# Auditory Evoked Potentials in Panic Disorder

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**Neuroimaging studies of behavioral-induced anxiety in non-patients and of lactate-induced anxiety in panic disorder patients have indicated that normal and pathological anxiety may share a common pathway involving the temporal poles. As panic-related anxiety may reflect faulty temporopolar evaluative processing of input, the objective of this study was to examine sensory reactivity in panic disorder patients via scalp recordings of the late auditory evoked 'vertex' potential (LAEP) which appears to have a predominantly temporal lobe origin. Twelve patients diagnosed according to DSM-III criteria as panic disorder and ten normal controls served as subjects in this study. EEG was recorded from 16 scalp sites using a monopolar fronto-occipital derivation and LAEPs were separately averaged in response to four acoustic intensities. Analysis focused on group and electrode-site differences in the negative ($N_1$) and positive ($P_2$) component amplitudes of the LAEPs. Panic disorder patients were found to exhibit significantly larger $N_1$ amplitudes across all stimulus intensities and across all recording sites. No significant group differences were observed with $P_2$. Although the results provide indirect support for a temporal focus, other modulating influences must be considered in data interpretation.**

*Keywords:* panic, auditory evoked potentials

## INTRODUCTION

Although our current understanding of the neural substrates of anxiety remains incomplete, recent applications of high-resolution functional and structural brain imaging techniques have provided critical insight into putative neurobiological elements involved in the generation of panic (Gorman et al 1989). Specifically, positron emission tomography (PET) evaluations of panic disorder patients in non-panic states have indicated several abnormalities, including asymmetry of parahippocampal blood flow, blood volume and oxygen metabolism, and abnormally high whole brain metabolism (Reiman et al 1984, 1986). During panic states, blood flow increases were involved in several brain regions, with the largest and most localized increments being identified in temporal poles, bilaterally (Reiman et al 1989a).

The implication that the temporopolar cortex, otherwise known as the 'paralimbic area' because of its anatomical connections to both limbic structures (eg., parahippocampal region) and sensory association areas, may be involved in panic is supported by animal investigations which have reported anxiety-associated autonomic and behavioral states concomitant with temporopolar stimulation (Kaada 1960; Mesulum 1986; Wall and Davis 1951) and by reports of experienced fear during temporal lobe stimulation in humans (Penfield and Jasper 1954). Based on these and additional observations, a neuroanatomical model of panic disorder has been proposed (Reiman et al 1986) whereby the temporopolar cortex, a region directly involved in the integration of/and evaluative response to novel or unpleasant environmental stimulation (Gray 1982; Mesulum and Mufson 1982), may, through activation by ascending brain stem noradrenergic projections (Charney et al 1984; Price and Marall 1981; Smith and De Vito 1984), be involved in panic by its heightened sensitivity to incoming cues which are then characterized as potentially threatening and dangerous events.

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Although this model of a faulty 'evaluative' temporopolar cortex in panic disorder is partially supported by PET monitored findings of exaggerated bitemporal blood flow increases during anticipation of electric shock (Reiman et al 1989b), more convincing support might be marshalled if patients were to evidence augmented reactivity to seemingly neutral, non-noxious sensory stimulation. With this in mind, the present study examined the scalp-recorded, late averaged auditory evoked electrical potential (LAEP) to tone stimuli in panic disorder patients and non-psychiatric controls. The transient LAEP is composed of a number of components amongst which is a biphasic complex with a major negative ($N_1$) and positive ($P_2$) potential peaking between 70 and 220 ms post-stimulus. As several lines of evidence have supported the contention for an origin of the $N_1$-$P_2$ complex predominantly in the superior temporal cortex (Scherg and von Cramon 1990; Wood et al 1984), and as the amplitudes of this complex have been shown to vary not only as a function of stimulus properties, but psychological properties, notably arousal and attention, as well, the LAEP was deemed an appropriate measure for the indirect assessment of temporopolar reactivity in panic disorder patients.

## METHODOLOGY

### Subjects

Twelve patients (9 female) were drawn from a consecutive sampling of actively symptomatic panic disorder outpatients. All patients met DSM-III criteria for panic disorder with agoraphobia and had a mean age of 34.4 years (range 23-52). Prior to testing, patients were shifted from their current medication to Lorazepam (up to a maximum of 3 mg, t.i.d.) for 3 days and were then tapered down to 1 mg (t.i.d.) over an additional 3 days. At the end of this period medication was prescribed on a p.r.n. basis up to 48 hours prior to laboratory testing at which time medication was stopped. Ten (6 female) hospital staff, with no psychiatric history and with a mean age of 31.3 years (range 24-40), served as normal controls. Patients and controls with histories of alcohol/drug abuse and neurological trauma/disease were not included in the study.

### Procedure

Subjects were seated in a sound-attenuated chamber immediately adjacent to the control room housing EEG, stimulator, computer and video monitors. Throughout the recordings subjects sat in a semi-reclining position with eyes closed, legs elevated and neck and arms supported. LAEPs were recorded in response to 4 auditory intensities, each intensity being presented in a 'block' of 100 repetitions at 1.0 sec intervals. Intensity blocks were randomized and counterbalanced across subjects using Latin square procedures. All testing took place in the afternoon and subjects were required to abstain from caffeine and nicotine 2 hours prior to testing, and from alcohol and drugs beginning at 12:00 a.m. on the previous evening.

### Apparatus

LAEPs were recorded from 16 scalp sites (Figure 1) using a monopolar fronto-occipital derivation according to the International 10-20 System. Electrodes were applied with an electrode cap (Blom and Anneveldt 1982) and were referenced to linked earlobes. All electrodes impedances, including a mid-forehead ground, were kept below 5 K.

Stimulus intensities of 60, 70, 80 and 90 db (SPL) were presented binaurally through headphones, with stimuli for each intensity consisting of 1000 Hz, 50 msec duration tones with 5 msec rise and decay times.

Electrical activity was recorded with a band pass setting of 0.5-40.0 Hz and averaging was carried out on-line by directly feeding stimulus-locked activity to an A/D converter which digitized at 1000 Hz for a 550 msec epoch beginning 50 msec pre-stimulus onset. Single sweeps with frontal lead ($F_{p1}$, $F_{p2}$, $F_{pz}$) amplitudes exceeding a peak-to-peak value of + 90 uV were automatically eliminated from the averaging, and the separately averaged LAEPs for each intensity were stored on disk for later off-line analysis.

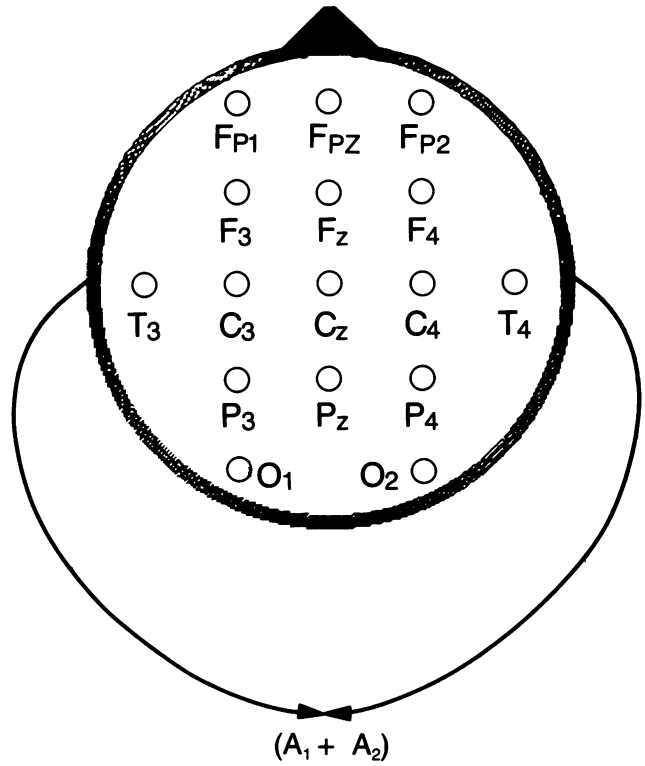


**Fig. 1. Electrode placement for LAEP recordings, based on the 10-20 System, is depicted within a graphic representation of the top of the head. The 16 recording sites, indicated by circles, were referenced to linked earlobes ($A_1$ + $A_2$).**

### Measurements

The main components of a typical LAEP for a normal subject are shown in Figure 2. The separate $N_1$ and $P_2$ peaks for each of the 16 channels were identified by visual inspection and the amplitudes of each peak were scored relative to pre-stimulus baseline via a computer cursor program.

The 16-lead referential averaged recordings and the resulting peak amplitudes allowed construction of topographic maps for depiction and visual assessment of LAEPs across the scalp. The mapping procedure involved the overlapping of a two-dimensional representation of the head surface, as viewed from above, with a 200 x 200 grid matrix producing a CRT image with 40,000 picture elements (pixels), with values for 16 points of the grid map being generated by the actual LAEP peak values. Values for points in the map at other than actual recording locations were computed by rectangular interpolation from the nearest 4 electrodes. The values were then color-coded to display maps for each separate LAEP peak (eg., Figure 3). The topographical maps were only used for illustration purposes and statistical analysis was carried out only on the 16 actual data points of each LAEP peak.

Statistical analysis of each LAEP peak was carried out via separate 2 (Group) x 4 (Intensity) x 16 (Channels) split-plot, repeated measures analysis of variance procedures, and any follow-up tests were carried out with t-tests.

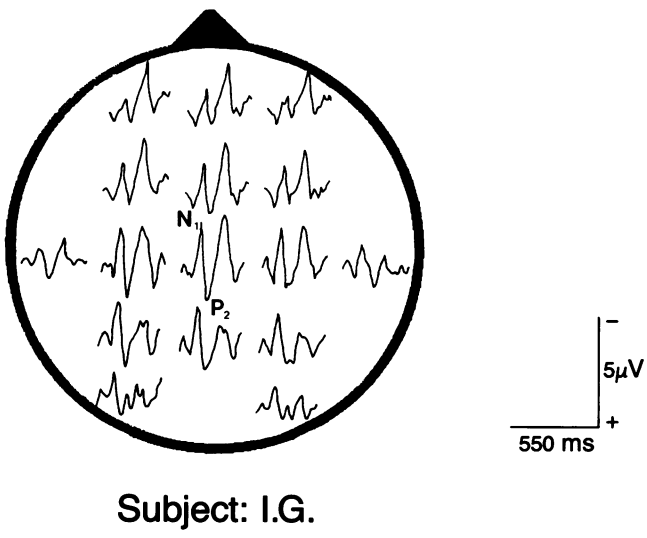


**Fig. 2. Examples of LAEPs recorded from 16 scalp sites of a normal control subject. The $N_1$ and $P_2$ peaks, prominent at the central sites ($C_3$, $C_z$, $C_4$), were identified and scored for each of the 16 channels.**

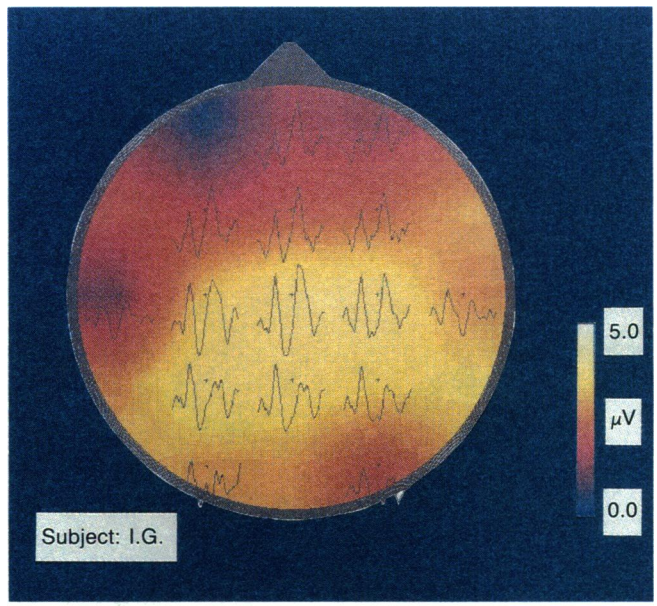


**Fig. 3. Example of topographical LAEP color mapping of the amplitude of the $N_1$ potential.**

## RESULTS

Analysis of $N_1$ data indicated the presence of a significant Group effect ($F(1/19)=9.96$, $p=.005$), and as the Intensity effect did not quite reach significance ($F(3/37)=2.67$, $p=.06$), the group-averaged, topographically mapped $N_1$ data, were collapsed across intensities, as shown in Figure 4. As can be seen, the patient group exhibited significantly larger $N_1$ amplitudes across the entire scalp. Although a significant Channel effect emerged ($F(15/285)=5.16$; $p=.0001$), reflecting the maximal central-frontal distribution of this peak, group differences were not dependent upon recording location.

Shown in Figure 5 are $P_2$ amplitude maps. Analysis did result in a significant Channel effect ($F(15/300)=8.54$, $p=.0001$), but no significant Group differences emerged with respect to this peak.

## DISCUSSION

The main finding of this study is the increased $N_1$ amplitude of the LAEP seen in panic patients in comparison with non-patient controls. Although the $N_1$ peak typically exhibits a vertex ($C_z$) maxima, both group averaged topographical maps indicated, as with previous studies (Picton et al 1974), that this potential was widespread in its distribution over the frontal-central scalp area, and that augmented $N_1$ amplitudes observed in patients were not localized to any specific scalp region. A question may arise on the role of benzodiazepine and dosage reduction in these patients as it may be expected that the presence of anxiolytic

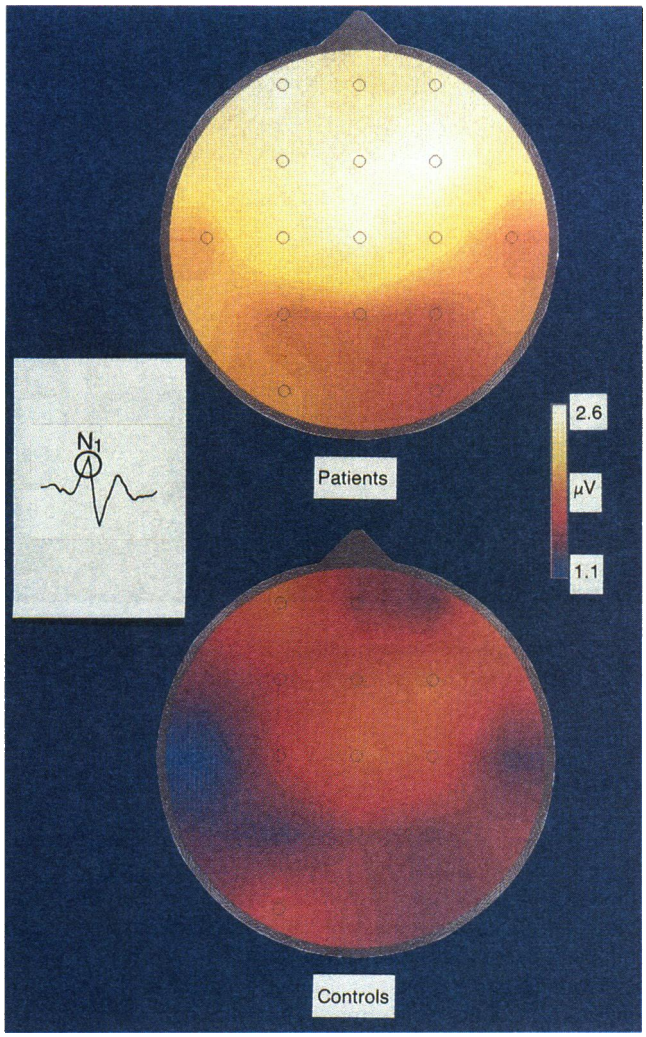


**Fig. 4. Grand (group) averaged topographic LAEP maps for the $N_1$ potential for panic patients and normal controls.**

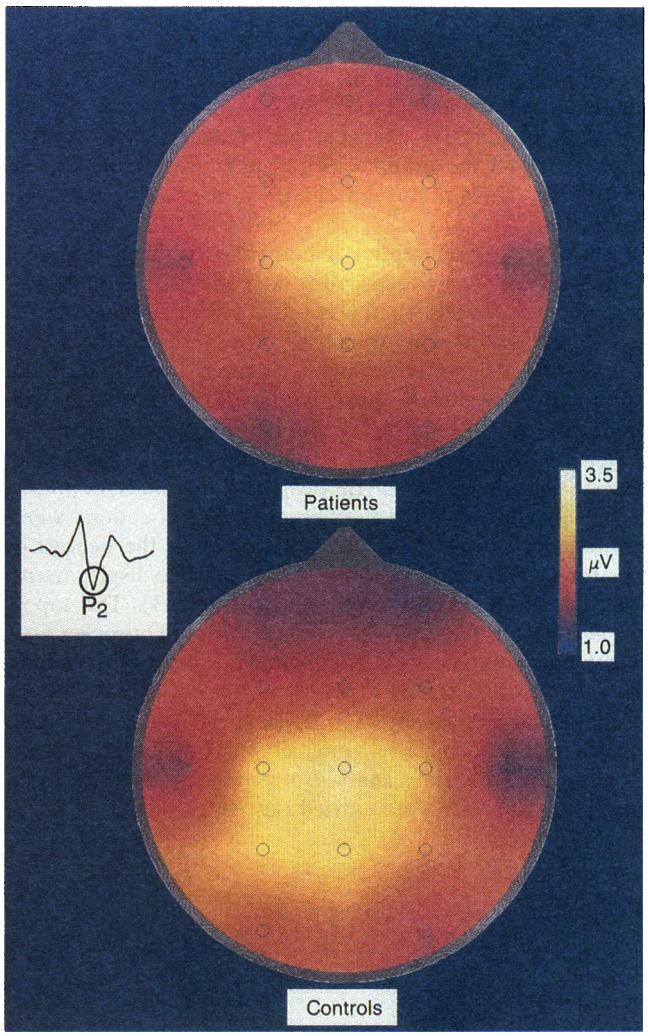


**Fig. 5. Grand (group) averaged topographic LAEP maps for the $P_2$ potential for panic patients and normal controls.**

medication and medication withdrawal may be a contributing factor in this neurophysiological profile. At this point it can only be stated that a short half-life benzodiazepine, lorazepam, was specifically chosen to reduce the influence of a drug effect, and with respect to this group of patients there was no clinical evidence of benzodiazepine 'rebound' anxiety at the time of testing.

As mentioned previously, evidence strongly suggests that LAEP components are generated from the primary auditory cortex of the temporal lobes and, given that this region is anatomically connected to the parahippocampal gyrus which play a major role in receiving and responding to input from sensory association areas, the enlarged $N_1$ findings may reflect the initiation of a marked 'defensive' response precipitated by projections from hyper-excitable noradrenergic brainstem nuclei and/or septoamygdalar centers (Fontaine et al 1990; Van Hoesen 1982; Smith and De Vito 1984). Although the precise mechanism mediating abnormal paralimbic processing is not yet known, it is reasonable to suggest, given the varied nature of putative panicogenic stimuli (eg., extereoceptive, visceral and perceptual) and the complex 'unimodal', 'polymodal' and 'supramodal' sensory projections to the connecting parahippocampal region, that more than one neural pathway may be involved in the initiation of faulty temporopolar processing (Le Doux 1987; Reiman 1988). It follows, of course that despite evidence of a temporal lobe origin for the $N_1$ peak, the present finding of larger $N_1$ amplitudes in panic patients does not necessarily implicate deviant processing in this region. This resultant effect could be modulated, for example, by any one of a number of brainstem nuclei (eg., preolivary, superior olivary and trapezoid) which differentially receive and process auditory input prior to higher order cortical processing (Moller and Janetta 1982).

Alternatively, one might hesitantly suggest that because $N_1$, but not the $P_2$ component, has been intimately linked to attentional processes, with larger $N_1$ amplitudes being observed in response to attended vs non-attended stimuli (Schwent et al 1976a, 1976b), that the enhanced $N_1$ amplitudes may reflect a frontally-mediated, attentional-cognitive dysfunction whereby long-standing panic disorder patients selectively 'over-attend' to certain environmental stimuli and to their resultant physiological impact (Clark 1986; Gorman et al 1989). As both animal (Alexander et al 1976; Skinner and Yingling 1977; Yingling and Skinner 1977) and human investigations (Knight et al 1980, 1981) have indicated that the frontal cortex may exert inhibitory influences on LAEPs (Bruneau et al 1985), the larger $N_1$ amplitudes observed in patients may reflect a hypo-frontal cortex with reduced descending inhibitory action on ascending reticular responsivity to acoustic stimuli (Picton et al 1970).

Finally, higher $N_1$ amplitudes observed in panic patients may simply reflect a diffuse, non-specific arousal process or a state-dependent 'anxiety' response of the patient group at the time of testing and may not, as the PET abnormalities of non-panic states have been interpreted, be tapping a trait-dependent vulnerability marker of panic disorder per se. Future studies may attempt to examine this latter possibility by monitoring, in addition to LAEPs, multi-response measurement strategies which attempt to compare subjective as well as peripheral and central nervous system arousal indices in these patient groups and in generalized anxiety disorders. Testing during passive vs active and attending vs non-attending conditions, and, as with previous studies, during both acute laboratory-provoked anxiety states (Knott 1990; Knott et al 1981; Knott and Lapierre 1986; 1988; Lapierre et al 1984) and during sleep-related panic attacks (Campbell and McGarry-Roberts 1991; Mellman and Uhde 1989a, 1989b) so as to enable a better separation of endogenous and exogenous influences on the $N_1$ potential, would help to delineate the functional role of the temporal lobes in panic disorder.

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