Anatomic Bases of Event-Related Potentials and Their Relationship to Novelty Detection in Humans

Robert T. Knight and Donatella Scabini

Department of Neurology, Center for Neuroscience, University of California, Davis, Veterans Medical Center, Martinez, California, U.S.A.

Voluntary or involuntary detection of an infrequent stimulus generates a large scalp P300 response. This P300 ERP (P for positive; 300 for the approximate peak latency poststimulation) has been widely used to study phasic attention and memory mechanisms. The P300 phenomenon, first reported in 1965 (Desmedt et al., 1965; Sutton et al., 1965) has been the subject of extensive research in normal, neurologic, and psychiatric populations. P300-like potentials have been described in rats (Ehlers et al., 1991; Yamaguchi et al., 1993), cats (Katayama et al., 1985; O’Connor and Starr, 1985; Wilder et al., 1991), and monkeys (Arthur and Starr, 1984; Neville and Foote, 1984; Paller et al., 1988; Pineda et al., 1989) supporting a broad ethologic significance of this electrophysiological marker of cognition (Fig. 1) (Swick et al., 1994).

Theorists have focused on attention and memory formulations to account for the cognitive basis of the P300, although no clear consensus has emerged (Donchin and Coles, 1988; Verleger, 1988). Some of this disagreement results from the fact that the P300 does not represent a unitary brain potential arising from a discrete brain region or cognitive process as initially proposed. Instead, scalp positivities generated in the 300- to 700-ms poststimulus delivery measure activation of multiple neocortical and limbic regions dependent on the degree of voluntary and involuntary attention allocated to a stimulus. Support for this contention is provided by scalp topographic studies in normal subjects (Courchesne et al., 1975; Squires and Hilliard, 1975; Ruchkin et al., 1990a, 1992; Yamaguchi and Knight, 1991a; Bruyant et al., 1993), intracranial recording in epileptic patients (McCarthy et al., 1989; Puce et al., 1991; Paller et al., 1992; Baudena et al., 1995; Halgren et al., 1995a,b) and lesion studies in neurologic patients (Knight, 1984, 1997a; Knight et al., 1989; Yamaguchi and Knight, 1991b, 1992; Scabini, 1992).

VOLUNTARY DETECTION AND THE TARGET P3B

Voluntary detection of an infrequent and task-relevant stimulus generates a large amplitude (5–15 μV) P300 response maximal over parietal scalp sites (target P3b). This effect is observed in the auditory, visual, somatosensory, and olfactory sensory systems. The modality-specific nature of the P3b has been extensively studied. Topographic EEG studies in normal subjects (Barrett et al., 1987; Johnson, 1989b; Nau mann et al., 1992), patients with temporal lobectomy (Johnson, 1989a) and patients with callosotomy, in addition to magnetoencephalographic studies in normal subjects (Rogers et al., 1991, 1992, 1993a,b), demonstrate that there are modality-specific contributions to the P3b. Scalp topography and intracranial recording indicate that longer latency (~600 ms) scalp positivity generated during recognition memory tasks predicts subsequent memory for the eliciting stimulus and appears to be distinct from the P3b (Fabiani et al., 1986; Paller et al., 1987; Puce et al., 1991).

P3b amplitude and latency is responsive to stimulus probability, subjective probability, stimulus meaning, and task relevance (Donchin and Coles, 1988; Johnson, 1988) and is linked behaviorally to a range of cognitive processes. One theory proposes that the P3b represents closure of an epoch of voluntary stimulus processing in association cortex (Verleger, 1988; Schupp et al., 1994). According to this theory, the P3b is generated...
during completion of a discrete epoch of stimulus processing and measures inhibition of regional activity involved in processing of expected stimuli (Heit et al., 1990; Schupp et al., 1994). The strength of this theory is that it is directly testable in animal P300 models, although no such data are available at present. Another major theory supported by extensive cognitive psychophysiology research is that the P3b indexes updating of activity in corticolimbic circuits during attention and working memory (Donchin and Coles, 1988; Ruchkin et al., 1990b,1992). Other proposals such as those linking P3b and template matching may be subsumed under the concept of context updating in working memory (Chao et al., 1995).

Ruchkin et al. (1990a,1992) provided evidence that longer latency scalp positivities index activity in phonologic and visuospatial systems of working memory. Working memory refers to the on-line ability to manipulate information generated by either external sensory events or internal mental activity. The concept of working memory encompasses a range of cognitive processes (Baddeley, 1992a,b). A trivial example is one’s rehearsal of a new phone number while waiting to dial. A more complex example is the cognitive process involved in comparing the experience of a new event with a past situation or in the prediction of a future outcome. Dorsolateral prefrontal cortex including areas 9 and 46 in humans and the corresponding sulcus principalis region in monkeys functions as a central executive to control the distributed neocortical networks engaged during working memory (Goldman-Rakic, 1987; Jonides et al., 1993; Petrides et al., 1993a,b; Knight, 1994). At intervals of <5 s working memory is largely independent of access to the long-term store and relies predominantly on distributed neocortical networks (Nielsen-Bohlin and Knight, 1994). Working memory is intact in patients with diencephalic or hippocampal amnesia.

The concept of working memory is particularly applicable to sustained performance in delayed response tasks classically associated with prefrontal cortex (PFCx) damage in monkeys (Jacobsen, 1935). Evi-
idence from single-unit recording, ERPs (Knight, 1994), lesion analysis, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have shown that areas 9 and 46 in humans and the corresponding sulcus principalis region in monkeys control distributed neocortical and limbic networks engaged during delay tasks (Jonides et al., 1993; Petrides et al., 1993; Wilson et al., 1993; Nielsen-Bohlman and Knight, 1994). The degree of PFCx activation is dependent both on the delay interval and task difficulty, indicating that sustained attention is critical for normal performance. The problem in distinguishing between the concepts of attention and working memory has prompted cognitive theorists to adopt the definition of working attention/memory. Indeed, several PFCx-mediated regulatory functions probably are engaged during working attention/memory tasks.

Large field potentials are recorded in the hippocampal region during tasks that generate scalp P3b responses (Halgren et al., 1980). However, scalp P3b peaks 30–50 ms before intracranial field potentials (McCarthy et al., 1989) and are intact in patients with mesial temporal damage due to hypoxia (Polich and Squires, 1993), anterior temporal lobectomy (Johnson, 1988; McCarthy et al., 1989; Rugg et al., 1991a), herpes simplex encephalitis (Onofrj et al., 1992; O’Donnell et al., 1993), tumor (Rugg et al., 1991) and hippocampal infarction (Knight, 1996). These results indicate that the brunt of the scalp P3b is not due to volume conducted field potentials from hippocampal regions. Anterior temporal lobectomies (McCarthy et al., 1989), bilateral mesial temporal lesions due to herpes simplex encephalitis (Onofrj et al., 1992), and unilateral posterior hippocampal infarctions (Knight, 1996) result in significant P300 reductions at far lateral temporal and frontal sites, which suggests that mesial temporal structures may either generate field potentials that propagate to the surface at these lateral scalp sites or are providing modulatory input necessary for P300 generation in these regions.

Discrete damage in the temporoparietal junction including posterior temporal plane and superior temporal sulcus (STS) results in severe reduction of P3b activity at posterior scalp sites in both the auditory (Knight et al., 1989) and somatosensory modalities (Yamaguchi and Knight, 1991b, 1992) and in partial reductions in the visual modality (Knight, 1997a) (Fig. 2). Verleger et al. (1994) independently confirmed that the auditory P3b was disproportionately reduced in comparison to the visual P3b after temporoparietal damage. These data, combined with magnetoencephalographic (MEG) studies in normal subjects (Rogers et al., 1991, 1992, 1993a,b), suggest that modality-specific regions contribute to the P3b. Intracranial recording showed P3b potentials in posterior cortical sites, including the STS, in further accord with the results of lesion studies (Smith et al., 1990; Halgren et al., 1995a,b).

Subregions of the human temporoparietal junction may correlate anatomically to multimodal area cSTP (Hikosaka et al., 1988) and auditory association area Tpt in monkeys. These multimodal regions located in the posterior STS of monkeys have bidirectional connections to area TH in the parahippocampal gyrus and have been implicated in learning and memory in animals and humans (Amaral et al., 1983). The P3b reductions in patients with temporoparietal lesions are accompanied by attention and memory deficits (Woods et al., 1993; Knight, 1994). Temporoparietal lesions in monkeys also result in auditory memory deficits (Colombo et al., 1990). The convergence of results from these human and monkey studies suggests that the posterior scalp P3b component marks activity in posterior association cortex generated during engagement of early attention and memory processes. This posterior neocortical system may interact with hippocampal regions during encoding of sensory inputs and updating of working memory (Eichenbaum et al., 1994). For instance, hippocampal field potentials are generated ~50 ms after the posterior scalp P3b (McCarty et al., 1989), supporting the notion that the scalp P3b may index readout of cortical information to limbic regions for memory updating.

**IN VOLUNTARY DETECTION AND THE NOVELTY P3A**

Novelty detection and novelty seeking are fundamental behavioral properties of mammalian species and are critical to both survival (Sokolov, 1963) and creative behavior. In 1933, Von Restorff showed that novel stimuli are better remembered but remarkably little attention has been paid to the neural circuits responsible for this powerful behavioral effect.

Involuntary orientation to an unexpected and novel stimulus generates a P300 response (P3a) that is recorded over widespread anterior and posterior scalp sites (Knight et al., 1989; Yamaguchi and Knight, 1991a). The P3a has a more frontocentral scalp distribution than the P3b and peaks 60–80 ms earlier in all sensory modalities. Intracranial recordings in the visual, auditory, and somatosensory modalities have shown that multiple neocortical and limbic regions are activated during tasks that generate scalp novelty-dependent P3a potentials (Halgren et al., 1995a,b;

*J Clin Neurophysiol, Vol. 15, No. 1, 1998*
Baudena et al., 1995; Scabini and McCarthy, 1993). Intracranial areas with novelty-related activity include frontal and posterior association cortex in addition to cingulate and mesial temporal regions encompassing posterior hippocampus and adjacent tissue. These intracranial novelty-related P3a potentials have been proposed to measure neural activity in a distributed multimodal corticolimbic-orienting system that processes novel events. Similar theories have been suggested for the scalp novelty P3a response (Courchesne et al., 1975; Squires et al., 1975; Knight, 1984). In intracranial studies, Scabini and McCarthy reported that limbic target and novelty ERPs have differential habituation properties (Fig. 3). The target ERP recorded from electrodes in hippocampal sites, like the scalp target response, does not habituate over repeated detection of the attended stimulus. Conversely, the hippocampal novelty ERP response, similar to its scalp electrophysiological counterpart, undergoes rapid amplitude reduction over repeated trials (Knight, 1984; Yamaguchi and Knight, 1991a). The novelty scalp P3a habituation is particularly prominent over prefrontal regions. The scalp and intracranial data are in accord with proposals that the novelty ERP is an electrophysiological manifestation of the orienting response.

Prefrontal damage results in differential effects on scalp P3a and P3b responses. The parietal maximal P3b generated to task relevant, correctly detected stimuli in simple sensory discrimination tasks is unaffected by prefrontal damage. However, parietal P3b reduc-
FIG. 3. Intracranial waveforms recorded in response to novel and target stimuli shown according to the sequence of stimulus presentation. Somatosensory event-related potentials (ERPs) were recorded to mechanical taps of the fifth finger (target, \( p = 0.10 \)), the middle finger (frequent, \( p = 0.80 \)), and to unexpected mild shock stimuli applied to the wrist (shock novel, \( p = 0.10 \)). All stimuli were randomized. The electrode tract entered the brain near the occipitoparietal border, penetrated the hippocampus along its length, and terminated at or beyond the amygdala. ERPs to target and novel stimuli were maximal in posterior hippocampal contacts. First row: Effect of habituation of the novel response from an electrode implanted in the posterior hippocampus across the first three blocks of stimulation for continuous stimulation of either the right or left hand. Second row: The novel response returned to full amplitude when the stimulation is switched to the other hand and then habituates again over repeated stimulation blocks. The target ERP amplitude remained constant across recording blocks and hands of stimulation and had a longer latency than the novel ERP (from Scabini and McCarthy, 1993).

Solutions after prefrontal damage are observed in more complex tasks (Swick and Knight, 1993, 1994). Conversely, P3a responses to both simple and complex unexpected novel stimuli are markedly reduced by prefrontal lesions. Comparable P3a decrements have been observed in the auditory (Knight, 1984; Scabini and Knight, 1989; Scabini, 1992), visual (Knight, 1997a) and somatosensory modalities (Yamaguchi and Knight, 1991b) in human subjects with PFCx damage. In addition to P3a reductions over prefrontal scalp sites subsequent to focal prefrontal damage, the P3a is also reduced throughout the lesioned hemisphere (Figs. 4 and 5). The P3 data, in conjunction with additional contingent negative variation (CNV) (Rosahl and Knight, 1995) and visual attention results (Swick and Knight, 1996), provide strong evidence that dorsolateral prefrontal regions modulate neural activity in posterior association cortex. The human ERP results in conjunction with neuropsychological observations (Mesulam, 1981), and monkey single-unit and metabolic data (Friedman and Goldman-Rakic, 1994) support an interaction between prefrontal and posterior regions during both voluntary and involuntary attention and working memory.

The ERP findings indicate a dorsolateral prefrontal source for the frontal scalp component of the novelty P3a and, with the intracranial data, clinical observations, and animal experimentation, support a critical role of prefrontal structures in the detection of novel stimuli (Kimble et al., 1965). Temporoparietal damage reduces the amplitude of both P3a and P3b potentials over lesioned cortex, suggesting that posterior cortex is engaged by phasic attention to all deviant stimuli independent of the degree of stimulus novelty.

Unilateral damage centered in the posterior hippocampal region has no significant effect on parietal P3b activity generated to auditory, visual, and somatosensory stimuli, but reduces frontocentral P3 activity to both target and novel stimuli in all modalities. Reductions are most prominent over frontal regions and for novel stimuli (Knight and Grabowecky, 1994; Knight, 1996) (Figs. 5 and 6). These reductions are comparable.
to and in some instances greater in amplitude than those observed after focal prefrontal damage is sustained. However, unilateral hippocampal damage reduces P300 potentials over both prefrontal cortices, whereas prefrontal damage results in predominantly unilateral reductions over the lesioned hemisphere. These observations support involvement of a prefrontal–hippocampal system in the detection of deviances in the ongoing sensory stream and show that the hippocampal formation has bilateral facilitatory input to prefrontal cortex. Positron emission tomography (PET) studies have also documented frontal hypometabolism in patients with medial temporal amnesia (Perani et al., 1993). Reciprocal intra- and interhemispheric pathways (Goldman-Rakic et al., 1984; Suzuki and Amaral, 1994) coursing through retrosplenial cortex or the cingulate (Shallice et al., 1994) may provide the anatomic substrates for prefrontal–hippocampal interactions during novelty detection and memory processing.

The amplitude and habituation characteristics of peripheral autonomic sympathetic skin responses (SSRs; also termed the galvanic skin response or GSR) to random wrist shocks are also altered by hippocampal damage. The SSR is a well-studied peripheral marker of the orienting response. SSR amplitude is reduced and patients with hippocampal lesions exhibit a flat habituation curve. Such patients show reductions in SSR amplitude to orienting stimuli presented ipsilaterally and contralaterally to the lesion (Knight, 1996). These results of ERP and SSR studies indicate that both peripheral and central orienting responses are impaired by mesial temporal damage. In a previous study of normal subjects, correlations between the amplitudes of the P3a and the SSR, were reported, indicating

FIG. 4. Scalp event-related potentials (ERPs) to rare unexpected novel auditory stimuli not requiring a behavioral response (p = 0.10). The data represent a grand average from 10 patients with a focal prefrontal lesion (3 right, 7 left). Scalp sites are indicated as ipsilateral (l) or contralateral (c) to the side of the lesioned hemisphere. Frontal lesions reduced the amplitude of the P3a component throughout the lesioned hemisphere, with reductions most prominent over frontal sites (Fl vs. Fc) (from Scabini, 1992).
that these potentials measure combined central and peripheral orienting responses to novel or sufficiently deviant stimuli (Halgren and Marinkovic, 1995). The SSR to auditory orienting stimuli is also reduced by prefrontal and posterior association cortex damage (Tranel and Damasio, 1994), providing evidence that distributed cortical and limbic regions are engaged in novelty processing. Recently described hippocampal-hypothalamic pathways may subserve the peripheral autonomic orienting response (Risold and Swanson, 1996).

Single-unit (Miller et al., 1991), PET (Tulving et al., 1994) and neural modeling studies (Metcalf, 1993) have also implicated prefrontal and mesial temporal regions in novelty detection. These observations, along with the ERP results, provide strong evidence of involvement of a prefrontal–hippocampal system in the detection of deviances in the ongoing sensory stream. Prefrontal–hippocampal interactions during orientation to novel stimuli may underlie the classic von Restorff memory effect wherein novel or out of context stimuli are better remembered (von Restorff, 1933; Karis et al., 1984; Metcalfe, 1993). Recent observations show that the amplitude of the novelty P3a at encoding predicts subsequent recall of items (Stevens and Knight, 1997), which provides an additional link between the novelty P3a and the von Restorff effect. Neural circuits dependent on the hippocampal region appear to maintain a template of the recent past for comparison with incoming sensory stimuli. Deviation from this template activates a distributed limbic-neocortical orienting system that facilitates behavioral response to and memory storage of discrete novel events.

**FIG. 5.** Scalp voltage topographies for target and novel stimuli in controls. The increase in prefrontal activity in controls to the novel stimuli in all sensory modalities was marked. **Right:** Effects of prefrontal or hippocampal lesions on the brain novelty response. Unilateral prefrontal damage results in multimodal decrease in the novelty response maximal over lesioned cortex (all lesions are projected onto the left side). Unilateral hippocampal damage results in severe bilateral reductions in the novelty response maximal at prefrontal sites. These findings implicate a prefrontal–hippocampal network in the detection of perturbations in the environment (from Knight, 1997b).
Results of a behavioral study conducted in the 1930s (von Restorff, 1933) and subsequent behavioral-electrophysiologic data (Karis et al., 1984) support the notion that stimulus novelty enhances recall. PET studies provide further support for the idea that stimulus novelty activates distributed brain regions engaged in memory storage (Tulving et al., 1996). As documented and described above, lesion and intracranial ERP data document multimodal activation of bilateral prefrontal, cingulate, temporoparietal, and hippocampal regions during processing of novel events, whereas in PET studies predominantly bilateral posterior cortical and right hippocampal involvement has been demonstrated. This divergence may result from the fact that PET integrates peaks of activation over sustained temporal epochs, whereas ERPs measure phasic neural activity specific to the novel stimulus. Differences in tasks used may also contribute to the different observations.

The ERP data provide evidence that the Pa, like the P3a component, is not a unitary phenomenon but instead represents distributed neural activity in corticolimbic regions engaged during involuntary response to discrete environmental events. Although this view is more complicated than initial proposals of a unitary nature for P300 activity, it strengthens the potential utility of scalp ERP recording since it provides a means for measurement of neural activity in distributed brain regions in the time domain of cognitive processing.
P3a-like potentials have been reported in many mammalian species, also suggesting that this hippocampal–neocortical network may provide a core substrate for orientation to novelty.

Acknowledgments: This work was supported by NINDS Grants No. NS21135 and PO NS17778 and the Veterans Administration Medical Research Service. We thank Clay C. Clayworth for technical assistance in all phases of the work.

REFERENCES


Rosahl S, Knight RT. Role of prefrontal cortex in generation of the contingent negative variation. *Cerebral Cortex* 1995;5:123–34.


Wilder MB, Farley GR, Starr A. Endogenous late positive compo-


