

Perceiving patterns in random series: dynamic processing of sequence in prefrontal cortex

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We demonstrate that regions within human prefrontal cortex develop moment-to-moment models for patterns of events occurring in the sensory environment. Subjects viewed a random binary sequence of images, each presented singly and each requiring a different button press response. Patterns occurred by chance within the presented series of images. Using functional magnetic resonance imaging (fMRI), we identified activity evoked by viewing a stimulus that interrupted a pattern. Prefrontal activation was evoked by violations of both repeating and alternating patterns, and the amplitude of this activation increased with increasing pattern length. Violations of repeating patterns, but not of alternating patterns, activated the basal ganglia.

Extracting regularities from temporal sequences of events is central to human cognition. By identifying patterns, people form predictions about upcoming events. If, when waiting at a train crossing, one first feels the ground shake, then hears a low rumbling, and finally sees flashing lights in the distance, the consistency of that pattern with past experience allows one to predict that the train will soon arrive. Most sequences of events contain a mix of regular patterns and un-patterned, random variability. A daily cognitive challenge, therefore, is to predict future events on the basis of temporal sequences that may contain both patterns and mere random variability.

Behavioral evidence indicates that the identification of patterns within event sequences is automatic and obligatory. When presented with visual stimuli that alternate between the left and right sides of a display, infants two months of age make anticipatory eye movements to the next event in the series after only a few minutes of exposure¹. By three months of age, infants anticipate events within more complex patterns (for example, left-left-right-left-left-right)¹. Further evidence comes from studies of implicit sequence learning, which show improvements in task performance even when subjects are not aware that temporal patterns exist^{2–5}. Finally, people identify structure in temporal sequences despite the sometimes negative consequences of wrongly expecting a pattern⁶, such as predicting slot machine or lottery number outcomes⁷. The human cognitive system identifies patterns in sequences of events, regardless of whether a pattern truly exists.

That people identify patterns in order to predict future events is well established. Less understood, however, are the brain regions underlying the development and maintenance of dynamic prediction of event patterns. Electrophysiological, neuroimaging and neuropsychological evidence suggests that prefrontal cortex (PFC) may be central to dynamic prediction. Novel stimuli, including those that violate a preceding pattern of events, elicit a large positive potential in PFC measured by electroencephalogram (EEG),

which peaks around 300 ms after stimulus onset^{8–10}. Functional MRI studies of target detection have identified similar transient activation in response to infrequent target stimuli within the PFC, notably in the anterior middle frontal gyrus (MFG) and posterior inferior frontal gyrus (IFG)^{11,12}. Furthermore, patients with focal PFC damage show both behavioral impairments in the use of patterns to predict visual targets (F. Barcelo-Galindo and R. T. Knight, *Soc. Neurosci. Abstr.* 26, 839.11, 2000) and reductions in an electrophysiological component associated with stimulus deviance¹³. Though these studies suggest a role for the PFC in processing global stimulus context (for example, overall probability), they do not address whether the PFC forms predictions about stimuli based on local context (the pattern of events preceding a stimulus). An additional shortcoming of these experimental designs is the association of infrequent stimuli with infrequent responses, so that the identification of pattern violations is confounded with response dishabituation.

To investigate whether the PFC processes moment-to-moment changes in event patterns, we conducted a speeded classification task while measuring subjects' brain activity using fMRI. We presented a random series of two stimuli, a circle and a square, each requiring a different response. This binary choice–response design allowed ready analysis of stimulus sequence. We refer to the stimuli as 'A' and 'B', and a string of 'A's and 'B's denotes a sequence with the current stimulus underlined. We considered circles and squares to be equivalent in all analyses. For example, 'AAB' describes both 'circle-circle-square' and 'square-square-circle'. Within the overall random sequence, we identified segments of up to eight stimuli that followed a repeating or alternating pattern. Based on previous behavioral studies^{14–18}, we expected that subjects would respond differentially to stimuli that reinforced or disrupted a local pattern, even though they were explicitly told that stimuli were presented randomly. This expectation was strongly supported by the response time data.



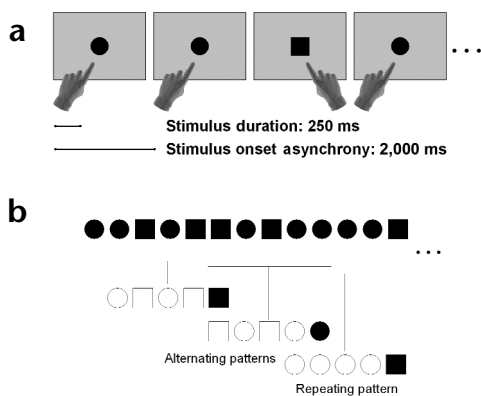


Fig. 1. A schematic representation of the experimental design and sequence analyses. (a) Two shapes, each requiring a different response, were presented in random order over many trials. The interval between successive stimuli was fixed at 2,000 ms to facilitate analysis. (b) We identified short-term patterns occurring by chance within the overall random sequence. Shown is a sample stimulus order, with the order of shapes representing the stimuli presented on successive trials. We identified two types of stimulus events: violations of repeating patterns and violations of alternating patterns. Left, two sample violations of a length-4 alternating pattern; right, an example of a violation of a length-4 repeating pattern. The filled symbols indicate the events that violate the preceding pattern. Each event may be part of more than one pattern, and patterns may overlap.

We expected that the PFC would be activated by violations of both repeating and alternating patterns if, and only if, these regions were critical for the generation of predictive models from observed events. Whereas a violation of a repeating pattern involves a stimulus and response that are different from those of the previous trial [AAAAAB], a violation of an alternating pattern repeats the stimulus and response from the previous trial [BABABB]. Significant activation evoked by violations of alternating patterns discriminates brain regions involved in moment-to-moment prediction from those involved in stimulus or response habituation. We also expected activation amplitude in these regions to vary according to the length of the preceding stimulus sequence. Our hypotheses were supported, as we found significant PFC activity in response to violations of both repeating and alternating patterns.

RESULTS

Brain activity was measured with fMRI while participants classified rapidly presented circles and squares (Fig. 1a). Our analysis focused on repeating and alternating patterns that occurred by chance within the overall random sequence (Fig. 1b). Repeating patterns consisted of trials in which *n* sequential stimuli were identical. We examined violations of length-1 repeating patterns [AB] through length-8 repeating patterns [AAAAAAAAB]. Alternating patterns consisted of trials in which *n* sequential stimuli alternated between circles and squares. We examined violations of length-2 alternating patterns [ABB] through length-8 alternating patterns [ABABABABB]. Because the overall presentation of stimuli was random, the frequency of each type of sequence depended on its length (for example, one-quarter of stimuli start a length-3 repeating sequence, one-eighth for length 4, and so on). Sequence lengths longer than eight stimuli were not analyzed because of their rarity. For example, there were only about seven instances of each type of length-9 sequences in the 1,800 experimental trials.

Behavioral measures

Measurement of subject response time demonstrated that the speed of categorical judgment depended on the sequence of preceding stimuli (Fig. 2). Mean response time across all trials was 408 ms. If a stimulus continued a preceding repeating pattern [AAAA], response time decreased with increasing pattern length to approximately 375 ms for patterns of length 6 or greater. However, if a stimulus violated a preceding repeating pattern [AAAA], response time increased with increasing pattern length, to more than 500 ms for length 8.

Alternating patterns also induced changes in subject response time. There was no effect of pattern length for stimuli that continued an alternating pattern [ABABA], as response times were about 410 ms for all pattern lengths tested. For stimuli that violated an alternating pattern [ABABB], response times were unchanged across pattern lengths 2–5, but increased thereafter to a maximum of 445 ms at length 8.

Functional magnetic resonance imaging

Violations of repeating patterns evoked activation in regions within the PFC, including the MFG, IFG and inferior frontal sulcus (IFS); in the anterior cingulate gyrus (ACG); and in the neighboring insular cortex (INS) and basal ganglia (Fig. 3a and b; Table 1). These activations were not related to the particular stimulus presented or the particular response made; nor did they result from the explicit demands of the task, as subjects were told that the stimuli would occur in a random order (they were not

Fig. 2. Behavioral results across stimulus sequences. Response time is shown as a function of the length of the preceding stimulus pattern. Events that violate the preceding pattern are indicated by the dark bars, whereas events that continue the pattern are shown by the light bars. (a) As the length of a repeating pattern increases, response time decreases to events that continue that pattern [AAAA], but response time increases to events that violate that pattern [AAAA]. The average response to all stimuli is shown at pattern length zero. (b) For increasing length of an alternating pattern, response time does not change to events that continue that pattern [ABAB], but increases for violations of patterns of length 6 or greater [ABABABB]. As a minimum of two events is needed to establish an alternating pattern, the lower chart begins with length-2 patterns.

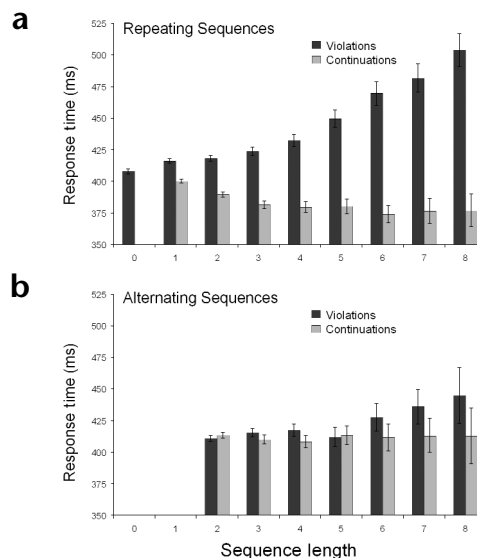
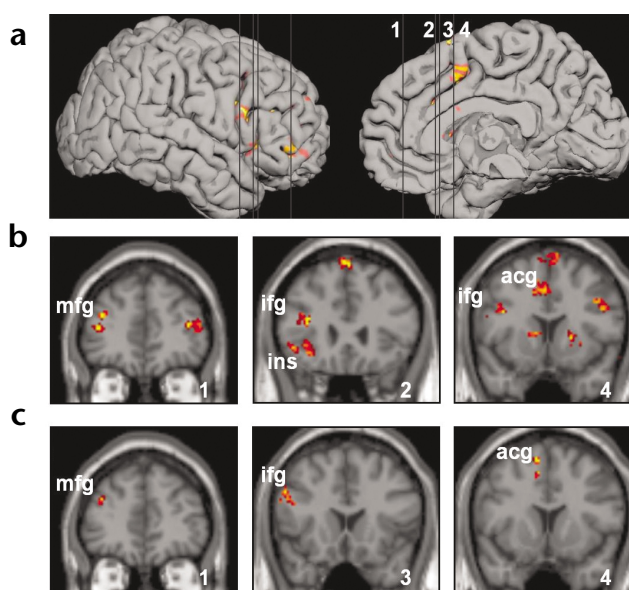


Fig. 3. Brain regions associated with violations of stimulus pattern. (a) The overall pattern of activation to violations of a repeating pattern (minimum *t*-value of 6.5), rendered using FreeSurfer (Cortechs, Charlestown, Massachusetts; MGH NMR center, Boston, Massachusetts). Numbered bars indicate locations of coronal slices (shown in b and c) in radiological convention. (b) Areas active to violations of a repeating pattern. Left, activation foci exceeding the minimum cluster size threshold in the middle frontal gyrus and inferior frontal sulcus (1), in the right insula and inferior frontal gyrus (2, middle) and in the caudal inferior frontal gyrus, anterior cingulate gyrus, caudate and putamen (4, right). (c) Areas active to violations of an alternating pattern. Left, activation in the middle frontal gyrus (1), in the inferior frontal gyrus (3, middle) and in the anterior cingulate gyrus (4, right).



instructed to consider stimulus sequence). These activations must therefore reflect the automatic identification of events that violate repeating patterns.

Similarly, violations of alternating patterns evoked activation in PFC regions including the MFG, IFG and IFS, and in the ACG (Fig. 3c). The center voxel (centroid) of activation in MFG for alternating-pattern violations was within one voxel ($3.75 \times 3.75 \times 5$ mm) of the centroid for repeating-pattern violations. The activation centroids in the IFS and IFG for alternating-pattern violations were within the active regions for repeating patterns. In the ACG, the activation for violations of alternating patterns was located superior to that for violations of repeating patterns. In each case, the activation was lateralized to the right hemisphere. To verify that these PFC regions responded to both repeating- and alternating-pattern violations, we conducted a masking procedure in which we measured, in voxels active to one violation type, the response to the other violation type. All regions activated by violations of repeating patterns were also activated to a significant degree by violations of alternating patterns (*P*-values, MFG = 0.002, IFG = 0.002, IFS = 0.004). Conversely, all regions activated by violations of alternating patterns were also activated to a significant degree by violations of repeating patterns (*P*-values, MFG = 0.0002, IFG = 0.0004, IFS < 0.0001).

We defined, for subsequent analyses, regions of interest (ROIs) based on the voxels active to violations of repeating pat-

terns. Within these ROIs, activation amplitude was graded according to the length of the preceding pattern [AAB < AAAAB < AAAAAAB]. A repeated-measures ANOVA with factors of pattern length (0–7) and time point (3–9 s, post-stimulus) showed that this parametric effect was significant in all regions indicated in Table 1 (all *P*-values < 0.00005). The fMRI hemodynamic responses (HDRs) in a representative ROI for patterns of length 1–7 are shown (Fig. 4). Note the monotonic change in signal amplitude, from little or no change for short patterns to large responses for longer patterns. The signal-evoking stimulus was identical for each curve. The length-6 and length-7 patterns, for example, differed only in the stimulus that was presented on the seventh preceding trial, which occurred 14 s before the violation event plotted here.

We then measured the extent to which HDR amplitude depended on sequence length. For repeating patterns, the HDR amplitude increased with pattern length before violation (Fig. 5a). In all ROIs, the HDR peaked significantly above baseline (cross-subjects random-effects *z*-tests, all *P* < 0.05) for patterns of two to eight stimuli; ACG, IFG, caudate and putamen were also significantly above zero for length-1 patterns. This suggests that formation of an implicit predictive model, whose violation evokes PFC activation, occurred after two or more stimulus repetitions. Significant PFC activation was also evoked by violations of alternating patterns (Fig. 5b), but with different effects of sequence length. At short pattern lengths (two or three stimuli), HDR amplitude was either significantly below baseline (INS, ACG, MFG; *P* < 0.05) or not different from baseline (all other *P*-values > 0.05). HDR amplitude was significantly above baseline for violations of length 6 or greater alternating patterns in MFG, IFS, IFG, ACG and INS (*P* < 0.05).

No significant effects of alternating-pattern violations were measured in the caudate or putamen. The distributions of voxel significance in the basal ganglia for alternating and repeating pat-

Table 1. Areas of significant activation associated with pattern violations.

Region	Laterality	MNI coordinates			Maximum <i>t</i> -value
		<i>x</i>	<i>y</i>	<i>z</i>	
Repetition violations					
Middle frontal gyrus (MFG)	Left	-42	32	32	11.3
	Right	34	46	22	10.4
Inferior frontal sulcus (IFS)	Left	-48	42	10	12.6
	Right	34	44	8	11.5
Inferior frontal gyrus (IFG)	Left	-60	6	8	11.7
	Right	54	16	16	10.8
Cingulate gyrus (CNG)	Right	6	6	44	10.9
Insula (INS)	Right	38	22	-10	14.8
Caudate	Right	12	12	4	11.4
Putamen	Left	-20	10	0	10.8
Alternation violations					
Middle frontal gyrus (MFG)	Right	36	44	24	10.2
Inferior frontal sulcus (IFS)	Right	41	37	16	12.1
Inferior frontal gyrus (IFG)	Right	48	16	25	11.3
Cingulate gyrus (CNG)	Right	8	11	52	11.7



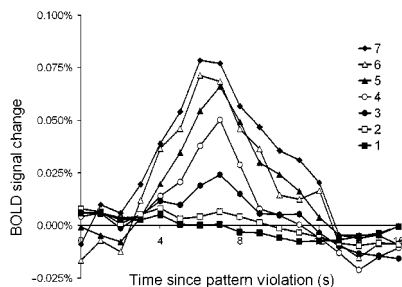


Fig. 4. fMRI responses observed for violations of length 1–7 repeating patterns. As shown for a representative brain region (right IFS), response amplitude systematically increased with pattern length, with small responses to violations of shorter patterns and larger responses to violations of longer patterns. Note the regularity of the HDR change with pattern length, and the lack of overlap between the response curves. This pattern is typical of all regions listed in Table 1 under repetition violations.

tern violations were significantly different, as shown by Kolmogorov-Smirnov testing ($D_k = 0.43, P < 10^{-10}$). In addition, we investigated whether there was evidence for sub-threshold activation to the alternating patterns. At the threshold for significance ($t > 6.58$), repeating-pattern violations evoked activation in 134 voxels, whereas alternating-pattern violations evoked activation in only 7 voxels (out of 1,729 in the ROI). When this threshold was lowered ($t > 3.0$), the numbers of active voxels for repeating and alternating patterns were 778 and 156, respectively. Thus, there is no evidence that the difference between the alternating and repeating patterns in the basal ganglia is an artifact of threshold selection.

Comparison of behavioral and fMRI measures

We found a striking correspondence between HDR amplitude and response time. For violations of repeating patterns, these measures were highly correlated across pattern lengths (mean HDR across ROIs, $r = 0.90$). For violations of alternating patterns, the correspondence between the measures was also very good, with both measures showing an inflection point at length 5 ($r = 0.92$). The only difference between the behavioral and HDR measures was found at length-8 patterns, for which the HDR was unchanged from length 7 (possibly owing to a ceiling effect) and the response time increased from length 7. This correspondence indicates that the observed fMRI activity likely reflects cognitive processes directly involved in the dynamic processing of sequence.

DISCUSSION

The present study demonstrates that (i) violations of sequential patterns evoke fMRI activity in prefrontal and interconnected subcortical regions previously associated with target

detection, task switching and working memory; (ii) HDR amplitude in these regions depends on the length of the sequence before violation; (iii) repeating and alternating pattern violations evoke activity in similar prefrontal regions; and (iv) sequence-related changes in HDR amplitude matched changes in behavioral response time.

Pattern violations evoked activity in PFC, including the anterior MFG and posterior IFG, and in the basal ganglia (caudate and putamen), which are anatomically and functionally interconnected with PFC^{19,20}. These regions have been implicated previously in target detection^{11,12,21,22}, task switching^{23,24} and active manipulation of information^{25,26}, all of which require moment-to-moment changes in cognitive processes. In target detection tasks, for example, infrequent targets but not frequent non-targets are found to activate PFC. Likewise, in task-switching experiments, PFC activation is transiently evoked when subjects change from performing one behavior to performing another. Our results presented here indicate that this activation does not result from simple changes in response or from changes in stimulus properties. Instead, we conclude that it is evoked by moment-to-moment updating of mental models for pattern.

Activation during this pattern violation task differs from that associated with explicit sequence learning tasks. When subjects explicitly learn a sequence of motor actions, such as a pattern of finger movements, activation is evoked in parietal and premotor brain regions^{27,28}, but not in prefrontal regions as observed here. We informed subjects that the stimuli were presented in a random sequence, that there was no need to make explicit predictions and that there was no benefit in doing so. Many subjects reported, during post-experiment debriefing, that although they understood that the stimuli were presented in a random order, they still noticed patterns in the sequence. Thus, we believe that the recognition of event pattern is obligatory, in that it occurs without any conscious attentional effort and in that the identified set of prefrontal regions is distinct from that active when consciously learning stimulus sequences.

Violations of a repeating pattern evoke PFC activation in ‘oddball’ target detection tasks, in which infrequent targets require a different response than frequent non-target stimuli^{11,12}. Furthermore, electrophysiological studies using oddball tasks suggest that global stimulus context, as manipulated by

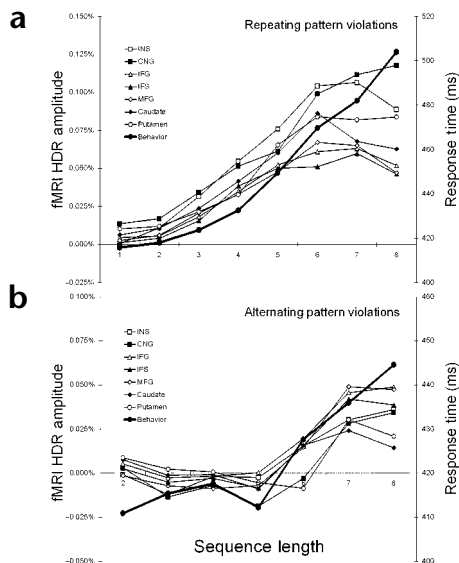


Fig. 5. Dependence of HDR amplitude on stimulus pattern. Each line indicates the mean amplitude of the HDR from 5–7 s after stimulus onset (left), as a function of pattern length before violation, for prefrontal ROIs specified in the key. Right, behavioral response time is shown for comparison. (a) For events that violated a repeating pattern, HDR amplitude increased with sequence length, reaching a plateau at pattern lengths 6–8. (b) For events that violated an alternating pattern, HDR amplitude did not change for pattern lengths 2–5, but increased for lengths 6 and larger.



discriminability between stimuli, influences the amplitude of prefrontally generated evoked potentials^{29,30}. Here we have demonstrated that PFC activation is also influenced by local stimulus context, as determined by the length of the preceding pattern. This result has both theoretical and technical implications. We designed the experiment so that subjects were faced with the same task on every trial. The same stimulus, therefore, elicits a large-amplitude HDR or a small-amplitude HDR (Fig. 4) depending on which stimuli previously occurred. In addition, the correspondence between stimulus sequence and HDR amplitude was remarkable, in that the HDR amplitude in most brain regions was dependent on the identity of the seventh preceding stimulus, which was presented 14 seconds earlier. As discussed above, subjects do not consciously rehearse the contents of the preceding seven stimuli; indeed, such a task would be impossible without training. Instead, there is an implicit representation of the preceding sequence that contains information, at least for the structured repeating and alternating patterns measured here, about the previous seven or eight stimuli.

The presence of significant effects, here lateralized to the right hemisphere, for alternating patterns conclusively demonstrates sensitivity to pattern structure, not just simple stimulus or response dishabituation. A similar right-hemisphere lateralization for processing complex patterns has been identified in auditory music perception³¹, and this lateralization may require the presence of short-term pattern violations³². Beyond differences in lateralization, repeating and alternating patterns have different moment-to-moment effects upon the PFC. Models for repeating patterns are established rapidly, in that only a few (one or two) repetitions are needed before a violation evokes prefrontal activation. In contrast, a longer series of alternations (six or seven) is required to establish a model for an alternating pattern. We predict that future studies will find activation in response to violations of any sequential pattern (for example, ABBABBABA, which occurs only about 6 times during 1,800 trials), but that more complex patterns will require a greater number of occurrences before a predictive model is established.

We found a dissociation between violations of repeating and alternating patterns in the basal ganglion structures, which are important in the control of voluntary and goal-directed motor movements and in related cognitive processes^{33–35}. Significant activation in the caudate and putamen was found for violations of repeating sequences, but not for violations of alternating sequences. This dissociation suggests that, in the present experimental context, the basal ganglia are involved in changing response modes (preparing and/or executing a new motor behavior) but not specifically in the recognition of complex event patterns.

Finally, the demonstration of changes in PFC activation with stimulus sequence complements decades of behavioral studies of sequence effects. In choice tasks that present stimuli in a random order, there are marked effects of stimulus sequence on behavior^{15,16} that may extend across multiple trials¹⁷ and are present for both repeating and alternating patterns¹⁸. Although EEG studies show a correspondence between behavioral response time and amplitude of the P300 event-related potential³⁶, until now no similar correspondence has been identified using fMRI or other techniques that localize brain activity. The current results demonstrate that, across sequence lengths, response time closely matches HDR amplitude. Most notably, violations of alternating patterns do not affect either measure for sequences of length 5 or shorter, but significantly affect both for longer sequences. We interpret this convergence as strong evidence for the role of these brain regions in identifying structure in sequences of events.

We conclude that brain regions within the PFC, specifically posterior-inferior and anterior dorsolateral regions, evaluate predictive mental models of upcoming events on a moment-to-moment basis. The cortical representation of the mental model strengthens with further consistent incoming information, as in the current experiment when a pattern extended over many stimuli, so that violations of well-established models evoke more brain activation than do violations of weak models. Thus, the recognition of patterns is an obligatory, dynamic process that includes the extraction of local structure from even random sequences.

METHODS

Participants. Sixteen healthy volunteers (18–32 years old; 9 female, 7 male) gave written consent to participate in the study. This project was approved by the Institutional Review Board of Duke University Medical Center.

Experimental design. On each trial, a single circle or square (about 6° of visual angle) was presented at fixation for 250 ms (Fig. 1a), with stimulus-onset asynchrony fixed at 2,000 ms. The shapes were presented in random order over approximately 1,800 trials. Subjects were instructed to press a single button for each shape on a fiber-optic response box (circle, left; square, right), responding as quickly as possible while maintaining a low error rate. Behavioral data from two subjects were not recorded because of equipment problems. All response time analyses use data from the remaining 14 subjects.

Our analyses were time-locked to the events that violated preceding stimulus patterns (Fig. 1b). Two types of violations were identified: violations of repeating patterns [AAAAB] and violations of alternating patterns [ABABAA]. Analyses were independent of stimulus and response hand, in that the patterns [AAAB] and [BBBA] were considered to be equivalent. All repeating and alternating patterns from length 2 to length 8 were analyzed, and the same stimulus may be part of more than one pattern. The overall sequence of stimuli was completely random; each stimulus had a 0.5 probability of being presented on each trial. The identified short-term patterns occurred by chance, and were not inserted into the sequence.

fMRI methods. Functional images encompassing the PFC were acquired using blood oxygenation level-dependent (BOLD) contrast T2*-weighted echoplanar MRI (TR, 1,000 ms; TE, 40 ms; flip angle, 81°; voxel size, 3.75 × 3.75 × 5 mm) on a 1.5-T GE (Waukesha, Wisconsin) scanner. To sample brain activity at the high temporal resolution necessary to fully characterize the fMRI hemodynamic response, our imaging volume was restricted to twelve 5-mm slices, perpendicular to the line connecting the anterior and posterior commissures. We focused on PFC because of previous research implicating it in the processing of infrequent target stimuli. Owing to the constraints upon our imaging volume, no fMRI data was recorded from parietal, temporal or occipital cortices.

High-resolution spin-echo images (coplanar with functional images) and spoiled gradient-recalled acquisition (SPGR) images (three-dimensional, full-brain) were acquired to aid in normalization and coregistration. We applied, to each subject's time series, a low-pass Butterworth filter (9th-order; zero phase forward and reverse digital filter; MATLAB software, Mathworks, Natick, Massachusetts) with a cut-off frequency of 0.415 Hz. Functional images were corrected for subject motion and time of acquisition within a TR and were normalized into a standard stereotaxic space (Montreal Neurological Institute, Montreal, Canada) for intersubject comparison, using SPM99 software (Wellcome Department of Cognitive Neurology, London, UK).

In all analyses, active voxels were identified by cross-correlation of signal time courses evoked by violations of length-5 repeating patterns [AAAAAB] or of length-6 alternating patterns [ABABABB] to an empirical reference waveform that was lagged from 4 s to 9 s, latency to peak. The significance threshold was determined by Bonferroni correction for multiple comparisons at $P < 0.05$ ($t > 6.58$). Each ROI consisted of a set of active voxels within a single anatomical region (minimal cluster size was three adjacent active voxels, uninterpolated)^{37,38}.



Brain regions that showed systematic changes in activation amplitude with sequence length are indicated in Table 1. The MNI coordinates indicate the centroid of the active region. One additional brain region, the medial frontal gyrus ($x, y, z = 0, 18, 62$), had significant activation to violations of repeating patterns. However, visual inspection of the waveforms revealed a greater HDR latency (peak at 9 s) as compared with the other activated regions, and no significant effects for alternating sequences. Therefore, this region was not included in the table of significant activations.

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Competing interests statement

The authors declare that they have no competing financial interests.

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