

NEURAL MECHANISMS FOR DETECTING AND REMEMBERING NOVEL EVENTS

Charan Ranganath* and Gregor Rainer‡

The ability to detect and respond to novel events is crucial for survival in a rapidly changing environment. Four decades of neuroscientific research has begun to delineate the neural mechanisms by which the brain detects and responds to novelty. Here, we review this research and suggest how changes in neural processing at the cellular, synaptic and network levels allow us to detect, attend to and subsequently remember the occurrence of a novel event.

COGNITIVE NEUROSCIENCE

Imagine that you are in a classroom listening to a lecture. As you pay attention to the speaker, you might fail to notice other ongoing events, such as the students taking notes next to you or the flickering of a fluorescent light. Then, suddenly, your attention is diverted when a naked man enters the room.

This anecdote was drawn from the experiences of one of the (fully-clothed) authors while he was an undergraduate at the University of California, Berkeley. Suffice to say, the entrance of the ‘naked guy’ was a novel event in that it was unexpected and out of context. The story illustrates two points — novel events attract attention and they are more effectively encoded in memory than are predictable events.

In nature, the ability to respond rapidly to novel events is fundamental to survival, but little theoretical work has been carried out to establish how the brain processes novelty. Recent research has shown that the occurrence of a novel event triggers a cascade of neural events that are relevant to perception, attention, learning and memory. Although several models have been used to study the effects of novelty, the results from these different approaches might reveal common underlying mechanisms by which the brain responds to novel events. First, we discuss research into how the brain responds to two types of novelty — stimulus novelty and contextual novelty. Next, we review research revealing the neural mechanisms by which novel events

are encoded into memory. Finally, we consider the role of neurotransmitter systems in coordinating a wide range of neural responses to novel stimuli.

Stimulus novelty

One type of novelty that has been studied extensively in humans, non-human primates and rodents is stimulus novelty. The effects of stimulus novelty can be seen as changes in behavioural and neural responses to a stimulus as it is repeated. Behaviourally, repetition often results in priming — that is, repeated items are often processed more fluently and efficiently¹. In addition, studies of perceptual learning that involve extensive repetition of stimuli during training have documented improvements in identification or classification of learned items². Stimulus repetition is often (but not always) accompanied by reductions in associated neural activity in cortical and subcortical brain regions^{3,4}. Note that a reduction of activity for repeated items is equivalent to increased activation when these items are novel⁵. The systematic repetition-related differences in neural and behavioural responses can therefore be thought of as effects of repetition, as has usually been done in previous studies, or as effects of stimulus novelty, as we do here.

Single-unit recording studies have shown that repetition suppression — the reduction of neural activity with repetition of a stimulus across a brief interval — is a common feature of neurons in inferior temporal, medial

*Center for Neuroscience and Department of Psychology, University of California, Davis, 1544 Newton Ct., Davis, California 95616, USA.
‡Max-Planck-Institute for Biological Cybernetics, Spemannstrasse 38, D-72076 Tübingen, Germany
e-mails: cranganath@ucdavis.edu; gregor.rainer@tuebingen.mpg.de
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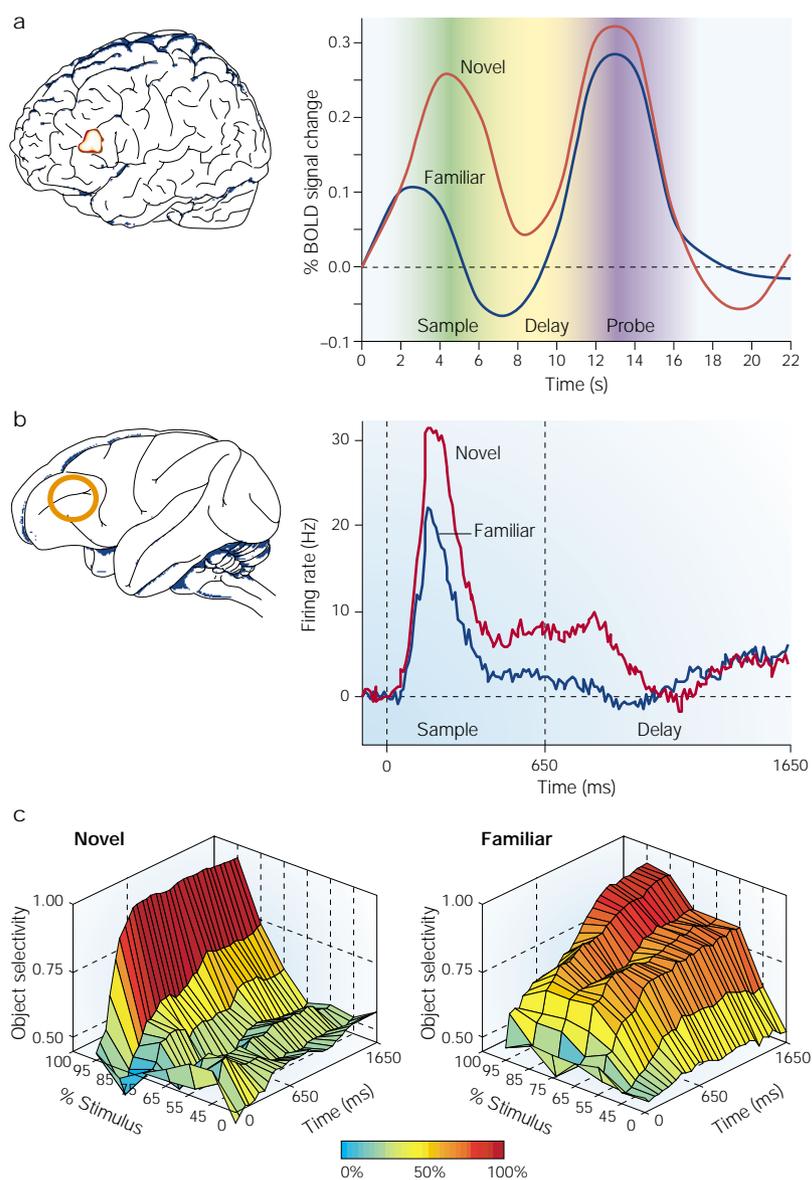


Figure 1 | Stimulus novelty effects in humans and monkeys. a | Results of a blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) study, in which activity during a delayed matching-to-sample task was compared between trials involving novel or familiar stimuli³². Activity is shown for a region in the lateral prefrontal cortex that had a greater delay-period activity during ‘novel’ trials than during ‘familiar’ trials. The coloured gradient in the background of the graph shows when a peak in activity would be expected if it related to encoding of the sample stimulus (green), rehearsal of the stimulus (yellow) and stimulus recognition (purple), assuming a 4–6 s time lag in the BOLD response. BOLD responses during the sample and delay periods were larger during ‘novel’ trials (red line) than during ‘familiar’ trials (blue line). Parts **b** and **c** are results of single-unit recordings from the sulcus principalis of the monkey lateral prefrontal cortex during a delayed matching-to-sample task with novel and familiar stimuli. Reproduced, with permission, from REF. 43 © (2000) Elsevier Science. **b** | Average firing rates across the population of sampled neurons (novel objects: $n = 160$; familiar objects: $n = 164$) during the sample and delay periods. Neural activity in the prefrontal cortex, during the sample and delay periods, was enhanced for novel relative to familiar objects. **c** | Although familiar objects activated fewer neurons than did novel objects, neurons coding for familiar objects showed more robust tuning in the face of stimulus degradation. Object selectivity of single neurons is shown for familiar and novel objects as a function of time during the trial and stimulus degradation by noise interpolation. The time period consists of stimulus presentation (0–650 ms) followed by a 1 s delay. 100% stimulus represents undegraded stimuli and 0% represents pure noise. Object selectivity had a steep slope for novel objects, whereas it resembled a broad plateau for familiar objects. Visual experience resulted in a smaller population of selective neurons, but this smaller population coded the familiar information more robustly.

temporal and prefrontal cortices. This effect occurs in a wide variety of tasks, including DELAYED MATCHING-TO-SAMPLE^{6–9} and classification¹⁰, as well as during passive viewing and even under general anaesthesia¹¹. The effects of repetition suppression are stimulus specific, in that a particular neuron will show reduced responses to repeated stimuli whereas the responses of the same neuron to novel stimuli will be largely unaffected. These effects occur over short timescales — it is estimated that neurons recover their responsiveness after about six seconds in awake monkeys¹¹. Finally, because the effects of repetition suppression carry information about recently seen stimuli, it has been proposed that they might be a passive mechanism for short-term memory^{9,12}, but only in simple tasks without intervening distractors.

A largely separate body of work deals with a property of neurons in sensory visual areas known as adaptation. Adaptation is the reduced response of cortical neurons to a particular stimulus after previous exposure to that stimulus^{13,14}. Although adaptation has generally been studied with long-adapting stimulus durations of several seconds in the anaesthetized cat, it also affects neural responses in the visual cortex of awake monkeys¹⁵. Adaptation seems to share many of the features of repetition suppression, as described above. For example, it operates over short timescales (of the order of seconds), it is at least partly stimulus specific¹⁶ and it seems to be automatic.

Recent work has identified a cellular mechanism that contributes to both adaptation and repetition suppression. An intracellular recording study identified a calcium-dependent potassium current as an important contributor to adaptation in the primary visual cortex¹⁷. The same current was identified as a plausible mechanism for repetition suppression in a study that used a neural network model of the inferior temporal cortex¹⁸. So, adaptation and repetition suppression might be two instantiations of the same cellular mechanism. The effects of this mechanism on neural activity might be compounded at higher levels of the visual processing hierarchy. This could help to explain the relatively high level of repetition suppression that is seen in some perirhinal cortex neurons¹⁹, in which a single repetition of a stimulus can sometimes lead to marked attenuation of neural responses. Interestingly, whereas repetition suppression is thought to contribute to short-term recognition memory¹², adaptation has been linked to various perceptual illusions, such as the TILT AFTER-EFFECT, and to optimization of information transmission through TEMPORAL DECORRELATION²⁰. So, the same biophysical mechanism seems to contribute to two different behavioural effects depending on where in the brain it operates. This mechanism might therefore reflect an inherent property of cortical neurons rather than being a specialized feature designed to solve a particular task.

Reductions in neural activity with repetition have also been observed over longer timescales, as documented by trends observed in a session lasting several hours or as systematic changes across training days. In the inferior temporal cortex, neural responses decline systematically over several hours in a delayed matching-to-sample task²¹, and similar effects are seen in neurons in the

Box 1 | Stimulus novelty, synaptic plasticity and memory formation

Most investigators studying the effects of stimulus repetition frame their results in terms of the effects of repetition, rather than the effects of novelty. However, investigations of field potentials recorded from the human medial temporal lobes during performance of verbal memory tasks indicate that some neural mechanisms might specifically affect the processing of relatively novel information. In these studies, field potentials were recorded in patients with severe epilepsy who had electrodes placed in their medial temporal lobes for presurgical evaluation. Several previous intracranial event-related-potential studies observed a potential generated in the anterior medial temporal cortex, known as the AMTL-N400, the amplitude of which is sensitive to the novelty of a word^{41,133–138}. One study found that epilepsy patients with hippocampal sclerosis had a reduced N400 response to novel words, relative to epilepsy patients without hippocampal sclerosis¹³⁴. By contrast, the N400 response to familiar words was not affected by hippocampal sclerosis, indicating that integrity of the hippocampus was crucial specifically for the enhanced N400 response to novel stimuli. A follow-up study showed that the magnitude of the N400 response to novel words was directly correlated with neuronal density in the CA1 subfield of the hippocampus⁴¹. In addition, administration of the NMDA (*N*-methyl-*D*-aspartate) receptor antagonist ketamine selectively attenuated the N400 response to novel words⁴¹. Collectively, these results indicate that there is a link between hippocampal NMDA receptor function and the encoding of novel stimuli.

DELAYED MATCHING-TO-SAMPLE TASKS

Recognition memory tasks in which presentation of a stimulus is followed by a delay, after which a choice is offered. In matching tasks, the originally presented stimulus must be chosen; in non-matching tasks, a new stimulus must be selected. With small stimulus sets, the stimuli are frequently repeated and therefore become highly familiar. So, typically, such tasks are most readily solved by short-term or working memory rather than by long-term memory mechanisms.

TILT AFTER-EFFECT

If you stare at a set of lines that are tilted in one direction from upright, upright lines will subsequently look as though they are tilted in the opposite direction.

TEMPORAL DECORRELATION

Small eye movements made during free viewing of natural scenes tend to expose neurons to similar but not identical structure. Adaptation can reduce responses to structure that is similar across fixations, removing correlations.

EYE FIELD

An area that receives visual inputs and produces movements of the eye.

superior temporal sulcus during passive viewing²² and in the medial temporal cortex during a serial recognition task²³. Robust reductions in activity have also been seen in the prefrontal cortex²⁴ and in the frontal and supplementary EYE FIELDS²⁵ during CONDITIONAL OCULOMOTOR LEARNING, reflecting many weeks of training. Familiarity-dependent reductions in neural activity have also been revealed in early visual areas by two perceptual learning studies^{26,27}. Monkeys were trained on a task that involved repeated presentation (and discrimination) of gratings of a particular orientation in one part of the visual field. After many months of training, the monkeys' perceptual ability to discriminate gratings around the trained location and orientation was greatly improved²⁶. In addition to other effects not discussed here, both studies found a slight reduction of V1 neural population activity for the trained orientation at the trained location. Unlike repetition suppression, these 'familiarity effects' are long-lasting. Although familiarity effects can be detected after only minutes of experience, they probably continue to develop over longer periods of time (hours to days) and are thought to be mediated by synaptic plasticity²⁸.

Effects that are similar to the repetition-related phenomena observed in neural activity can also be seen in activity-dependent correlates, such as the blood oxygenation level-dependent (BOLD) signal measured in functional magnetic resonance imaging (fMRI) studies of human subjects⁴. Reductions in BOLD signal levels with stimulus repetition have been observed in several studies in prefrontal, medial temporal and inferior temporal regions^{29–33}, as well as in sensory areas^{34,35} (FIG. 1). It is probable that adaptation of the BOLD signal is in part due to the same mechanisms that give rise to the stimulus novelty effects described above. However, it is important to keep in mind that, in addition to local activity, other mechanisms such as intracortical feedback contribute to the BOLD signal. Because BOLD signals correlate better with local field potentials (which

largely reflect the synaptic inputs to a given region) than with spiking activity (which reflects the region's output)³⁶, such modulatory influences might be relatively amplified in BOLD signal levels compared with spiking activity³⁷.

To link the generally observed reductions in neural activity in response to repetition with improved processing of these repeated stimuli, several authors have suggested that neurons showing repetition effects are 'dropping out' of the object representation^{38,39}. One way in which this might occur is through synaptic plasticity⁴⁰. Consistent with this hypothesis, one study found that blocking NMDA (*N*-methyl-*D*-aspartate)-receptor-dependent synaptic plasticity eliminated medial temporal lobe field potentials that were correlated with stimulus repetition⁴¹ (BOX 1).

The models described earlier indicate not only that stimulus repetition produces less overall activity, but also that the net effect of this reduction is a more finely tuned object representation. Direct evidence for this idea comes from a study of the prefrontal cortex, in which familiarity resulted in a reduction in the population-level activity in a delayed matching-to-sample task (FIG. 1b). As shown in FIG. 1c, the smaller population of neurons that responded to familiar objects coded these objects more robustly with respect to stimulus degradation^{42,43}.

However, this account cannot explain activity reductions in early visual areas. It would predict that neurons that represent non-optimal orientations or locations might become less responsive with training, which would cause a reduction in their activity. However, activity reductions with perceptual learning are seen specifically for neurons at the trained location and orientation^{26,27}. What might be the source of these reductions? We suggest that the slight reductions in early sensory areas result from a network effect. That is, reductions in early sensory areas might reflect reduced feedback coming from higher areas as a result of a sparser representation of the learned stimuli in those higher areas.

The results reviewed above show that repetitive presentation of a stimulus facilitates the processing of that stimulus and leads to reductions in the average neural activity in many cortical regions. Reductions are seen for timescales ranging from seconds to many months of training, and they reflect distinct mechanisms operating at the cellular, synaptic and network levels. These findings indicate that, in one sense, novel stimuli might be less efficiently processed than familiar or repeated stimuli. As described later, however, the increased activity elicited by novel stimuli can confer other processing advantages.

Contextual novelty

Another type of novelty that has been researched extensively is contextual novelty. A stimulus or event can be thought of as contextually novel if it arises in an unexpected context (for example, the 'naked guy' entering the classroom). When an event is particularly novel or surprising, it will elicit an orienting response⁴⁴, with

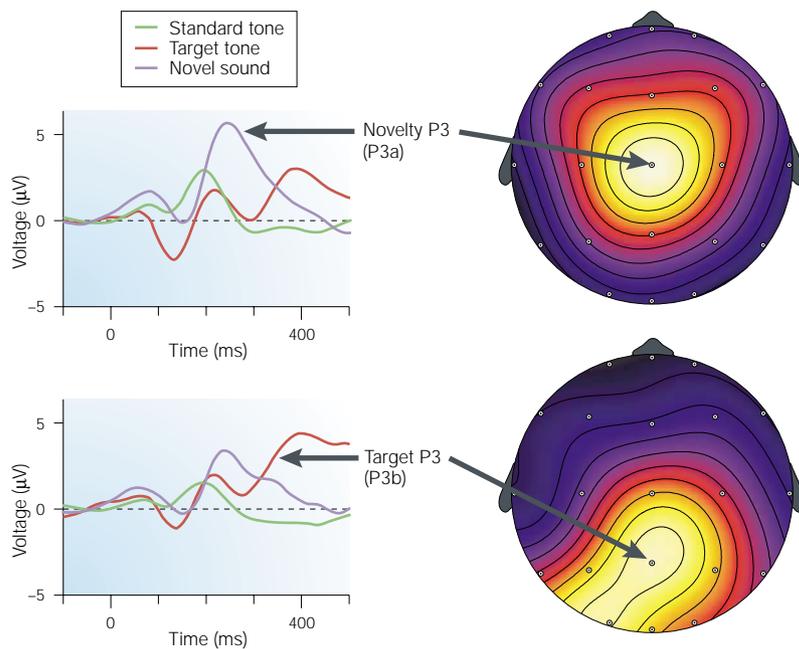


Figure 2 | **The novelty P3.** In typical experiments used to investigate contextual novelty, event-related potentials are recorded during an auditory target-detection task. For example, subjects might be instructed to respond to an infrequent target tone amidst a series of frequent 'standard' sounds and infrequent novel distracter sounds (such as a dog's bark). Scalp-recorded brain potentials elicited during one such study are shown in the plots on the left. Infrequent novel sounds (purple line) elicited a novelty P3 potential at anterior scalp sites that peaked ~240 ms after the sound. Reproduced, with permission, from REF. 58 © (1999) MIT Press. A topographic ERP amplitude map (right) illustrates the relatively anterior topography of the novelty P3 potential on the scalp (as viewed from above). This potential was not elicited by the standard sounds, which were also task-irrelevant, or the target sounds, which were also infrequent. Target sounds did, however, elicit a positive potential that peaked ~400 ms after the sound over posterior scalp sites. The map (right) illustrates the relatively posterior topography of the target P3 (also called the P3b).

attentional resources being automatically diverted towards the stimulus⁴⁵.

Substantial insights into the nature of the orienting response have come from studies of scalp-recorded **EVENT-RELATED POTENTIALS (ERPs)** in humans. An ERP associated with contextual novelty — the P300 or P3 — was first described by Sutton and colleagues in 1965 (REF. 46). Although the P3 has been studied most extensively in humans, 'P3-like' potentials have been recorded from macaque and squirrel monkeys, cats, rabbits, rats, dogs and dolphins, indicating that the P3 might represent processes that are conserved across mammalian species⁴⁷. Four decades of research have shown that the P3 probably reflects a family of potentials that are related to different types of attentional processes^{48–56}. The potential that is most directly linked with novelty is the P3a (REF. 49) or 'novelty P3' (REF. 48). In a typical novelty P3 experiment, a subject will perform an auditory target detection task with simple pure tone stimuli, and will occasionally hear a contextually novel sound (such as a dog bark) amidst these tones. Unlike the standard and target tones, these novel sounds elicit a scalp-recorded potential that peaks about 200–300 ms after the stimulus and that is largest over the central and frontal scalp electrodes (FIG. 2). The early latency of this potential indicates that novel stimuli rapidly modulate cognitive processing.

The functional characteristics of the novelty P3, and the cognitive processes it might index, have been a topic of active investigation⁵¹. Results from these studies have shown four important characteristics of the P3a. First, novelty P3 responses habituate across successive presentations of novel items, indicating that as these stimuli become more predictable, the magnitude of the response wanes^{57–61}. Second, novelty P3 responses are not tied to any particular modality — similar novelty P3 responses have been observed for novel visual, auditory and somatosensory events^{57,62,63}. Third, although the novelty P3 is typically elicited experimentally by complex sounds, similar potentials can be derived with simple stimuli, provided that they are contextually deviant^{49,64}. Fourth, although task manipulations can affect the magnitude of the novelty P3 (REFS 65–68), a stimulus can elicit a robust novelty P3 even if it is task-irrelevant⁴⁸ or if it is ignored^{49,58,69}. The early latency of the novelty P3, together with the functional characteristics described above, indicate that the novelty P3 reflects the activity of a general network for rapidly orienting to novel stimuli or events^{51,52}.

Several sources of evidence implicate regions in the prefrontal cortex and the medial temporal lobes as important components of the network that generates the novelty P3. For example, evidence has come from studies of patients with epilepsy in whom intracranial electrodes have been implanted for presurgical evaluation. Intracranial ERP studies in these patients have reported cortical-field potentials that have properties analogous to those of the scalp-recorded P3 (REFS 54,70–78; BOX 2). These field potentials have been most commonly observed in the dorsolateral, ventrolateral and orbital prefrontal cortex, cingulate cortex, lateral temporo-parietal cortex, hippocampus and parahippocampal cortical regions. Using an experimental design to elicit responses specific to novel stimuli^{73–75}, Halgren and colleagues observed field potentials generated in orbital, ventrolateral and dorsolateral prefrontal regions that were temporally and functionally similar to the novelty P3 (REF. 75). Outside the prefrontal cortex, similar field potentials were recorded from sites in the medial temporal (perirhinal and posterior parahippocampal) cortex, subicular complex (in the hippocampal formation), temporoparietal cortex and cingulate gyrus^{73,74}.

As shown in FIG. 3, studies of patients with focal brain lesions also indicate that prefrontal, temporo-parietal and medial temporal cortical regions are important for responding to contextual novelty. For example, patients with lateral prefrontal^{57,63,79–82}, lateral temporoparietal^{63,81,83} or posterior medial temporal lobe lesions^{62,82} resulting from strokes have attenuated novelty P3 responses to novel auditory, visual or somatosensory stimuli. Further studies have shown that patients with prefrontal or medial temporal lesions also do not show peripheral indices of orienting to contextually novel events, as indexed by skin conductance responses^{62,84}. In addition, some findings indicate that patients with lateral prefrontal lesions divert less attention towards novel stimuli, and this reduction is directly correlated with the attenuation of

CONDITIONAL OCULOMOTOR LEARNING

An association between a set of stimuli and a set of eye movements has to be learned by trial and error, where each stimulus is associated with a particular eye movement.

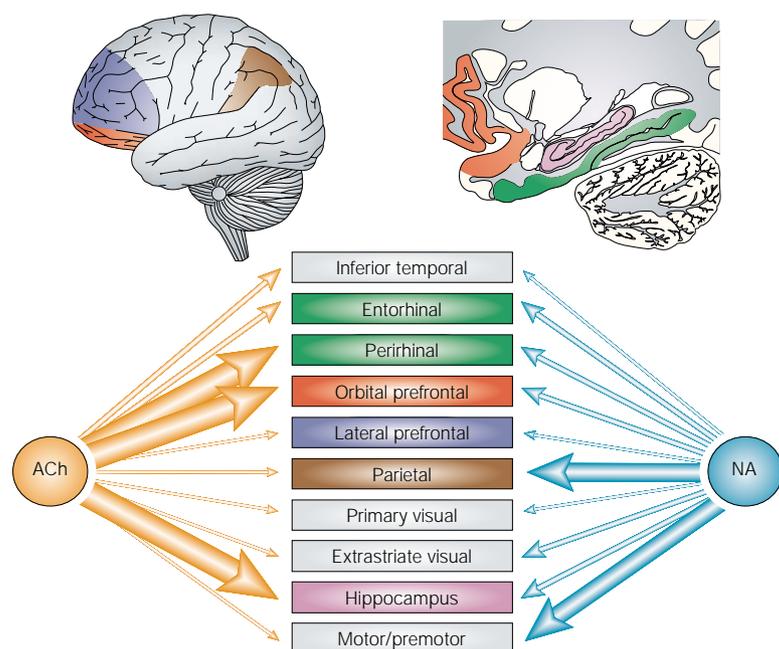
EVENT-RELATED POTENTIALS

Electrical potentials that are generated in the brain as a consequence of the synchronized activation of neuronal networks by external stimuli. These evoked potentials are recorded at the scalp and consist of precisely timed sequences of waves or 'components'.

Box 2 | Brain regions implicated in novelty processing

Several brain regions have been implicated in novelty processing, leading some researchers to suggest that these regions represent a distributed network for novelty detection^{50,52}. This network includes areas in the lateral prefrontal cortex (blue), orbital prefrontal, anterior insular and anterior temporal cortex (red), temporoparietal cortex (brown), medial temporal areas along the parahippocampal gyrus (including the perirhinal and posterior parahippocampal cortices, dark green), and hippocampal formation (including the entorhinal cortex, dentate gyrus, CA1-3 subfields and subicular complex, purple). Other areas implicated in novelty processing (not shown) include the amygdala and the cingulate gyrus.

These areas correspond relatively well to the projection zones of two neurotransmitter systems: acetylcholine (ACh) and noradrenaline (NA). In the lower panel, the thickness of the arrows corresponds to the relative strength of projections to each region. Although both ACh and NA project widely across the cortex, the strengths of these projections vary — ACh projections are strongest to orbital prefrontal and medial temporal regions¹¹³, whereas NA projections are strongest to parietal and motor areas^{128,139,140}. Activity in both ACh and NA neurons that project to the cortex is sensitive to novelty, indicating that these neuromodulatory systems are crucial for orienting attention to and enhancing memory for novel stimuli.



the novelty P3 (REFS 79,80,85). In contrast to the effects of lateral prefrontal lesions, which reduce or eliminate the novelty P3 response, the results of one study indicate that damage to the orbital prefrontal cortex enhances the novelty P3 (REF. 86). These investigators concluded that the orbital prefrontal cortex might suppress or modulate the novelty response, although further evidence is required to confirm this finding.

Functional neuroimaging — particularly EVENT-RELATED fMRI — has been another valuable tool in identifying the neural sources of the scalp-recorded novelty P3. However, correspondence between fMRI and ERP studies must be interpreted with caution. Whereas ERPs directly index electrophysiological activity with a high degree of temporal resolution, the BOLD response reflects changes in blood oxygenation that occur several seconds after the corresponding neural events. As we noted earlier, BOLD responses detected by fMRI

correlate well with local field potentials⁸⁷, indicating that they might also correlate well with scalp-recorded field potentials. Nonetheless, because of the different time-scales of ERP and fMRI methods, these two measures might not always be in close correspondence.

With these caveats in mind, results from fMRI studies of contextual novelty have generally corresponded well with results from intracranial ERP and lesion studies. In event-related fMRI experiments similar to ERP studies used to evoke a novelty P3, novel stimuli elicit BOLD responses in the inferior frontal gyrus, insula, temporoparietal junction and anterior cingulate^{87–92}. One limitation of these studies, however, is that it was unclear whether activations in response to novel stimuli were due to the contextual novelty of the items or whether they were due to other factors related to the lower-level features of the novel stimuli. Nonetheless, in accordance with previous ERP results⁶⁴, the results of two fMRI studies indicate that this network responds robustly to violations of stimulus context, even when stimulus factors are well controlled^{93,94}.

In each of these fMRI studies^{93,94}, a train of simple stimuli were presented, and brain responses were examined in response to events that violated a pattern of preceding events. In one study⁹⁴, subjects were presented with a random string of two shapes, each requiring a different response. Response latencies to an item that violated a pattern in the previous trials (for example, a square presented after three circles) increased linearly with the length of the preceding pattern. Activation in the middle and inferior frontal gyri, anterior insula and dorsal anterior cingulate regions showed a similar pattern, indicating that activity in these regions was sensitive to contextual novelty. In another study⁹³, subjects passively experienced simultaneous trains of auditory, visual and somatosensory stimuli. These stimuli were repeated except for at certain times, when a stimulus in one modality would change. Such changes were associated with enhanced activity in the inferior frontal gyrus, anterior insula and dorsal anterior cingulate, regardless of the modality in which the deviation occurred. These results strongly implicate regions in the ventrolateral prefrontal cortex, cingulate gyrus and anterior insula in orienting to contextually novel events.

Few functional imaging studies have found evidence for medial temporal responses to contextual novelty, despite the evidence from ERP and lesion studies. However, most fMRI studies that have investigated responses to contextually novel events did not examine the dynamics of activity over the course of stimulation. One study that did find evidence of medial temporal lobe activation⁹⁵ specifically investigated whether responses to novel events habituated over time. Consistent with the previous ERP results^{57–61}, these investigators found evidence for initial activation of the hippocampus upon presentation of contextually novel stimuli, and this activation habituated with repeated presentations. This finding converges with results from three other studies using different models that also found evidence for initial activation and rapid habituation of hippocampal activation^{96–98}.

EVENT-RELATED fMRI

A variant of functional magnetic resonance imaging (fMRI) methods that allows neural correlates of individual trials or classes of trials to be isolated and compared.

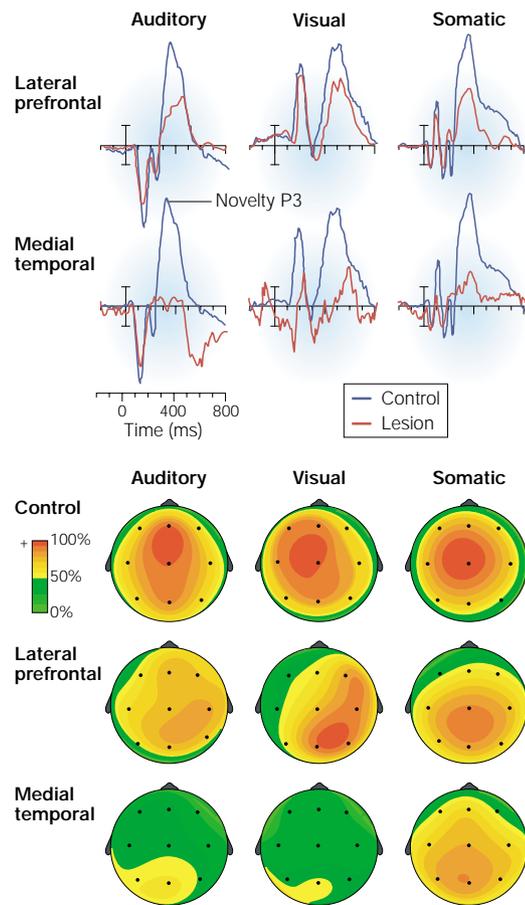


Figure 3 | Effects of lateral prefrontal or posterior medial temporal lesions on the P3. Results from several studies indicate that lateral prefrontal and posterior medial temporal regions are crucial for the generation of the scalp-recorded novelty P3^{62,63,81,82}. Upper part shows plots of the novelty P3 elicited in the auditory, visual and somatosensory modalities in patients with lateral prefrontal or posterior medial temporal lesions (red lines) and matched control groups (blue lines). Positive is plotted upwards. Scale bar for the auditory and somatosensory plots, 2 μ V. Scale bar for the visual plots, 1 μ V. Lower part shows topographic maps illustrating the scalp topography of the novelty P3 in the two patient groups and the control group. For illustration purposes, a subset of the electrode locations used to calculate each map are shown as black circles. The novelty P3 had a frontal topography in control subjects across all modalities whereas the novelty P3 topography was more posterior in patients with prefrontal lesions, and was virtually eliminated in patients with medial temporal lesions.

So, converging evidence indicates that a network of brain regions responds to stimuli that are contextually novel. This network includes areas in the prefrontal cortex, anterior insula, cingulate gyrus, temporoparietal cortex, medial temporal (entorhinal, perirhinal and parahippocampal) cortex, and the hippocampal formation (BOX 2). Although the results reviewed earlier indicate that these regions are recruited during the processing of novel stimuli, a subset of these regions, as we review below, might also be crucial for encoding novel events into memory.

Novelty and memory

As well as diverting attentional resources, contextually novel events tend to be encoded in memory more effectively than events that are less distinctive. Contextual novelty might contribute to the ‘primacy effect’ described in behavioural studies of memory — in which items that are presented first in a list are remembered better than subsequently presented items.

Enhanced memory for contextually novel items has been studied most directly in experiments using variants of a model developed by von Restorff⁹⁹. In these studies, a few contextually novel items are studied amidst a group of relatively homogeneous items (for example, a word printed in red among a series of words printed in blue). Several such studies have shown that memory is enhanced for contextually novel items relative to the less distinctive items^{99–102}, regardless of in what way the event is novel. Collectively, these findings indicate that contextually novel events recruit a neural network that diverts attention towards the salient event⁴⁵ and modulates the encoding of this event in memory^{103,104}.

As we noted earlier, the novelty P3 can be thought of as an index of the diversion of attentional resources towards contextually novel stimuli. If the corticolimbic network that generates the novelty P3 modulates memory encoding, it might be predicted that the magnitude of the P3 response to a contextually novel event would correlate with the degree to which that information is subsequently remembered. ERP studies indicate that this is the case — contextually novel stimuli elicit a large P3 response relative to homogeneous items, and the magnitude of this response correlates with subsequent memory for these items^{105–107}.

Consistent with the results of studies on the neural substrates of orienting responses, results from one lesion study indicate that interactions between prefrontal and medial temporal lobe regions might be crucial for the generation of enhanced memory for contextually novel items¹⁰⁰. In this study, the authors developed an analogue of the von Restorff model and showed that both humans and intact monkeys had enhanced memory for contextually novel stimuli. They also found that lesions that disconnected the frontal and perirhinal cortices in the same hemisphere (that is, lesioning the perirhinal cortex in one hemisphere, and lesioning the prefrontal cortex in the other hemisphere) eliminated the memory enhancement. Recent findings from another group indicate that amnesic patients with extensive medial temporal lesions and patients with lesions limited to the hippocampus do not show a von Restorff effect (Kishiyama, M., Yonelinas, A. and Lazzara, M. submitted). These results underscore the importance of prefrontal and medial temporal regions for the encoding of contextually novel stimuli.

Results from a human neuroimaging study provide further support for this point¹⁰⁸. Volunteers were scanned while studying a series of scenes and words, and BOLD responses were compared between words and scenes that were relatively novel — not encountered before in the session — and words and scenes that were highly familiar — encountered several times just before

the scanning session. Regions in the ventrolateral prefrontal, parahippocampal and fusiform cortices and the posterior hippocampus showed greater activity in response to novel items than familiar items. Each of these regions showed greater activity for novel items that were successfully recognized than for novel items that were later forgotten. These two findings indicate a potential link between the sensitivity of these regions to stimulus novelty and their role in encoding information in memory. These findings, together with those in REF. 100, strongly implicate prefrontal and medial temporal lobe regions in a circuit that mediates the enhanced encoding of novel stimuli and events¹⁰⁹.

Neuromodulatory influences

The idea that prefrontal and medial temporal cortical regions modulate encoding of novel events indicates that there must be a mechanism by which these regions influence the rapid encoding of events that are processed across various cortical regions. One mechanism by which these regions might influence the processing and encoding of novel information is through regulation of neurotransmitter modulation of cortical processing^{47,110} (BOX 2). Several neurotransmitter systems have been implicated in the generation of responses to novelty, but various lines of evidence indicate that acetylcholine (ACh) has a particular role in modulating the encoding of novel events.

ACh tends to elevate the baseline firing rate while enhancing stimulus-evoked activity in certain brain regions, as well as facilitating NMDA-receptor-dependent synaptic plasticity¹¹¹. The main source of cortical ACh is the nucleus basalis of Meynert (NBM), which receives inputs from only a few cortical regions, including the orbital prefrontal, medial temporal (including perirhinal and entorhinal) and anterior insular cortex¹¹². However, the NBM provides ACh input to almost the entire neocortical mantle, with the orbital prefrontal, perirhinal, entorhinal and insular cortex receiving the strongest projections as assessed by ACh-related enzymatic activity¹¹³. By modulating ACh release from the NBM, prefrontal and medial temporal regions can modulate memory encoding across many brain regions.

Several studies have implicated this pathway in learning and memory. For example, disconnection of either the frontal or the temporal cortex from ACh afferents leads to deficits in visual recognition memory and object–reward association learning^{114,115}. In addition, immunotoxic lesions of the NBM lead to reductions in the level of ACh in frontal and temporal cortices, the extent of which are correlated with concurrent behavioural impairments in a learning task¹¹⁶.

These links between ACh and learning are consistent with a view in which ACh systems are preferentially activated by novel stimuli and are instrumental in consolidating memories about such novel stimuli¹¹⁷. Consistent with this view, single-unit recordings from monkeys show that neurons in the NBM have enhanced firing rates to novel stimuli that decline with repetition^{118,119}. Direct evidence for novelty-associated enhancement of cortical

ACh comes from an *in vivo* microdialysis study in freely behaving rats, which found robust increases in cortical levels of ACh while rats explored novel environments¹²⁰. The increases were not correlated with motor activity and there was no change in average glutamate release.

In humans, two studies found that administration of scopolamine, an anticholinergic agent, attenuated behavioural indices of repetition priming and BOLD correlates of stimulus repetition (leading to a reduced difference in the BOLD signal between novel and repeated items)^{121,122}. Administration of scopolamine was associated with impaired learning of novel face–name associations and reduced the BOLD signal in ventrolateral prefrontal, inferior temporal and hippocampal regions¹²³. Although one study reported behavioural impairments in a short-term memory task after scopolamine administration in monkeys¹²⁴, the study failed to find a robust effect of scopolamine on the responses of inferotemporal neurons. Finally, administration of scopolamine in humans reduced frontal P300 responses to infrequently occurring target stimuli^{125,126}. These findings support a direct link between cholinergic neuromodulation and neural responses to novel or contextually deviant stimuli.

Other neuromodulators are probably also involved in generating novelty responses. For example, noradrenaline has similar biophysical properties to ACh, in that it tends to enhance stimulus-evoked activity and promote NMDA-receptor-dependent plasticity¹¹¹. The strong reciprocal interactions between the ACh and noradrenaline systems¹²⁷ indicate that these systems are highly interconnected and are often activated together. Noradrenaline projections originate in the locus coeruleus, and unlike ACh projections, these projections particularly target structures that are involved in attention, such as the parietal cortex¹²⁸ (BOX 2). The noradrenaline system might therefore also contribute to the novelty P3 (REFS 129,130). Single-unit evidence from freely moving rats confirmed that, similar to neurons in the perirhinal cortex²³, locus coeruleus neurons fire in response to novel objects and that this firing habituates rapidly, leading to the release of noradrenaline on just the first few trials¹³¹.

The projection patterns of noradrenaline (focusing on the parietal cortex) and ACh (focusing on frontal and anterior medial temporal cortices) could account for the topography of cortical generators of the novelty P3. Consistent with this idea, an ERP study has found a double dissociation between two components of the novelty P3 centred on frontal and parietal cortical areas⁵⁹. Furthermore, administration of a noradrenaline antagonist in monkeys selectively abolishes the parietal P3, but leaves the P3 in other regions unaffected¹³². By contrast, administration of an ACh antagonist in humans attenuated frontal, but not parietal, P3 responses^{125,126}.

An integrated account of novelty responses
The evidence cited in this review highlights the seemingly contradictory effects of novelty on behaviour. The stimulus novelty effects show that novel stimuli can be at a disadvantage compared with familiar ones. Behavioural evidence indicates that processing of familiar stimuli is

facilitated, and this is usually accompanied by reductions in neural activity across several cortical areas — particularly in prefrontal and medial temporal cortical regions. The available evidence indicates that at least two mechanisms contribute to these effects, one operating over short timescales (seconds) and the other over longer timescales (minutes to days).

Conversely, the contextual novelty effects reviewed earlier indicate that novel stimuli also have advantages over repeated items. For example, novel items tend to attract attention and are encoded into memory more efficiently than are familiar items. These contextual novelty effects have been associated with increases in neural activity across a distributed cortical network that includes frontal, parietal and medial temporal areas. We have hypothesized that neuromodulators — in particular ACh — might provide the means by which this occurs³⁸.

Prefrontal and medial temporal areas receive highly processed information from many modalities. Assuming that activity in these regions reflects summated inputs from lower-level processing areas, we would expect activity in these regions to be most sensitive to the relative familiarity of a stimulus¹⁹. So, when a novel stimulus is encountered, an increase in activity would be expected in these areas. The unique connectivity of prefrontal and medial temporal areas with cholinergic neurons in the NBM might provide a mechanism by which these regions can cause ACh release to target regions of the NBM, thereby directing attentional and mnemonic resources towards novel events. The relative increase in activity in response to novel stimuli in prefrontal and medial temporal regions would therefore lead to the release of greater amounts of ACh from the NBM when compared with amounts that are released in response to familiar stimuli.

By this account, during a typical task used to study contextual novelty, repeated stimulation of neurons representing the standard or target items will — through stimulus repetition effects — lead to reductions in neural activity that will be most robust in prefrontal and medial temporal regions. The occurrence of the infrequent novel item will elicit relatively higher amounts of activity — leading, for example, to release of ACh through interactions of the prefrontal and medial temporal cortices with the basal forebrain. The resultant cascade of activity prompted by cholinergic as well as noncholinergic modulation results in the diversion of attentional resources (as indexed by the novelty P3) and enhanced memory encoding elicited by novel events.

So, stimulus novelty effects are constantly at work at all levels of the processing hierarchy to reduce mean

activity for familiar inputs, so that when novel stimuli are encountered these can cause the release of modulatory neurotransmitters. Familiar stimuli are processed more efficiently because synaptic plasticity produces a smaller population of neurons that represents these familiar stimuli more robustly. By contrast, novel stimuli cause activation in a larger network, leading to release of the neuromodulators ACh and noradrenaline. This results in attention being directed towards processing these novel stimuli, and in more successful memory formation.

Conclusions

The evidence we have reviewed indicates that the occurrence of a novel stimulus elicits a cascade of neural responses that results in enhanced attention to and memory for that stimulus. Recent research has begun to reveal the complex mechanisms by which these changes occur, and we have suggested a tentative model to account for these findings. Nonetheless, substantial work remains to be carried out. Research on stimulus effects and contextual novelty effects has proceeded largely independently of each other. For example, there are very few single-unit studies of contextual novelty effects in monkeys, compared with the wealth of information that has been gathered in ERP studies of human subjects. Filling this gap, and assembling a more unified picture of the various phenomena observed at different timescales and using different techniques, might lead to important breakthroughs in our understanding of basic neural mechanisms for memory and attention. We have advanced the hypothesis that the neuromodulatory transmitters ACh and noradrenaline are closely involved in novelty processing. Although this hypothesis can account for a wide range of findings, further experiments are required to directly test and refine it. In particular, although the anatomical connections between the orbital prefrontal cortex, perirhinal cortex and NBM have been documented, these connections have yet to be functionally characterized.

Finally, we note that the tentative account we have offered to explain novelty processing is a relatively mechanistic model of neural processing. To characterize novelty processing more fully, it will be necessary to clarify these mechanisms at the cognitive level. Associating the effects of novelty at these levels with subjective experience will be a daunting task and might require the development of new psychological constructs. Such an occurrence might turn out to be the most significant benefit to emerge from the development of a cognitive neuroscience of novelty processing.

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