

UC Irvine

UC Irvine Previously Published Works

Title

Middle and long latency auditory evoked potentials in cat. I. Component definition and dependence on behavioral factors

Permalink

<https://escholarship.org/uc/item/8kj8c80p>

Journal

Hearing Research, 10(2)

ISSN

0378-5955

Authors

Parley, Glenn R
Starr, Arnold

Publication Date

1983-05-01

DOI

10.1016/0378-5955(83)90049-7

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at

<https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Middle and long latency auditory evoked potentials in cat. I. Component definition and dependence on behavioral factors

Glenn R. Farley * and Arnold Starr **

Departments of Psychobiology and Neurology, University of California, Irvine, CA 92717, U.S.A.

(Received 5 April 1982; accepted 30 November 1982)

Middle (10–50 ms) and long (50–600 ms) latency auditory evoked potentials (AEPs) were investigated in artificially respired, muscle-paralyzed cats. Similarity to human potentials of comparable latencies was examined in two ways: (1) the similarity of waveform features such as peak amplitude, polarity and latency, and (2) the effects of task-related variables on these various waveform features. Four behavioral variations of a classical pupillary conditioning paradigm were used to vary attention and arousal. Twelve peaks and troughs were identified in the AEP: P10, N13, P17, N22, P31, N41, P55, N70, N100, N140, P260 and N520. Principal components analysis (PCA) defined 7 AEP components, some of which spanned several peaks. Analysis both of peak latencies and amplitudes, and of principal component scores, revealed differential effects of the behavioral manipulations on these components: those with latencies longer than 50 ms were strongly influenced by behavioral variations, while earlier components were relatively immune to these effects. On the basis of these findings, several relationships between cat and human AEP components were suggested. Specifically, peaks P10–P41 in the cat were thought related to human middle latency components, cat P55 to human P50, cat N140 to human N300, and cat P260 to human P300. Cat N520 was comparable to several long latency components in humans. No obvious correspondences between cat AEP components and human N90 and P170 were identified.

Key words: auditory evoked potential; cat; middle latency; long latency; behavior.

Introduction

The human auditory evoked potential (AEP) is easily recorded from the scalp using signal averaging techniques, and has proven useful both for clinical diagnosis [36] and for the study of neural correlates of cognitive processes [7,13]. Animal models of the short latency human AEP components known as the auditory brainstem response (ABR) have been developed, and have proven useful in depth mapping and lesion studies directed towards neural generator localization

* Present address: Boys Town Institute, 555 No. 30th Street, Omaha, NE 68131, U.S.A.

** Send requests for reprints to: A. Starr, Department of Neurology, University of California, Irvine, CA 92717, U.S.A.

[1,2,5,10,15,19], although some inter-species discrepancies remain [14]. Likewise, very delayed AEP components, including the contingent negative variation and readiness potential, have been studied extensively in animals (e.g. [20]) and in man. However, between these responses are a series of 'middle and long latency components' which have only recently begun to be analyzed in animals [4,16,34,41].

Human AEP components are distinguishable along three dimensions. First, the components' amplitudes, latencies, and shapes vary. Second, components differ in their 'functional relationships'; e.g. middle latency components are strongly influenced by stimulus variables such as intensity, but are little influenced by behavioral task, and are thus considered 'exogenous' in character, whereas later components, such as P300, are stimulus independent but task dependent, and thus 'endogenous' [28,29]. Finally, components differ in their topographic distribution; many middle and long latency AEP components have frontal and central maxima, while others, such as P300 and the T-complex, are localized over other scalp regions including parietal or temporal areas [29,31,43].

In this paper, we investigate the cat AEP along two dimensions: (1) the waveform features (components), and (2) their relationship to behavioral task. We have chosen a classical pupillary conditioning task in paralyzed cats [26,27,40] because of the need to control both muscle artifacts known to contaminate human AEP recordings (e.g. [3]) and likely to contaminate similar recordings in cats, and acoustic input variables that can also affect AEPs. Procedures used on humans, including instructions to relax, monitoring of muscle potentials with rejection of trials showing significant electromyographic activity, and discrimination of muscle artifacts on the basis of spatial distribution, cannot be considered adequate for animals, especially in initial attempts to define potentials. In a companion paper [39] we report on the surface distribution of and effects of stimulus intensity on cat AEP components.

Methods

Subjects and surgery

Nine adult male and female cats weighing between 1.8 and 5.0 kg were studied; five in preliminary experiments and four in the data collection sequence. Each animal was free from ear lice infestation and had normal ABR thresholds to clicks.

Seventeen stainless-steel screw recording electrodes, an Amphenol connector to provide connections from the electrodes to the recording apparatus, and a head holder were implanted in each animal under sodium pentobarbital anesthesia (40 mg/kg). The first electrode (V1) was placed 1.0 cm anterior to Bregma on the midline; the second (V5) was 0.5 cm anterior to the ridge behind the lambdoidal suture. The inter-electrode distance for remaining electrodes was defined as 20% of the V1-V5 distance (typically 1.1 cm). The remaining fifteen electrodes were placed in a pattern (Fig. 1A), which, except for the curvature of the skull, locates electrodes on the intersections of a rectangular grid. The approximate locations of the electrodes over the brain surface are shown in Fig. 1B.

Following surgery, cats were allowed at least one week to recover before undergoing a series of training and testing procedures.

Data recording procedures

All experimental procedures occurred in a double-walled sound room. The cats were paralyzed with gallamine triethiodide (20 mg/kg), intubated, and artificially respired. They were placed on a warmed, soft cushion with their heads held securely by the previously implanted skull device. There were no pressure points. The left eye was fixed open and a pupillometer [6] was placed to measure task performance. Both eyes were coated with a thin layer of Terramycin eye ointment to prevent corneal drying.

Electrical activity was recorded from the screw electrodes in the cranium referenced to a needle electrode inserted in the skin 2.0 cm caudal to the occiput. A second needle electrode, inserted 2.0 cm caudal to the reference electrode, was grounded. The amplifiers had a gain of 2000, with a bandpass between 0.1 and 3000 Hz.

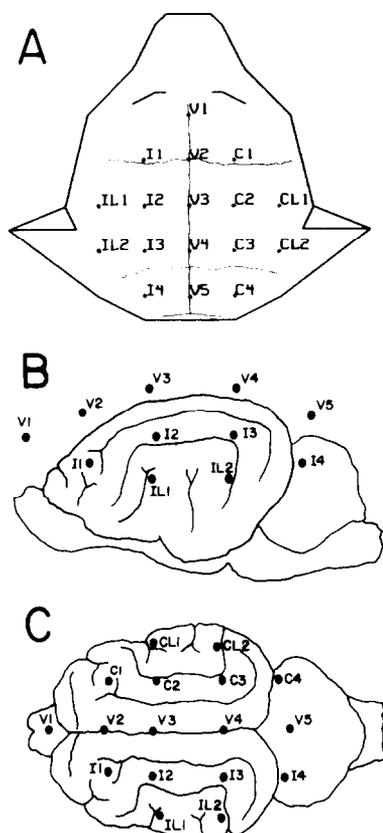


Fig. 1. Electrode locations in relation to skull and brain surface landmarks. (A) Diagrammatic representation of electrode locations relative to skull sutures (light lines). Electrode V2 was located very close to Bregma, while V5 was located between the lambdoidal suture and post-lambdoidal ridge. Shortest inter-electrode distances were typically 1.1 cm. (B) Electrode locations relative to the brain surface ipsilateral to acoustic stimulation. (C) Electrode locations relative to the dorsal surface of the brain.

Amplifier outputs were recorded on an FM tape recorder along with the output of the pupillometer and pulses indicating the occurrence of stimuli. The electrical activity of the VI electrode was also recorded on a polygraph to monitor the electroencephalogram (EEG). Heart rate, body temperature and expired carbon dioxide were maintained within normal physiological limits.

Stimuli

Two acoustic stimuli were used in this study: a click and a noise burst. They were presented monaurally by a Beyer earphone coupled to the ear by a short piece of plastic tubing. The click had substantial power in a band from 0.5 to 3.5 kHz, with predominant energy at 1.4 kHz. Peak SPL of the click was 113 dB SPL. The noise was presented as a burst of 500 ms duration with a 5 ms rise and fall time. The intensity of the noise stimulus was 83 dB SPL.

For behavioral reinforcement, a 250 ms electric shock train of 25 pulses (3 mA, 2 ms duration) was delivered to the tail through a pair of ring electrodes. These were spaced 2.0 cm apart on the shaved tail, and moistened with electrode jelly. The tail shock routinely produced a moderate pupillary dilation in each animal when delivered alone. Prolonged dilations or heart rate changes were not observed.

Behavioral paradigms

The four related behavioral tasks used in this study are summarized in Fig. 2.



Fig. 2. Behavioral paradigms and elicited pupillary dilations. The behavioral paradigms used are schematically represented along with the pupillary dilation response. On the abscissa, click stimuli (delivered continuously every 999 ms) are represented by upward directed marks. Once every 25–65 s, a click is replaced by a noise burst (shaded box). Depending on the paradigm, shock stimuli, represented by an S with an arrow drawn through it, are presented. (H) The pupillary dilation elicited by ‘habituation’ is very small. Note that shock is not delivered here. (B) In ‘backward conditioning’, a shock is delivered coincident with the eighth click preceding noise. There is a moderate pupillary dilation that starts after the shock is given (not shown) and decays over the course of a few seconds. Noise delivery elicits a relatively small, short-lasting dilation. (S) In ‘sensitization’ the shock stimulus can be delivered at any time, as symbolized by the arrows pointing left and right from the shock symbol. Noise evokes a relatively small, short-lasting dilation. (C) In ‘conditioning’, shock follows noise onset by 5 s. Noise delivery elicits a large, sustained dilation which peaks at shock delivery.

Each typically required three to four training sessions of 100–150 trials before a stable pupillary response and pattern of EEG activity were achieved.

In ‘habituation’ (Fig. 2H), there was no tail shock. Only a minimal pupillary dilation was evoked by the noise. The EEG consisted mainly of spindles and slow waves suggesting the animals to be asleep.

For ‘sensitization’ (Fig. 2S), tail shocks were delivered once per trial, triggered at the onset of an acoustic stimulus. Within a trial, each acoustic stimulus had an equal probability of being chosen for shock delivery. Noise stimuli typically elicited a small pupillary dilation after noise burst onset which rapidly decayed to baseline. EEGs consisted of low-voltage, high-frequency activity, compatible with a state of high arousal. Only trials where shock occurred 5 s before or 10 s after the noise onset were analyzed to avoid including shock artifact and evoked somatosensory activity.

In ‘conditioning’ (Fig. 2C), the tail shock invariably followed noise onset by 5 s. Noise thus signalled impending shock and typically elicited an initial dilation followed by a large sustained dilation which grew until shock delivery. The shock elicited a further dilation which decayed rapidly back to baseline. The EEG was similar to that of sensitization, suggesting that the animals were aroused. Training on this task required a shaping procedure in which the animals were exposed initially to a noise stimulus of 5 s duration which was gradually shortened to the final 500 ms duration while maintaining the 5 s noise–shock interval.

In ‘backwards conditioning’ (Fig. 2B), the tail shock occurred 8 s before noise onset. Pupillary responses consisted of a moderate dilation to the shock stimulus (not shown) which decayed rapidly to baseline. The dilation to noise was similar in shape to, but smaller than, that elicited during sensitization. The EEG desynchronized at the shock, but rapidly resynchronized, so that, in the peri-noise period, the animals typically appeared to be in a relaxed state similar to habituation.

Testing procedures

On recording days, animals were refamiliarized with the paradigm by delivery of around 10 trials, and then subjected to three sets of trials (25 to 35 per set) which were recorded on tape. Seven EEG channels were recorded per trial set. Electrode locations for the first, second and third sets were randomly chosen, with the constraints that a left side electrode be matched with its right side counterpart, and that all electrodes be represented at least once in the three sets. One electrode (V1) was common to all sets to insure that AEPs were consistent between sets.

Data retrieval and analysis

Data were digitized off-line and averaged across trials to form 16 different waveforms: 15 for the clicks and 1 for the noise stimuli in the period from 5 s before to 10 s after the noise onset. For each waveform, digitization commenced at click or noise onset, and consisted of 256 samples 40 μ s apart, followed by 1024 samples 600 μ s apart, giving a total sampling interval of 625 ms. The five click waveforms preceding and the second to fourth following noise proved comparable within a trial set. They were thus averaged to give pre- and post-noise click waveforms, respec-

tively. These, together with the noise waveform, provided three traces for each cat, electrode location and behavioral condition, and formed the data on which later analyses were based.

The pupillary dilation was retrieved from tape and filtered (0–50 Hz bandpass). For each trial, digitization (512 samples, 31.25 ms inter-sample intervals) commenced with the fifth pre-noise click. These 512 samples were stored separately on a trial by trial basis, and later averaged across trials within a recording set to give that set's average pupillary dilation.

The EEG was filtered in a 0–50 Hz band, and two periods of 512 samples per trial were taken at 5.0 ms intervals, giving a sampling period of 2.56 s. The first (pre-noise) period was initiated 3 s before noise onset, while the second (post-noise) was initiated 2 s after noise onset. Each of these traces was stored separately on a trial-by-trial basis to allow measurements of the power spectrum of the EEG on each trial.

Further analyses from the digitized AEP data included (1) principal components analysis (PCA) of AEP waveforms, (2) calculation of principal component scores, (3) measurement of peak amplitudes and latencies of AEPs, and (4) statistical tests of the relationships of these scores with various dependent and independent variables. A description of PCA as applied to AEPs can be found in [8].

Principal components of the AEP were derived as follows. A set of 80 time samples, spaced 7 ms apart and thus spanning a 560 ms range, was selected from each AEP waveform. The pre-stimulus baseline voltage was subtracted from each point, which was then entered into a data matrix (204×80), separately for each cat. To represent earlier, higher frequency portions of the AEP better, a second data matrix containing 80 samples from each AEP at 1.2 ms intervals (spanning the first 100 ms) was similarly compiled for each cat.

Variance–covariance matrices were then calculated from these data matrices, and principal components derived. Components accounting for at least 1/80th of the variance in their data matrices were retained for further analysis. Varimax rotation, which tends to localize components into discrete time regions, was performed. This yielded a set of seven components for the 560 ms span, and five components for the 100 ms span for each cat. Each such set accounted for at least 95% of the total variance of its data matrix. Components were sorted and labelled in order of increasing latency of peak loading, except for components 7 of the 560 ms span and 5 of the 100 ms span, which were polyphasic and required special treatment. Components from different animals were quite comparable, except for component 5 of the 100 ms span, which proved variable in both amplitude and latency.

Care for animals

Because this experiment involved chronic use of animals which were periodically paralyzed and subjected to aversive conditioning, special attention to the animals' well-being was maintained. During the experiment proper, cats were held directly by the implanted atraumatic head holder, insuring that there were no painful pressure points. Care was taken to alleviate any postural strain by careful positioning of the animals, and the body rested on a cushioned surface. The eyes were protected from

drying. There was no tension on the subcutaneous needle electrodes. Training and recording sessions lasted a maximum of 3 h; supplemental doses of gallamine were not given. In general, heart rate remained constant, pupillary dilation occurred only in the time period associated with the shock stimulus, and the animals, when not anticipating shock, showed high-voltage, low-frequency EEG activity compatible with sleep.

During the course of the study, animals generally gained or maintained a stable body weight and were free from infection and disease. Signs of extreme fear were not evident when they were being prepared for daily sessions; there was no hissing, piloerection, or attempt to escape or attack during the preparation procedure. Further, cats willingly entered and explored the experimental chamber on their own. Overall, the cats remained healthy and friendly during the course of the experiment.

Results

Typical waveforms and components

AEPs from the V1 electrode of one cat during conditioning evoked by clicks (Fig.

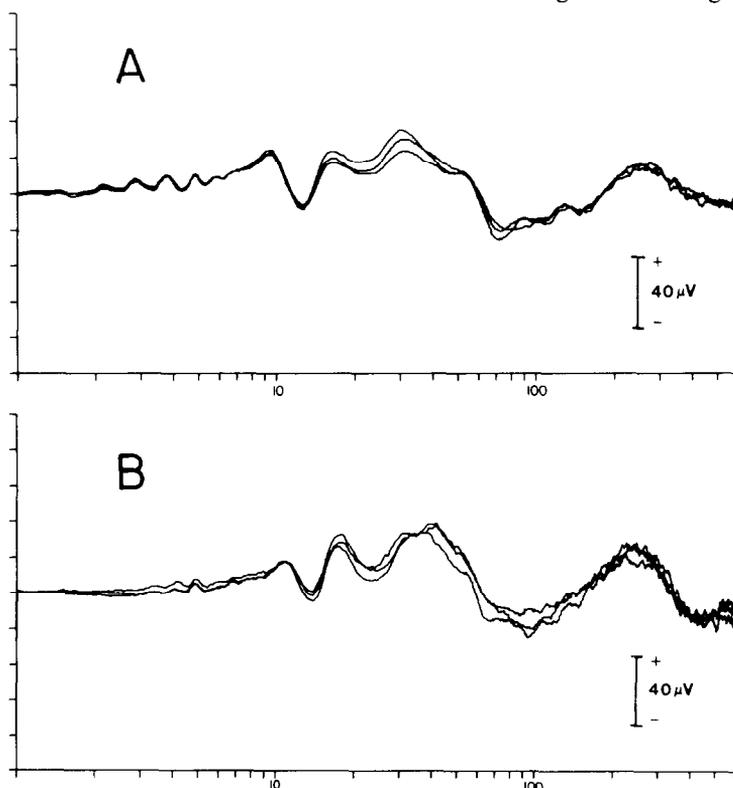


Fig. 3. Reproducibility of the cat AEP. Displayed on a logarithmic time base are AEPs evoked by clicks (A) and noise stimuli (B) as recorded from the V1 electrode site, from one animal, in one behavioral condition. The similarities in the replicated waveforms suggest a good degree of reproducibility in the cat AEP. Abscissa units are in ms; ordinate units spacing is 20 μV .

3A) and noise bursts (Fig. 3B) are shown to provide an estimate of the replicability of waveforms.

Two methods for identifying AEP components were used. The first used approximate peak latency and polarity of peaks and troughs at the V1 electrode site for identification (Fig. 4A). The peaks and troughs chosen had relatively large amplitudes and stable latencies across cats and conditions. The means and standard deviations of these latencies across all cats and experimental conditions are shown in Table I. The ABR comprises the first 8 ms and its major component, P4, is labelled. Six peaks and troughs of 8–50 ms latency are tentatively considered ‘middle latency’ components. Finally, the ‘late components’ encompass the six peaks and troughs of 50–600 ms latency. N100 (indicated by a dashed line), is not strongly apparent at V1, but is a large *positive* peak at lateral electrodes (especially CL1).

The second method of component definition, PCA, is illustrated in Fig. 4B. Principal components have been averaged across cats and are displayed with an example AEP (upper tracing). The middle traces contain the five components for the 100 ms span, while the lower contain the seven components for the 560 ms time span. The numbers designate individual components; components 7 of the 560 ms time span and 5 of the 100 ms span are represented by darker traces. A marked similarity is apparent between the first four components of the 100 ms time span and those of the 560 ms time span. However, component 4 in the middle traces is also similar to parts of component 7 in the lower set. Component 5 of the 100 ms span is not clearly related to any of the 560 ms span components.

Components 1–3 of the 100 ms span and 4–7 of the 560 ms span were chosen for score calculation. The first six components loaded strongly at about 25, 45, 65, 140, 260 and 500 ms. The seventh component was polyphasic, with strong loading from 50 to 200 ms, and a maximum at about 100 ms. Components can be thought to represent latency epochs in the AEPs, and their variation to contribute to the

TABLE I

LATENCIES OF CAT AUDITORY EVOKED POTENTIAL PEAKS (in ms)

Peak name	Mean latency	Standard deviation
P4	4.65	0.54
P10	9.83	1.07
N13	13.09	1.07
P17	17.39	1.27
N22	22.45	1.00
P31	30.18	4.05
N41	39.33	5.39
P55	49.23	6.68
N70	68.73	11.21
N100	97.93	18.01
N140	162.58	22.54
P260	272.27	27.82
N520	498.45	3.05

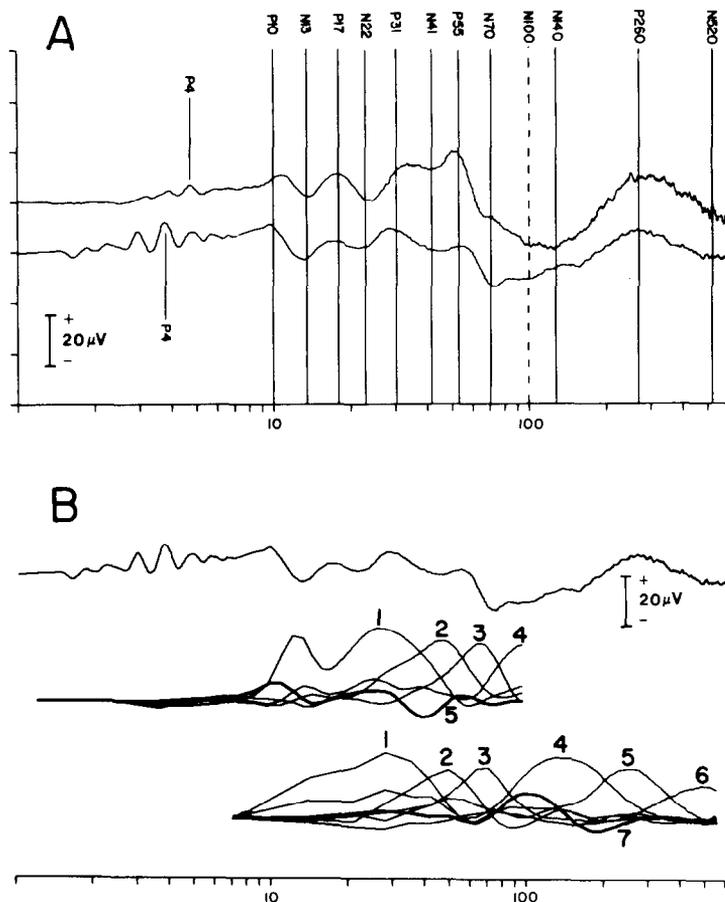


Fig. 4. AEP component identification. (A) Representative AEPs evoked by noise (upper trace) and clicks (lower trace) for which the major peaks and troughs have been labelled. The location of N100, seen mainly over temporal areas, is indicated by the dashed line. (B) Principal components derived for 1.2 ms (middle traces) and 7.0 ms (lower traces) sampling intervals are numbered. An AEP waveform is provided in the top trace to allow comparison between principal components and waveform features.

behavior of the peaks and troughs subsumed within those epochs. Thus, the relationship between principal components versus the peaks and troughs of the AEP is as follows: component 1 includes P10, N13, P17, N22 and P31, and component 2 spans N41 and P55, while component 3 corresponds best to N70, component 4 to N140, component 5 to P260, component 6 to N520, and component 7 to N100.

Behavioral effects examined qualitatively

Behavioral manipulations most affected the later AEP components (especially from 60 ms on), as illustrated in Fig. 5. In the upper plate of Fig. 5, AEPs to pre-noise clicks (light traces) and post-noise clicks (dark traces), are compared, while in the lower plate, noise-evoked AEPs are displayed. Each trace has been averaged

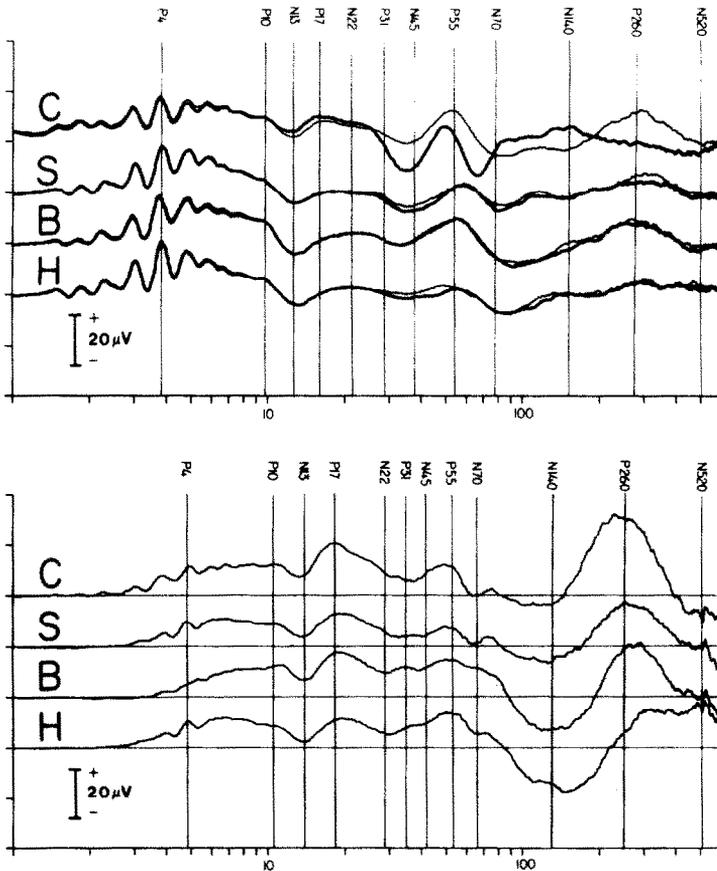


Fig. 5. Effect of behavioral state and stimulus on AEP waveforms. AEPs have been averaged across midline electrode locations (V1–V5) for pre-noise clicks (light traces, upper plot), noise bursts (lower plot), and post-noise clicks (dark traces, upper plot), separately for each behavioral condition. Major waveform peaks and troughs are labelled. (H) Habituation. (B) Backward conditioning. (S) Sensitization. (C) Conditioning.

across cats and the five midline electrodes (V1 to V5). Note especially that (1) the click evoked AEPs are quite similar in all behavioral conditions except for the 30–500 ms period during conditioning, when pre- and post-noise click AEPs obviously differ (Fig. 5, upper plate, C), and (2) that noise AEPs differ across conditions, particularly for components N140 and P260 (Fig. 5, lower plate).

Behavioral effects on peak measures

The peaks and troughs shown in Fig. 4A were measured for baseline to peak amplitude and peak latencies for the V1 electrode. Each measure was subjected to a two-way repeated measures analysis of variance (CONDITION, 4 levels; STIMULUS, 3 levels), whose results are shown in Table II. The significant effects are generally apparent in Fig. 5; when they are not, it should be remembered that Fig. 5

shows the mean of all midline electrode sites, while the effects tested in Table II were from only the V1 electrode.

For all components up to P55, noise bursts evoked a slightly longer (typically 1 ms) latency than clicks. Also, latencies for peaks P10 through N22 were slightly shorter during conditioning than those during sensitization or backward conditioning, which in turn were shorter than habituation. These differences were usually around 2 ms. Finally, P260 latencies had a significant condition–stimulus interaction. They were longest for all habituation responses and for noise responses during backward conditioning, but shortest for noise during conditioning.

The amplitudes of a number of peaks and troughs were larger for noise than for click stimuli. Three peaks showed condition effects: N13 was least negative during conditioning, N70 was most negative with conditioning and least negative during habituation, and N520 was positive for habituation but negative for all other conditions.

TABLE II
ANOVA ON PEAK AMPLITUDE AND LATENCY

COND = condition; STIM = stimulus.

Peak	Latency			Amplitude		
	COND (3,9 df)	STIM (2,6 df)	COND–STIM (6,18 df)	COND (3,9 df)	STIM (2,6 df)	COND–STIM (6,18 df)
P4	1.02	25.56 < 0.01	1.12	1.59	67.32 < 0.001	1.75
P10	4.14 < 0.05	42.75 < 0.001	1.12	2.13	0.30	0.04
N13	7.02 < 0.01	12.10 < 0.01	1.46	6.29 < 0.025	9.38 < 0.025	2.08
P17	5.93 < 0.025	3.83	0.68	1.18	11.66 < 0.01	0.46
N22	3.89 < 0.025	38.84 < 0.001	1.78	1.03	12.83 < 0.01	0.46
P31	2.60	30.61 < 0.001	1.55	1.84	3.43	0.96
N45	0.95	4.96	1.51	0.58	7.55 < 0.025	0.75
P55	2.29	0.96	1.13	1.91	10.60 < 0.025	3.33 < 0.025
N70	1.81	0.93	0.88	4.61 < 0.05	4.94	2.02
N140	0.78	0.16	2.02	2.28	12.97 < 0.01	4.10 < 0.01
P260	1.35	0.35	2.86 < 0.05	0.64	47.66 < 0.001	6.14 < 0.01
N520	1.41	3.41	0.70	4.48 < 0.05	0.70	0.51

In addition, the amplitudes of three peaks showed significant condition–stimulus interactions. P55 evoked by noise was largest for conditioning and habituation, and smallest for backward conditioning. Amplitudes were similar for all clicks in all conditions, except the post-noise click during conditioning, where it was much smaller. N140 evoked by clicks had similar amplitudes across all conditions except conditioning, where post-noise click N140s became positive. N140 amplitude evoked by noise was smaller during conditioning and sensitization than during backward conditioning and habituation. P260 evoked by noise was largest during conditioning, approximately half that size during sensitization and backward conditioning, and almost undetectable during habituation. A similar pattern was evident for click AEPs except that, for post-noise clicks during conditioning, P260 became slightly negative.

Analysis of effects on PCA component scores

Component scores were calculated for each of the seven principal components derived for each cat. These were subjected, component by component, to a three-way repeated measures analysis of variance, the outcome of which is shown in Table III. The three factors were (1) the four levels of behavioral condition (COND), (2) the seventeen skull electrode locations (LOC), and (3) the three ‘stimuli’ (STIM), being the pre- and post-noise clicks and the noise.

Note that all components except 1 and 7 showed effects involving the condition factor, especially components 3 through 6. Plots of the significant condition and condition–stimulus effects for these latter four components are presented in Fig. 6. All components showed a significant location effect. Moreover, for all components except 6, there was a highly significant location–stimulus interaction, indicating that different stimuli evoked either (1) the accentuation of a basic skull topographic distribution or (2) the formation of a totally different skull topographic distribution. In fact, the first alternative was usually the case. Presentation of results involving the location effect is deferred to a companion paper [39].

Correlations with behavioral state indices

We examined the relationship between the AEP principal component scores and two indices of behavioral state: arousal level (as defined by EEG), and behavior (defined by pupillary dilation). Examples of the three types of data, averaged across animals, are shown in Fig. 7.

‘EEG scores’, derived by taking the value in the 0–12 Hz band of the average EEG magnitude spectrum (Fig. 7B, shaded region), reflect the relative prominence of low-frequency, high-voltage activity. Pre-noise EEG scores were often larger than post-noise scores, except during backward conditioning, where they were quite similar. Habituation scores were generally largest, while the other behavioral conditions were grouped together at considerably lower values.

‘Pupil scores’, derived by calculating the average dilation from 465 and 940 ms after noise presentation (shaded region, Fig. 7C), relative to the pre-noise baseline, reflect the amplitude of the initial pupillary dilation to noise. Pupil scores were largest for conditioning, relatively equal valued for sensitization and backward

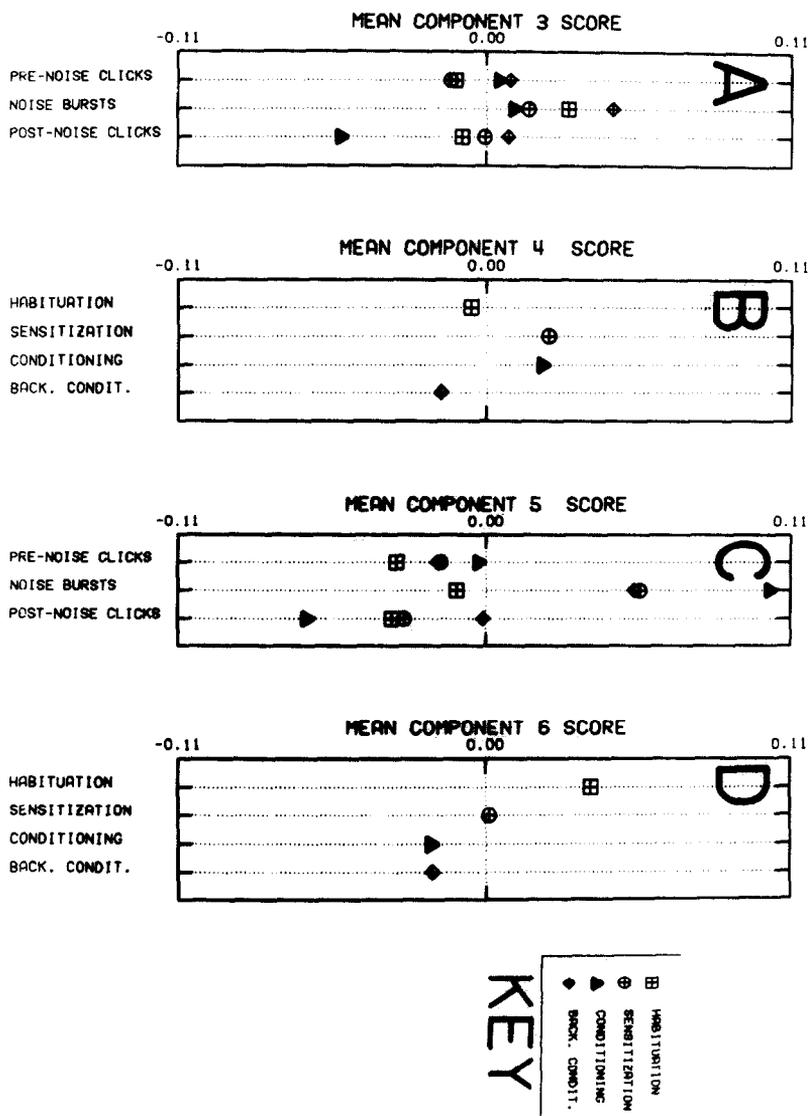


Fig. 6. Some effects of behavioral condition on principal component scores. Mean component scores are plotted for the simpler effects of behavioral condition (including interactions with stimulus) for those principal components showing significant effects for these factors. (A) Condition-stimulus interaction for component 3. (B) Condition effect for component 4. (C) Condition-stimulus interaction for component 5. (D) Condition effect for component 6.

conditioning, and smallest for habituation.

Correlations (see Table IV) were calculated on a replication by replication basis between the EEG and pupil scores, and the noise evoked potential component scores from the V1 electrode. Pre- and post-noise EEG scores were collapsed to give a

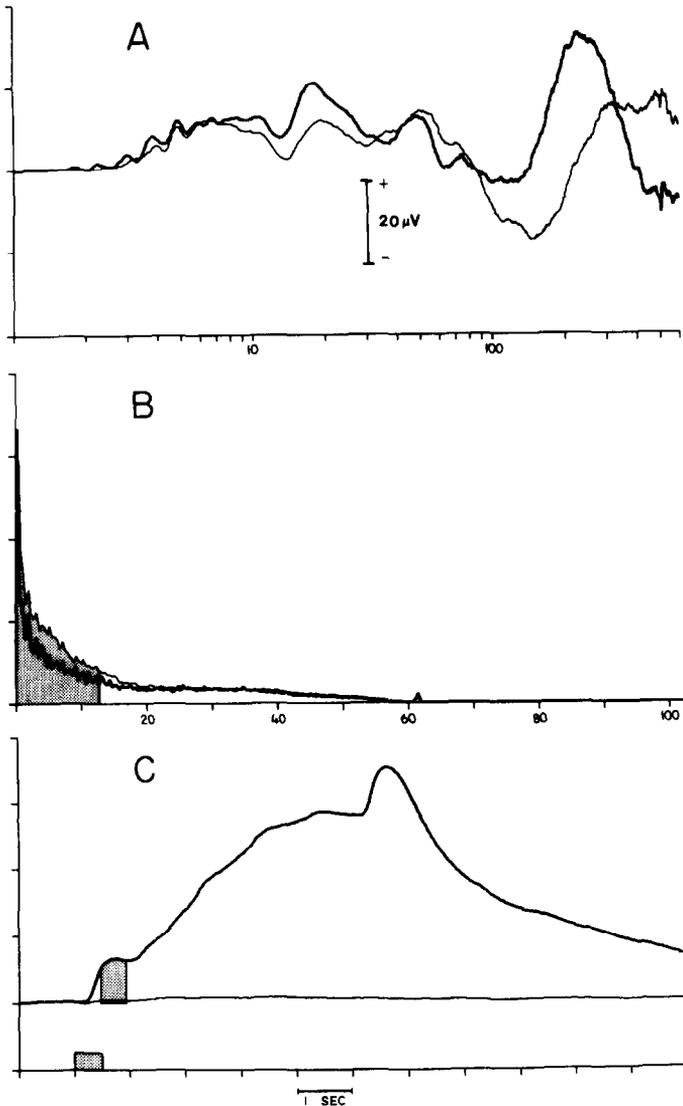


Fig. 7. AEP and behavioral measures used in correlations are shown for two behavioral conditions: habituation (light traces) and conditioning (dark traces). (A) AEPs to noise stimuli averaged across animals. Ordinate unit spacing is $20 \mu\text{V}$. Principal component scores were used in correlations. (B) The average magnitude spectrum of the EEG (averaged across animals, replications, and pre- versus post-noise periods) is plotted against frequency on the abscissa (units in Hz). An area measurement (represented by shading) was taken in the 0 to 12 Hz band to form the basis for an 'EEG score' used in the correlations. (C) Average pupillary dilation is plotted against time for the peri-noise period starting 999 ms before noise onset and ending 10989 ms after noise onset. Noise stimuli were delivered in the period shown by the shaded box. An area measurement was taken during the peak of the initial dilation (indicated by the shaded bar) and formed the basis for a 'pupil score' used in the correlations.

TABLE IV
CORRELATIONS OF PRINCIPAL COMPONENTS WITH BEHAVIORAL INDICES

	Correlation (46 df) with	
	Pupil score	EEG score
Component 2	0.078	-0.375 < 0.01
Component 3	-0.306 < 0.05	0.348 < 0.05
Component 4	0.514 < 0.01	-0.623 < 0.01
Component 5	0.518 < 0.01	-0.117
Component 6	-0.240	0.130
Pupil score	1.000 < 0.01	-0.428 < 0.01
EEG score	-0.428 < 0.01	1.000 < 0.01

single EEG score for this purpose. Note that components 3 and 4 were correlated with both behavioral indices, although the relationship was slightly stronger for the EEG score in both cases. The EEG and Pupil scores were, themselves, significantly correlated.

Discussion

In this study in cats, a complex series of AEP components occurred for up to 600 ms following auditory stimulation. These components were distinguishable along the same dimensions that have been investigated for humans.

Limitations of cat as an AEP model

Before considering human and cat AEP correspondences, we note several ways this study differs from those reported in the human literature. These include dissimilarities in (1) brain structures, (2) training strategies, and (3) response measures.

There are several major differences between cat and human brains, including the overall brain size, the proportion of tissue devoted to various regions, and the orientation of various structures. These differences might change potential field distributions and temporal sequencing of waveform features. A non-human primate would, of course, be less troublesome in these regards. However, the cat has advantages in cost, availability, and knowledge of its neurophysiology. It is also important to know the phylogenetic generality of middle and long latency AEP components.

Second, training procedures differ between animals, which require conditioning

techniques, and humans, who are often given verbal instructions. Such differences could activate different cognitive and neural processes, with consequences for the AEP. Exact comparison between humans and animals is possible only if humans are trained by procedures applicable to animals. However, valid comparisons might be made if superficially different training techniques elicit similar behavioral and cognitive processes. Fortunately, many processes thought to affect human AEP components, including arousal, attention, and expectancy, also seem affected by conditioning procedures. The current autonomic conditioning task was chosen because of (1) extensive evidence that it behaves the laws of classical conditioning [26,27,40], (2) the fact that classical conditioning appears able to manipulate variables [30] thought to affect the human AEP, (3) the ease of training and recording from animals performing this task, and (4) importantly, the control of acoustic inputs and muscle artifacts (including middle-ear muscle contractions, post-auricular reflexes and eye movements), known to interfere with human and animal AEPs [3,37]. Possible task drawbacks are that (1) components might be task specific and not comparable across species and (2) paralysis might radically alter the behavioral context of the situation, restricting meaningful comparison with human studies. The first of these limitations seems unlikely since middle and late human AEP components occur in variety of behavioral tasks, and could be eliminated from consideration by demonstrating that they occur during classical conditioning in humans. The paralysis issue is less significant for the middle latency components, since they have been elicited in human subjects paralyzed with succinylcholine [12]; a similar demonstration is lacking for the late AEP components.

Finally, different response measures between human studies, where button presses and silent stimulus counting are common, and this study in cats, in which pupillary dilation was measured, might cause apparent species AEP differences. For instance, neural or autonomic muscle events underlying pupil dilations might have contributed to the form of the AEP. However, correlations between pupil dilation and P300 amplitude have been reported in humans [9], suggesting that the use of this autonomic measure is not an issue. Second, paralysis might cause AEP differences by preventing muscle artifact contamination. Finally, certain neural mechanisms reflected in the AEP might be differentially activated based on response system used. At present, we can only note that human middle and late AEP components are thought to be (1) neurally generated, (2) stimulus bound or due to attentive and cognitive processes, and (3) elicited in a variety of tasks having differing response requirements. We have limited our recordings to neural (and autonomic) potentials, to at least the degree of human AEP studies. However, we did not directly vary response system, and cannot thus rule out its contribution to some of our AEP components.

Behavioral indices and their meanings

We used two measures to provide insight into our cats' behavioral states. First, pupillary dilation provided an index of training and performance. We suggest that the pupillary response amplitude to a given stimulus might be considered an index of attention to it. The other behavioral index was the EEG. This index varied both

between conditions and over time within a condition. We suggest that these variations indicate arousal level fluctuations, and that predominantly low-frequency, high-voltage activity, including spindling, might indicate sleep.

Implications of behavioral and waveshape criteria for correspondences

The cat AEP waveform much resembles that described for humans, with notable exception of the human N90-P170 components. Since behavioral effects were seen only in later AEP components, the exogenous–endogenous distinction described for humans [7] seems also to apply to cats. Waveform and behavioral criteria for correspondence are discussed below for various AEP components. In a companion paper [39], implications of stimulus effects on and topographic distributions of AEP components are discussed, and a summary interpretation of our findings is offered.

Exogenous components. The ABR (latencies less than 10 ms) components showed relatively little variation during the behavioral study when compared with other parts of the waveform. This might have been predicted based on their immutability even during drug induced coma in humans [38].

Five peaks and troughs with latencies of 10–50 ms were treated by PCA as primarily due to a single source of variation. Their latencies and polarities correspond well with human middle latency AEP components, although one complex of peaks (presumably N13–P17–N22) was more consistently recorded in this study than has been reported for humans [22]. Human components at these latencies were relatively insensitive to the behavioral manipulations [21], although deep sleep often caused small amplitude reductions in some peaks [22–24]. For the most part, these findings are true of these cat AEP components, as well. However, we note small latency changes in these components between behavioral conditions, a difference from human middle latency components that bears further examination.

The latency and polarity of cat N41 and P55 suggest that they best correspond with human N45 and P50. However, this correspondence might be questioned, since one of the main distinguishing features of human P50 is its occurrence just before a large N90 wave, which is not obvious in the cat AEP. Human N45 and P50 are less studied than either the N90–P170 vertex response or the middle latency components up through P30, and thus other distinguishing criteria are lacking.

Endogenous components. On behavioral grounds, cat N140 best corresponds with human N300, although their latencies are quite different. The main evidence in this regard is the strong association of large cat N140 amplitudes with low arousal levels (i.e. sleep), similar to that described for human N300 [18,29,42].

P260, and its associated principal component 5, probably corresponds to human P300. Their polarities and latencies correspond well, especially for easily distinguishable stimuli [11,33,35]. P260's complex interaction of controlling factors (component 5 condition–location–stimulus interaction) is comparable to that of human P300 (e.g. [32]). Human P300 is evoked by rare, task-relevant stimuli, and its size is controlled by the interaction of stimulus probability and task relevance [7]. In this study, the largest potentials were elicited by rare noise stimuli during condition-

ing (when noise stimuli had signal value), while potentials to clicks and task-irrelevant noise stimuli were much smaller. Further, this component's correlation with pupillary dilation, but not EEG synchrony, suggests an involvement of attentional rather than arousal processes in its production. Finally, we show in another study [41] that P260's amplitude varies with stimulus probability. We also demonstrated that P260 is elicitable by light flashes, as well as tone and noise bursts, and thus is relatively stimulus independent, like human P300 [41]. Similar results have been reported in cat [34], with the addition that a P260 wave was elicited to a task-relevant, missing stimulus.

N520 might correspond to one or more human components of similar latency and amplitude. First, as Keidel [17] pointed out, cat auditory cortical potentials evoked by long duration stimuli resemble human slow potential shifts, including termination by an off response. Some features of our N520s to noise stimuli behave in this manner. Second, the late positive (their P3) wave described by Williams et al. [42] grew greatly during deep sleep. We note that N520 is most positive during habituation, and that this is the condition in which our cats could be in deepest sleep, since conditioning and sensitization EEGs indicated high arousal, while animals during backward conditioning were in transition from an aroused state, having just been shocked. Finally, latency criteria suggest a possible relationship between cat N520 and the slow wave following P300 reported occasionally in humans [7].

Missing components

N90 and P170 in humans are usually four or five times larger than preceding middle latency components [44]. In this study, such peaks are not obvious, although minor features (N70 and N100) of proper latency can be seen. Thus, one might suggest that cat N70 (and associated principal component 3) corresponds either with human N90 or with its closely associated "N100 processing negativity" [25], while cat N100 (and associated principal component 7) may relate somehow to any or all of human components N90, P170, and the T-complex [43]. It is also possible that N90 and P170 are missing in the cat.

Effects on AEPs during the noise-shock interval

AEPs evoked by post-noise clicks during conditioning differed dramatically from other click evoked AEPs, especially at latencies greater than 30 ms. This is not explained by noise-burst induced fatigue, which would be present in other conditions, nor by arousal level (reflected by the EEG), which resembled that of sensitization. Based on one classical conditioning theory [30], one might speculate that this phenomenon involves attentional changes, since the shaping procedure used during training should remove signal value from everything but the interval between noise onset and shock onset. However, whatever its behavioral correlates, this striking phenomenon might prove useful in further identifying human and cat AEP counterparts.

Acknowledgements

This work was supported in part by grants from the National Institutes of Health (NS11876), and by graduate training support (to G.R.F.) from the National Institute of Mental Health (5 T32 MH 14599-03 & 04) and the National Science Foundation (SMI-76-22511). Portions of this material have been published on microfilm as G.R.F.'s doctoral dissertation with University Microfilms, Inc., Ann Arbor, Michigan.

The authors gratefully acknowledge the help received in the course of this work from Dana Grenier, Jay Manago, Keith Manahan, Shirley Adams, Dr. Len Kitzes and Dr. Mike Cassaday.

References

- 1 Achor, L.J. and Starr, A. (1980): Auditory brain stem responses in the cat. I. Intracranial and extracranial recordings. *Electroenceph. Clin. Neurophysiol.* 48, 154-173.
- 2 Achor, L.J. and Starr, A. (1980): Auditory brain stem responses in the cat. II. Effects of lesions. *Electroenceph. Clin. Neurophysiol.* 48, 174-190.
- 3 Bickford, R.G. (1972): Physiological and clinical studies of microflexes. *Electroenceph. Clin. Neurophysiol.* 31 (Suppl.), 93-108.
- 4 Buchwald, J.S., Hinman, C., Norman, R.J., Huang, C.-M. and Brown, K.A. (1981): Middle- and long-latency auditory evoked responses recorded from the vertex of normal and chronically lesioned cats. *Brain Res.* 205, 91-110.
- 5 Buchwald, J.S. and Huang, C.-M. (1975): Far-field acoustic responses: origins in the cat. *Science* 189, 382-384.
- 6 Cassaday, J.M., Farley, G.R., Weinberger, N.M. and Kitzes, L.M. (1982): Pupillary activity measured by reflected infra-red light. *Physiol. Behav.* 28, 851-854.
- 7 Donchin, E., Ritter, W. and McCallum, W.C. (1978): Cognitive psychophysiology: the endogenous components of the ERP. In: *Event Related Potentials in Man*, pp. 349-411. Editors: E. Callaway, P. Teuting and S.H. Koslow. Academic Press, San Francisco.
- 8 Donchin, E. and Heffley, E.F., III (1978): Multivariate analysis of event-related potential data: a tutorial review. In: *Multidisciplinary Perspectives in Event-Related Brain Potential Research*, pp. 555-572. Editor: D.A. Otto, U.S. Government Printing Office, Washington, D.C.
- 9 Friedman, D., Hakerem, G., Sutton, S. and Fleiss, J.L. (1973): Effect of stimulus uncertainty on the pupillary dilation response and the vertex evoked potential. *Electroenceph. Clin. Neurophysiol.* 34, 475-484.
- 10 Goldenberg, R.A. and Derbyshire, A.J. (1975): Averaged evoked potentials in cats with lesions of auditory pathway. *J. Speech Hear. Res.* 18, 420-429.
- 11 Gomer, F.E., Spicuzza, R.J. and O'Donnell, R.D. (1976): Evoked potential correlates of visual item recognition during memory scanning tasks. *Physiol. Psychol.* 4, 61-65.
- 12 Harker, L.A., Hosick, E., Voots, R.J. and Mendel, M.I. (1977): Influence of succinylcholine on middle component auditory evoked potentials. *Electroenceph. Clin. Neurophysiol.* 103, 133-137.
- 13 Hillyard, S.A., Picton, T.W. and Regan, D. (1978): Sensation, perception and attention: analysis using ERPs. In: *Event-Related Potentials in Man*, pp. 223-321. Editors: E. Callaway, P. Teuting and S.H. Koslow. Academic Press, San Francisco.
- 14 Huang, C.-M. (1980): A comparative study of the brain stem auditory response in mammals. *Brain Res.* 184, 215-219.
- 15 Jewett, D.L. (1970): Averaged volume-conducted potentials to auditory stimuli in the cat. *Electroenceph. Clin. Neurophysiol.* 28, 609-618.

- 16 Kaga, K., Hink, R.F., Shinoda, Y. and Suzuki, J. (1980): Evidence for a primary cortical origin of a middle latency auditory evoked potential in cats. *Electroenceph. Clin. Neurophysiol.* 50, 254–266.
- 17 Keidel, W.D. (1976): The physiological background of the electric response audiometry. In: *Handbook of Sensory Physiology*, Vol. V/3, pp. 105–231. Editors: W.D. Keidel and W.D. Neff. Springer-Verlag, New York.
- 18 Kevanishvili, Z.Sh. and von Specht, H. (1979): Human slow auditory evoked potentials during natural and drug-induced sleep. *Electroenceph. Clin. Neurophysiol.* 47, 280–288.
- 19 Lev, A. and Sohmer, H. (1972): Sources of averaged neural responses recorded in animal and human subjects during cochlear audiometry (electrocochleography). *Arch. Klin. Exp. Ohr. Nas. Kehlkopf.* 201, 79–90.
- 20 Macar, F. and Vitton, N. (1979): Contingent negative variation and accuracy of time estimation: a study on cats. *Electroenceph. Clin. Neurophysiol.* 47, 213–228.
- 21 Mendel, M.I. and Goldstein, R. (1969): The effect of test conditions on the early components of the averaged electroencephalic response. *J. Speech Hear. Res.* 12, 344–350.
- 22 Mendel, M.I. and Goldstein, R. (1971): Early components of the averaged electroencephalic response to constant level clicks during all night sleep. *J. Speech Hear. Res.* 14, 829–840.
- 23 Mendel, M.I., Hosick, E.C., Windman, T.R., Hirsh, S.K. and Dinges, D.F. (1975): Audiometric comparison of the middle and late components of the adult auditory evoked potentials awake and asleep. *Electroenceph. Clin. Neurophysiol.* 38, 27–33.
- 24 Mendel, M.I. and Kupperman, G.L. (1974): Early components of the AER to constant level clicks during rapid eye movement sleep. *Audiology* 13, 23–32.
- 25 Naatanen, R. and Michie, P.T. (1979): Different variants of endogenous negative brain potentials in performance situations: a review and classification. In: *Human Evoked Potentials: Applications and Problems*, pp. 251–267. Editors: D. Lehmann and E. Callaway. Plenum Press, New York.
- 26 Oleson, T.D., Westenberg, I.S. and Weinberger, N.M. (1972): Characteristics of the pupillary dilation response during Pavlovian conditioning in paralyzed cats. *Behav. Biol.* 7, 829–840.
- 27 Oleson, T.D., Vododnick, D.S. and Weinberger, N.M. (1973): Pupillary inhibition of delay during Pavlovian conditioning of paralyzed cats. *Behav. Biol.* 8, 337–346.
- 28 Picton, T.W. and Hillyard, S.A. (1974): Human auditory evoked potentials. Part II: Effects of attention. *Electroenceph. Clin. Neurophysiol.* 36, 191–199.
- 29 Picton, T.W., Hillyard, S.A., Krausz, H.I. and Galambos, R. (1974): Human auditory evoked potentials. Part I: Evaluation of components. *Electroenceph. Clin. Neurophysiol.* 36, 179–190.
- 30 Rescorla, R.A. and Wagner, A.R. (1972): A theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement. In: *Classical Conditioning II*, pp. 64–99. Editors: A. Black and W.F. Prokasy. Appleton-Century-Crofts, New York.
- 31 Snyder, E., Hillyard, S.A. and Galambos, R. (1980): Similarities and differences among P3 waves to detected signals in three modalities. *Psychophysiology* 17, 112–122.
- 32 Squires, K.C., Donchin, E., Herning, R.I. and McCarthy, G. (1977): On the influence of task relevance and stimulus probability on event-related-potential components. *Electroenceph. Clin. Neurophysiol.* 42, 1–14.
- 33 Squires, K.C., Hillyard, S.A. and Lindsay, P.H. (1973): Vertex potentials evoked during auditory signal detection: relation to decision criteria. *Percept. Psychophys.* 10, 445–452.
- 34 Squires, N.K. and Buchwald, J.S. (1981): Endogenous auditory evoked potentials in the cat. *Neurosci. Abstr.* 7, 452.
- 35 Squires, N.K., Donchin, E. and Squires, K.C. (1977): Bisensory stimulation: inferring decision-related processes from the P300 component. *J. Exp. Psychol.* 3, 299–315.
- 36 Starr, A. (1978): Sensory evoked potentials in clinical disorders of the nervous system. *Annu. Rev. Neurosci.* 1, 103–127.
- 37 Starr, A. (1964): Influence of motor activity on click-evoked responses in the auditory pathway of waking cats. *Exp. Neurol.* 10, 191–204.
- 38 Starr, A. and Achor, L.J. (1975): Auditory brain stem responses in neurological disease. *Arch. Neurol.* 32, 761–768.
- 39 Starr, A. and Farley, G.R. (1983): Middle and long latency auditory evoked potentials in cat. II. Component distributions and dependence on stimulus factors. *Hearing Res.* 10, 139–152.

- 40 Weinberger, N.M., Oleson, T.D. and Haste, D. (1973): Inhibitory control of the conditional pupillary dilation response in the paralyzed cat. *Behav. Biol.* 9, 307-316.
- 41 Wilder, M.B., Farley, G.R. and Starr, A. (1981): Endogenous late positive component of the evoked potential in cats corresponding to P300 in humans. *Science* 211, 605-607.
- 42 Williams, H., Tepas, D. and Morlock, H. (1962): Evoked responses to clicks and electroencephalic stages of sleep in man. *Science* 138, 685-686.
- 43 Wolpaw, J.R. and Penry, J.K. (1975): A temporal component of the auditory evoked response. *Electroenceph. Clin. Neurophysiol.* 39, 609-620.
- 44 Zerlin, S. and Nauton, R.F. (1974): Early and late averaged electroencephalic responses at low sensation levels. *Audiology* 13, 366-378.