two hundred simulations, assuming an abundance of 0.0001 in one sample and 0.0006 in a second sample, revealed a significant difference [ $P < 0.01$  (8)] 95% of the time.
  10. This analysis revealed 208 transcripts that were significantly decreased in CR cancer cell lines as compared with normal colon cells and 228 transcripts that were increased. Venn diagrams and tables illustrating the relation between the *in vivo* and *in vitro* differences are available through the Internet at <http://welchlink.welch.jhu.edu/~molgen-g/home.htm>.
  11. It is not possible to obtain pancreatic duct epithelium, from which pancreatic carcinomas arise, in sufficient quantities to perform SAGE. It is therefore not possible to determine whether these transcripts were derived from genes that were highly expressed

- only in pancreatic cancers or that were also expressed in pancreatic duct cells.
12. Total RNA isolation and Northern blot analysis were performed as described [W. S. el-Deiry *et al.*, *Cell* **75**, 817 (1993)].
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27. In the case of normal and neoplastic colon cancer tissue, 548 differentially expressed transcripts were identified among the 36,125 different transcripts.
28. We thank K. Polyak and P. J. Morin for providing colon cancer cell lines; G. M. Nadasdy for providing pancreatic primary tumors; and J. Floyd, C. R. Robinson, and Y. Beazer-Barclay for technical assistance. Supported by the Clayton Fund and by NIH grants GM07309, CA57345, and CA62924. B.V. is an investigator of the Howard Hughes Medical Institute.

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## Brain Regions Responsive to Novelty in the Absence of Awareness

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Brain regions responsive to novelty, without awareness, were mapped in humans by positron emission tomography. Participants performed a simple reaction-time task in which all stimuli were equally likely but, unknown to them, followed a complex sequence. Measures of behavioral performance indicated that participants learned the sequences even though they were unaware of the existence of any order. Once the participants were trained, a subtle and unperceived change in the nature of the sequence resulted in increased blood flow in a network comprising the left premotor area, left anterior cingulate, and right ventral striatum. Blood flow decreases were observed in the right dorsolateral prefrontal and parietal areas. The time course of these changes suggests that the ventral striatum is responsive to novel information, and the right prefrontal area is associated with the maintenance of contextual information, and both processes can occur without awareness.

The detection of novelty is a cognitive operation necessary to survival and requires an assessment of both expectedness and context. Events can be familiar in one context but novel in another. More precisely, novelty represents a deviation from the expected likelihood of an event on the basis of both previous information and internal estimates of conditional probabilities (1).

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Novelty detection has typically been linked to consciousness because novel events often capture attention. For similar reasons, studies of novelty have often been confounded by awareness (2). Here, we sought to determine whether the response to novelty can occur without awareness and, if so, to identify the associated brain regions in a manner unconfounded by awareness. To do so, we used an implicit learning task.

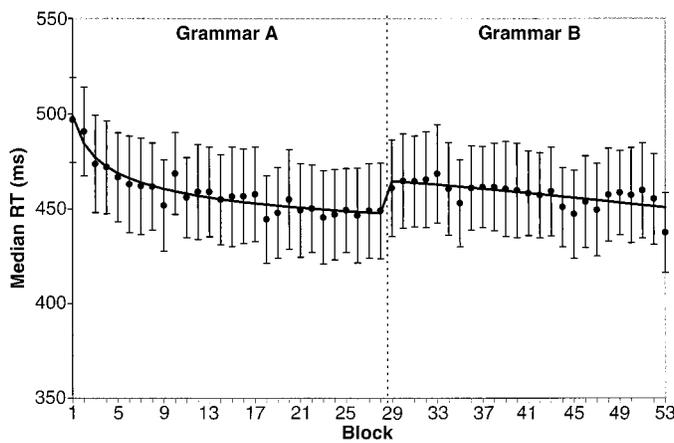
A large body of research has examined learning mechanisms that operate below the level of awareness. This type of learning is said to occur implicitly because behavioral measures indicate that learning takes place, even though the individuals are unaware of this or are unable to report it explicitly (3). A frequently used paradigm is

based on a serial reaction-time task, in which participants observe sequences of visual stimuli and must press buttons corresponding to these. Unknown to the participants, the sequence of stimuli is predetermined by a fixed, repeating order. With practice, reaction times improve (compared with randomly sequenced stimuli), indicating that the participants have learned about the sequential order. However, they are not always conscious of this. When the sequence is sufficiently complex, individuals are unaware of the sequential regularities or that they have learned anything specific about the stimuli, even though their reaction times have improved significantly (4). This indicates that sequential information can be both learned and used in the absence of awareness.

One type of sequence that has been well studied is based on finite-state grammars (5). Such grammars can be used to generate highly complex, context-dependent sequences. With enough practice, individuals show improvements consistent with implicit learning of such grammars. However, because such grammars are typically probabilistic, specific repeating sequences rarely occur, further reducing the likelihood of awareness of the sequential regularities.

Implicit learning of finite-state grammars means that participants have developed expectations for each stimulus, on the basis of the specific stimuli that preceded it in the sequence (that is, its context). Under such conditions, changing the rules of the grammar will cause subsequent stimuli to violate these expectations, by appearing in novel contexts. Thus, a switch in grammars

**Fig. 1.** Average median reaction times (RT)  $\pm$  SE as a function of trial block. The average of the median RTs across participants is shown with separate regression curves that followed a power law for each grammar. The switch from grammar A to grammar B resulted in a 15-ms increase in median RT. There was no significant change in accuracy across the grammar change.



during a rest condition (staring at a box on the screen) before the task was begun and after completion of it. Areas of significant difference in rCBF after the grammar change were identified with statistical parametric maps (10).

The median reaction time (RT) for the 10 participants declined from an initial average of 500 ms to 450 ms at the end of grammar A (Fig. 1). When the grammar changed, RT increased to 465 ms and then declined again. The average RT increase of 15 ms, although statistically significant, was undetected by the participants, as was the change in grammar (11). After the initial block of stimuli, the accuracy remained stable at 92% and showed no significant change from grammar A to grammar B.

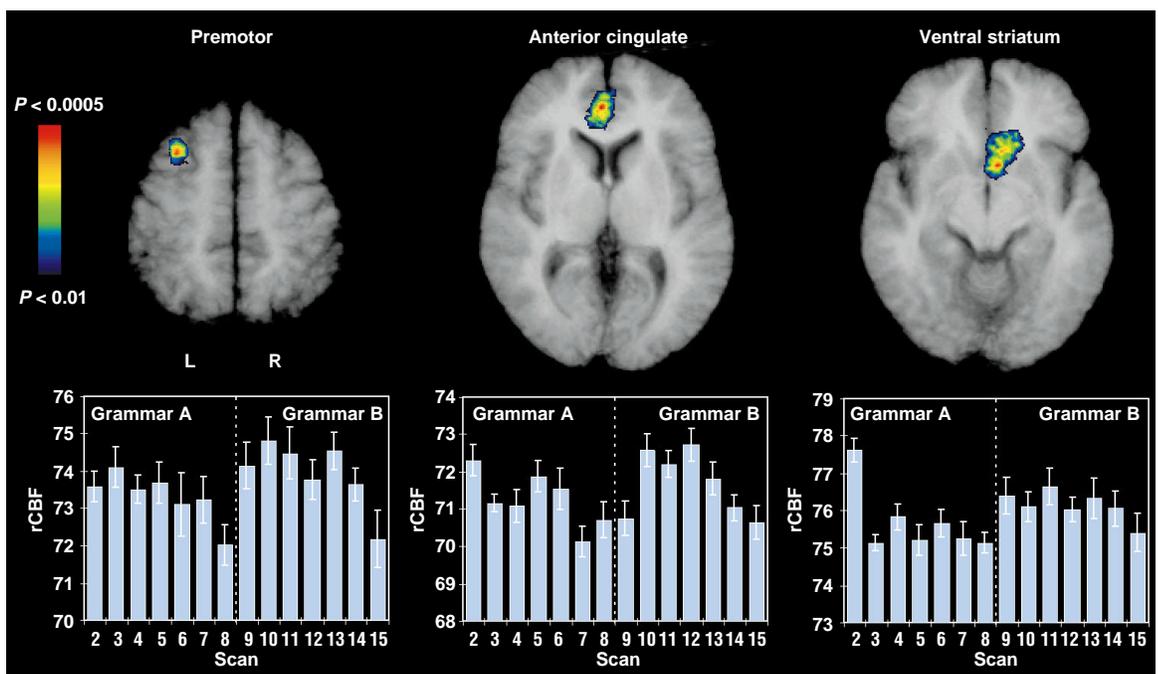
Areas of significantly increased rCBF after the grammar change are shown in Fig. 2 (12). Three areas of focal increase were noted: left premotor area, left anterior cingulate, and right ventral striatum and nucleus accumbens. The scan-by-scan plots of rCBF indicate that the increase in blood flow in these areas was clearly related to the grammar change, with the ventral striatum showing the most significant increase in response to the grammar change. The most prominent areas of decreased rCBF (Fig. 3) were in the right dorsolateral prefrontal cortex (Brodmann area 45/46) and right inferior parietal and superior temporal areas. These areas were also negatively correlated with

should engage mechanisms sensitive to novelty. Furthermore, if participants are unaware of both the initial grammar and the switch, then changes in behavior and regional brain activity associated with the switch should represent processes occurring without awareness.

Ten normal, right-handed volunteers performed a serial reaction-time task while regional cerebral blood flow (rCBF) was mapped by positron emission tomography (PET) (6). The task consisted of a number (1, 2, or 3) appearing on a computer screen, and the participant was instructed to press the corresponding key on the number pad with the right hand as quickly and as accu-

rately as possible. The sequence of stimuli was determined by a finite-state grammar and appeared every 700 ms in 90-s blocks with 45-s rests between blocks. A total of 53 blocks were performed (7). For the first 28 blocks the sequence of stimuli followed one grammar (grammar A), after which the sequence was switched, without telling the participants, to a second grammar (grammar B), and another 25 blocks were presented (8). PET scans were performed starting with the first block and every fourth block thereafter (9). Fourteen scans were obtained during the course of the task, and participants continued to perform the task between scans. Two additional PET scans were taken

**Fig. 2.** Statistical parametric maps (SPMs) for areas of increased blood flow after the grammar change (upper row) and the corresponding time course of rCBF  $\pm$  SE for the significant area in each slice (lower row). Contrasts between the end of grammar A and the beginning of grammar B were performed by subtracting the activity maps from the four final scans of grammar A from the four beginning scans of grammar B and performing paired *t* tests on each voxel. Only differences that were significant at  $P < 0.001$  were considered in the interpretation, but voxels significant at  $P < 0.01$  are shown for demonstration of the extent of the activity differences. The SPMs are superimposed on the average MRI for the cohort of 10 participants. This blood-flow contrast isolates those brain regions showing significant rCBF changes related to changing stimulus probability, which occurred largely without awareness. Areas of significant increase in blood flow included, from left to



right [Talairach-Tournoux (TT) coordinates; peak Z values]: left premotor area (-28, 6, 52;  $Z = 3.10$ ), left anterior cingulate (-4, 38, 12;  $Z = 3.36$ ), and right ventral striatum and nucleus accumbens (4, 10, -4;  $Z = 3.40$ ). The ventral striatum displayed a time course consistent with response to novelty.

RT and displayed a different time course from the other areas (13).

Different regions showed different time courses of rCBF during task performance, which can be used to distinguish the functions of the regions. For example, the right cerebellum showed a constant elevation of rCBF during task performance relative to rest, consistent with a role in sensory or motor processes associated with task execution. Other areas, such as left premotor cortex, showed a pattern that varied during each grammar but was similar for both. This could reflect an involvement in the implicit learning of each grammar, with greatest activity early when learning was the greatest.

The striatum exhibited a different pattern: an increase in rCBF early during each grammar that lasted significantly and substantially longer during the second grammar. This pattern is consistent with a response to novelty. This area was transiently activated at the beginning of the first grammar, when the task itself was novel; however, the basic task was simple and easily learned, so this was a brief response. With practice, stimuli came to be associated with the particular sequential contingencies of the first grammar. When the grammar was switched, these contingencies were violated. This violation of the learned contingencies by the stimuli was a more powerful elicitor of novelty than their appearance at the very beginning of the experiment, when they were not associated with any specific expectations. Previous brain mapping studies have pointed to the role of the right ventral striatum in implicit sequence learning (14); however, the time course of the rCBF observed in our experiment, particularly its strong response to the grammar

switch, support a more specific response to novelty (15). This sensitivity to novelty may also explain the known dopaminergic response to errors in reward prediction (16). The striatum is reciprocally connected to the dopamine neurons of both the substantia nigra and ventral tegmentum, so the striatal response could signal prediction errors of reinforcing stimuli.

Our findings identified regions involved in processing novelty of a particular type. An event can be novel because the stimulus has never been seen before, or because it is being seen in a new or unexpected context. Furthermore, individuals may or may not be aware of the novelty of a stimulus. Previous imaging studies of novelty detection have focused primarily on the conscious processing of unfamiliar stimuli. These studies found activation of a number of limbic structures, including hippocampus, parahippocampal gyrus, medial dorsal thalamus, and medial frontal cortex (2), that differ from the regions identified in our experiment. These differences may be due to the fact that our experiment involved familiar rather than unfamiliar stimuli, and unconscious rather than conscious detection of novelty. Thus, the structures we identified could participate in a system specialized for the detection of familiar stimuli that violate expectations, novelty in the absence of awareness, or both.

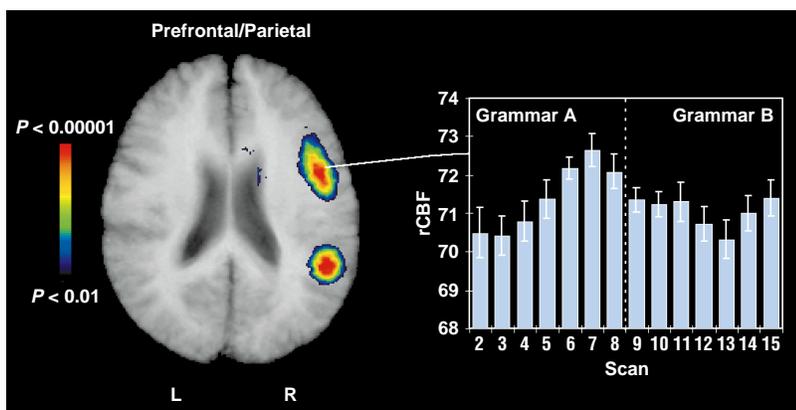
A different profile of rCBF was observed in the right dorsolateral prefrontal cortex (DLPFC). This region showed a progressive increase in rCBF during the first grammar, with a decrease after the grammar switch and then an increase late during the second grammar. Several studies have implicated DLPFC in the active maintenance of task-relevant information (17) and, in particular, the main-

tenance of context information (18). Superficially, our task did not require the maintenance of such information. Participants simply responded to the current stimulus. However, the improvements in RT indicate that they were learning sequential dependencies among the stimuli and using these to anticipate the next stimulus. With practice, participants both learned and maintained longer, and more predictive, sequences.

The changes in rCBF that occurred in right DLPFC during the first grammar are consistent with the operation of maintenance mechanisms. The progressive increase in rCBF could reflect the increase in maintenance requirements associated with longer sequences as these were learned and used (19). This is consistent with studies demonstrating that activation of a similar region of DLPFC increases progressively as memory load for sequential information is increased (20). Blood flow within this region initially decreased during the second grammar, presumably because the sequences learned during the first were no longer informative. Eventually, rCBF began to increase again, as the new sequences were learned and used.

Our findings also address an important question regarding the relation of active maintenance, prefrontal function, and awareness. Previous studies implicating prefrontal cortex in active maintenance have involved circumstances in which individuals were aware of the need to maintain information. This is consistent with the belief that active maintenance requires conscious mental effort. Our findings call this idea into question. The participants in our study were not aware of either the grammars or the switch and therefore had no conscious reason to maintain information about prior stimuli. Therefore, our findings suggest that the prefrontal mechanisms involved in active maintenance, like those responsive to novelty, can operate independently of awareness.

In summary, we have identified structures associated with performance in an implicit learning task that, by their profile of activity, can be associated with specific cognitive functions. Our findings are consistent with the view that DLPFC is involved in the active maintenance of context information used for prediction, and that the ventral striatum monitors the reliability of such predictions, becoming activated when these are violated by stimuli that appear in an unexpected context. We found that both mechanisms can operate without awareness.



**Fig. 3.** SPM for areas of blood flow negatively correlated with RT (left). The ventral region extends from the right dorsolateral prefrontal cortex (DLPFC) (Brodmann area 45/46; TT coordinates: 36, 20, 16) posteriorly to primary sensory area (TT coordinates: 44, -16, 20). The posterior region is centered on the junction of the right inferior parietal lobule and superior temporal gyrus (TT coordinates: 44, -50, 16). The rCBF time course of the DLPFC (right) is consistent with the encoding and maintenance of contextual information during the first grammar, which declines with the grammar switch and increases again as the second grammar is learned.

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5. Finite-state grammars consist of nodes connected by allowable transitions, with each transition corresponding to one of the stimuli (3). With complex grammars, individuals learn the dependencies after ~30,000 trials (as evidenced by decreased reaction times compared with trials with random stimuli) without developing awareness of the grammar's presence [A. Cleeremans and J. L. McClelland, *J. Exp. Psychol. Gen.* **120**, 235 (1991)]. In pilot studies, we found that simpler grammars can be learned in shorter periods of time without individuals developing awareness of the grammar.
6. There were five male and five female participants, average age = 26.0 years (SD = 6.4, range 20 to 39). Informed consent was obtained from all participants after the nature and possible risks of the experiment were explained. Before the study the participants current and past medical histories were reviewed to exclude those with neurologic, psychiatric, or active medical disorders. The protocol was approved by the University of Pittsburgh Medical Center institutional review board.
7. Stimuli appeared every 700 ms regardless of whether the response was correct. Stimuli were determined by a five-node finite-state grammar similar to those of previous studies [A. S. Reber, *J. Verb. Learn. Verb. Behav.* **6**, 317 (1967)]. From a given node, one of the available transitions was randomly chosen and the corresponding stimulus was displayed. This was then repeated from the new node. The final node in the grammar was the same as the first. Stimuli associated with the transitions were set up so that the overall probability of each stimulus was 1/3. Thus, any learning that occurred used information about second-order or higher probabilities. To maintain a general level of motivation, the participants were informed at the beginning of the task that they would earn monetary bonuses for better performance, and accuracy was more important than speed.
8. The architecture of grammar B was the same as that of grammar A except that the stimuli associated with the node transitions were permuted so that 1 became 2, 2 became 3, and 3 became 1.
9. The individual's head was positioned in the PET scanner aperture by adjusting the scanner gantry such that the most inferior scanning plane was both parallel to and level with the canthomeatal line. After positioning, a 10-min transmission scan was obtained. For each PET scan, individuals received a 7-mCi bolus of  $^{15}\text{O}$ -water through an automated injector. A 60-s scan commenced 30 s after the start of the bolus. Scans were obtained with a Siemens ECAT 951R in 3D mode [S. R. Cherry, R. P. Woods, E. J. Hoffman, J. C. Mazziotta, *J. Cereb. Blood Flow Metab.* **13**, 630 (1993)] and reconstructed with a Hanning filter with a cut-off frequency of 1.0. This "autoradiographic" approach results in images of  $^{15}\text{O}$ -water activity that are closely proportional to rCBF [M. E. Raichle, W. R. W. Martin, P. Herscovitch, M. A. Mintun, J. Markham, *J. Nucl. Med.* **24**, 790 (1983); P. Herscovitch, J. Markham, M. E. Raichle, *ibid.*, p. 782].
10. Scans were realigned to each individual's structural magnetic resonance image [R. P. Woods, J. C. Mazziotta, S. R. Cherry, *J. Comput. Assisted Tomogr.* **17**, 536 (1993)] and subsequently transformed to a standard atlas [J. Talairach and P. Tournoux, *Coplanar Stereotaxic Atlas of the Human Brain* (Thieme, Stuttgart, 1988)]. With SPM95 [K. J. Friston, C. D. Frith, P. F. Liddle, R. S. J. Frackowiak, *J. Cereb. Blood Flow Metab.* **11**, 690 (1991)], analyses of variance (ANOVAs) were performed at each voxel in the PET space. To control for global differences in blood flow both within and between individuals, we first normalized activity counts using analysis of covariance (ANCOVA) to a mean of 50 ml per 100 ml per minute. Activity maps were smoothed with a 20 mm by 20 mm by 12 mm Gaussian kernel to increase the signal-to-noise ratio and account for interparticipant anatomic variability. The time required for learning each grammar precluded a balanced experimental design, so effects confounded with time may be significant (such as fatigue). We therefore included scan number as a covariate of noninterest in the ANOVA model, and only the remaining voxels with significant changes across the whole study at  $P < 0.05$  were used for further specific  $t$  tests. To identify rCBF changes due to the grammar change, we performed contrasts between the end of grammar A (scans 5 through 8) and the beginning of grammar B (scans 9 through 12). Two one-tailed paired  $t$  tests identified those voxels with significant increases or decreases, respectively. A conservative threshold of significance was used ( $P < 0.001$ ).
11. Participants were formally debriefed after completion of all PET scans with a series of general ("Did you notice anything about the sequence of numbers?") to specific questions ("Halfway through the task, the sequences changed. Did you notice this?"). No one reported awareness of sequential structure to the stimuli. One of the 10 participants reported that something may have changed during the course of the task, but the other nine denied being aware of the grammar change.
12. When compared with the scans taken at rest, several other regions (particularly the right cerebellum and left sensorimotor areas) had significant increases in blood flow during the entire task; however, these areas did not show a statistically significant difference in blood flow when the grammar was changed.
13. Reaction time is a surrogate measure of learning, so any regions that show either positively or negatively correlated blood flow are potentially involved in the learning of the contextual information. Significant positive correlations were limited to the right ventral striatum and left parahippocampal region.
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15. Other cognitive processes occurring at the grammar change may also contribute to the pattern of rCBF changes. Overriding the response tendencies from the first grammar may be significant, even if the individual is not conscious of it. Our study does not allow for the separation of the novelty from the process of overriding responses. However, the ventral striatal activation, being more transient, may be more related to novelty sensitivity, and the left anterior cingulate activation, because it peaks after the grammar change and not during the first grammar, may be more related to overriding prepotent responses.
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21. We would like to thank M. B. Wiseman for assistance with computer processing and C. S. Carter and J. L. McClelland for comments on the manuscript. Supported by the Functional Brain Imaging Center (MH 49815).

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