Cortico-limbic Circuits and Novelty: A Review of EEG and Blood Flow Data

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SYNOPSIS

Novelty detection is a fundamental capacity of all mammalian nervous systems /64/. The ability to orient to unexpected events is critical for both survival and normal memory function /82/. The mechanisms whereby the brain detects and responds to novelty have become of increasing interest to neuroscientists. A review is provided of human electrophysiological and blood flow data focused on delineating the neural systems engaged by novelty. Electrophysiological recording of event-related potentials (ERPs) has shown that novel stimuli activate a distributed network involving prefrontal and posterior association cortex as well as the hippocampus /4,23,24,32,33,36,86,88/. Activation of this network facilitates subsequent memory for novel events /27/. Neural modeling provides additional support for a prominent role of novelty in normal memory function /43/. Blood flow studies employing PET and fMRI have also begun to define the neural regions activated by novelty. The blood flow data provide converging evidence on the role of the hippocampus and cortical association regions in the processing of novelty /30,66,75,76/. The results of the behavioral, ERP and blood flow research confirm that a distributed neocortical-limbic circuit is activated by stimulus novelty. These distributed circuits maintain a template of the recent past /74/. Deviations from the template activate a neocortical-limbic network facilitating behavioral response to and memory storage of novel events.

KEY WORDS

novelty, hippocampus, prefrontal cortex, ERPs, fMRI, memory, attention

INTRODUCTION

The ability to detect and respond to new information is one of the highest evolved traits in humans. In lower mammalian species detection and response to deviant environmental events is critical for survival /64/. In humans the role of novelty detection remains crucial for the orienting response and adaptation. However, in humans the ability to process novelty has evolved into a central influence for a wider range of cognitive processes such as memory encoding and creative behavior. In a seminal series of experiments in the 1930s Von Restorff provided experimental evidence that discrete novel stimuli are better remembered /82/. Subsequent behavioral-electrophysiological experiments provided /27/ further support for the notion that stimulus novelty enhances recall.

The novelty of a given stimulus or event also has a powerful effect on memory for everyday events outside the laboratory setting. For instance, unique personal events such as the birth of a child or a death are deeply encoded. Similarly, rare but engaging events such as assassinations are better remembered. Several factors influence this effect. Repetition of the news of Kennedy’s assassination
in part drives deep encoding of that event. However, the first moments a person became informed about Kennedy’s death are also well remembered by most individuals. Indeed, many people remember the exact place and people they were with when news of his death broke. This is a clear example of how the novelty of a discrete situation can have a profound influence on the depth of subsequent memory encoding. Novelty also influences other human behaviors. Creative behavior is routinely defined in direct proportion to its novelty. This relationship extends to all fields of endeavor with typical examples including distinguished performance in art and science. Great art is by definition defined by originality.

In recent years the neural mechanisms of both novelty detection and generation of novel behavior have become of increasing interest in neuroscience. Multiple experimental approaches have focused on the biological mechanisms of novelty processing. For instance, genetic studies of novelty seeking behavior in humans have provided a link to the short arm of chromosome 11 and the dopamine D₄ receptor gene /6,13/. Approaches including classic neuropsychology, electrophysiology and cerebral blood flow have been increasingly employed in an effort to delineate the neural mechanisms engaged during novelty detection or production of novel behaviors in humans. These techniques have revealed that a widely distributed neural network including dorsolateral prefrontal cortex, temporal-parietal junction, hippocampus and cingulate cortex is engaged by both novelty detection and during production of novel behaviors. This is not surprising given the fact that novelty has such a profound effect on human behavior. The current review focuses on behavioral and physiological studies in humans of the cortico-limbic circuits engaged during the processing of novel events.

**ERPs, fMRI and Voluntary Attention**

In everyday life humans are routinely required to detect and respond to environmental events. Examples of voluntary attention might include simple tasks such as looking for a pencil on one’s desk or more complicated tasks such as finding one key reference in a large pile of papers. Both tasks involve the ability to maintain a template of what one is looking for, and when that template is found to mount an appropriate behavioral response. Both these tasks generate large scalp recorded electrical activity to the correctly found stimulus. In the 1960s advances in computer developments permitted development of evoked potential averaging techniques. Evoked responses, now referred to as event-related potentials (ERPs), were employed to study a wide range of sensory and cognitive processes including attention, motor performance, memory and language. In 1965 two separate laboratories described a large parietal maximal positive scalp potential (P300) peaking in amplitude from 300-500 milliseconds after stimulus delivery when a subject voluntarily detected a task relevant event such as a pencil on the desk /10,67/. This ERP is referred to as a P3b response to distinguish it from scalp positive potentials (P3a) generated by novel stimuli which will be discussed in turn. P300 responses to task relevant targets (P3b) and task irrelevant novel stimuli (P3a) are generated in all sensory modalities. P3b responses can even be recorded to the detection of a missing stimulus in a train of irrelevant stimuli.

Researchers studying voluntary attention have operationalized detection behavior to the “oddball task”. In the oddball task a subject is asked to detect an infrequent and low probability event. The detected or target stimulus is referred as the “oddball” stimulus in a series of background stimuli. Detection of the oddball generates a prominent parietal maximal P3b. Theories focused on attention and memory have been proposed to account for the cognitive basis of the P3b although no clear consensus has emerged /12,79/. The most widely held view is that the P3b indexes updating of activity in cortico-limbic circuits during voluntary attention and working memory /12,55,56,79/. Other proposals such as those linking P3b and template matching may also be subsumed under the concept of context updating in working memory /8/. There is an extensive literature on the P3b including electroencephalographic and magnetoencephalographic work in normals, intracranial ERP data from epileptic patients, and lesion and neuropharmacological studies in humans and animal models. These will not be reviewed in detail since several
extensive reviews are available /51,71/. The basic conclusions are that a distributed circuit, including multi-modal posterior association cortex, hippocampus, cingulate cortex and prefrontal cortex, is engaged during voluntary detection tasks. The degree of prefrontal activation as measured by ERPs increases with task difficulty and may be minimal when employing easy detection tasks /70, 72/ or with tasks with minimal working memory load /50/.

Recent event-related fMRI studies have provided additional evidence on P3b sources. Four separate visual or auditory studies employing 1.5T or 4T magnets have reported inferior parietal, superior temporal plane, thalamic and cingulate activations to correctly detected oddballs. Inferior parietal activation was reported by all groups with other regions of activation seen only with the 4T magnet /76/. The degree of prefrontal activation has also varied between different laboratories independently of the size of the magnet /30,41,42,76/. Differences in task design, sensory modality and magnet strength may all contribute to the variability in the results.

Although intracranial recording has provided clear evidence of generation of large hippocampal electrical fields to voluntarily detected stimuli /63/, this activation is not readily apparent with fMRI. One possibility may relate to magnetic susceptibility effects. The authors of one report suggested that differences in sensitivity between ERP and fMRI techniques or differential degrees of sustained activation in cortical versus hippocampal regions could also contribute to the lack of significant activation of the hippocampus /41/.

P300 potentials both to voluntarily detected stimuli and to unexpected task irrelevant novel stimuli are recorded in multiple mammalian species. This ubiquitous brain electrical response has been observed in rats /15,87/, cats /28,46,83/, dolphins /84/ and monkeys /3,45,47,48,52/, supporting a broad ethological significance. The continued development of animal models will be critical for defining the cellular and pharmacological basis of the P300 phenomenon. It is likely that the animal ERP work will converge with ongoing lesion and neuropharmacological research in humans in an effort to delineate the contributions of hippocampal and cortical regions to novelty detection /1,7,31,73/.

**ERPs AND NOVELTY**

In the ensuing decades after Von Restorff’s seminal contribution on the relationship of novelty and memory performance relatively little attention was directed towards understanding the neural basis of this powerful behavioral effect. In the mid-1970s this situation changed with the publication of two papers reporting generation of scalp potentials to novel or deviant stimuli /9,65/. Involuntary orientation to an unexpected and novel stimulus generates a P300 response similar in some regards to that generated by a voluntarily detected stimulus. However, the novel response differs in three important aspects from the voluntary attention related P3b. The novelty P300, referred to as a P3a, has a more fronto-central scalp distribution than the P3b, peaks 60-80 msec earlier in all sensory modalities and undergoes rapid habituation over the first 5-10 stimulus presentations /32,33,36,85/ (Fig. 1). Intracranial recordings of ERPs in the visual, auditory and somatosensory modalities have shown that multiple neocortical and limbic regions are activated during tasks that generate scalp recorded novelty dependent P3a potentials /4,21,23,24,25,40,60/. Single unit recording in humans has also reported novelty related activity in the hippocampus /17/.

Intracranial areas with novelty related activity include frontal and posterior association cortex in addition to cingulate and mesial temporal regions encompassing the hippocampus and adjacent tissue. Scalp and intracranial novelty related ERPs have been proposed to measure neural activity in a distributed multi-modal cortico-limbic orienting system that processes novel events /9,32,65/. Intracranial recordings in humans have shown that limbic recorded voluntary attention and novelty ERPs have differential habituation properties /38,60/ (Fig. 2). The hippocampal recorded target ERP, like the scalp target response, does not habituate over repeated detection of the attended stimulus /38/. Conversely, the hippocampal novelty ERP response, similar to its scalp electrophysiological counterpart, undergoes rapid amplitude
reduction over repeated trials /32,86/. These data provide further support for the theory that the novelty P3a is a central nervous system marker of the orienting response.

FOCAL CORTICAL LESIONS AND NOVELTY

Patients with damage in dorsolateral prefrontal cortex have impairments in both sustained and phasic attention /34/. Neuropsychological testing has documented additional problems with the solving of novel problems /18,19/. Simple attention tasks are typically performed normally by prefrontal patients. Advanced prefrontal disease manifests several classic clinical problems including indifference, loss of creativity, deficits in orienting to novel stimuli and abulia in severe disease. In accord with clinical observations, prefrontal damage results in differential effects on scalp P3a and P3b responses. The parietal P3b and concomitant behavioral performance in simple sensory discrimination tasks is unaffected by prefrontal damage. However, P3b reductions after prefrontal damage are observed in more complex tasks /70,72/, supporting the notion of increasing prefrontal involvement in more difficult tasks.
Conversely, P3a responses to unexpected novel stimuli are markedly reduced by prefrontal lesions. Novelty ERP reductions are observed in the auditory /32,58,59/, visual /36/ and somatosensory modalities /86,88/ after prefrontal damage. The ERP findings in conjunction with the neuropsychological observations support a critical role of prefrontal cortex in the processing of novelty /18,19,29/. Temporal-parietal damage reduces both P3a and P3b potentials, suggesting that posterior cortex is engaged by phasic attention to both task relevant and irrelevant novel stimuli irrespective of stimulus modality /33,36,80,86/. Temporal-parietal damage results in equivalent novelty related P3a
reductions across modalities. In monkeys, multimodal single unit activity is observed in the superior temporal sulcus /26/. This region is lesioned by strokes in the temporal-parietal region. Thus, activity in the STS region may contribute to the posterior scalp component of the novelty P3a. Temporal-parietal damage reduces both auditory and somatosensory P3b activity but has less effect on the visual P3b /80/. Since AII and SII are lesioned by temporal-parietal strokes but VII is less affected, additional activity in secondary association cortex may contribute to the scalp recorded P3b /36/.

FOCAL HIPPOCAMPAL LESIONS AND NOVELTY

The hippocampus is well known to be involved in memory encoding. The fact that stimulus novelty enhances memory for novel events suggests that the hippocampus is likely involved in novelty processing. This possibility has been examined in patients with focal damage in the hippocampal region. Patients with unilateral infarction of the artery of Uchimura present a unique opportunity to study hippocampal contributions to a variety of behaviors /77/. The artery of Uchimura is a branch of the posterior cerebral artery. Damage from artery of Uchimura occlusion centers in the posterior hippocampal region including hippocampus proper, dentate gyrus, subiculum, parahippocampal gyrus, entorhinal cortex and fornix /16/. The degree of damage to adjacent fusiform, lingual and calcarine gyri observed in individual patients is dependent on the degree of associated posterior cerebral artery occlusion. Post-mortem analysis of complete mesial temporal stroke due to posterior cerebral artery occlusion has shown that fornix infarction results in macroscopic post-mortem atrophy of the mammillary body unilateral to fornix damage /14/. This medial mammillary atrophy is due to reduction in cell size, not number. Unilateral mammillary body atrophy secondary to fornix infarction can be visualized in vivo with MRI scanning. Bilateral mammillary body atrophy is also observed in patients with amnesia due to Wernicke-Korsakoff syndrome /62/. This suggests that the amnesia in both conditions is due to disruption of a hippocampal-diencephalic encoding network. PET scanning employing [18F]-fluorodeoxyglucose in patients with mesial temporal infarction reveals additional hypometabolism in anterior mesial temporal and neocortical regions not structurally damaged by infarction, supporting additional hippocampal-cortical dysfunction after mesial temporal infarction /53/. Recent PET studies have confirmed more extensive cortical hypometabolism in patients with mesial temporal amnesia from other causes, such as Herpes simplex encephalitis and hypoxia-induced CA1 damage /49/. The remote metabolic evidence of cortical dysfunction after mesial temporal damage may be due to effects in several neural pathways including bi-directional cortical-hippocampal connections coursing through entorhinal cortex /78/, hippocampal-prefrontal connections synapsing in retrosplenial cortex, or dysfunction in fornix-mammillothalamic-cortical pathways.

The complete mesial temporal infarction syndrome results in verbal and spatial memory deficits after left mesial temporal infarction and predominantly spatial non-verbal deficits after right sided infarction /11,81/. Patients occasionally have additional combined calcarine and splenial involvement resulting in the behavioral syndrome of alexia without agraphia /11/. Other cognitive deficits reported in mesial temporal infarction patients include problems with recognition and familiarity memory which are partially dependent on stimulus novelty /89/ and failures in the binding of memory elements resulting in illusory memory conjunctions /39/.

Patients with discrete damage centered in the posterior hippocampal region have normal parietal P3b activity and intact behavioral indices of detection ability. Conversely, fronto-central P300 activity to both target and novel stimuli is markedly reduced by hippocampal damage in all sensory modalities. Novelty related ERP activity reductions are most prominent over frontal regions and for novel stimuli irrespective of stimulus modality /35,36/. These reductions are comparable and in some instances greater in amplitude to those observed after focal prefrontal damage (Figs. 1 and 3). However, unilateral hippocampal damage reduces P300 potentials over both prefrontal cortices whereas prefrontal damage results in
Fig. 3: Group averaged ERP data from controls and hippocampal lesioned patients (n=7) for auditory, visual and somatosensory target and novel stimuli. Subjects were seated in a sound attenuated booth and instructed to press a button upon detection of a designated target stimulus during each experiment. Auditory stimuli consisted of blocks of repetitive standard 1000 Hz monaural tone bursts (60 dB HL, 50 msec duration, 1 sec ISI). Tone bursts of 1500 Hz occurred randomly on 10 percent of the trials and served as targets. Unexpected novel tones consisting of complex computer generated sounds and environmental noises such as bells or barks were randomly delivered in 10% of the trials. A similar paradigm was employed in the visual modality. Visual stimuli consisted of repetitive presentation of triangles. In 10% of the trials inverted triangles served as target stimuli. In an additional 10% of trials random line drawings or pictures of irrelevant stimuli served as novel events. Somatosensory stimuli consisted of repetitive taps to the index finger with targets being random taps to the ring finger that occurred in 10% of the trials. Novel stimuli consisted of brief random shocks to the median nerve in 6% of the trials. ERPs are shown from the electrode where maximal response was recorded (Pz for targets; Fz for novels). The novelty P3a is markedly reduced at prefrontal sites in all three modalities and the target P3b is spared /38/. 

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predominantly unilateral reductions over the lesioned hemisphere. These observations support selective involvement of a prefrontal-hippocampal network in the detection of novelty in the ongoing sensory stream and suggests that the hippocampal formation has bilateral facilitatory input to prefrontal cortex. As noted above PET studies have also documented frontal hypometabolism in patients with medial temporal amnesia /49/. Reciprocal intra- and inter-hemispheric pathways /2,20,69/ coursing through retrosplenial cortex or the cingulate /61/ may provide the critical anatomical substrates for prefrontal-hippocampal interactions during novelty detection and memory processing. However, contributions from cortico-limbic connections through entorhinal cortex or fornix-mammilothalamic-cortical pathways cannot be eliminated.

In addition to central ERP measures of novelty detection/orientation, peripheral measures of orientation are also impaired by hippocampal damage. Both the amplitude and habituation characteristics of peripheral autonomic sympathetic skin potentials (SSRs; also referred to as the GSR: galvanic skin response) to infrequent wrist shocks are reduced and a flat habituation curve is observed in hippocampal patients /35/ (Fig. 4). The results of the ERP and SSR studies provide evidence that both peripheral and central orienting responses to novel stimuli are impaired by hippocampal region damage. Previous studies in normals have reported correlations between the amplitudes of the N2, P3b, P3a ERPs and the SSR, indicating that these potentials measure combined central and peripheral orienting responses to novel or sufficiently deviant stimuli /5,22/. Hippocampal-hypothalamic pathways may subserve the peripheral autonomic orienting response /54/. Single unit data in monkeys reveal that novelty related cells in inferior temporal cortex fire within 100 msec /44/ suggesting that stimulus processing antecedent to P3a generation may contribute to novelty related activation in humans. Delineation of the precise timing of interactions between different brain regions will be critical for modeling of the distributed network interactions underlying novelty processing. This

![Sympathetic Skin Responses](image)

Fig. 4: Sympathetic skin responses (SSRs) (a) and the habituation of the SSR with repetition (b) are shown. Wrist shocks set to elicit an opponens pollicis twitch were delivered at a random ISI varying from 12-30 seconds while subjects watched a silent movie. The amplitude of the positive component of the SSR was reduced for stimuli delivered to a limb either ipsilaterial or contralateral to hippocampal damage. The hippocampal patients had an abnormal flat habituation curve over blocks of trials /35/.
work will be facilitated by contributions from animal research.

In addition to the influence on memory processing, novel stimuli have other reliable effects on behavior. In a normal individual a deviant stimulus has systematic effects on the reaction time to a subsequent target stimulus. Presentation of an unexpected novel stimulus typically increases the reaction time to a subsequent target. In visual attention tasks the predictive value of a novel stimulus has been shown to have reliable effects on behavior. Novel stimuli that do not have signal value for a subsequent target prolong the RT to a target if they occur immediately and unexpectedly before the target /68/. These novel stimuli without predictive value also have larger novelty ERP responses. Conversely, a novel visual stimulus that always predicts a subsequent target is reliably associated with shorter RTs to the target. This suggests that humans are able to modify their response to novel events dependent on behavioral needs. Thus, unlike lower mammals, in humans the response to novel events likely includes both automatic and controlled components. The identical novel stimulus can serve as either an alerter or a distractor dependent on behavioral context. We assessed this phenomenon in controls and in a patient with mesial temporal damage. In the experiment a target tap to one finger was delivered either without a preceding shock or with an opponens pollicis shock delivered 1000 or 200 milliseconds prior to a target. As predicted closer shock-target pairings decreased reaction times. However, this shortening of reaction time was not observed after hippocampal damage (Fig. 5). Thus, the normal arousal related response cueing effect is compromised by hippocampal damage. These data provide additional behavioral support for a defect in the orienting response after hippocampal damage.

**PET AND fMRI STUDIES OF NOVELTY**

PET studies have provided support for the idea that stimulus novelty activates distributed brain regions known to be engaged during memory storage /75/. As discussed previously, lesion and intracranial ERP data document multi-modal activation of bilateral prefrontal, cingulate, temporal-parietal and hippocampal regions during the processing of novel events. PET studies report predominantly bilateral posterior cortical and right hippocampal involvement. This divergence of findings between electrophysiology and blood flow measures may be due to the fact that PET integrates peaks of activation over sustained temporal epochs which may include additional cognitive processing of the novel event, while ERPs measure phasic neural activity specific to the novel stimulus. Differences in tasks employed may also contribute to the different observations.

Recently fMRI has also been used to study novelty related processing. A study looking at generation of novel words reported activation in the posterior hippocampus in the same area lesioned in the hippocampal stroke patients with novelty ERP and SSR reductions /66/. Another study employing event-related fMRI techniques with a 1.5 T magnet failed to find significant visual novelty related
activation in either prefrontal or hippocampal regions known by ERP and lesion techniques to be engaged by novelty, but did find posterior cortical activation /30/. Event-related fMRI research with a 4T magnet has reported prefrontal and temporal activation to auditory novel stimuli /76/. As with the discussion of the detection/P3b/fMRI results, several factors including task design, modality and field strength could contribute to the lack of convergence between ERP and fMRI approaches.

We employed event-related fMRI with a 3T magnet to examine the blood flow response to novel visual stimuli inserted in an “oddball” task. This high field fMRI experiment has provided preliminary evidence of selective novelty related activation of prefrontal and posterior association cortex in accord with the ERP and 4T data (Fig. 6). The hippocampal region was not examined in this study.

**Fig. 6:** Event-related fMRI activations in a visual detection task recorded in a 3T magnet. Gradient echo echo-planar images were obtained utilizing a General Electric Signa 3.0& system equipped with an Advanced NMR (ANMR) EPI module using the following parameters: FOV 40 cm X 20 cm; matrix 128 x 64; slice thickness 5 mm; inter-slice gap 2.5 mm; TR 2 sec. Spatial resolution was approximately 3 mm x 3mm x 5 mm. Sessions with subject motion exceeding 0.1 pixel were repeated to avoid fictional activation from pixel misalignment. fMRI time series data consisting of 500 consecutive EPI images for each slice (n=4) were analyzed utilizing SPM96 (the Wellcome Department of Cognitive Neurology). After application of spatial and time smoothing in order to conform to Gaussian field theory, statistical analysis was performed using a modified delayed boxcar hemodynamic model function. Hemodynamic changes were assessed within 4-10 seconds post-stimulus delivery. To minimize effects of physiological noise, a high pass filter of 50 seconds and global normalization were applied within the design matrix. fMRI images were made with contrast between 2 stimuli specified. The images demonstrate activated areas which conform to statistical criteria of significance. Activations are superimposed on structural MRI images from the same subject. Subjects were asked to count infrequent target stimuli presented pseudorandomly with a mean ISI of 23 seconds. The targets were simple black and white inverted triangles. Background stimuli consisting of upright triangles were presented at a one second ISI throughout the 16 minute recording session. Task irrelevant novel visual stimuli consisting of colored pictures of various objects and scenes were randomly delivered at a mean ISI of 23 milliseconds. A comparison between novels and targets is shown for two subjects. Selective prefrontal-posterior association cortex activations were observed for the novel stimuli.
CONCLUSIONS

Behavioral, ERP and blood flow data reveal that a distributed neural circuit including the hippocampal region is crucial for responding to novel events. This network maintains a template of the past for comparison with incoming sensory stimuli. Different templates could include either real events from the recent past as those employed in short experimental sessions or idealized models of events from remote experience. Detection of significant deviations from these templates activates a distributed limbic-neocortical orienting system. Engagement of this network by perturbations in the environment facilitates behavioral response to and memory storage of novel events.

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