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THE EFFECTS OF ALCOHOL UPON SENSORY EVOKED AND SPONTANEOUS CEREBRAL POTENTIALS

A DISSERTATION

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AND SPONTANEOUS CEREBRAL POTENTIALS

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CHAPTER 1

INTRODUCTION

Although Hans Berger (1929) is credited with being the first to identify and categorize certain spontaneous cerebral rhythms, reports of "feeble" electrical currents emanating from the brain had actually been published by Caton as early as 1875 (Caton, 1875). It was not, however, until the confirmation of Berger's findings by Adrian and Mathews in 1934 that human electroencephalography, a powerful tool for the study of neuronal processes, was launched as a formal discipline. The tonic potential flux recorded from the cortical surface of laboratory animals as well as through the calvarium and scalp of man have come to be known as the electroencephalogram or EEG. Lindsley (1969) points out that Caton, according to the description of his own data, was, in fact, monitoring sensory evoked potentials. Evoked potentials or evoked responses (used interchangeably) are distinguishable from the more or less random and/or oscillatory variations detected by Berger and his contemporaries in that they are temporally related to the onset of a given stimulus. Moreover, they are discrete rather than autonomous or "ongoing" as is the EEG. An evoked response (ER) may therefore be re-

garded as that observable change in electrical potential in any region of the central nervous system (CNS) following sudden peripheral (externally presented stimulus, e.g., click, flash, shock) or central (e.g., electrical or chemical stimulus applied directly to spinal or brain tissue) stimulation (Chang, 1959).

The correlation between a particular sensory signal and the ensuing electrical response of the brain was firmly established in the mid and late 30's (Adrian, 1936; Bartley and Heinhecker, 1938; Bishop and O'Leary, 1938; Davis, Davis, Loomis, Harvey, and Hobart, 1939; Davis, 1939; Forbes and Morrison, 1939). Today these potential fluctuations can be recorded either intra or extracellularly from single neurons (units) or small groups of cells, from nuclei and nerve tracts deep in the brain, epicortically and, of course, from the surface of the scalp. As such the ER technique has greatly assisted neurophysiologists in tracing sensory impulses through specific afferent systems to their terminals in the cortex. Even transcranially, ER's picked up through the intact skull show a topographical distribution in accordance with the sensory pathways being activated (Gastaut, Regis, Lyagoubi, Mano and Simon, 1967). However, because the sensory ER, as recorded from the scalp, is relatively small (1-15 μv) with respect to the background EEG (20-100 μv), the accurate mapping of the minute potential fields set up by deliberate stimulation of a sense organ had to await the development of special purpose computers (averagers). With these devices, repetitive samples of EEG are automatically summated. Electrical activity unrelated to the onset of a stimulus tends to cancel with successive sweeps while the response initiated by the stimulus

(the evoked potential) reinforces itself. In this way the signal-to-noise ratio can be sufficiently resolved to permit quantification of the ER. With the aid of advanced computers ER methodology has emerged from its beginnings as a means of assessing sensory transmission to a potent investigative technique for the understanding of the brain mechanisms underlying behavior.

The Average Cortical Response

The average cortical response (ACR) presents itself as a complex sequence of polarity reversals which may endure for up to 500 msec. Each deflection varies somewhat depending on the modality stimulated and on the locus from which it was recorded. Although there is some specificity of response following auditory, somatosensory and visual stimulation, a certain degree of similarity across modalities is also apparent. Numerous classification systems have been devised to describe the various undulations of the ACR (Williams, Morelock and Lubin, 1964; Ciganek, 1961; Allison, 1962). The simplest and possibly most universal scheme divides the ER waveform into the early (usually the first 50-100 msec.) and late (the remainder of the response) occurring deflections. This dichotomy is based on the observation that the early portion of the response is localized to the respective sensory receiving area of the cortex whereas the more slowly developing waves are diffusely represented over the entire scalp. Each segment of the ER waveform may contain one or more functionally related or independent components of varying amplitude and duration. Because some of the individual components have been shown to differ in terms of latency and cranial distribution they have been assumed to represent unitary

physiological events. The early components, for example, are thought to originate in fast conducting (oligosynaptic) sensory pathways . Since they are limited to the cortical projection field of specific thalamic relay nuclei, they are believed to reflect cellular excitation in the primary cortex. These short latency components are most pronounced in post-rolandic and occipital regions of the scalp following stimulation of the appropriate sense receptors (Bergamini and Bergamasco, 1967; Allison, 1962). Differences in the recovery cycle and phase relationships among the early components of the scalp recorded somatosensory ER suggest that they may further be divided into presynaptic and postsynaptic constituents (Allison, 1962; Rosner, Goff and Allison, 1963a; Rosner, Goff and Allison, 1963b).

On the other hand, the late components are thought to arise from impulses propagated in more medial lying (extralemniscal) pathways reaching all parts of the cerebral mantle through activation of midline, intralaminer and reticular thalamic structures (Allison, 1962; Goff, Rosner and Allison, 1962). These long latency components are largest in the nonspecific frontal and central areas of the scalp and are considered to be polysensory, since they can be elicited by stimulation in any sense modality. Unlike the early components they are easily influenced by a wide range of organismic and extrinsic variables and have been said to reflect psychological aspects of the experimental situation. Furthermore, they are differentially sensitive to pharmacological manipulation. It was in the deeply barbiturized preparation (cat) that Derbyshire, Rempel, Forbes and Lambert (1936) first observed what was later termed the "secondary discharge" (Forbes, et al., 1963).

A predominantly monophasic positive response with roughly the same time characteristic can be recorded in man (Allison, 1962). Chloralose administration in the cat enabled Amassian (1954) and other workers, Albe-Fessard and Rougurl (1958), Buser and Borenstein (1959) and Thompson and Sindberg (1960) to identify a potential evoked response in the association cortex. This "association response" disappears upon barbiturization, as do components of similar latency and phase in man (Allison, et al., 1963). A similar potential has been likened to the response of the ascending reticular system reported by Brazier (1960). In this regard, changes in the amplitude, latency or waveform of the different components have been taken as the manifestation of neurotrophic action upon central modulating structures as well as on classical sensory pathways (Winters, 1968).

Following pentobarbital infusion or ether inhalation in the cat and monkey, French, Verzeano and Magoun (1953), Arduini and Arduini (1954) and Rosner, et al. (1963) demonstrated that potentials initiated by peripheral nerve or acoustic stimulation were suppressed along multisynaptic (extralemniscal) routes. Evoked responses in the mid-brain reticular formation, pons, centre median nucleus and cortical late components progressively declined with deepending anesthesia. In contrast, conduction along oligosynaptic (lemniscal) pathways remained unimpaired as the primary response in the post-central gyrus and auditory cortex showed no effect or became enhanced. Behaviorally, the effect resembled that produced by electrolytic destruction of medial brain stem structures. This functional blockade of afferency ascending in the centrecephalic system was postulated as the basis of the

anesthetic state (French, et al., 1954). The slight potentiation of the early components was construed as a release from tonic reticular inhibition. In man some long latency components are similarly affected. With increasing depths of anesthesia perirolandic and vertex late components were shown to decrease and ultimately vanish whereas early components were unchanged or became slightly enhanced (Allison, et al., 1963; Abrahamian, Allison, Goff and Rosner, 1963).

The Effects of Alcohol on the Sensory Evoked Response

Attempts to localize the pharmacological action of alcohol within the central nervous system have also relied on the evoked potential technique.

By implanting electrodes at successive locations along the somatosensory pathway in the cat, DiPerri, Dravid, Schweigerdt and Himwich (1968), Himwich, DiPerri, Dravid and Schweigerdt (1966) and Dravid, DiPerri, Morillo and Himwich (1963) were able to demonstrate a differential susceptability to ethanol among the various recording stations. Potentials evoked in the midbrain reticular formation to radial or sciatic nerve stimulation were markedly depressed by the dosage used (1g./kg.) while the primary cortical receiving area and the specific thalamic relay nucleus (posterior lateral ventral nucleus) were barely affected. The most pronounced effect, however, as judged by relative amplitude loss, was observed in the somatosensory association area (Schweigerdt, Dravid, Stewart and Himwich, 1965; DiPerri, et al., 1968). Experiments with photic stimulation revealed that under alcohol, the late components of the homolateral visual cortex were

severely attenuated at a time when little change was seen in the early components or lateral geniculate potentials. The cortical response to acoustic stimulation was also more resistant to alcohol, showing only a transitory effect compared to the prolonged depression of evoked activity in the inferior colliculus. Because those structures with the most extensive synaptic development were influenced to the greatest degree, the synapse was assumed to be the most vulnerable neural element to the narcotic action of alcohol.

Following alcohol loading in human subjects, Lewis, Dustman and Beck (1970) found that the polysensory response to either light or shock stimuli became significantly reduced whereas occipital potentials were not affected. Speculating that those components having latencies in excess of 80 msec. arrive over nonspecific pathways, they concluded that suppression of collateral output from the reticular formation was the probable site of the pharmacological block. Gross, Begleiter, Tobin and Kissin (1966) observed that all waves of the auditory evoked response were obtunded 15-30 minutes after the inges tion of 100 cc of whiskey. These investigators hypothesized that conduction along lateral as well as medial pathways was impaired by alcohol.

Pharmacological Differentiation Of Response Components

The data thus far presented, although indirect, favors the contention that the early and late components of the ACR represent respectively the specific and nonspecific activation of the cerebral cortex. Additional findings with various pharmacological agents lend further support to this distinction. Numerous studies with animal and

human subjects have demonstrated that the different components are selectively sensitive to a wide range of anesthetic compounds.

In doses sufficient to produce clinical anesthesia, diethyl ether and cyclopropane suppressed all components of the visual ER, nitrous oxide occasionally enhanced the primaries while methoxflurane and halothane enchanced the secondary components. The barbiturates in high doses led to the obliteration of the late components and reduced the earlier ones. The phenothiazines seemed to exert little influence on either visual or somatosensory ER's (Domino, Corssen and Sweet, 1963; Allison, et al., 1962; Rosner, et al., 1963). The degree of modification (potentiation or attenuation), however, depended not only on the drug given but on the dose level as well. In light barbiturate anesthesia (pentobarbital, thiopental, amobarbital, thiomyal) the early components showed a slight augmentation; at intermediate stages, the secondary components grew larger or became unmasked whereas surgical doses depressed the entire response (Domino, et al., 1963; Ciganek, 1961; Rosner, et al., 1963). This diminution of evoked activity followed a progression from the slowest to the fastest components, the former being the most susceptible showing some reduction upon premedication (Abrahamian, et al., 1963). The stimulant effects seen at low levels of barbiturate anesthesia are also apparent in the spontaneous rhythms of the brain which exhibit marked hyperexcitability. The delta-wave pattern associated with deep narcosis becomes evident only at high concentrations.

There is an abundance of evidence demonstrating a similar biphasic effect of alcohol on the nervous system. Gallego (1948) and

Posternak and Mangold (1949) found that alcohol tended to decrease the resting membrane potential of isolated frog nerves. Small amounts of alcohol led to a slight depolarization thereby lowering the threshold for stimulation. Extreme depolarization in the face of high concentrations rendered the nerve inexcitable. An increase in the random release of transmitter (acetylcholine, ACh) at the frog neuromuscular junction, as indicated by a corresponding increase in the frequency of miniature end plate potentials, has also been observed with low concentrations of alcohol (Gage, 1965; Okada, 1967). Facilitation of impulse transmission from nerve to muscle was noted by Blume (1925) at low alcohol levels, with inhibition occurring at higher concentrations. An increase in the oxygen consumption of rat and guinea pig brain slices was shown to precede the usual respiratory depression seen at higher blood alcohol levels (Wallgren, 1970). This increase in oxygen uptake, however, can be seen at concentrations exceeding that considered to be lethal in vivo (Wallgren, 1970). Nevertheless, a small but significant rise in the cerebral blood flow of the paralyzed cat was demonstrated by Hadji-Dimo, Ekberg and Ingver (1968).

A brief period of activation at low blood alcohol concentrations (BAC) is also revealed by the EEG of the acutely alcoholized subject (Hadji-Dimo, et al., 1968). Furthermore, local injections of small quantities of alcohol (0.1-0.2 parts/1000) were shown to increase the excitability of neurons in the cruciate cortex and hypothalamus of the cat (Masserman and Jacobson, 1940). The analeptic effects of alcohol have also been observed in the response of the cortex to direct electrical stimulation (DCR) in the cat (Grenell, 1959; Caspers, 1958;

Story, Eidelberg and French, 1961), although agreement on the dose level has not been reached. Temporary potentiation of the auditory ER in the cat has been reported by Grenell (1959) following the infusion of small amounts of ethanol, methanol and propanol. In most ER studies, though, only a monotonic decline in response amplitude was noted with the rising concentration of alcohol in the blood. It could be that ER's were sampled at BAC's too high or alcohol loads too great to reveal any facilitation.

Behaviorally, improvement in perception (Grenell, 1959) and some motor skills (Tollend, 1966) as well as performance on complex intellectual tasks (Carpenter, Moore, Snyder and Lisansky, 1961) has been reported at relatively low BAC's. Once reached, however, the disturbance threshold is more pronounced when the BAC is still climbing than when it is falling. It should be pointed out that both neurological and behavioral signs of intoxication are themselves poorly correlated with BAC. Mersky, Piker, Rosenbaum and Lederer (1941), Newman and Abramson (1941), Rosenbaum (1942) and Goldberg (1943) have shown that deficits observed during the acclivous phase of the blood alcohol curve returned to normal at BAC's well beyond those at which the impairment was first noted.

Purpose of Dissertation

From the preceding research it is evident that the effects of a given drug on the sensory evoked potential depend not only upon the segment of the response waveform examined but on the dose level at which the observations were made as well. Behavioral experiments have further shown that following alcohol administration the point on the

slope of the blood alcohol curve at which measurements were obtained must also be taken into account. Evoked responses, however, have generally been sampled only at peak BAC's, although different dosages have been used. Moreover, it is not clear in the human literature whether the effects of alcohol on the ER are modality or component specific.

The purpose of the first experiment is to describe in more detail the effects of alcohol on the average cortical response during both ascending and descending stages of alcoholization and to establish the dose-response curve for the various components of the somatosensory evoked potential (SEP).

The SEP is a complex multiphasic response lasting some 300-400 msec. (Allison, 1962; Goff, et al, 1962; Shagass and Schwartz, 1963; Schwartz and Shagass, 1964). Since the early components are best recorded from post-rolandic regions and the late components are visualized easiest over the vertex, both scalp placements will be used to better assess the drug effects.

The somatosensory system was selected for study for several reasons: somatic afferent stimulation affords the experimenter a high degree of stimulus control. The cortical response to this form of stimulation is not so easily influenced by end organ or perceptual adjustments as is true of the auditory and visual apparatus. More importantly transcutaneous stimulation, as opposed to light or acoustic stimuli, is known to yield the clearest expression of the postsynaptic primary discharge (Allison, 1962; Bergamini, et al., 1967; Lindsley, 1969). Parallel studies conducted on monkey and man have further shown

that an early brief deflection recorded from the human scalp corresponds in polarity and time course to the thalamocortical radiation response (presynaptic response) recorded from the brain of monkey (Goff, et al., 1962; Rosner, et al., 1963). It is this component that reportedly becomes enhanced upon light barbiturization but has heretofore been neglected in alcohol work.

A second experiment will specifically examine the effects of small amounts of alcohol on this fast potential.

The possibility that the depressive effects of alcohol seen at the cortex could, in part, be due to a reduction of afferency in peripheral nerves has also eluded systematic investigation. Action potentials elicited by shock stimuli can be recorded through the skin overlying the large nerves of the limbs and provide an index of peripheral neurophysiological events. A third experiment will therefore be carried out to monitor sensory transmission in the median nerve of the alcoholized subject.

CHAPTER II

METHODS AND PROCEDURES FOR EXPERIMENTS I, II AND III

The Effects of Alcohol on the Average Somatosensory Evoked Response (Experiment I)

Subjects

Five male graduate and medical students at the University of Oklahoma Medical Center between the ages of 24-30 years served as subjects. All subjects attested to have had at least "social" experience with alcohol.

Recording Apparatus

Cortical potentials evoked by somatosensory stimulation were recorded from two scalp locations: a post-rolandic parasagittal site (one electrode 4 cm. posterior to an imaginary line in the interaural plane and 7 cm. lateral to the midline, and a reference electrode 4 cm. anterior to this line) roughly corresponding to the contralateral sensory hand area, and a central (CZ) lead referred to linked ears. Both electrode pairs were led into a Grass EEG machine (model 6) for amplification with band pass specifications of 1-70 Hz.

Evoked potentials were automatically summed with a Fabritek

series signal averager (model 1062) and displayed with an X-Y plotter (Hewlett Packard, 7004B).

Stimulus

The stimulus consisted of brief (500 μsec.) rectangular pulses (8-11 ma) delivered to flat silver disk electrodes (11 mm in diameter) applied precutaneously to the median nerve at the wrist. The palmaris longus tendon served as a landmark. The anode lay at the flexion crease of the wrist with the cathode 3 cm proximal to it. To minimize ohmic resistance at the site of the stimulus leads, the skin was rubbed with Sanborn Redux until slight erythema was visible. The electrodes were covered with Grass electrode paste and held in place with Blenderm surgical tape. The stimulus was produced by a Grass S8 stimulator and isolated from ground by a Grass Isolation Unit (SIU5).

The intensity of the stimulus was determined for each subject by first ascertaining his sensory threshold (modified ascending method of limits) and then adjusting the voltage upwards until motor threshold was reached. Motor threshold was defined as a just perceptible thumb twitch. This assured us that the median nerve received adequate stimulation.

To reduce stimulus artifact, a silver ground plate, 2 cm by 4 cm, was placed in the middle of the forearm.

Procedure

Initially five subjects were run on two nonsuccessive days. In each instance they were required to fast for at least four hours prior to the onset of the experiment. Upon arrival at the laboratory

each subject was weighed and assigned to either a control or drug condition. Grass silver disk (9 mm diameter) electrodes were affixed with gauze and collodion. Grass electrode paste served as the conducting medium. Several preliminary average evoked potential samples were then collected. As during the subsequent experimental sessions, cortical potentials evoked by randomly (average interstimulus interval 4.5 sec.) presented shocks to the median nerve were averaged in blocks of 32 trials. The drinks were then administered.

On the control day the subject was given a placebo which consisted of a standard dose (200 ml) of gingerale or orange juice depending on the subject's preference. A minute quantity of alcohol (2-3 ml), just sufficient to exude the distinct odor of ethanol, was floated on the surface. Subjects imbibed three separate drinks of equal volume and were allowed 10 minutes per drink for ingestion.

On the test day, 0.5 ml USP 95% ethyl alcohol per pound of body weight was also provided. The total alcohol content was again distributed in three separate drinks. This amount of alcohol raised each S's blood alcohol concentration (BAC) to about 100 mg percent. A reading of 0.1% on the breathalyzer scale is equivalent to 100 mg ethanol/100 ml plasma thus, 100 mg percent.

Following the 30 minute absorption period evoked potentials were averaged in blocks of 32 trials. Stimuli were presented only if the ongoing EEG showed the typical waking rhythms. After each recording session, which took about five minutes, a determination of the subject's BAC was made with a Stephenson Breathalyzer. During this time the subject was disconnected from the headboard and given a five

minute break before recording resumed. This sequence was then repeated every half hour until the subject's BAC had returned to zero.

Evoked Response Measurements

Analysis of the early components was confined to the initial positive-negative-positive complex of the post-rolandic response and the late components to the large negative-positive-negative complex of the vertex response. The peak-to-peak amplitudes were measured in microvolts commencing from the peak designated as '0' in Figure 1. Figure 1 identifies the components measured and gives the alphanumeric classification used. The upper line in Figure 1 shows the vertex response, the lower line the post-rolandic recording. Peak latency was measured in milliseconds from the stimulus onset.

The Effects of Small Amounts of Alcohol on The Initial Spike (Experiment II)

Subjects

In this experiment five additional subjects were run. All were paid volunteers and had previously participated in alcohol experiments at the Medical Center.

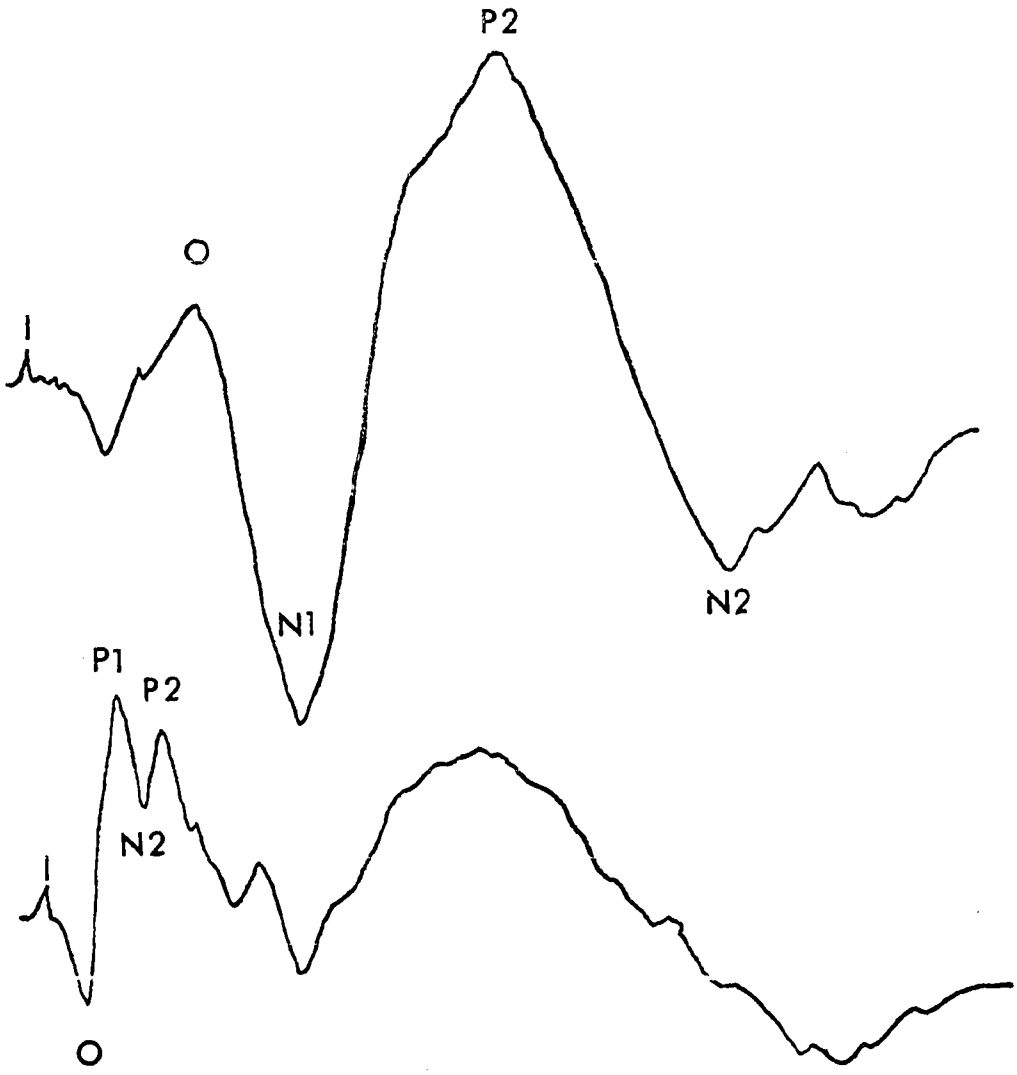
Recording Procedure

Cortical potentials were derived exclusively from the post-rolandic placement used in the first experiment. The raw EEG signal was amplified by a Grass polygraph (model 7) with a frequency response of 1 Hz-3000 Hz. The stimulus production mechanisms and stimulus parameters were identical to those used in Experiment I.

Figure 1. Alphanumeric Classification of Evoked Response Components.

The upper trace shows the vertex potential, the lower trace the post-rolandic response.

Amplitude measurements were made in microvolts from O-N1, N1-P2, P2-N2 for the vertex and O-P1, P1-N2, and N2-P2 for the rolandic recording. Latencies were measured from stimulus onset, indicated by the vertical bar, to peak.


P2
O
I
N1
N2
P1
P2
N2
I
O

Experimental Procedure

Once the electrodes were in place three baseline averages (Fabritek, 1062 averager) of 64 evoked responses were written out (Hewlett Packard X-Y plotter, model 7004B). The subject then received one drink containing .3 ml/lb ethyl alcohol in 100 ml's of gingerale. Subjects were required to imbibe the substance within a period of 3 minutes. Immediately following ingestion, during the rising phase of the blood alcohol curve, evoked responses were repeatedly sampled until the peak BAC (30-40 mg%) had been attained. The sampling procedure was interrupted, at the end of each average of 64, just long enough to permit a breath analysis to be made (Stephenson Breathalyzer).

The Effects of Alcohol Upon Sensory Transmission in the Median Nerve (Experiment III)

Subjects

Subjects were three healthy adult males, all of whom had some familiarity with grain alcohol. The stimulus apparatus was the same as that used in the first two experiments.

Recording Procedure

Compound action potentials elicited by electric shocks to the wrist (as in experiment I) were recorded precutaneously from the median nerve in the upper arm (Dawson, 1947; Shagass and Schwartz, 1963). The median nerve was identified by systematically moving a stimulus probe over the brachiallis in the region of the medial epicondyle process until the subject reported feeling radiations in those fingers innervated by the median nerve. Grass silver disk electrodes were then at-

tached with tape to that locus. An approximate distance of 4 cm separated the recording electrodes.

Evoked potentials from the post-rolandic scalp placement as described in experiment I were also recorded. Biopotentials were amplified by a Grass polygraph (model 7) set to pass a frequency band of 1 Hz-3000 Hz. As in the previous experiments, cortical and peripheral responses were electronically summated with a Fabritek (model 1062) averager.

Experimental Procedure

Once the subjects were prepared two baseline samples each consisting of 32 averaged cortical ER's and 32 simultaneously recorded median nerve action potentials were collected about 10 minutes apart. Again, stimulus pulses were presented more or less randomly within an interval of 2-6 sec. A standard dose (.5 ml/lb) of ethyl alcohol (USP 95%) mixed with gingerale was then administered in three equally potent drinks. Ten minutes per drink was allotted for ingestion. A breath test (Stephenson Breathalyzer) was made every 15 minutes until the subject reached his peak blood alcohol level. Cortical and nerve potentials were sampled once at a low BAC (20-30 mg%) and again at peak BAC (around 100 mg%). One subject voluntarily agreed to take a supplementary dose of alcohol which further elevated his BAC to 145 mg percent.

CHAPTER III

RESULTS OF EXPERIMENTS I, II AND III

The Effects of Alcohol on the Average Somatosensory Evoked Response (Experiment I)

Consistency of Evoked Response Waveform in Alcoholized and Nonalcoholized States

Under control conditions cortical potentials averaged from two scalp locations, the vertex and the parasaggital site overlying the sensory hand area, were found to be fairly reproducible over time. Figure 2 illustrates this reliability. Each superimposed trace in the upper part of this figure represents an average of 32 vertex responses. Each average was obtained about 1.5 hours apart during a single session. The lower portion of this figure shows average rolandic potentials recorded simultaneously. As an index of stability, voltage points measured from 20 to 400 msec. in 10 msec. steps along the extent of the evoked response waveform were correlated (Pearson product moment correlation) between the second baseline sample and the sample collected at the peak blood alcohol level on the drug day. The same analysis was performed for two baseline samples obtained on the control day. Selection of these samples was based on the time required for each subject

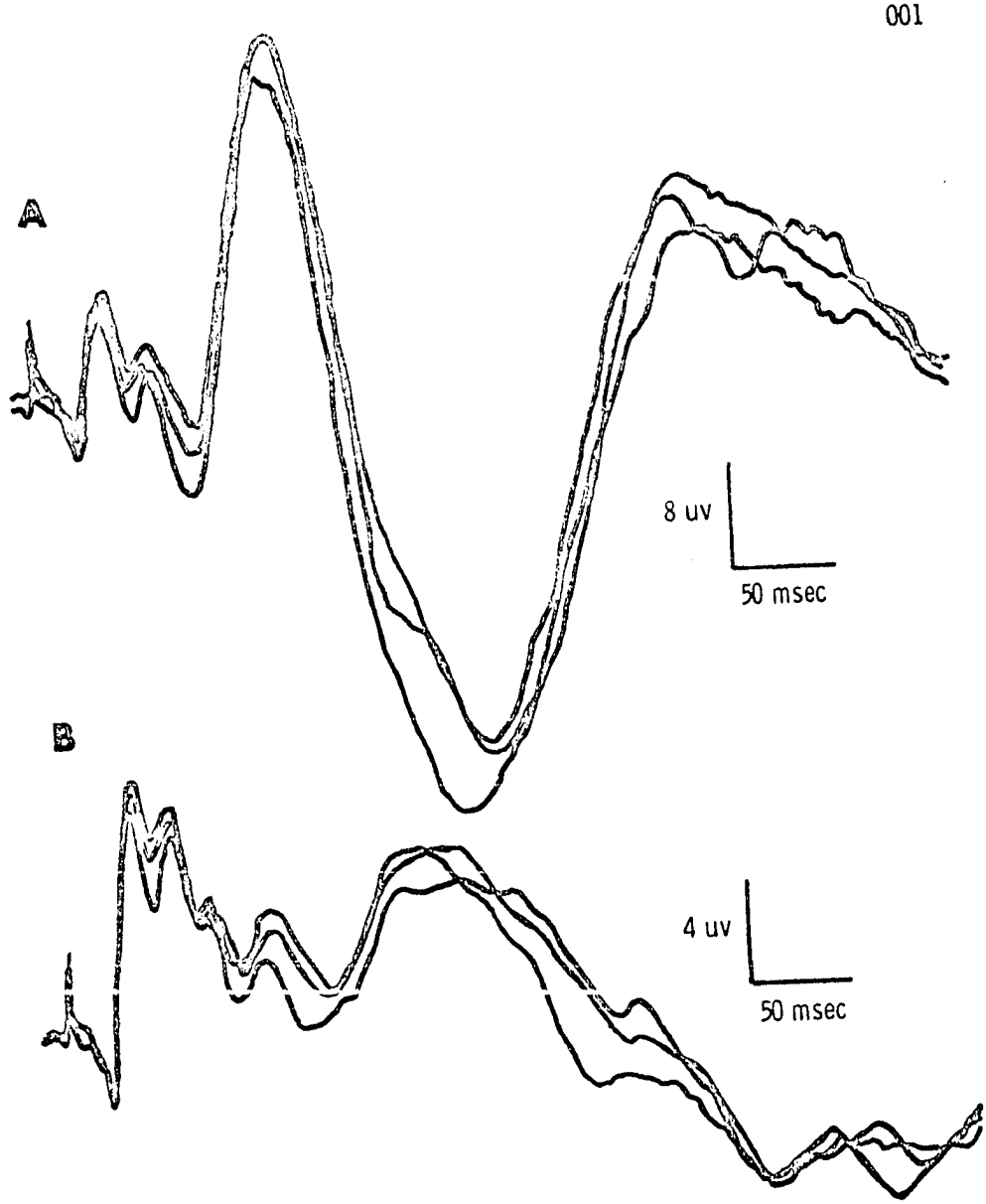
Figure 2. Consistency of Average Evoked Response Waveforms in Nonalcoholized States.

Each superimposed trace represents an average of 32 responses obtained approximately 1.5 hrs. apart from one subject.

A. Three averages recorded from the vertex. Downward deflection indicates relative positivity at the vertex.

B. Three averages recorded post-rolandically. Downward deflection indicates relative negativity at the active electrode.

001



to reach his maximum blood alcohol concentration (BAC). The two baseline samples which best corresponded to this interval were used. The correlation coefficients, experimental conditions, and recording sites are presented in Table 1. Correlations were also computed for the early (20-100 msec. of the vertex response and 20-70 msec. of the post-rolandic response) and for the late (100-400 msec. for both placements) segments of the ER waveform. These values are also given in Table 1.

In the nonalcoholized state the overall wave patterns of the paired responses were highly correlated for both vertex ($t=10.80$, $p < .01$) and post-rolandic ($t=12.73$, $p < .01$) recordings. Similarity of waveforms was also demonstrated for the early vertex ($t=6.44$, $p < .01$) and post-rolandic ($t=4.55$, $p < .05$) components as well as for the late vertex ($t=10.66$, $p < .001$) and post-rolandic ($t=14.34$, $p < .001$) components. Table II shows the 'Z' transforms for the correlations derived from the total, early and late segments of the evoked response waveform. In contrast, when the correlations obtained from the two baseline samples were compared to those taken from the predrug and peak drug samples, the difference proved substantial. As can be seen in Table III the effect of alcohol was apparent at all segments of the evoked response waveform with the exception of the so called primary discharge (20-70 msec.) specific to the post-rolandic derivation. Table III gives the t values (t for correlated means) for each segment of the evoked response for the respective recording sites.

In summary, the slow components of the average evoked response were markedly affected following alcohol consumption regardless of electrode position. The form of the evoked response, however, maintained

Table 1

PEARSON CORRELATION COEFFICIENTS BETWEEN TWO BASELINE SAMPLES OBTAINED ON CONTROL DAYS AND PREDRUG - PEAK DRUG SAMPLES OBTAINED ON TEST DAYS

Subject	Waveform Segment	Vertex Baseline-Baseline	Vertex Baseline-Alcohol	Rolandic Baseline-Baseline	Rolandic Baseline Alcohol
S1	Early[a]	.878	.478	.550	.144
	Late [b]	.950	.852	.970	.338
	Total[c]	.943	.816	.948	.430
S2	Early	.793	.227	.931	.822
	Late	.988	.934	.940	.512
	Total	.984	.880	.935	.509
S3	Early	.749	-.739	.873	.116
	Late	.915	.685	.928	.821
	Total	.907	.647	.934	.768
S4	Early	.965	-.030	.997	.965
	Late	.984	.765	.977	.948
	Total	.983	.686	.983	.933
S5	Early	.740	.344	.895	.880
	Late	.949	.635	.919	.691
	Total	.941	.562	.915	.830

a - 20-100 msec. vertex, 20-70 msec. rolandic.
b - 100-400 msec. both placements.
c - 20-400 msec. both placements.

Table 2

R-Z TRANSFORMS FOR CORRELATIONS DERIVED FROM THE TOTAL, EARLY AND LATE SEGMENTS OF THE EVOKED RESPONSE WAVEFORM

	Vertex Baseline - Baseline			Rolandic Baseline - Baseline		
	Early[a]	Late[b]	Total[c]	Early[d]	Late[e]	Total[f]
S1	1.37	1.83	1.77	2.99	2.10	1.81
S2	1.08	2.56	2.41	1.23	1.74	1.70
S3	0.97	1.56	1.51	1.11	1.64	1.69
S4	2.01	2.41	2.38	1.23	2.23	2.38
S5	0.95	1.82	1.75	1.44	1.58	1.56
	Baseline - Alcohol			Baseline - Alcohol		
	Early	Late	Total	Early	Late	Total
S1	0.52	1.26	1.15	1.59	0.35	0.46
S2	0.23	1.69	1.37	0.69	0.57	0.56
S3	-0.95	0.84	0.77	1.58	1.16	1.02
S4	0.00	1.01	0.84	0.95	1.81	1.69
S5	0.36	0.75	0.64	1.36	0.85	1.19

a - 20-100 msec.
b - 100-400 msec.
c - 20-400 msec.
d - 20-70 msec.
e - 100-400 msec.
f - 20-400 msec.

Table 3

COMPARISON OF CORRELATIONS[a] FOR WAVEFORM SEGMENTS OBTAINED ON CONTROL AND ALCOHOL DAYS

Vertex	df	t	p
Early	4	4.17	.02
Late	4	6.41	.01
Total	4	6.28	.01
Rolandic			
Early	4	1.23	NS
Late	4	3.67	.05
Total	4	4.78	.01

a - computations made on Z scores.

its general predrug configuration. That is to say, the correlations between the baseline and peak drug averages, although reduced, were still significant. Table I provides these correlation coefficients. The major effect of alcohol then, appeared to be a supp ression of evoked activity.

The Relationship between Evoked Response Amplitude and Blood Alcohol Concentration

To establish the dose-response relationship for the various components of the evoked response the peak-to-peak amplitudes and peak latencies of the individual waves were correlated with the percentage of alcohol in the blood. Measurements were made from the early positive-negative-positive components of the rolandic response and the late negative-positive-negative complex of the vertex response. Figure 1 shows the labeling scheme employed for the primary rolandic and secondary vertex components.

The long latency potentials were found to be extremely sensitive to the depressant effects of alcohol. The amplitude of the triphasic vertex spike was shown to be inversely related to the concentration of alcohol in the blood, the correlation being highly significant. The correlation coefficients, their Z transforms and the t values (one sample t) for each vertex component are given in Table 4. As the content of alcohol in the blood rose to about 100 mg percent these late components underwent a proportional diminution of voltage. Figure 3 depicts this inverse relationship during the ascent of the BAC. As alcohol dissipated from the blood the evoked response recovered in the same inverse fashion. The close correspondence between peak amplitude

and BAC during the ascending and descending limbs of the blood alcohol curve is shown in Figure 4.

Conversely, the post-rolandic primary response was highly resistant to alcohol showing a decrement only at fairly high BAC's (120-150 mg%). The persistence of these early components at moderate blood alcohol levels is exemplified in Figure 5. It can be seen that even at these relatively low BAC's the later components have already begun to diverge from baseline amplitudes. Table 5 gives the significance levels for each of the waves of the post-rolandic recordings.

Effects of Alcohol on Peak Latency

The latencies of each of the vertex and post-rolandic components were also correlated with the concentration of alcohol in the blood. These data are presented in Table 6. As can be seen in this table, only the latencies of the N1 and P2 vertex components were found to vary directly with BAC.

The Effects of Small Amounts of Alcohol on the Initial Spike (Experiment II)

Just preceding the primary post-rolandic response, a very fast diphasic, negative-positive deflection occurs. The negative phase is almost always apparent in human recordings. The positive phase, being very brief (1-3 msec.) and of low amplitude (2-4 μv) is either masked by the rapidly rising postsynaptic discharge or otherwise technically obscured, e.g., filtered out (cf. Allison, 1962). This component, altogether absent in animals, can be visualized as a monophasic positivity upon direct stimulation of the thalamic relay nuclei (Dempsey and Mor-

Figure 3. Inverse Relationship Between Peak Amplitude and Blood Alcohol Concentration (BAC).

Each trace represents an average of 32 vertex potentials recorded before alcohol was given, BAC 00 mg% and at three dose levels, 50 mg%, 80 mg% and 95 mg%. Downward deflection indicates positivity of vertex electrode.

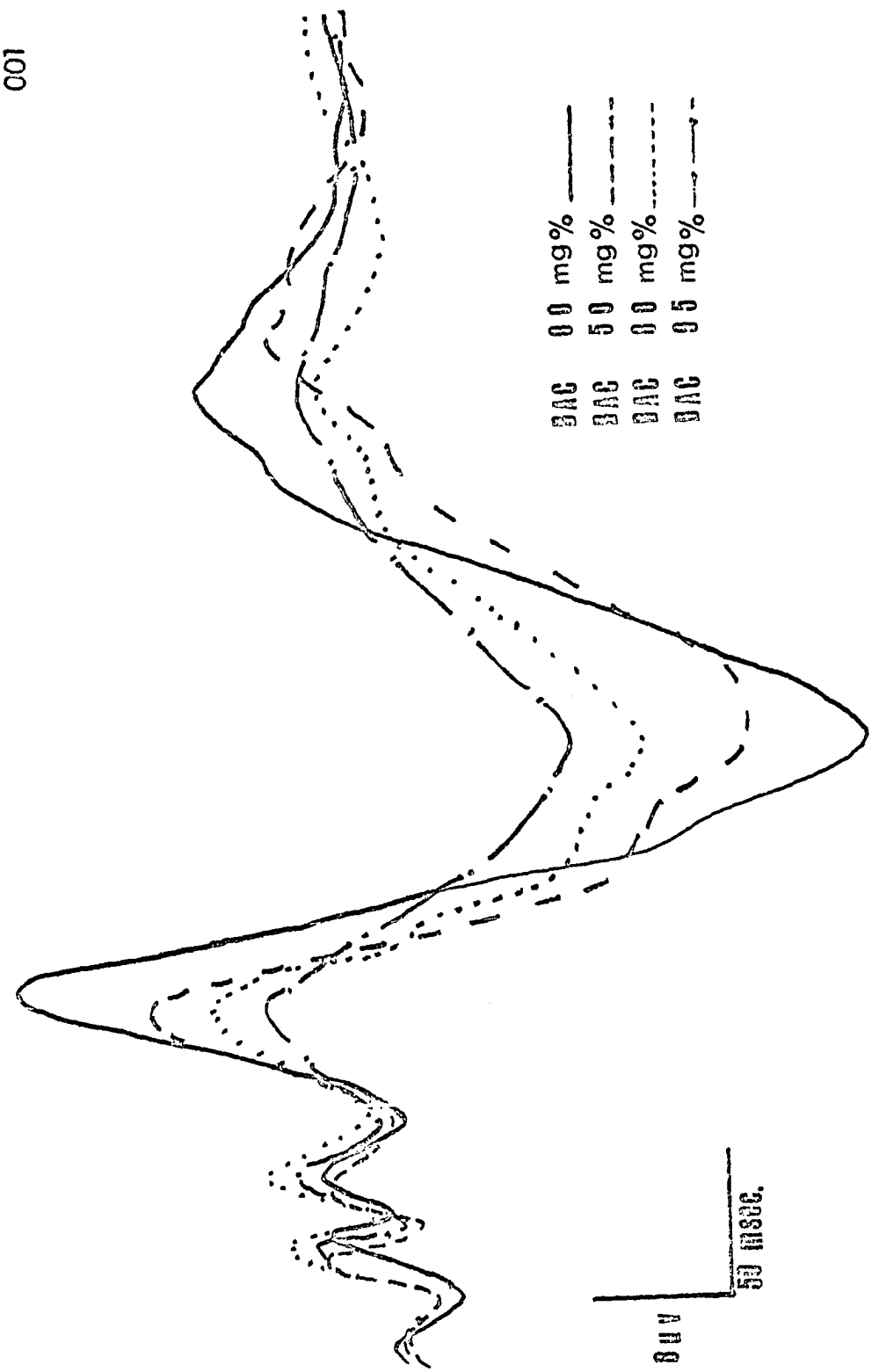

100
BAC 0.0 mg%
BAC 5.0 mg%
BAC 0.0 mg%
BAC 9.5 mg%
8 mV
50 msec.

Figure 4. Correspondence Between Evoked Response Amplitude and BAC During Ascending and Descending Phases of Alcohol Intoxication.

This figure shows the close correspondence of peak amplitude of the vertex response and BAC during the ascending and descending limbs of the blood alcohol curve.

A. Averaged evoked responses recorded at a BAC of 70 mg%, during the ascending (solid line) and descending (dotted line) BAC.

B. Average evoked responses recorded at a BAC of 35 mg%, during the ascending (solid line) and descending (dotted line) BAC.

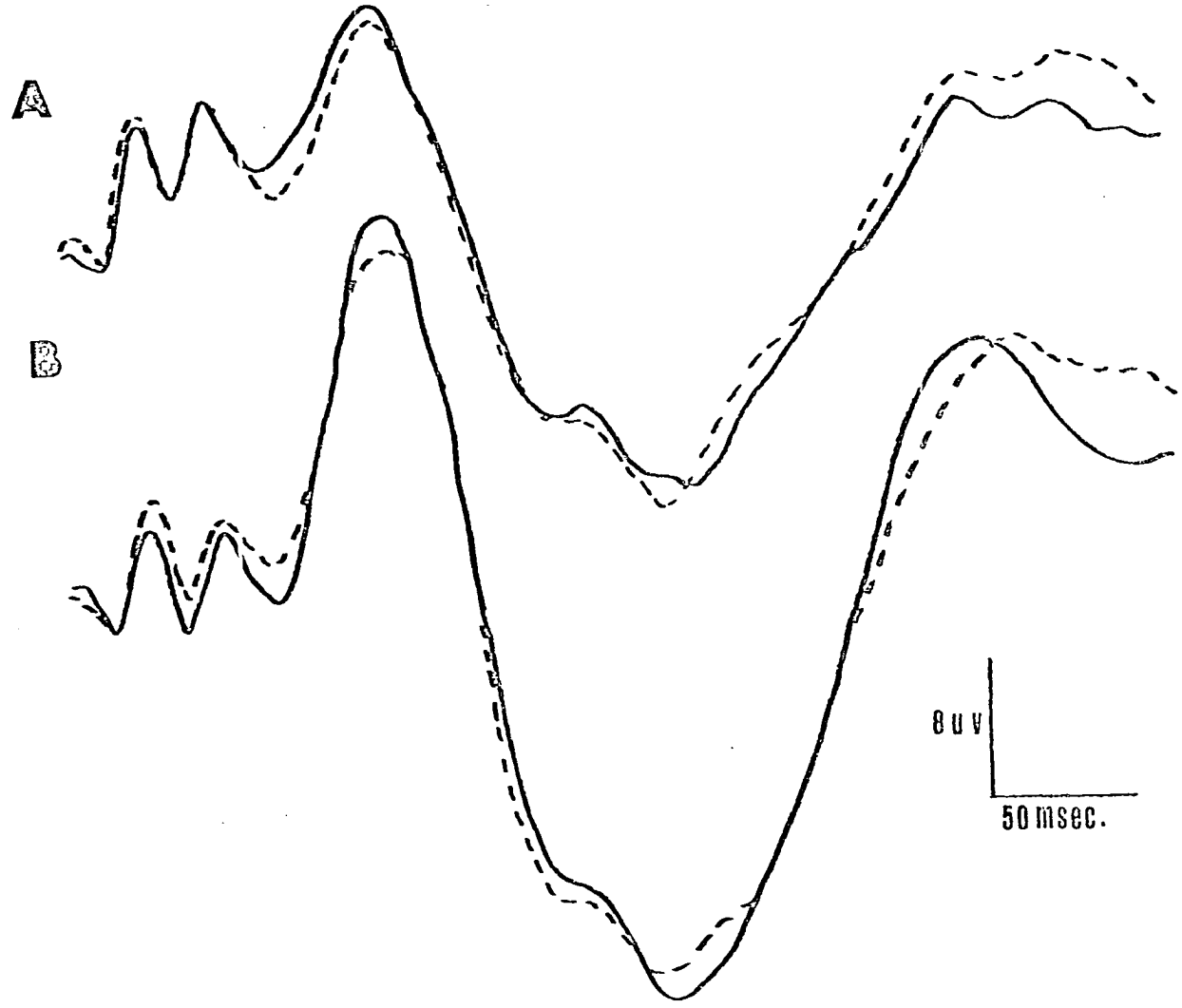
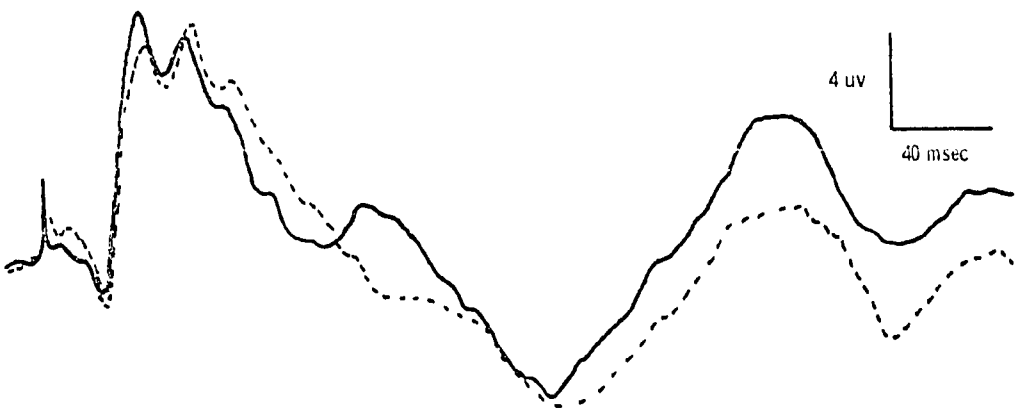

A
B
8 u v
50 msec.

Figure 5. Resistance of Early Components at Moderate BAC's.

This figure illustrates the resistance to alcohol of the early components (first 50 msec.) for two S's, of the post-rolandically recorded average evoked response. Solid trace represents an average of 32 ER's obtained on the control day. Dotted trace also represents average of 32 taken at moderate BAC's (60-80 mg%). Note that the secondary portion of the response has already begun to diverge from pre-drug amplitudes.

009



007

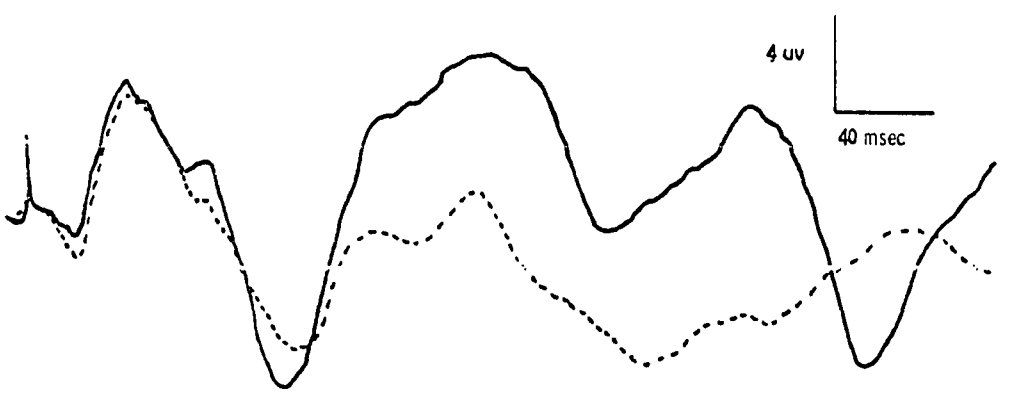


Table 4

CORRELATIONS BETWEEN INDIVIDUAL VERTEX COMPONENTS AND BLOOD ALCOHOL CONCENTRATION

Subject		Component N1[a]	P2[b]	N2[c]
S1	R	-0.733	-0.943	-0.649
	Z	-0.98	-1.77	-0.77
S2	R	-0.954	-0.966	-0.895
	Z	-1.87	-2.02	-1.44
S3	R	-0.775	-0.885	-0.984
	Z	-1.03	-1.40	-2.39
S4	R	-0.964	-0.964	-0.775
	Z	-2.00	-1.68	-1.03
S5	R	-0.822	-0.709	-0.147
	Z	-1.16	-0.89	-0.15

a - $t=-4.91$, $p < .005$

b - $t=-6.63$, $p < .005$

c - $t=-3.162$, $p < .01$

Table 5

CORRELATIONS BETWEEN POST-ROLANDIC COMPONENTS AND BLOOD ALCOHOL CONCENTRATION

Subject		Component P1[a]	N1[b]	P2[c]
S2	R	-0.311	-0.294	0.754
	Z	-0.32	-0.30	0.98
S3	R	-0.071	-0.586	0.056
	Z	-0.07	-0.56	0.06
S5	R	-0.623	0.259	-0.181
	Z	-0.73	0.26	-0.18

a - t=1.94 NS b - t=.83 NS c - t=.81 NS

Table 6

CORRELATIONS BETWEEN EVOKED RESPONSE LATENCY AND BLOOD ALCOHOL CONCENTRATION

Subjects		Components					
		Vertex				Rolandic	
		N1[a]	P2[b]	N2[c]	P1[d]	N1[e]	P2[f]
S1	R	0.799	0.421	0.293			
	Z	1.09	0.43	0.30			
S2	R	0.559	-0.091	0.625	-0.257	-0.462	-0.332
	Z	0.63	-0.09	0.73	-0.26	-0.50	-0.35
S3	R	0.437	0.686	0.146	0.442	0.048	0.137
	Z	0.47	0.84	0.15	0.48	0.04	0.14
S4	R	0.411	0.442	-0.583			
	Z	0.43	0.48	-0.67			
S5	R	0.466	0.423	0.694	-0.183	-0.125	-0.050
	Z	0.51	0.45	0.86	-0.19	-0.13	-0.05

a - t=5.19 p< .005 b - t=2.84 p< .025 c - t=1.01 p NS d - t=.042 p NS e - t=-1.59 p NS

f - t=-.607 p NS

rison, 1943; Perl and Whitlock, 1955; Landau and Clare, 1956) and persists after complete excision of the cerebral cortex (Bishop and O'Leary, 1952; Bishop and Clare, 1953; Bremer, 1958). The physioanatomical characteristics of this potential, as seen at the scalp surface, suggest that it represents the arrival of impulses traveling in axons and nerve terminals.

Figure 6 depicts the first 60 msec. of the average rolandic response. The arrows indicate the so-called presynaptic component. Each superimposed trace represents an average of 64 ER's taken before alcohol administration, at a BAC of 10-20 mg percent and again at peak BAC, 30-40 mg percent. As can be seen in Figure 6, small doses of alcohol were ineffective in producing any notable change in this early component. In particular, there was no evidence of a transitory potentiation at low BAC's. Table 7 presents the mean negative-positive peak amplitudes for the baseline and two alcohol samples for each subject. The averages were not significantly different ($t=1.03$, $p > .05$).

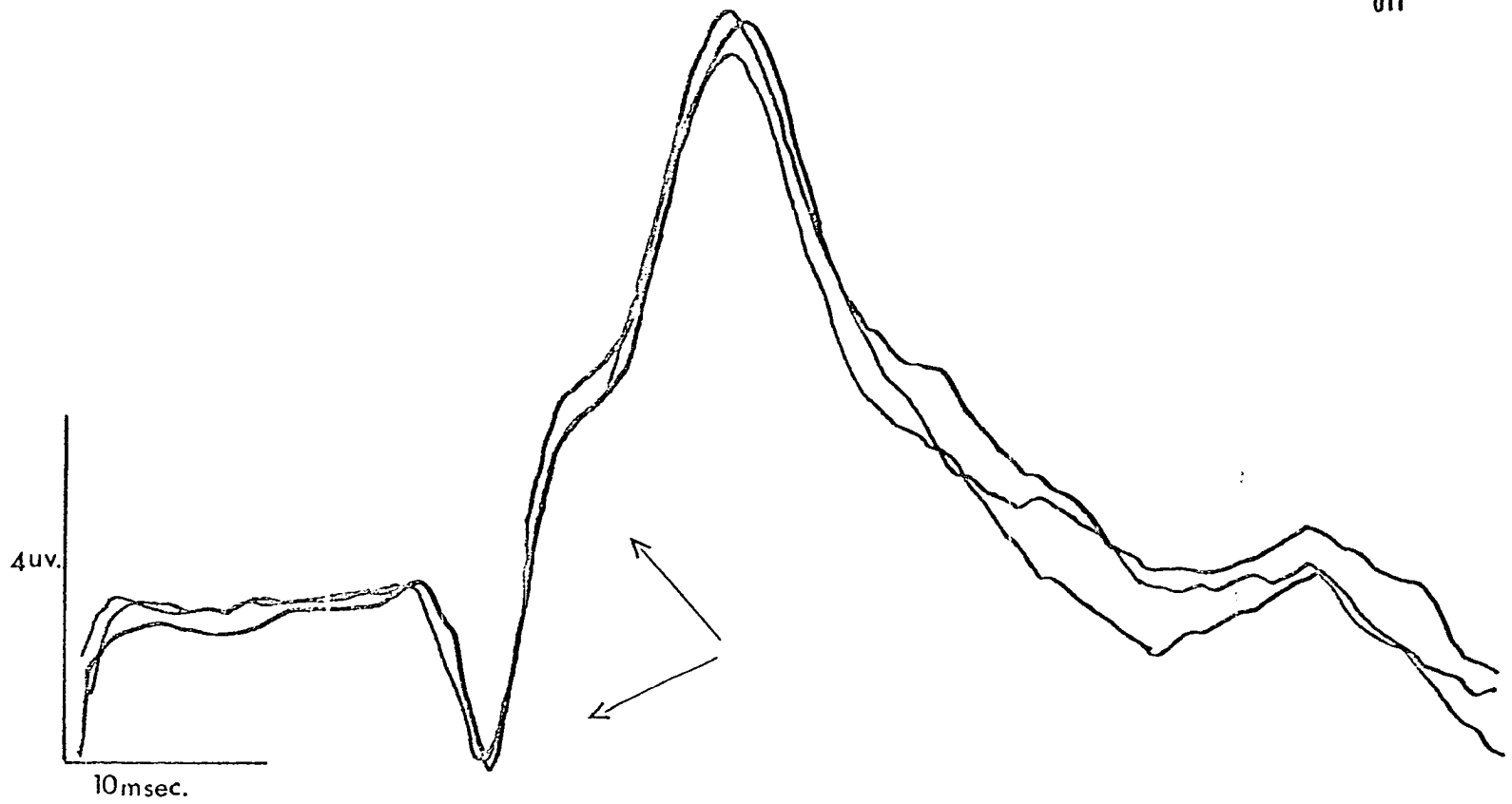
Effects of Alcohol Upon Sensory Transmission in the Median Nerve (Experiment III)

To explore the possibility that peripheral events could have been, in part, responsible for the effects seen at the scalp, action potentials to the shock stimuli were recorded from the median nerve in the upper arm of three subjects. Cortical responses were simultaneously recorded before alcohol was given and at the peak BAC reached. Figure 7a shows the first 50 msec. of the post-rolandic response of one subject; the solid line is the predrug average, the dotted line an equal number of trials (32) sampled at a blood level of 145 mg percent. As

Figure 6. Initial Spike of the Post-Rolandic Response.

This illustration shows the first 60 msec. of the average rolandic response. The arrows point to the diphasic negative (downward deflection) and positive response that precedes the large postsynaptic discharge. The positive notch is often masked by the much larger successive positivity.

Each superimposed trace represents an average of 64 ER's obtained before alcohol administration, at a BAC of 10-20 mg% and again at peak BAC, 30-40 mg%. No evidence of early potentiation is evident.


4uv.
10msec.

can be seen, with this high concentration, even the primary response is severely attenuated. Figure 7b shows the median nerve action potentials; the predrug and peak drug samples are superimposed. As can be seen, they are virtually indistinguishable. Thus, even at the highest dosage used, sensory transmission in the median nerve was not detectably altered.

Ohmic resistance as measured at the site of the stimulating electrodes was also shown to bear no systematic relationship to BAC.

Table 7

MEAN AMPLITUDE[a] OF INITIAL SPIKE IN ALCOHOLIZED AND NONALCOHOLIZED STATES

Subject	$\bar{M}$ 3 Baseline Samples[b]	$\bar{M}$ 3 Alcohol Samples[c]
S1	3.025	2.683
S2	2.481	2.476
S3	3.231	3.251
S4	2.183	2.225
S5	3.666	3.533
	$t=1.03$, $p > .05$	

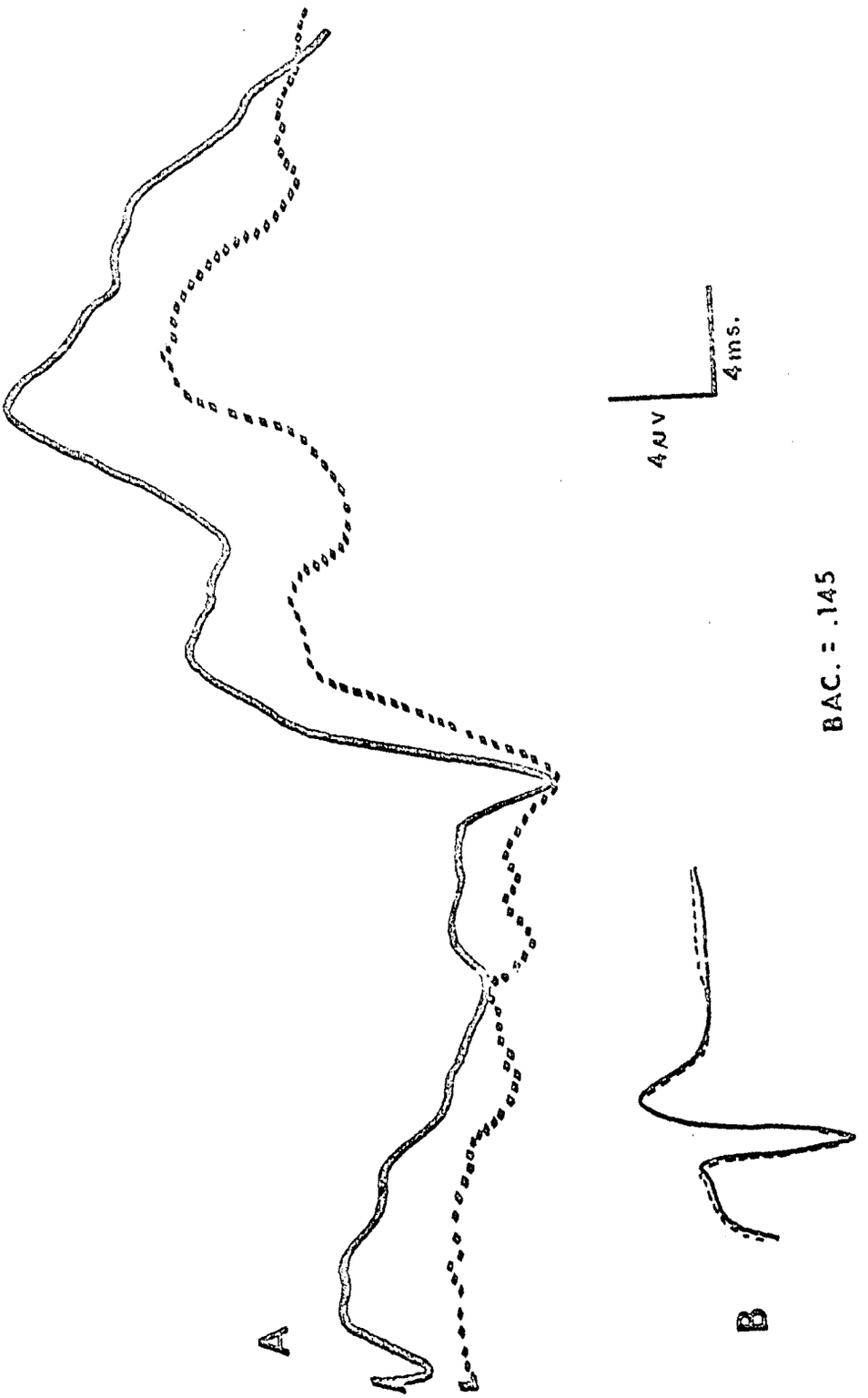
a - in microvolts
b - averages of 64
c - averages of 64

Figure 7. The Effects of Alcohol on Peripheral and Cerebral Transmission.

In this figure diminution of the primary discharge is evident at a high BAC whereas sensory transmission in the median nerve is unaffected.

A. First 50 msec. of the post-rolandic evoked response. Each trace represents an average of 32. The solid line is the predrug sample, the dotted line the average obtained at peak BAC. Note marked attenuation.

B. Action potentials measured from the median nerve in the upper arm recorded simultaneously with cortical ER's. Each superimposed trace represents an average of 32 taken before (solid line) alcohol and at peak blood level (dotted line). No difference can be detected in the two waveforms.


A
B
4μV
4ms.
BAC. = .145

CHAPTER IV

THE VALIDITY OF ER AND EEG PARAMETERS IN PREDICTING THE AVERAGE CORTICAL RESPONSE (EXPERIMENT IV)

Introduction

In the first two experiments the effects of acute alcohol administration on the somatosensory evoked response were described. The amplitude of the late components, particularly of the biphasic vertex response, were shown to decrease systematically with the rising concentration of alcohol in the blood. It was not possible, however, to determine the extent of drug action upon other neuroelectric parameters known or suspected to influence the amplitude of the average cortical response. The fourth experiment attempted to establish whether the decline in evoked cortical responsiveness was 1) merely a corollary of concomitant EEG alterations, 2) an inverse function of peak latency variability or 3) specifically a consequence of diminished brain potential.

The Effects of Alcohol on the Electroencephalogram

It must be recognized that the changes seen in the sensory evoked response occur at a time when the spontaneous cerebral rhythms are also undergoing modification by alcohol.

Initially, when the BAC is still low, below 50 mg%, the electro-

cortical activation response or desynchronization reportedly takes place (Gibbs, Gibbs, and Lennox, 1937; Hadji-Demio, et al., 1968; Horsey and Akert, 1953). Following this transitory phase of CNS excitation, as the BAC rises to 80-90 mg%, the EEG is characterized by a gradual slowing of the dominant frequency. With a further increase in the blood alcohol content to around 120 mg%, episodes of 4-8 Hz activity predominate in the bioelectric pattern. Coincident with these theta bursts are the usual behavioral signs of intoxication (Davis, Gibbs, Davis, Jetter and Trowbridge, 1940; Newman, 1959). Further elevation of the BAC to 150 mg% will produce high voltage delta waves with subsequent loss of consciousness (Davis, et al., 1940; Newman, 1959).

By applying spectral analysis to the EEG of alcoholized subjects, Davis, et al. (1949), were able to examine the distribution of various frequency bands with respect to the total energy of the EEG at different BAC's. Predrug recordings revealed a sharp energy drop on the fast side of the frequency spectrum (10-13 Hz), while the reverse was true on the slow side of the alpha peak (6 Hz). At relatively low blood levels (35 mg%) this trend became more pronounced. As the concentration of alcohol in the blood approached 120 mg%, rhythmic 4-8 Hz bursts appeared. Accompanying these intrusions was an increase in energy in the corresponding frequency band. Spectral analysis of the component frequencies within the alpha band further disclosed a sharp increase in energy at the low end of the alpha range (8-9 Hz) while intermediate activity (10-11 Hz) decreased substantially. No change in the fast end of the alpha spectrum (12-13 Hz) was observed (Docter, Naitoh and Smith, 1966). The major effect of alcohol, then, seemed

to be a potentiation of frequencies on the slower side of the alpha distribution.

Whether the altered sensory response is just an epiphenomenon of changes taking place in the tonic potential flux or represents an independent process raises the more fundamental issue of association between intrinsic and extrinsic cerebral events.

The Relationship Between Discrete Electrical Events and Ongoing Phenomena

Because of the averaging process used to identify evoked potentials (see page 2), the background EEG is tacitly disregarded as unwanted "noise." Whether or not this implicit assumption is warranted remains an open question. When the average evoked potential was compared to the average EEG recorded just prior to stimulus delivery, a direct relationship between the amplitude of the two measures was found (Dustman and Beck, 1963; Rodin, Grisell, Gudobba and Zachary, 1965; Shagass, Haseth, Callaway and Jones, 1968). In one study where background EEG was analyzed over a 40 sec. interval the highest positive peak of the visual evoked response was shown to be positively correlated to the amount of energy in the alpha, theta and delta frequency bands (Rodin, et al., 1965). Furthermore, the energy content in the 13-30 Hz band width (beta) was positively related to the amplitude of the largest negative component as well as to the amplitudes of other smaller waves. Weiss (1969) found that the average amplitude and standard deviation of the auditory evoked response were linearly related to the root mean square (RMS) of the prestimulus EEG in the implanted cat. The strongest correlation was between the standard deviation of the evoked response

and RMS. The relationship between RMS and response magnitude was also significant. Generally speaking, though, it is the after discharge or late components of the visual evoked potential that correlate best with EEG amplitude (Dustman and Beck, 1963; Kooi and Bagchi, 1964).

Using the background EEG frequency as the criterion, Spilker, Kamiya, Callaway and Yeager (1969) found that subjects trained to "control" their alpha rhythm (e.g., Kamiya, 1968) produced larger evoked potentials to flashes and sine wave light in the presence of the induced rhythm. On the other hand, click evoked responses showed no correlation with the alpha state. Levonian (1966) reportedly could distinguish visual evoked potentials on the basis of a high or low alpha index occurring subsequent to the stimulus.

In behavioral states of attentiveness or expectancy, the amplitude of the EEG is appreciably reduced. The conclusions drawn from the studies mentioned above are not consistent with the fact that during attentive states numerous investigators report augmentation of the average evoked response (see Naatanen, 1967, for a review). Moreover, Fruhstorfer and Bergstrom (1969) demonstrated that an inverse relationship holds between the power of the prestimulus EEG and the amplitude of the auditory evoked response. Using single unaveraged ER's and a two second epoch of EEG just prior to the click stimulus, they found that when low voltage fast activity covered the entire convexity single robust ER's could be consistently visualized. An eventual decline in voltage and increase in variability of the ER waveform coincided with the appearance of the occipital alpha rhythm and its subsequent spread to parietal and central regions. In the somatic sensory modality,

Shagass, Overton, Bartolucci and Straumanis (1971) were unable, for the most part, to detect changes in ER amplitude corresponding to significant alterations in background EEG. When correlations were found they were usually of low order and negative for most response components. Finally, several investigators have failed to establish any relationship whatsoever between ER and EEG variables (Chapman and Bragdon, 1964; Garcia-Austt, 1963; Werre and Smith, 1964).

Variability of Peak Latency

When single unaveraged evoked potentials are scrutinized by superimposition, marked trial-to-trial variation becomes evident despite stability of sample-to-sample averages. Figure 8a shows eight consecutive single ER's while 8b shows eight averages of eight trials each. Attempts to explain this variability exclusively in terms of fluctuations in the gross EEG have not met with particular success (vide supra). The tendency on the part of investigators to use rather large EEG samples and large ER averages has, no doubt, contributed to the inconsistency of results. Averaging techniques employed to isolate evoked activity do not preserve information about the variability of the individual responses that make up the average. If the onset and/or duration of a specific component of the ER were to vary from trial-to-trial, then the average amplitude computed for that component by an automatic averaging device would be an underestimate of the true mean. If a second average could be computed by analysis of each evoked response, adjusting for small variations in latency, the degree of discrepancy between the two averages would be an increasing function of the trial-to-trial variation in response latency (or duration). Support

for this proposition is provided in Figure 9 which shows the relationship between the variance of response latency and the difference in peak-to-peak amplitude computed by the two averaging methods ($R = 0.536$, $p < .001$). Variation of peak latency could therefore be reflected as a depression of the average evoked response even though the absolute voltage was maintained at a fairly constant level. Thus, it was necessary to examine the possibility that the depression of ER amplitude found with alcohol in Experiment I was due to an increase in variability of latency of certain ER components.

One way to get at the problem of variability would be to examine the single unaveraged potentials that compose the average. Unfortunately, the scalp recorded ER is typically obscured by the higher amplitude background EEG and is difficult to detect. As already indicated (Introduction to Experiment I) this situation led to the use of automatic devices which by computing the algebraic sum of several trials, reveal the constant ER "signal" embedded in the "noise" of the ongoing EEG. However, long before computer-based techniques were available, electroencephalographers had observed discrete potential shifts time-locked to the onset of a sensory stimulus. This brief evoked response was first described as having a long latency and could be visualized following visual, auditory or somatosensory stimulation (Davis, 1939; Gastaut, 1953; Bancaud, Block and Paillard, 1953). Although this sensory response was diffusely represented over the scalp's surface, it was best recorded from the vertex (Zerlin and Davis, 1967; Davis and Zerlin, 1964; Gastaut, et al., 1953), and has come to be known as the "V" potential or vertex spike (Davis, 1965). In spite of its presence in the EEG tracing,

Figure 8. Variability of Single Potentials.

A. Eight superimposed single responses.

B. Eight superimposed averages of eight responses.

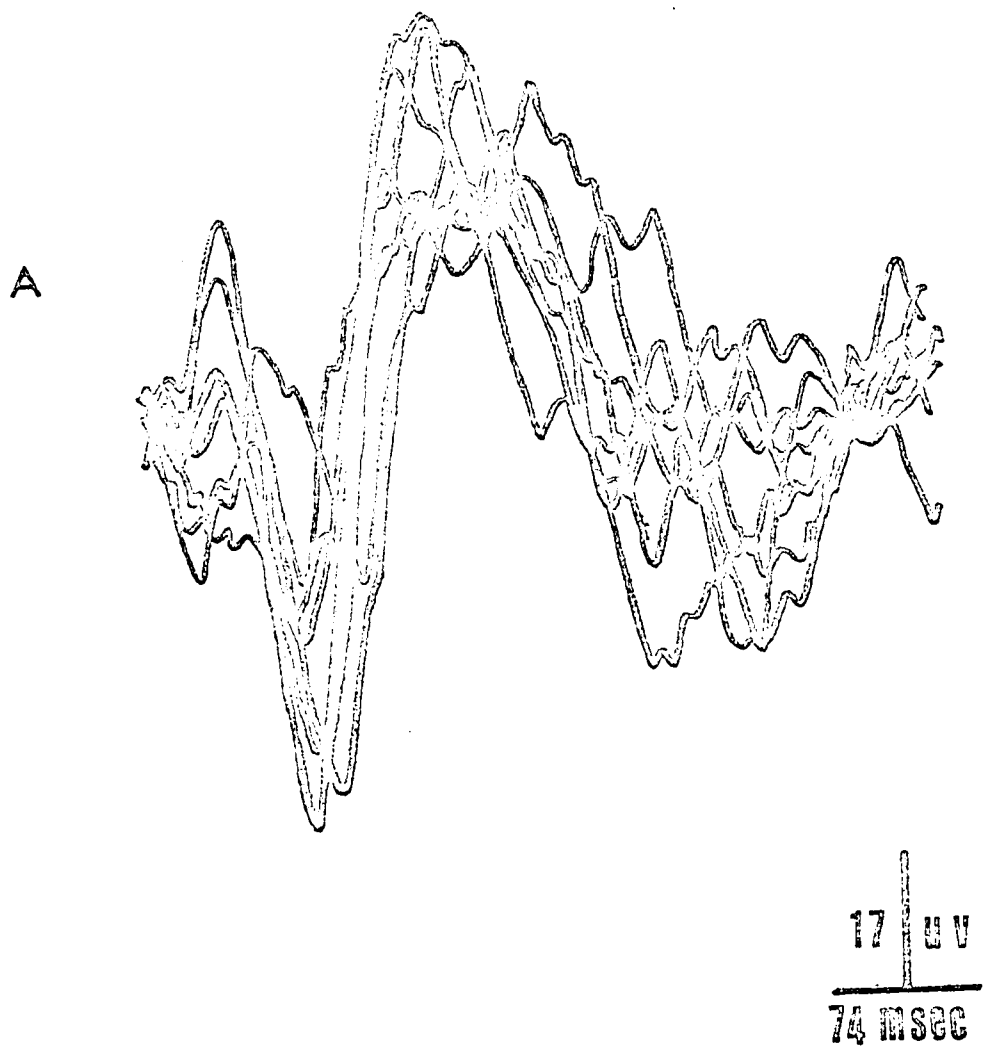
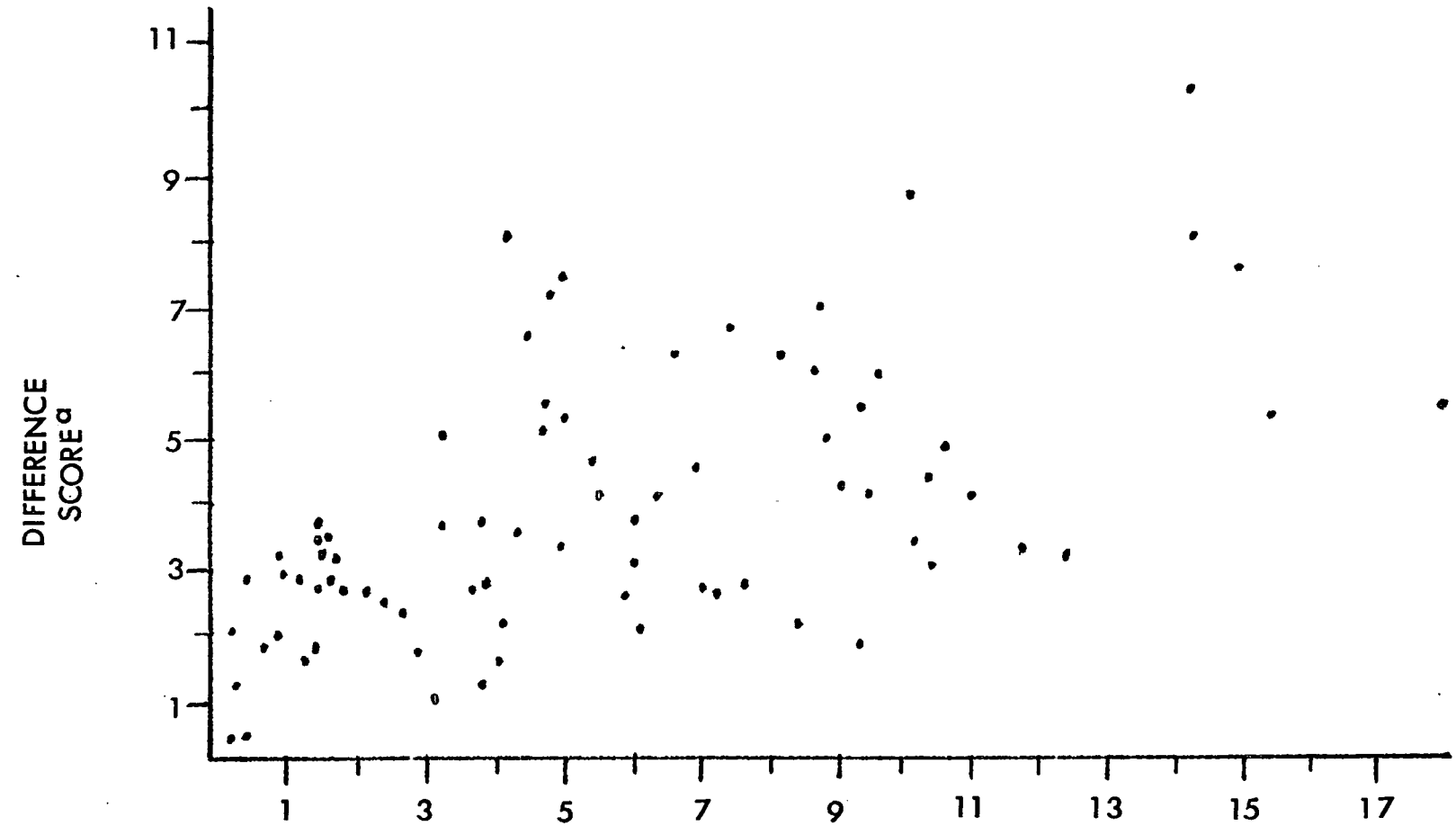

A
17 u V
74 m sec
B
S1

Figure 9. Relationship Between Peak Latency Variance and the Difference Between Peak-to-Peak Amplitude Computed by Automatic Summation and Analysis of Each Response.

This scatter-plot illustrates the positive relationship between the trial-to-trial variability in peak latency and the difference in peak amplitude computed by automatic summation and actual measurement of the single ER's. Each point represents a sample of 8 ER's.



a - in standard gradicules
b - based on samples of 8

rarely was the "V" potential persistent enough to allow accurate measurements to be made.

Recently there has been a resurgence of interest in single trial data with particular reference to the variability of various parameters of the sensory evoked response. Several investigators have successfully demonstrated the feasibility of the single sweep technique for the auditory and visual modalities (Davis, 1965; Zerlin and Davis, 1967; Ciganek, 1968; Donchin, 1969; Ruchkin, 1971; and Derbyshire, Osenar, Hamilton and Joseph, 1971).

Objectives of Experiment IV

The specific aims of this research were to 1) isolate the pharmacological effects of alcohol upon selected EEG and ER variables believed important in the evolution of the average cortical response; 2) to determine the interrelationships between these variables and the relative contribution of each to the amplitude of the evoked response; 3) to abstract from this group of independent variables the minimum set of effective predictors of evoked response amplitude (criterion) and 4) to establish the most valid measure of the biphasic vertex spike.

Selection of EEG Variables

As discussed earlier, studies purporting to demonstrate frequency dependence of the ER or to correlate ER amplitude with that of contiguous EEG have produced discrepant results. This is not surprising in view of the diversity of experimental methods employed. It seems likely that differences in modality tested, electrode placement, and segment of the ER waveform measured as well as the length of the pre-

EEG sampled have contributed to the protean findings. Nevertheless, while the precise properties of the electroencephalogram crucial to the elaboration of the evoked response are, as yet, far from understood, analysis of single unaveraged potentials must acknowledge preceding EEG activity.

Visual examination of the ongoing EEG has generally proved adequate for gross classification of steady states of consciousness such as waking, stages of sleep and arousal. In the ink written analogue record, however, it is most difficult to visualize nuances in the EEG wavetrain associated with a particular state or with transitions from state to state. This lack of precision in depicting subtle changes in the primary EEG tracing has led to the development of sophisticated quantitative techniques. With these methods a given electrophysiological state may be automatically summarized in terms of frequency (Dietsch, 1932; Grass and Gibbs, 1938; and Walter, 1943), phase (Darrow, 1967), period (Motokowa, 1941; Saltzberg and Burch, 1957; Burch, 1959), or amplitude (Drohocki, 1948; Goldstein and Beck, 1965). Unfortunately, a single procedure to completely portray the characteristics of a complex EEG pattern has yet to be devised. Current innovations in data reduction systems take a multidimensional approach in which several EEG parameters are considered simultaneously. In order to maximize quantitative efficacy in this experiment a combination of period analysis and amplitude integration was utilized.

The method of period analysis separates the waves of the EEG signal into intervals of their duration. A major period is defined as the number of counts per unit time at certain amplitude points, usually

baseline (zero voltage) crossings. The mathematical first derivative of the primary EEG trace yields an index of superimposed activity (i.e., the intermediate period) and represents the time between inflection points. Higher order derivatives (second derivative or minor period) can also be calculated if desired.

Since changes in the frequency composition of the EEG were anticipated as a consequence of alcohol administration, period analysis seemed particularly suitable to the purpose of this experimental situation. Frequency bands prominent in the waking EEG were made to correspond to the major periods of theta, 4-7 Hz, slow alpha defined as 8-10 Hz and fast alpha, 10.2-13 Hz as well as the intermediate period of beta, 16-30 Hz and read out "on line." Some advantages attributed to period analysis over other contemporary methods include 1) brief episodes of EEG may be analyzed without contamination from longer enduring electrical events; 2) equal weight is given to all waves irrespective of amplitude (MacIntyre, 1964), 3) it does not assume a periodic function (Saltzberg, 1957) and 4) it retains information about individual waves (Walter, 1967). On the other hand, failure to provide knowledge of amplitude variations may be regarded as a definite disadvantage of period analysis. Differences in the energy content of the EEG and its variation have been found to be extremely sensitive to a number of pharmacological and behavioral treatments (Goldstein, 1965). In order to gain perspective on these variables, automatic integration of the EEG was also performed. With this procedure the amplitude of the EEG is depicted as a series of spikes, the frequency of which is proportional to the cumulative voltage in a predetermined time period.

CHAPTER V

EXPERIMENT IV

Methods

Subjects

A search was undertaken to locate subjects who consistently displayed single unaveraged somatosensory evoked potentials large enough to permit quantification. Five healthy adult males whose ER's were easily visualized in the ongoing EEG were found. All were accustomed to alcoholic beverages.

Data Recording

Measurements of the unstimulated electroencephalogram and cortical evoked responses were made from the monopolar derivation used in Experiment I (vertex, CZ, referred to linked ears). Recordings were amplified by a Grass EEG machine (model 6) set to pass a frequency band of 1-70 Hz. The stimulus parameters and site of stimulating electrodes were the same as used in the first three experiments. All biological signals and synchronizing pulses were stored on magnetic tape (Ampex FM 1300) for later playback and analysis.

Procedure

Each subject visited the laboratory on three occasions, in each

instance he was required to fast for at least four hours prior to the onset of the experiment. All subjects agreed to abstain from alcohol or other drugs during the course of the experiment and to maintain a normal sleep schedule. Once the subject was weighed, a placebo or ethyl alcohol (USP 95%) mixed with orange juice and ice was administered. The alcohol load was appropriate to raise the subject's blood level to 50-65 mg% (low dose) or 95-110 mg% (high dose) according to his body weight. The placebo, as in Experiment I, consisted of a standard dose of orange juice (150 ml) with a minute quantity of alcohol, just adequate to exude the distinct odor of ethanol floated on the surface. Within each experimental condition, two drinks, equal in content, were provided and twenty minutes was allotted for the ingestion of the substance. During the following 40 minute absorption period the electrodes were attached.

Once the subject was prepared and the desired BAC had been reached (control, low dose or high dose) as indicated by a breath test (Stephenson Breathalyzer), he was brought into the dimly lit, sound attenuated experimental chamber and comfortably seated. To avoid movement artifact, the subject was asked to relax, remain as motionless as possible and to keep his eyes closed throughout the run. White noise was employed to mask distracting extraneous sounds. To maintain an acceptable level of consciousness in an environment otherwise conducive to rapid state shifts, the subject was instructed to count, to himself, every eighth stimulus pulse. Data collection then began.

Three hundred and twenty stimuli (interstimulus interval 6-24 sec.) were randomly presented in ten recording periods. During each

session the subject might receive as many as 58 shocks but only the first 32 were included in the analysis. Thus a given session lasted from five-ten minutes. Between each recording period, the subject was "disconnected" and allowed to walk about and converse with the experimenter for about five minutes. During this break, a breath sample to determine the BAC was made. To assure that the concentration of alcohol in the blood was maintained within the specified range (low dose/ high dose), supplementary doses were provided as prescribed.

This cycle was repeated until the completion of the experiment.

Analogue to Digital Conversion

Amplitude integration

In this experiment the continuous EEG was subjected to amplitude integration. This was accomplished by a modified method of Drohockie (Cowden, 1971), which automatically measures the energy content of the EEG. Successive samples of EEG are full wave rectified and a train of pulses is generated at a rate directly proportional to the area under the amended curve. Inasmuch as the EEG may be viewed as a change in voltage with respect to time, the subtended area represents the product of electrical potential times time. In this experiment one second epochs prior to stimulus presentation were selected as the unit of time for quantitative analysis. The number of pulses emitted during this period were counted, combined in sets of 8 and the means and variances computed.

Period Analysis

Period analysis of the ongoing EEG was also performed (Bio-

physical A-D converter). This technique allows for the separation of EEG waves according to intervals of their duration (periods). The number of baseline (zero) crossings corresponding to each band width are registered as vertical pen deflections. That is, the number of counts for a given wave defined by the time between two successive baseline crossings are written out on a separate channel of the electroencephalograph. The frequency bands (major periods) under study in this experiment were: theta (4-7 Hz), slow alpha (8-10 Hz), fast alpha (10.2-13 Hz) and beta (16-30 Hz). Since activity in the beta range often appears as "riding" activity, i.e., it does not cross the baseline, it was assessed by taking the first derivative of the primary signal (intermediate period). Again the number of spikes falling within the one second prestimulus epochs were accumulated for each of the three major and one intermediate periods.

Cortical Evoked Potentials

Evoked potentials occurring up to 500 msec. in the poststimulus interval were successively fed into the first, second and third quarters of the memory of a Fabritek special purpose computer (model 1062) and read out with a Hewlett Packard plotter (7004B). Each response was then additively transferred to the fourth quarter of the memory and summated in subsets of eight trials. In this way, a permanent record of evoked activity in averages of 8, 32 and 320 was obtained as well as each of the single sweeps.

Peak amplitude was measured as the absolute voltage from the highest positivity to the lowest negativity falling within a specified time "window." In this experiment only the N1 and P2 components of the

vertex response were of concern. The appropriate time windows for the designated waves were determined from the prototype response derived from the "overall" average (N-320) for each subject. A template of the prototype response obtained from the control average was then made and fitted over the single evoked potentials as well as over the averages of eight. Figures 10 and 11 demonstrate this process. Latency was taken as the temporal distance from the point of stimulus onset to the peak of the selected inflections (N1, P2).

Data Reduction

As already indicated the stimulus pulse served as the reference point for all analogue measurements. Three hundred and twenty shock stimuli were presented to each of five subjects under three alcohol treatments. Assessment of EEG variables (output of amplitude integrater and period analysis system) was made in the 1 second epochs preceding stimulus delivery and of the ER variables (amplitude and latency of components N1 and P2) in the 500 msec. following each stimulus pulse. The total counts for the three major periods and one intermediate period, as well as for the integrated EEG signal, falling within the 1 second prestimulus intervals were parcelled into sets of eight. The means and variances of these subsets were then computed. This gave 40 means and variances for each EEG parameter. Measurements of peak-to-peak amplitude in microvolts and peak latency in milliseconds of the N1 and P2 components of each of the 320 ER's were also divided into sets of eight and their means and variances calculated.

Figure 10. Method of Identification and Measurement of N1 and P2 Components.

A. Average of 320 somatosensory evoked responses recorded from the vertex.

B. Development of template. Horizontal line indicates estimated isolectric zero. Vertical lines delimit time "windows" for specific components.

C. Labeling scheme for components and illustration of peak-to-peak measurements.

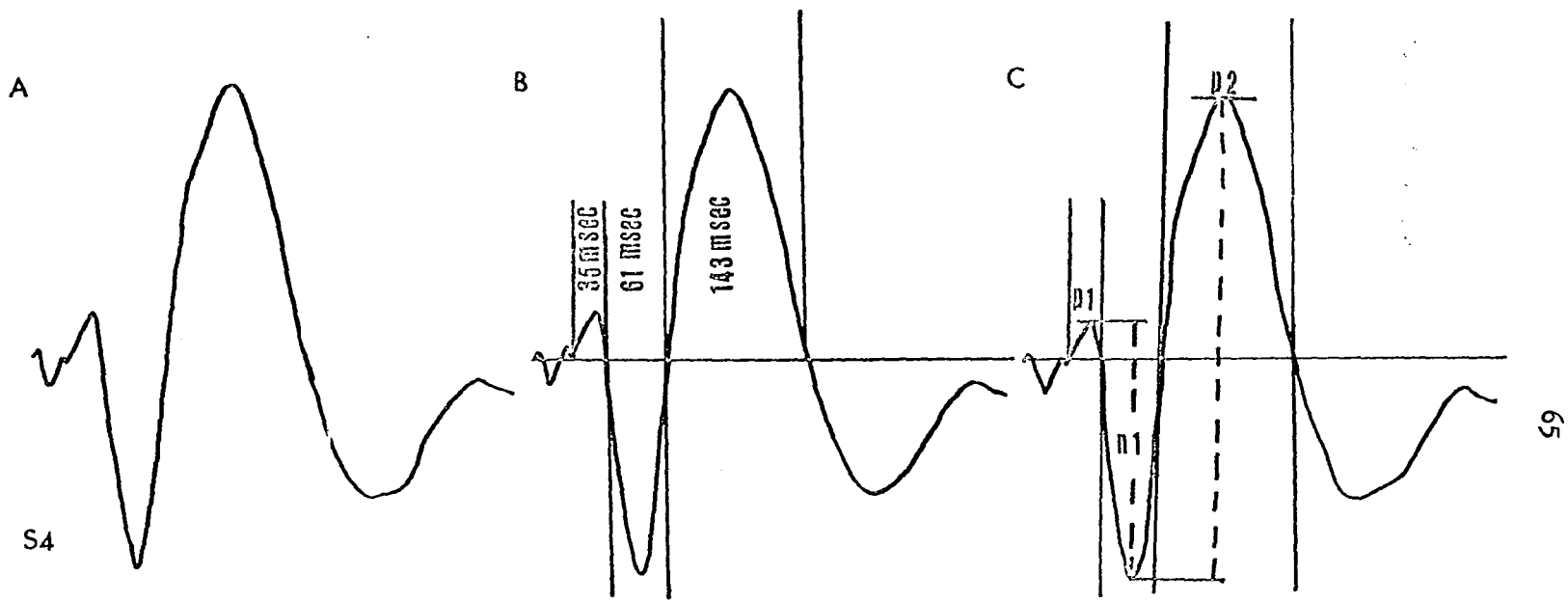
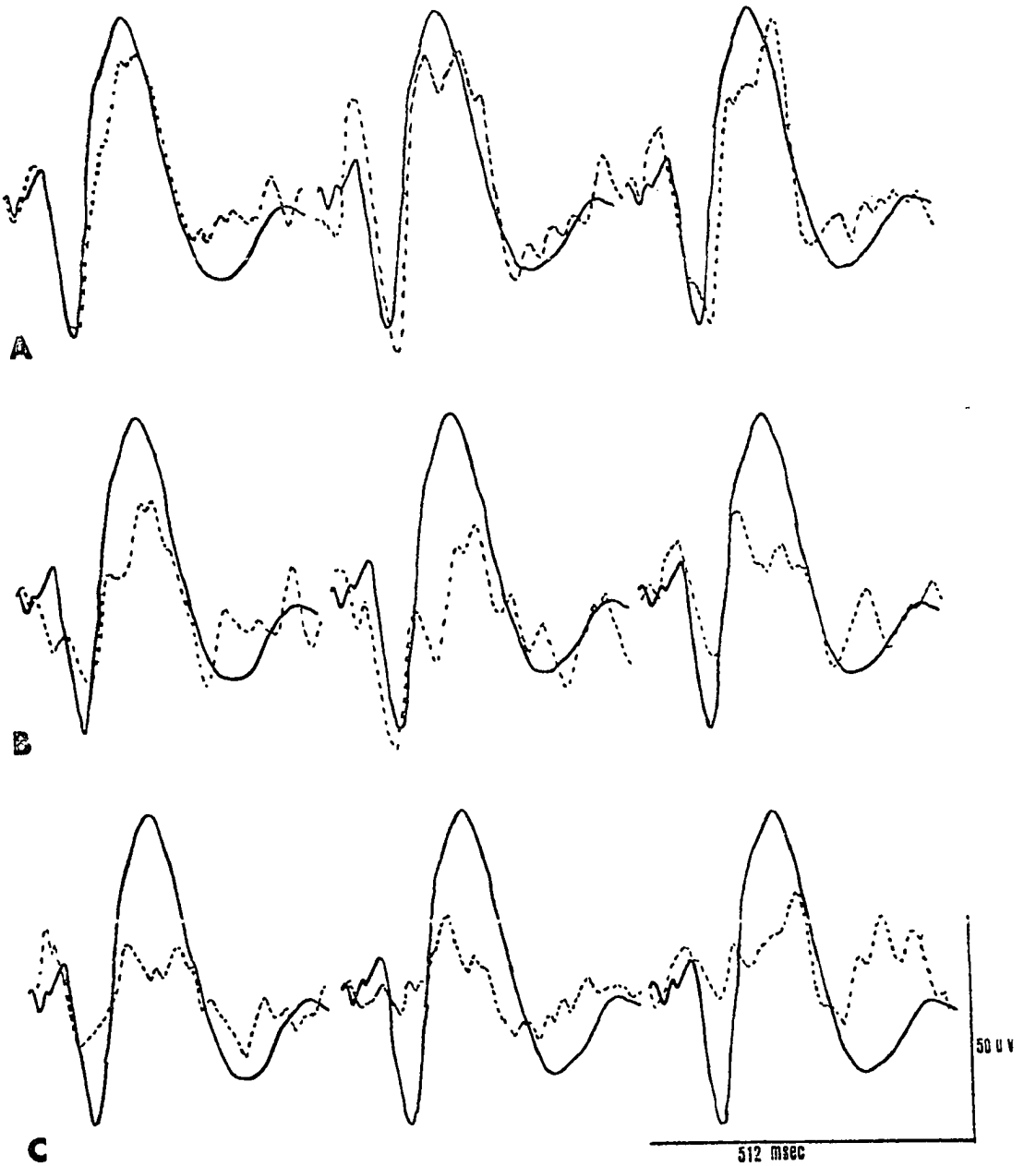

A
S4
B
35 msec
61 msec
143 msec
C
D1
D2
n1

Figure 11. Application of Template to Single Sweeps.

In this figure the use of the template is demonstrated in three alcohol conditions: A) placebo, B) low dose, C) high dose. Template (solid line) derived from average of 320 ER's for each subject is laid over single sweeps (dotted line). Note easy recognition of relevant peaks at high BAC's (C) when response amplitudes approach "noise" level.


A
B
C
50 u v
512 msec

Statistical Treatment

These data were then treated in a one-way repeated measures design analysis of variance in order to determine the effects of the three alcohol levels on each of the EEG and ER variables independently. Comparisons of the correlated treatment means with the small case t were made when significance was indicated.

Evoked potentials were also electronically averaged in samples of eight. The average amplitude of the N1 and P2 components of the vertex response served as dependent variables (criteria) to be tested separately against the battery of EEG and ER variables (independent variables) in a step-wise multiple regression procedure. The purpose of this analysis was to establish the effective predictors of the N1 and P2 components from among the entire set of EEG and ER parameters measured. Of special interest to us was the step in which each variable entered the regression equation, the multiple correlation squared (RSQ) of that variable (accountable variance) and whether the increase in RSQ at each successive step was significant. A regression analysis was computed for each subject under each of three alcohol treatments. The computations for this analysis were provided by the Biomedical package (BMD02R) (Dixon, 1967) and processed on an IBM 360-50 computer (Merrick Computing Center, University of Oklahoma).

CHAPTER VI

RESULTS OF EXPERIMENT IV

The Unaveraged (Single) Evoked Response

Single unaveraged potentials evoked by transcutaneous afferent stimulation were readily observable in the ongoing electroencephalogram. Despite variations in amplitude and waveform the individual ER's were consistent enough for easy recognition. Figure 12 exemplifies the prominence of these sensory responses with respect to the background EEG. This figure shows several ER's taken from the control (placebo) record of one subject along with a display of the ongoing EEG. Three hundred and twenty such responses were written out for each of five subjects under three levels of alcoholization; placebo, low dose and high dose. At low BAC's (50-60 mg%) single responses, although attenuated, could still be visualized in the EEG record (Figure 13). By the time the amount of alcohol in the blood had reached 95-110 mg% (high dose) the ER was reduced to "noise" level. This graded diminution of response amplitude from placebo-to low dose-to high dose is apparent in Figure 13.

Identification of specific components regardless of their magnitude was achieved by superimposing a template deduced from the grand sum (average of 320 ER's) over the individual responses. Only the first

Figure 12. Single Evoked Responses and Background EEG.

This figure illustrates the magnitude of the single ER's with respect to the ongoing EEG. Arrows indicate stimulus onset. Relative positivity at active site indicated by downward deflection.

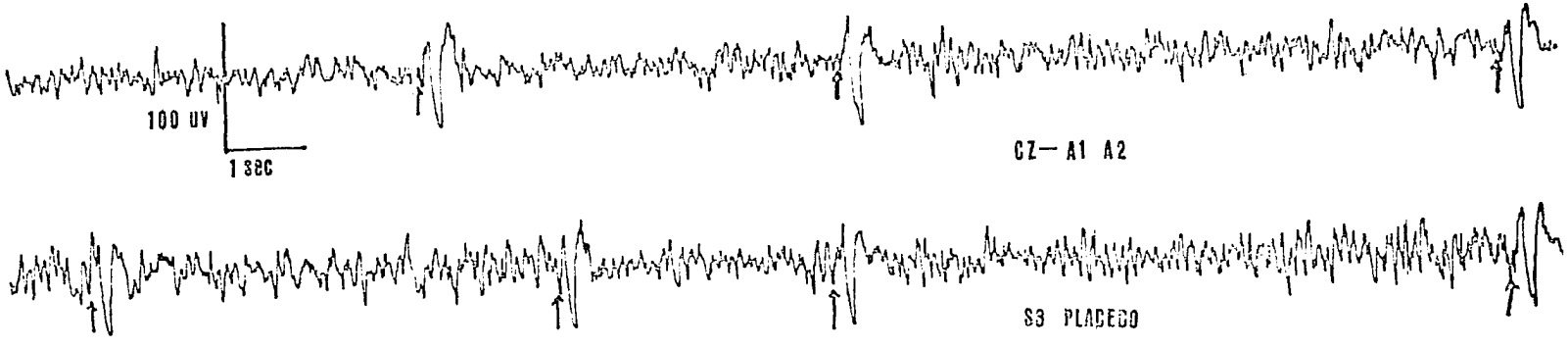
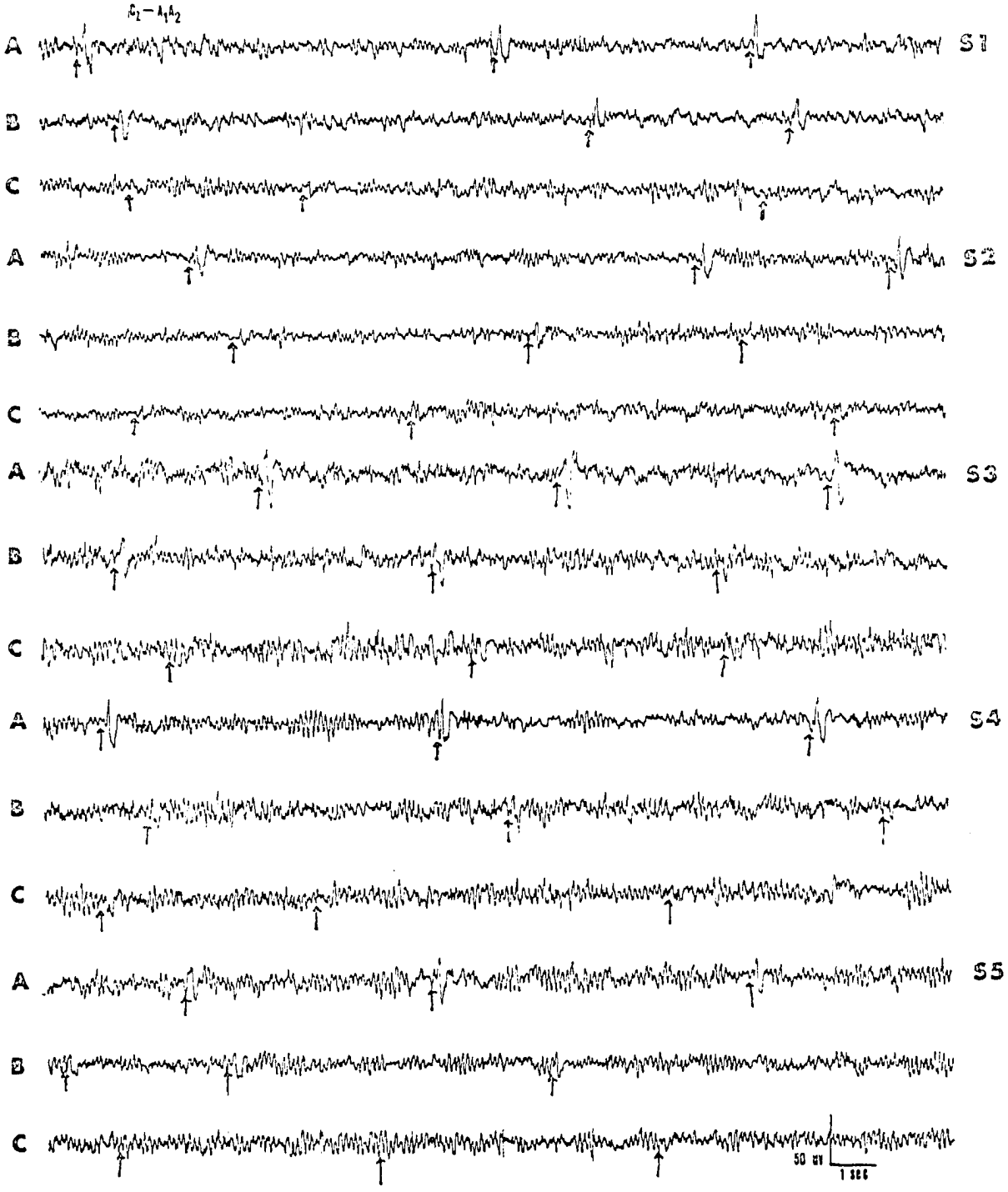

100 UV
1 SEC
CZ— A1 A2
S3 PLACEBO

Figure 13. Gradual Loss of Response Amplitude with Increasing BAC.

This figure shows single evoked responses embedded in background EEG for five subjects (S1-5) under three alcohol treatments; A) placebo, B) low dose, C) high dose. Note reduction of ER amplitude with increasing BAC, i.e., B. compared to A and C compared to B. Arrows indicate stimulus onset.


$A_2 - A_1A_2$
A
B
C
S1
S2
S3
S4
S5
50 uV
1 SEC

negative wave (N1) and the second positive wave (P2) were of concern in this study. It is these components that are most consistent across subjects. Peak amplitude was taken as the absolute voltage between the maxima and minima of two succeeding waves opposite in polarity falling within the limits predetermined by the model response. This procedure is illustrated in Figures 10 and 11. Latency was taken as the interval between stimulus onset and the point of inflection for the N1 and P2 components.

Evoked responses were also summed in blocks of 8 and 32 trials. As in Experiment I, average responses (samples of 32) were shown to be quite stable throughout the baseline period. Nine (of the 10) baseline (placebo) samples from one subject are displayed in Figure 14; each trace represents an average of 32 ER's taken every 10 minutes (approximately) with a five minute break between each recording session. Average ER's were also surprisingly uniform across subjects. In Figure 15 the sum of 320 superimposed ER's for the five subjects demonstrates this similarity of waveforms. Finally Figure 16 summarizes the effects of alcohol on the average cortical response.

Comment

It may be argued that using the template method, thereby imposing a tight limit on the freedom of each component to vary, defeats the purpose of tapping latency variability. Drug or behavioral treatments, however, are apt to increase the complexity of the ER or to reduce it to the extent that specific components can no longer be recognized. It then becomes impossible to determine whether the presence of a "blip" is, in fact, a new component or an old one displaced in latency.

Figure 14. Consistency of Average Evoked Response Throughout Control Period.

Each trace represents an average of 32 ER's. Each sample was obtained in successive sessions on the control (placebo) day. Positivity at vertex indicated by upwards deflection.

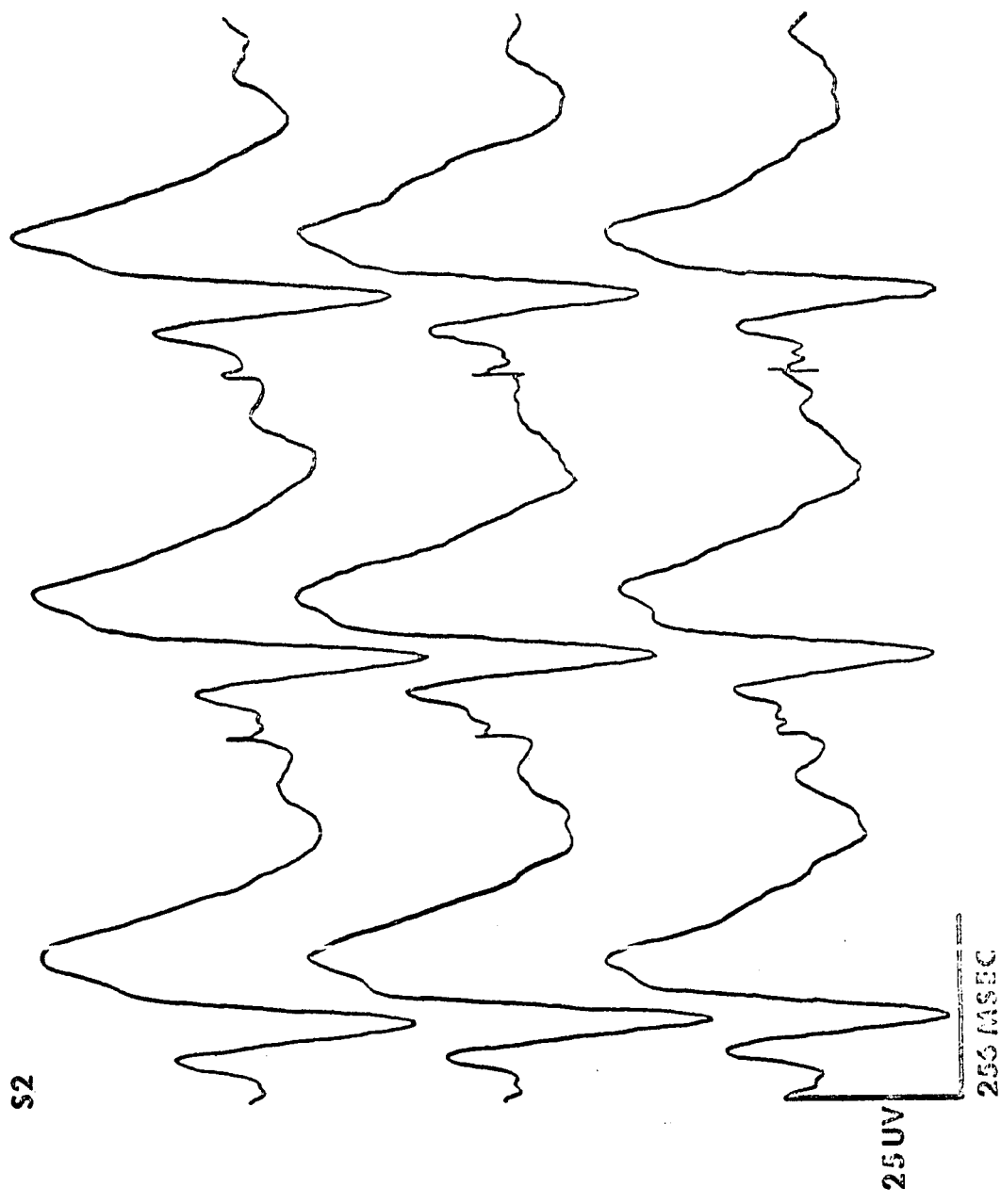

S2
25 UV
250 MSEC

Figure 15. Similarity of Evoked Response Waveforms Across Subjects.

This figure illustrates the striking similarity of ER waveforms across five subjects. Each superimposed trace represents an average of 320 ER's obtained on the control day.

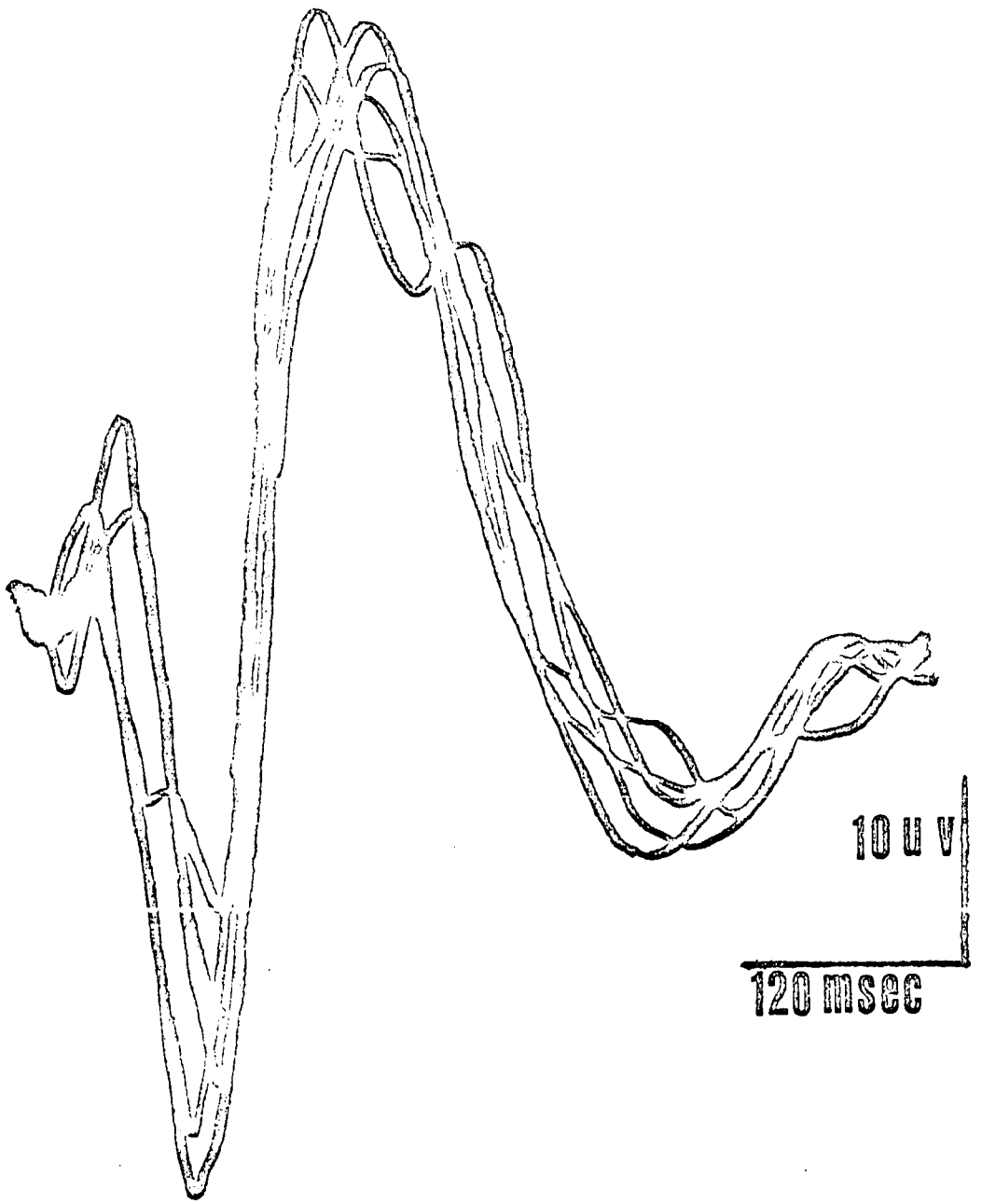

10 u v
120 msec

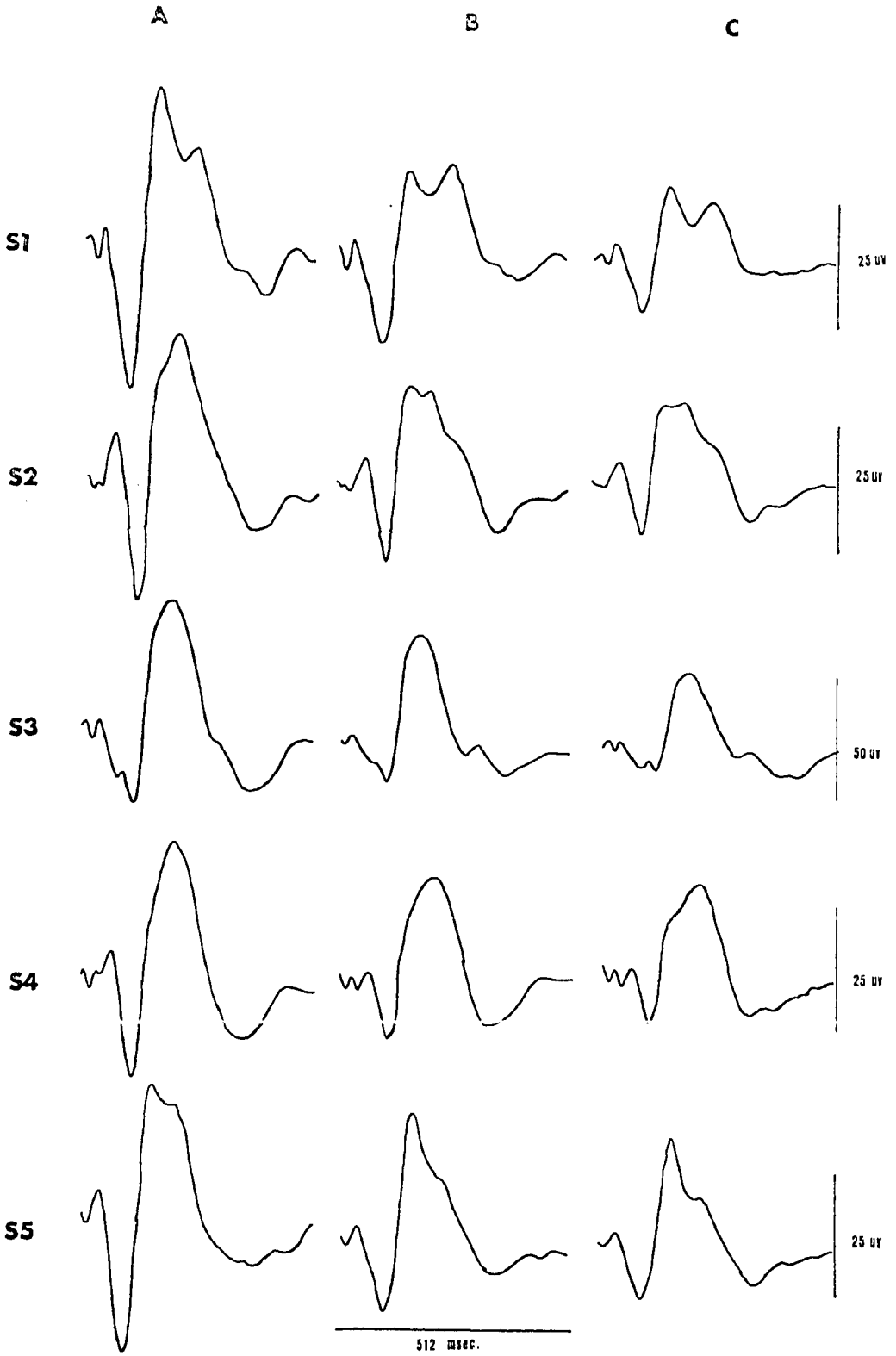
Figure 16. Summary of the Effects of Alcohol on the Average Evoked Response.

Each trace represents an average of 320 ER's obtained under three alcohol treatments:

A. placebo, BAC=00 mg%

B. low dose, BAC=50-60 mg%

C. high dose, BAC=95-110 mg%


A
B
C
S1
S2
S3
S4
S5
25 uv
25 uv
50 uv
25 uv
25 uv
512 msec.

This is particularly true of single trial data where the absence of activity is a likely outcome and where spontaneous excursions can easily be misinterpreted as an ER component. Although peak naming and the template method are both arbitrary, the former seems to introduce a greater opportunity for bias. As will be seen, the component with the narrowest time window (N1) showed the greatest variability.

The Effects of Alcohol on Evoked Response Parameters

The mean and average variance of the amplitude and latency of the N1 and P2 components were calculated from the 320 single sweeps for the three experimental conditions (Tables 8-15). The computed values were then subjected to a one-way repeated measures analysis of variance.* Results of these analyses revealed that the mean amplitude of both the negative and positive waves decreased significantly ($F=122$, $p < .001$; $F=136$, $p < .001$ respectively) with the rising concentration of alcohol in the blood. The variability of latency of the N1 but not the P2 component showed an increase following alcohol ingestion ($F=6.89$, $p < .05$). However, this effect was significant only at high BAC's ($t=5.34$, $p < .01$). Alcohol loading produced no apparent change in the mean latency of either component nor did it alter the variability of peak amplitude. F values are given in Tables 8-15.

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*Since the treatment means were correlated, a conservative test of significance is indicated (Greenhouse and Geisser, 1959). Thus, unless otherwise specified, all significant F values reported here are based on 1/4 degrees of freedom. Analysis of differences between pairs of treatment means was based on the t test for correlated measures.

Table 8

MEAN AMPLITUDE[a] OF COMPONENT P2 UNDER THREE ALCOHOL CONDITIONS: PLACEBO, A1; LOW DOSE, A2; HIGH DOSE, A3

Subjects	Treatments A1	A2	A3
S1	35.451	27.284	24.833
S2	37.630	26.468	22.737
S3	40.030	29.834	24.569
S4	53.121	43.459	37.549
S5	32.389	24.070	21.537

F=136.84, $p < .001$ 1/4 df.

a - measured in standard gradicules, one gradicule equals 1.5 microvolts.

Table 9

AVERAGE VARIANCE OF COMPONENT P2 AMPLITUDE UNDER THREE ALCOHOL CONDITIONS: PLACEBO, A1; LOW DOSE, A2; HIGH DOSE, A3

Subjects	Treatments A1	A2	A3
S1	100.516	79.627	72.996
S2	79.797	66.942	76.776
S3	90.678	74.399	79.908
S4	143.565	144.625	126.355
S5	48.179	51.749	41.252

$F=3.93$, $p > .05$, 1/4 df.

Table 10

MEAN AMPLITUDE[a] OF COMPONENT N1 UNDER THREE ALCOHOL CONDITIONS: PLACEBO, A1; LOW DOSE, A2; HIGH DOSE, A3

Subjects	Treatments A1	A2	A3
S1	19.824	13.002	12.175
S2	20.380	14.334	12.718
S3	24.108	15.986	12.387
S4	24.415	19.055	16.443
S5	21.152	14.200	12.343

$F=122.10$, $p< .001$, 1/4 df.

a - measured in standard gradicules, one gradicule equals 1.5 microvolts

Table 11

AVERAGE VARIANCE OF COMPONENT N1 AMPLITUDE UNDER THREE ALCOHOL CONDITIONS: PLACEBO, A1; LOW DOSE, A2; HIGH DOSE, A3

Subjects	Treatments A1	A2	A3
S1	87.970	63.268	68.998
S2	74.448	75.198	77.359
S3	108.680	79.528	64.301
S4	107.703	147.012	123.388
S5	56.515	50.728	43.533

$F=.89$, $p > .05$, 1/4 df.

Table 12

MEAN LATENCY[a] COMPONENT P2 UNDER THREE ALCOHOL CONDITIONS: PLACEBO, A1; LOW DOSE, A2; HIGH DOSE, A3

Subjects	A1	A2	A3
S1	25.180	24.159	24.823
S2	22.760	24.887	24.025
S3	23.972	21.103	20.819
S4	25.199	21.880	23.548
S5	25.381	24.340	25.749

$F=1.88$, $p > .05$, 1/4 df.

a - measured in standard gradicules, one gradicule equals 8 milliseconds.

Table 13

AVERAGE VARIANCE OF COMPONENT P2 LATENCY UNDER THREE ALCOHOL CONDITIONS: PLACEBO, A1; LOW DOSE, A2; HIGH DOSE A3

Subjects	Treatments A1	A2	A3
S1	9.170	13.047	18.581
S2	18.963	27.785	27.097
S3	12.905	12.390	10.935
S4	9.302	8.157	8.621
S5	8.977	12.623	15.404

$F=2.77$, $p > .05$, 1/4 df.

Table 14

MEAN LATENCY[a] OF COMPONENT N1 UNDER THREE ALCOHOL CONDITIONS: PLACEBO, A1; LOW DOSE, A2; HIGH DOSE, A3

Subjects	A1	A2	A3
S1	14.409	13.025	13.187
S2	12.165	11.933	12.356
S3	13.425	11.727	11.506
S4	14.150	12.965	13.391
S5	15.349	15.491	15.959

$F=3.42$, $p > .05$, 1/4 df.

a - measured in standard gradicules, one gradicule equals 8 milliseconds

Table 15

AVERAGE VARIANCE OF COMPONENT N1 LATENCY UNDER THREE ALCOHOL CONDITIONS: PLACEBO, A1; LOW DOSE, A2; HIGH DOSE, A3

Subjects	Treatments A1	A2	A3
S1	2.435	2.670	4.249
S2	1.639	3.127	4.141
S3	1.936	3.552	3.901
S4	4.356	3.060	7.018
S5	0.764	1.147	1.393

$F=6.89$, $p < .05$, 1/4 df.

The Effects of Alcohol on EEG Parameters

The integrated amplitude of the EEG and period analysis of theta (4-7 Hz), slow alpha (8-10 Hz), fast alpha (10.2-13 Hz) and beta (14-30 Hz) activity were tabulated in counts per/second for the 1 second epochs preceding each stimulus pulse. The means and variances of the total counts for each of these variables were calculated for each subject across all 320 trials under placebo, low dose and high dose conditions (Tables 16-25). Analysis of variance of these data disclosed that only the frequency band of theta was influenced by alcohol consumption. The F values are provided in Tables 16-25. Comparisons of the baseline (placebo) with the two alcohol dosages indicated that the number of theta waves tended to decrease at low BAC's ($t=2.762$, $p < .05$) and then returned to but did not exceed control levels at high BAC's ($t=-1.23$, $p > .05$). The increase from low to high BAC's was significant ($t=5.37$, $p < .01$). The remaining EEG bandwidths (mean beta, mean fast alpha and mean slow alpha), integrated amplitude and the variances of these measures were unaffected by the drug. Winer (1962) points out that the conservative test is all too often too conservative. Thus, as a back-up for the analysis of variances, Friedman's two-way analysis of variance (X^2_r) was performed. The X^2_r values presented in Table 26 show that only the strength of the effect on theta and latency variability of the N2 component improved; the other variables still did not reach significance.

The Relationships Among Variables Within Subjects and Treatments

The counts tallied for each EEG parameter in the one second

Table 16

MEAN THETA UNDER THREE ALCOHOL CONDITIONS

Subjects	Placebo	Low Dose	High Dose
S1	1.555	1.220	1.472
S2	1.658	1.615	1.686
S3	1.219	1.165	1.333
S4	1.368	1.177	1.412
S5	1.331	1.225	1.440

$F=11.326$, $p < .05$, 1/4 df.

Table 17

AVERAGE VARIANCE OF THETA UNDER
THREE ALCOHOL CONDITIONS

Subjects	Placebo	Low Dose	High Dose
S1	1.249	0.968	1.290
S2	1.336	1.232	1.315
S3	1.050	1.036	1.031
S4	1.027	1.077	1.170
S5	1.269	1.005	1.200

$F=3.890$, $p > .05$, 1/4 df.

Table 18

MEAN SLOW ALPHA UNDER THREE
ALCOHOL CONDITIONS

Subjects	Placebo	Low Dose	High Dose
S1	1.575	1.784	1.928
S2	1.909	1.875	2.058
S3	2.534	2.674	2.542
S4	1.902	2.146	2.083
S5	1.865	2.027	1.939

$F=4.868$, $p > .05$, 1/4 df.

Table 19

AVERAGE VARIANCE OF SLOW ALPHA UNDER THREE ALCOHOL CONDITIONS

Subjects	Placebo	Low Dose	High Dose
S1	1.949	1.904	2.037
S2	1.883	1.780	2.082
S3	2.634	2.912	2.680
S4	2.061	2.094	1.892
S5	2.031	2.171	1.911

$F=.295$, $p > .05$, 1/4 df.

Table 20

MEAN FAST ALPHA UNDER THREE ALCOHOL CONDITIONS

Subjects	Placebo	Low Dose	High Dose
S1	1.718	2.131	2.034
S2	1.928	1.868	1.824
S3	1.996	2.132	2.090
S4	1.906	2.150	1.797
S5	2.518	2.468	2.606

$F=1.391$, $p > .05$, 1/4 df.

Table 21

AVERAGE VARIANCE OF FAST ALPHA UNDER THREE ALCOHOL CONDITIONS

Subjects	Placebo	Low Dose	High Dose
S1	1.752	2.100	2.026
S2	2.014	1.825	2.087
S3	1.742	2.179	1.942
S4	1.764	1.902	1.729
S5	2.576	2.290	2.528

$F=.474$, $p > .05$, 1/4 df.

Table 22

MEAN BETA UNDER THREE ALCOHOL CONDITIONS

Subjects	Placebo	Low Dose	High Dose
S1	7.918	7.109	7.050
S2	6.640	6.619	7.168
S3	7.122	7.099	7.511
S4	8.769	8.943	8.656
S5	7.680	7.546	7.397

$F=.337$, $p > .05$, 1/4 df.

Table 23

AVERAGE VARIANCE OF BETA UNDER THREE ALCOHOL CONDITIONS

Subjects	Placebo	Low Dose	High Dose
S1	7.008	6.461	5.950
S2	5.346	5.235	6.484
S3	5.816	5.188	6.225
S4	7.370	7.585	9.591
S5	6.936	6.867	7.305

$F=2.333$, $p > .05$, 1/4 df.

Table 24

MEAN INTEGRATED AMPLITUDE UNDER THREE ALCOHOL CONDITIONS

Subjects	Placebo	Low Dose	High Dose
S1	4.171	4.699	5.537
S2	4.147	3.962	4.283
S3	4.649	4.699	4.477
S4	5.218	5.758	6.629
S5	3.565	3.396	3.581

$F=2.593$, $p > .05$, df. 1/4.

Table 25

AVERAGE VARIANCE OF INTEGRATED AMPLITUDE UNDER THREE ALCOHOL CONDITIONS

Subjects	Placebo	Low Dose	High Dose
S1	1.435	1.496	1.391
S2	0.893	0.856	0.960
S3	1.021	0.928	0.969
S4	1.394	1.795	2.389
S5	0.704	0.606	0.610

$F=.739$, $p> .05$, 1/4 df.

epochs prior to stimulus presentation were separated into sets of eight and their means and variances computed. The amplitude and latency of the N1 and P2 components of the poststimulus response were grouped in corresponding sets of eight and their means and variances obtained. This procedure yielded a composite of 14 quantitative EEG and ER variables based on N's of 40. A complete list of these variables is given in Table 27. The combined EEG and ER variables formed the battery of independent variables (predictors) in the multiple regression problem. The amplitude of the average cortical response as measured from the automatically summated single ER's (N=8) served as the dependent variable (criterion). The negative (N1) and positive (P2) components of the average response were tested as separate criteria against the entire set of predictors. Within each subject at each treatment level the relationships between the dependent variable and the set of independent variables was analyzed with a stepwise multiple regression procedure. As a first step towards the solution of the regression equation the intercorrelations among the independent variables as well as correlation coefficients with the dependent variable (N1 and P2 taken one at a time) were printed. Thus, a correlation matrix was generated for each subject in each of the experimental conditions. Appendix I shows the correlation matrices with the P2 component as the criterion and Appendix II with the N1 component as the criterion. In these appendices, each EEG and ER variable is numbered one through 14 as in Table 27. The criteria N1 and P2 are indicated by the number 15 in the respective appendices. Examination of column 15 then, shows the first order validities of each variable (designated by variable number)

Table 26

FRIEDMAN'S χ^2_r FOR ER AND EEG PARAMETERS

Evoked Response Parameters	
Variable	χ^2_r
Mean ER amplitude component P2	10.0*
Variance of ER amplitude component P2	3.6
Mean ER latency component P2	1.6
Variance of ER latency component P2	0.4
Mean ER amplitude component N1	10.0*
Variance of ER amplitude component N1	0.4
Mean ER latency component N1	2.8
Variance of ER latency component N1	8.4*

EEG Parameters	
Variable	χ^2_r
Mean integrated amplitude	2.8
Variance of integrated amplitude	1.2*
Mean theta	8.4
Variance of theta	1.4
Mean slow alpha	4.8
Variance of slow alpha	0.4
Mean fast alpha	1.2
Variance of fast alpha	0.4
Mean beta	1.2
Variance of beta	3.6

*.01

Table 27

EEG AND ER VARIABLES

Variable number	Variable	Alphanumeric designation
1.	Mean ER amplitude (P2, N1)	MERA (P2)(N1)
2.	Variance of ER amplitude (P2, N1)	VERA (P2)(N1)
3.	Mean integrated amplitude (P2, N1)	M-AI (P2)(N1)
4.	Variance of integrated amplitude (P2, N1)	V-AI (P2)(N1)
5.	Mean slow alpha (P2, N1)	M-LAL(P2)(N1)
6.	Variance of slow alpha (P2, N1)	V-LAL(P2)(N1)
7.	Mean fast alpha (P2, N1)	M-HAL(P2)(N1)
8.	Variance of fast alpha (P2, N1)	V-HAL(P2)(N1)
9.	Mean beta (P2, N1)	M-BET(P2)(N1)
10.	Variance of beta (P2, N1)	V-BET(P2)(N1)
11.	Mean theta (P2, N1)	M-THE(P2)(N1)
12.	Variance of theta (P2, N1)	V-THE(P2)(N1)
13.	Mean ER latency (P2, N1)	MERL (P2)(N1)
14.	Variance of ER latency (P2, N1)	VERL (P2)(N1)
15.	Average amplitude (P2, N1)	CAMP (P2)(N1)

with the criterion, the variable with the highest correlation being the most valid at this stage of the analysis.

Selection of the Minimal Set of Effective Predictors

A stepwise multiple regression technique was used to select the independent variables in the order of their importance. The variable making the greatest reduction in the error sum of squares was deemed to be the most important and entered the regression equation. At each step of the analysis the "F" ratio criterion was applied to determine when additional variables contributed significantly to the multiple correlation. Ultimately, only those independent variables which reliably improved the "goodness of fit" were included in the final regression.

In each of the analyses performed the mean amplitude of the signal sweep ER's (variable number 1) was found to have the highest independent validity (partial correlation) for predicting the dependent variable. This was the case for both the N1 and P2 criteria. In subsequent steps the variability of peak latency (variable number 14) of the negative but not the positive component was found to have independent validity. This held across subjects and treatments. The EEG variables and other ER variables entered the equation in a seemingly random order and did not reliably improve prediction. The optimal set of predictors and summary of the stepwise procedure is presented in Appendix III for the positive wave and Appendix IV for the negative component. In the left hand column of Appendix III and IV the variable number and the order in which it entered the regression equation for each subject

separately under each experimental condition is given. The next three columns provide the multiple correlation (R), the square of the multiple correlation (RSQ) and the increase in the RSQ added by each variable. In the last column, the F value of the gain added by the independent variables is given.

CHAPTER VII

DISCUSSION

The results of Experiments I and II demonstrate that while the various components of the somatosensory evoked response (SER) are not uniformly affected by alcohol, they do behave in a predictable way. At low to moderate BAC's the early components (primary discharge) confined to the post-rolandic site show little change. This is in agreement with the findings of Lewis, et al. (1969), who reported that the visual evoked response (VER) as recorded at the occiput was relatively resistant to comparable doses of alcohol, and indicates that this effect is not a modality specific phenomenon. In contrast to the VER, however, the rolandic late components were severely suppressed by the drug.

The initial spike which characteristically becomes enhanced following barbiturate anesthesia showed no such tendency at low BAC's, thereby distinguishing the action of the two compounds at intermediate stages of pharmacological metabolism. At what might be considered high blood alcohol levels (120 mg%) the entire early response showed marked attenuation, suggestive of general depression of the central nervous system.

Conversely, the late components with particular reference to the slow vertex response became significantly inhibited by even small amounts of alcohol. Strong negative correlations between the peak-to-

peak amplitudes of the individual components and BAC were found for each subject. In other words, as the volume of alcohol in the blood loomed upwards, the amplitude of the vertex response progressively declined. With the subsidence of the BAC, the ER gradually recovered its predrug magnitude. Thus, unlike other neurological or behavioral signs of intoxication, the SEP was found to be an extremely sensitive physiological index of BAC during both the ascending and the descending phases of the blood alcohol curve (see Figure 4).

The third experiment conclusively shows that sensory transmission in the median nerve proceeds, unimpaired, at high BAC's. Action potentials recorded from the upper arm of 5 subjects were not perceptibly different at peak BAC's from those obtained during the baseline run. One subject allowed his blood level to be pushed to 145 mg percent. Thus the alterations in amplitude and latency of the cortical ER cannot be attributed to changes in peripheral mechanisms.

The results of the foruth experiment indicate that the magnitude of the average cortical response relates best to the amplitude of the single unaveraged responses and is essentially independent of concurrent ongoing rhythms. This autonomy is demonstrated in the iterations of the multiple regression analysis. Referring to Appendix III and IV, it can be seen that the various EEG parameters enter the equation unsystematically and rarely contribute significantly to the prediction of the average response (N1 or P2). This was true of all subjects in both alcoholized and nonalcoholized conditions, thereby ruling out the possibility that the two measures became dissociated in the drug state. Furthermore, a test of the pooled residuals (EEG and ER variables) in

each case (subjects by treatments) inconsistently increased the gain in the multiple correlation squared (RSQ).

In contrast to previous reports, a generalized slowing of the EEG at high BAC's was not observed. However, activation reflected as a sharp decrease in theta activity was observed at low BAC's. Although changes in the EEG are usually slight, failure to detect even subtle effects at the high dose level (100 mg%) could have been due to several factors. First, recording was done during steady-state conditions, that is, the subject had attained his peak BAC and may have begun to normalize (c.f. Mirsky, et al., 1941), i.e., "adapt" already. Secondly, the subject's state of consciousness was carefully controlled in this experiment. In past studies subjects were allowed to lie passively for various lengths of time with eyes closed. It is conceivable that the action of the drug interacted with level of alertness to accentuate the sedative effects. Evoked responses too, are subject to modulation at different stages of wakefulness (Williams, et al., 1964). It is often difficult or impossible to distinguish specific effects. In this experiment subjects were required to count (by eights) the stimulus pulses. At the end of each run the subject would verbally report his tally. Performance under the three treatments was 100 percent. This low demand task therefore proved adequate to maintain the subject at a relatively constant behavioral and parenthetically electrophysiological state. This might also account for the stability of peak latency in Experiment IV. Thirdly, we recorded only from the vertex, which is not the optimal site to monitor changes in specific frequency bands such as alpha activity. We saw no evidence of a marked increase in alpha (slow

alpha) particularly at low BAC's as reported by Docter, et al. (1966), in alcoholic patients.

Significance of Differential Effects

Functional differences between the early and late components of the average cortical response as well as their anatomical distribution across the scalp strongly suggest that they arise from spatially separate generators in the brain. There is considerable agreement that short latency components (16-70 msec.), restricted to the posterior quadrant of the scalp contralateral to the stimulus, express activity in lemniscal pathways. Those components with longer latencies (70-300 msec.) show a more extensive distribution over the entire convexity and have therefore been ascribed to an extralemniscal source. Within this framework, the preservation of the early components and modification of the later ones implies that alcohol is acting on those structures mediating the diffuse response rather than upon classical sensory pathways. In this way the effect of alcohol appears to be similar to that of other central depressants.

The Central Effects of Alcohol

The finding that ER's in the midbrain reticular formation and somatosensory association area were markedly depressed compared to primary cortex and relay thalamus following alcohol infusion led DiPerri, et al. (1968), to postulate the synapse as having the greatest affinity to alcohol. This interpretation is in accord with the explanation offered by French, et al. (1953), of the anesthetic effects induced by barbiturates and ether administration. The polysensory character of the

human vertex potential suggests some degree of convergence upon a common neuron pool. Anatomically, the reticular formation (RF) of the brain stem is optimally situated to modulate complex sensory interactions. Aggregates of reticulo-petal fibers invade the lateral and ventral aspects of the stem at every level. It is well known, however, that the RF does not receive input from the medial lemniscal system (Bowsher, 1958; Nauta and Kuypers, 1958; Morillo and Baylor, 1963). Section of the fasiculus gracilis does not alter the reticular response to sciatic stimulation nor does direct stimulation of the dorsal column nuclei provoke such a response (Bowsher, 1958; Morillo, et al., 1963). Instead, activation of the RF following peripheral nerve stimulation takes place solely through collaterals branching from spinoreticular and spinothalamic tracts at all segments of the cord (Scheibel and Scheibel, 1958; Scheibel and Scheibel, 1967). Electrophysiological studies have repeatedly shown reticular potentials to be large slow waves with long recovery times (King, Naquet and Magoun, 1957). The long latencies of responses to sensory or cortical excitation are indicative of slow conduction rates. Intrareticular transport is even slower (French, et al., 1953). Such observations led early investigators to conclude that the delay in transmission through the brain stem reticular formation was due to multiple synaptic connections of short axonal cells (Magoun, 1950; French, et al., 1953). This served as a structural model for the interpretation of pharmacological selectivity.

There is an abundance of evidence demonstrating the modulatory role played by the RF. Autonomic and visceral functions (Pitts, Magoun and Randon, 1939; Pitts, 1940), spinal reflex and motor activity

(Magoun, 1944; Rhines and Magoun, 1946), thalamic excitability (King, et al., 1957), sensory gating (Hagbarth and Kerr, 1954; Killam and Killam, 1958), cortical tonus (Moruzzi and Magoun, 1949) and state of consciousness Galambos, Sheatz and Vernier, 1956) have all been shown to come under reticular control. Under barbiturate anesthesia this reticular influence becomes impaired or blocked altogether (Killam, 1962). Caspers (1958) examined the effects of alcohol on reticular regulation of cortical potentials. Alcohol given in low doses led to an increase in convulsive-like bursts induced by direct stimulation of the cortex. This effect could be counteracted by either central or peripheral activation of the RF. With high concentrations of alcohol the RF was ineffective in predisposing cortical discharge. The author suggested that alcohol may act directly on reticular inhibitory mechanisms.

In this context, Sauerland, Knauss and Clemente (1967) have shown that the masseteric and soleus reflexes normally evoked by electrical stimulation of the trigeminal nucleus are completely inhibited by a train of pulses applied to the orbital cortex of the cat. Since the projection fibers from the orbital gyri descend without synaptic interruption to the bulbar inhibitory center, the finding that small quantities of alcohol (480-540 mg/kg) interfered with this inhibitory process led the authors to conclude that the medullary RF was the primary target of the depression. Following 0.8 g/kg of alcohol in the rabbit, Ohga (1965) found that the threshold for the elicitation of the arousal reaction in the frontal cortex to be higher for RF stimulation than for stimulation of the medial thalamus or several hypothalamic

structures. The deleterious effect of alcohol was also apparent at the nonspecific thalamic site. Taken together, these studies plus the work of DiPerri, et al. (1968), mentioned in the introduction to Experiment I, implicate the RF of the brain stem with its polyneuronal organization as the preferential locus of alcohol depression.

That synaptic preponderance alone cannot account for the obtained results, however, was demonstrated by Domino (1955), King (1954), and King (1956). These investigators found that while several anesthetic agents were effective in raising the threshold for EEG arousal to RF stimulation, specific interneuronal depressants such as mephenesin and the benzazoles were not. Fiber diameter as the morphological substrate for drug effects has been emphasized by Randt, Collins, Davis and Dillon (1958). They found that evoked potentials in the posterioventral lateral nucleus of the thalamus and pretectal region of the midbrain were differentially affected by general anesthesia, although both responses are propagated through oligosynaptic systems. The extralemniscal spike potential transmitted over small slow conducting gamma-delta group afferents showed considerable attenuation, as did responses in the periaqueductal multisynaptic reticular formation. In contrast, impulses projected over large beta group fibers (lemniscal) were unaltered. The topical application of a local anesthetic (2% procaine solution) to the dissected sciatic nerve in the cat was shown by Morillo, et al. (1963), to depress the response in the RF, while the response in the nucleus gracillis remained essentially unchanged.

Wall (1967) and Killam (1962) suggest that an understanding of pharmacological action depends upon knowledge of synaptic organiza-

tion and of the disruption of spatial and temporal synaptic arrangements rather than merely the number of connections per se. Nauta and Kuypers (1958), using the silver impregnation method (Nauta-Gygax), surmised that the reticular tegmentum abounded with short fiber Golgi type II cells, as hypothesized by Moruzzi, et al. (1949). Contrastingly, the Scheibels (Scheibel, et al., 1967), using Golgi preparations, found no evidence of polyneuronal chaining, although most reticular neurones were characterized by dense collateralization. Instead, the axonal outflow of these cells was found to consist of long conductors projecting rostrally or caudally for some distance along the neuroaxis. Many large and medium size cells were shown to bifurcate, coursing in both directions. Some of the ascending fibers extended as far as the diencephalon, especially the nonspecific thalamic nuclei, without synaptic interruption. Nakai and Domino (1969) have recently gathered physiological evidence suggesting that the integrity of the RF is maintained under alcohol and that reticular facilitation is mediated by the axonal system described by the Scheibels (Scheibel, et al., 1967). In normal animals, the visual evoked potential (VEP) to a single optic tract volley becomes enhanced following a conditioning train delivered to the midbrain reticular formation. Subanesthetic doses of pentobarbitol and accumulative amounts of ethyl alcohol suppressed the post-synaptic components of the test response but had little influence presynaptically. Under pentobarbital the post-synaptic components of the VER, as well as reticular facilitation of the cortical potential, although still observable, were damped. On the contrary, ethanol (1600 mg/kg) failed to alter the VEP to electrical stimulation of the RF but did lead to a

decrease of the cortical response. A release phenomenon apparently resulting from suppression of tonic peripheral inhibition, restoring the VEP towards control levels, was seen with anesthetic doses of pentobarbital (33 mg/kg) but not with coma producing doses of ethanol (3.2 g/kg) further distinguishing the effects of the two agents. If, on the other hand, brain stem inhibitory centers are presumed to be selectively blocked by alcohol, sensory potentials in the cord dorsum and neocortex might be expected to show some enhancement, as occurs following barbituratization (French, et al., 1953). No such potentiation was observed in the lateral funiculus or primary cortex of the cat after alcohol infusion (DiPerri, et al., 1968). Moreover, Takaori, Nakai and Sasa (1966) examined the influence of both reticular facilitation and reticular inhibition on the cortical evoked response. They found that reticular domination was abolished by pentobarbital, chlorpromazine and chloralose anesthesia but maintained under alcohol.

Where in the central nervous system alcohol exerts its most pronounced effect, be it the RF or the cerebral cortex, cannot be determined from scalp recordings alone. Nevertheless, inferences about the pathways involved in corticopetal transmission can be drawn from the gross response pattern. For a more complete discussion of the meaning of evoked response components, see Appendix V.

Independence of ER and EEG

It is now widely accepted that the electrical response recorded as spontaneous EEG, like evoked activity, arises from the summation of excitatory and inhibitory postsynaptic potentials (Eccles, 1951; Li and Jasper, 1953; Purpura, 1959). The failure of alcohol to alter the EEG

implies that the presynaptic influx as well as the spatial and temporal pattern of depolarization-hyperpolarization sequences remains undisturbed as was said of the primary discharge. Considered with the concomitant reduction of ER amplitude, this intimates that the drug acts upon distinct neural aggregates within the cortical neuropile and that the cell population committed to the generation of random potentials does not participate in the mediation of the vertex late components.

A decline in ER amplitude to a highly synchronized afferent volley (median nerve shock) could signify a reduction in the number of units firing, a change in the interspike interval or a weakening of the repetitive discharge. The result would be to limit the transcortical spread of information (Robson, 1967). Association, commissural or projection elements or any combination of the three may be involved (see Appendix V). The diminished output of one cell group could be confounded with direct blockage of input to subsequent neuronal stations. Whether the effect of alcohol is to actually decrease excitatory activity or to increase inhibitory drive, or both, cannot be said.

CHAPTER VIII

SUMMARY

Ethyl alcohol, acutely administered to normal subjects, is known to alter the electrical response of the brain. Potentials evoked by sensory stimulation generally show a monotonic decline in amplitude with increasing concentrations of alcohol in the blood. Spontaneous fluctuations show a biphasic effect with cortical activation obtaining at low blood alcohol concentrations (BAC's) and slowing or hypersynchrony prevailing at higher BAC's.

Two experiments were carried out to delimit the action of alcohol, in varying concentrations, on the different components of the somatosensory evoked response (ER). Responses evoked by median nerve stimulation were recorded from two scalp locations (perirolandic and vertex) before alcohol was given and during the ascending and descending limbs of the blood alcohol curve. Breath analyses to determine the content of alcohol in the blood were regularly performed. Prior to alcoholization ER's were found to be relatively invariant over time. Following the ingestion of low to moderate doses the initial spike and primary discharge specific to the postrolandic site were demonstrated to be fairly resistant to the depressive effects of alcohol. In contrast, the late components as well as the vertex slow waves became markedly attenuated. The amplitude of the triphasic vertex response was

shown to be extremely sensitive to alcohol, decreasing proportionately to the rising concentration of alcohol and returning to normal with the clearance of alcohol from the blood.

In a third experiment, action potentials recorded from the median nerve in the upper arm at high BAC's (145 mg%) were found to be indistinguishable from those obtained during a control period. Since peripheral neurophysiological events were not responsible for the drug effects seen at the cortex, attention was turned to specific ER and EEG parameters.

Examination of single unaveraged vertex potentials revealed considerable variation from trial-to-trial. Unfortunately, information about the variability of the individual responses that make up the average cortical response (ACR) is lost in the automatic summation process. Thus the possibility that an alcohol induced increase in the latency variability of certain components could account for the depression of the average cortical response remained. Furthermore, coincident with the changes taking place in the sensory evoked response, the spontaneous rhythms of the brain also undergo systematic alterations following alcohol consumption.

A fourth experiment was therefore conducted in order to determine to what extent the depression in the ACR was either an inverse function of peak latency variability or dependent on the changing EEG pattern.

Three hundred and twenty <u>single</u> vertex potentials evoked by somatic afferent stimulation were recorded from five subjects under three alcohol treatments: placebo (00-BAC), low dose (50-60 mg% BAC)

and high dose (95-119 mg% BAC). The individual ER's were then parcelled into forty subsamples of eight trials each. The mean and variance of the amplitude and latency of the large negative (N1) and positive (P2) components of the vertex response was computed for each sample. Evoked responses were also electronically averaged in corresponding sets of eight. Period analysis and amplitude integration of the EEG was performed on the 1 second epochs immediately preceding each stimulus pulse and also tallied in sets of eight. This procedure yielded a composite of fourteen quantitative ER and EEG parameters.

Analysis of variance of these data revealed that the amplitude of both the negative and positive waves of the ER decreased significantly with increasing alcohol concentrations. However, only the latency variability of the negative component showed a sharp increase. Of the EEG parameters measured, only the number of theta waves (4-7.5 Hz) decreased at the low BAC and then increased following the high alcohol load. The remaining ER and EEG parameters were uninfluenced by the drug. In order to establish the interrelationships among the selected electrophysiological variables as well as their predictive validity with respect to the amplitude of the ACR, a step-wise multiple regression analysis was performed. With this procedure the entire battery of ER and EEG parameters (predictors) was tested against the average amplitude of the N1 and P2 components (criteria) separately. The results disclosed that the amplitude of the single ER's explained most of the variance in the respective criteria (N1, P2). Peak latency variability also reliably contributed to the prediction of the N1 but not the P2 component. Evoked response latency as well as the EEG

parameters did not possess independent validity.

These data indicate that the reduction of the ACR is an effect best accounted for by the suppression of the mechanisms underlying the single ER which appear to be independent of the background EEG. The finding that an alcohol associated increase in the latency variability of the N1 component significantly improved prediction demonstrates the importance of peak variance for a full understanding of response depression.

APPENDIX 1

CORRELATION MATRICIES FOR EEG AND ER VARIABLES

S1 Placebo, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	-.06	.04	-.03	.03	.17	-.19	.09	.17	.07	.19	-.03	.10	-.14	.86
2		1.00	-.27	-.22	-.33	-.10	-.05	-.07	-.48	-.10	.03	-.04	-.03	.12	.01
3			1.00	.48	.32	-.05	-.09	-.04	.19	.08	-.01	.08	-.24	.19	-.01
4				1.00	.04	-.24	-.11	-.21	.04	-.01	.07	.07	-.07	.30	-.13
5					1.00	.51	.26	.13	.08	.10	-.48	-.04	.13	.22	-.10
6						1.00	.01	.08	-.13	.16	-.21	.18	.09	-.10	.07
7							1.00	.59	-.21	.00	-.45	-.10	.06	.10	-.15
8								1.00	-.17	-.07	-.27	-.19	.14	.15	-.02
9									1.00	.19	.36	-.07	.13	-.06	.21
10										1.00	-.07	.24	.08	.03	.05
11											1.00	.06	-.10	-.16	.27
12												1.00	-.29	.03	-.02
13													1.00	.38	-.07
14														1.00	-.30
15															1.00

S1, Low Dose, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.30	.35	.29	.14	.27	-.17	.16	.39	.09	-.02	.05	.01	-.40	.92
2		1.00	.02	.12	.01	.04	.03	.07	.00	.41	-.07	-.15	.06	.08	.25
3			1.00	.50	.33	.25	.01	.26	.05	-.15	.13	-.01	-.31	-.20	.20
4				1.00	.45	.36	-.07	-.03	.28	.02	-.11	-.10	.02	-.13	.15
5					1.00	.43	-.22	-.31	.03	.03	-.09	-.15	-.04	-.01	.06
6						1.00	.00	-.20	.23	.05	-.01	-.04	-.07	-.10	.22
7							1.00	.49	-.09	.08	-.27	.05	-.03	-.10	-.15
8								1.00	-.02	-.06	-.02	.22	.02	.09	.11
9									1.00	.01	.11	-.25	.14	-.15	.32
10										1.00	-.17	-.21	-.13	-.20	.07
11											1.00	.22	.14	.31	-.08
12												1.00	.00	.17	.01
13													1.00	.18	.05
14														1.00	-.44
15															1.00

S1, High Dose, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.34	.32	.23	-.09	.13	-.14	.12	-.18	-.14	.30	.06	-.12	-.19	.88
2		1.00	.06	.10	-.05	-.17	.23	.12	-.02	-.04	.22	.09	.01	.11	.32
3			1.00	.40	.39	.25	.31	.03	-.33	.06	-.04	.01	-.09	-.35	.36
4				1.00	.08	.31	-.08	-.04	-.08	-.20	.10	.31	.12	-.16	.16
5					1.00	.20	.29	-.01	-.17	.20	-.56	-.17	-.16	-.38	.05
6						1.00	.03	.12	.01	.10	.03	.26	.07	-.33	.15
7							1.00	.45	-.29	.28	-.36	-.20	.11	.05	-.04
8								1.00	-.13	-.03	.08	.20	.11	.07	.21
9									1.00	.09	.10	.19	.07	-.03	-.12
10										1.00	-.03	-.25	.06	.00	-.18
11											1.00	.47	.17	.11	.17
12												1.00	-.13	-.17	.05
13													1.00	.13	-.05
14														1.00	.35
15															1.00

S2, Placebo, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.15	.03	-.02	.15	.16	.10	-.12	-.03	-.09	-.17	.03	.01	-.07	.88
2		1.00	-.02	-.05	.04	.08	-.06	-.21	.00	-.11	-.07	.00	.06	-.06	.18
3			1.00	.41	.00	.20	.30	.06	-.17	.17	-.14	.02	.26	.20	-.01
4				1.00	-.22	-.02	.03	.11	-.17	.23	.13	-.05	-.15	-.27	-.04
5					1.00	.57	.19	.01	.19	-.04	-.50	.00	-.04	.14	.27
6						1.00	-.09	.19	.28	-.03	-.05	.08	-.04	-.02	.23
7							1.00	.46	.10	.20	-.54	-.06	.42	.28	-.04
8								1.00	.07	.17	-.25	-.28	.20	.06	-.04
9									1.00	.07	-.15	-.40	-.13	.10	-.08
10										1.00	-.04	-.27	-.11	-.05	-.10
11											1.00	.16	-.16	-.15	-.26
12												1.00	.08	-.20	-.03
13													1.00	.68	-.24
14														1.00	-.19
15															1.00

S2, Low Dose, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.02	.64	.34	-.01	.17	.35	.28	-.22	.20	-.16	-.22	.05	-.16	.91
2		1.00	.12	.05	.17	.24	.03	-.03	-.02	-.17	.02	.12	-.31	.08	.07
3			1.00	.49	.17	.28	.42	.09	-.10	.12	-.18	-.06	-.07	-.16	.61
4				1.00	.02	-.02	.24	.05	-.25	.26	-.13	-.30	.15	.15	.43
5					1.00	.12	.28	-.07	-.15	-.05	-.55	-.34	-.16	-.11	.04
6						1.00	.32	.27	-.01	-.23	-.25	.28	-.23	-.06	.19
7							1.00	.26	-.17	-.14	-.43	-.10	-.12	-.37	.43
8								1.00	-.12	-.18	-.07	.13	-.10	-.01	.23
9									1.00	.10	.29	.26	.05	.03	-.28
10										1.00	.12	-.34	.55	.23	.22
11											1.00	.15	.13	-.03	-.16
12												1.00	.00	-.02	-.26
13													1.00	.04	.03
14														1.00	-.10
15															1.00

S2, High Dose, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.28	.33	.19	.00	-.08	.02	.18	.06	.23	.20	-.08	-.13	-.06	.87
2		1.00	.11	.05	-.17	-.18	-.10	.04	.31	.08	.14	.05	-.33	-.07	.19
3			1.00	.12	.08	-.14	.15	.10	.08	.22	.04	-.01	-.22	-.27	.34
4				1.00	.07	-.05	-.06	.27	.14	.04	-.07	.04	-.13	.05	.14
5					1.00	.37	.09	.06	-.16	.23	-.39	-.04	.08	.06	.06
6						1.00	.27	.11	-.06	-.07	-.38	.18	.02	-.24	-.24
7							1.00	.40	-.21	.06	-.40	-.01	-.18	-.37	.05
8								1.00	.26	.35	.14	.08	-.12	-.15	.09
9									1.00	.19	.25	.20	-.07	.17	-.06
10										1.00	.21	-.10	-.14	-.08	.25
11											1.00	.11	.00	.08	.09
12												1.00	.05	-.07	-.24
13													1.00	.54	-.21
14														1.00	-.12
15															1.00

S3, Placebo, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	-.24	.23	-.08	-.11	-.09	-.01	.13	-.09	-.01	-.09	-.32	.21	-.03	.83
2		1.00	-.12	.06	.08	-.04	-.10	.07	.10	-.12	.17	.38	-.34	-.05	-.21
3			1.00	.22	.22	.25	.06	.05	.03	-.17	-.29	-.29	-.06	-.12	.02
4				1.00	.08	.33	.20	.34	-.17	.00	.04	.25	-.13	-.09	-.21
5					1.00	.37	-.29	-.19	.39	.04	-.29	.19	-.08	.15	-.08
6						1.00	-.38	-.19	.08	-.02	-.14	-.08	.22	.05	.04
7							1.00	.47	.09	.11	.13	-.04	-.28	.01	-.17
8								1.00	-.07	-.24	.29	.27	-.13	.00	-.05
9									1.00	.39	-.13	.02	-.23	.00	-.10
10										1.00	-.02	.08	.15	.03	-.13
11											1.00	.51	.30	.03	-.02
12												1.00	.00	-.10	-.24
13													1.00	.21	.30
14														1.00	-.04
15															1.00

S3, Low Dose, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.11	.16	.06	-.09	-.17	.15	.12	.25	.13	.13	-.14	-.14	-.29	.77
2		1.00	-.08	.05	-.04	.05	-.17	-.15	-.02	-.15	-.01	.10	.04	.32	.03
3			1.00	.28	.44	.11	.14	.01	.32	.13	.01	-.21	-.09	-.33	.22
4				1.00	.19	.48	-.11	-.20	-.14	-.01	-.09	-.16	-.01	0.02	.00
5					1.00	.15	-.08	-.18	-.10	.04	-.45	-.36	-.12	-.16	.01
6						1.00	-.17	-.12	-.30	-.02	.02	-.09	.11	.12	-.19
7							1.00	.44	.31	.05	-.10	.02	-.09	-.08	-.01
8								1.00	.09	-.01	-.02	.07	-.14	-.05	.19
9									1.00	.11	.17	.07	-.01	-.23	.20
10										1.00	-.04	-.16	.00	.18	.09
11											1.00	.55	-.06	-.22	.18
12												1.00	.04	.10	-.11
13													1.00	.63	-.49
14														1.00	-.50
15															1.00

S3, High Dose, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.18	.23	.27	.23	-.22	-.11	-.13	-.28	.16	-.27	-.28	-.22	-.05	.95
2		1.00	.10	.37	.32	.00	.05	.08	-.03	.20	-.08	.08	-.04	-.04	.19
3			1.00	.10	.30	-.21	.00	-.21	-.19	.11	-.30	-.22	.01	.27	.19
4				1.00	.02	.06	.08	.15	.06	.06	-.04	.06	-.15	-.25	.26
5					1.00	.27	.05	.21	-.11	.48	-.43	-.04	.00	.24	.20
6						1.00	.03	.00	.21	.03	.27	.51	.00	-.11	-.14
7							1.00	.16	.00	.05	.12	-.17	.05	-.04	-.13
8								1.00	-.03	.09	-.21	.02	.13	.28	-.20
9									1.00	.07	.24	.44	.01	-.05	-.23
10										1.00	-.17	.07	-.02	.03	.11
11											1.00	.53	.32	-.10	-.24
12												1.00	.13	-.10	-.24
13													1.00	.70	-.22
14														1.00	-.06
15															1.00

S4, Placebo, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.13	-.37	-.34	-.17	.00	-.08	-.08	.08	.05	.18	.25	.41	-.33	.94
2		1.00	-.04	-.04	.08	.15	.03	.05	.19	.10	-.20	.29	.22	-.11	.01
3			1.00	.22	.25	.18	.27	.25	.01	.13	-.16	-.06	-.08	.10	-.46
4				1.00	-.03	-.16	-.02	.16	.18	.14	-.05	-.18	-.14	-.12	-.30
5					1.00	.43	-.03	-.24	-.17	.04	-.25	.27	-.22	.19	-.19
6						1.00	.03	.03	.07	.23	.13	.13	.17	-.08	-.03
7							1.00	.23	.03	.22	-.24	-.15	-.12	-.01	-.15
8								1.00	-.06	.10	.17	.13	-.11	-.15	-.02
9									1.00	.22	.00	-.06	.26	.06	-.03
10										1.00	-.22	.04	.17	.08	.03
11											1.00	.35	.01	-.27	.30
12												1.00	-.05	-.15	.32
13													1.00	-.18	.31
14														1.00	-.46
15															1.00

S4, Low Dose, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.01	.02	-.09	-.05	-.16	.08	.10	-.05	.09	-.02	.19	-.29	-.08	.75
2		1.00	.27	-.07	-.05	.20	.02	.08	.09	.09	-.01	-.02	-.13	.11	.02
3			1.00	.20	.12	-.20	.05	.04	.49	.29	-.22	-.17	.15	.34	-.15
4				1.00	.06	.12	-.07	-.03	.05	.27	-.02	-.03	.13	-.05	-.29
5					1.00	.29	-.20	.21	-.25	.06	-.22	-.03	.15	.01	-.10
6						1.00	-.17	-.14	-.10	.09	.01	-.06	.04	.00	-.29
7							1.00	.58	.23	.20	-.34	-.17	-.08	-.01	-.14
8								1.00	.02	.43	-.25	.10	.07	-.08	.07
9									1.00	.32	-.20	-.02	.14	.46	-.23
10										1.00	-.23	.05	.17	-.03	-.02
11											1.00	.40	-.15	-.10	.24
12												1.00	-.18	-.01	.32
13													1.00	.31	-.46
14														1.00	-.37
15															1.00

S4, High Dose, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.13	-.06	-.24	.16	.27	.09	-.15	-.33	-.13	.05	.08	.20	.01	.84
2		1.00	.18	.17	-.15	-.14	.05	-.17	.30	.35	-.22	.16	.02	-.11	.02
3			1.00	.55	.48	-.07	-.09	.02	.05	.37	-.03	-.01	.50	.22	-.37
4				1.00	.21	-.03	-.16	-.12	.03	.10	.01	-.14	.22	.24	-.35
5					1.00	.28	-.08	.17	-.10	-.03	-.12	-.24	.00	-.10	.11
6						1.00	-.07	.04	-.17	-.32	-.10	-.09	.11	-.09	.19
7							1.00	.32	.02	-.15	-.32	.24	-.19	-.01	.17
8								1.00	.06	.00	.07	.01	-.09	-.28	-.02
9									1.00	.52	-.15	-.15	.05	-.03	-.28
10										1.00	-.04	-.20	.21	-.04	-.21
11											1.00	.18	.32	.05	.10
12												1.00	.07	-.02	.08
13													1.00	.14	-.04
14														1.00	-.09
15															1.00

S5, Placebo, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	-.18	-.19	-.12	.19	-.08	.21	-.21	.28	.44	-.18	-.22	.16	.09	.93
2		1.00	-.19	-.22	.05	-.05	.12	-.24	-.27	-.12	-.25	-.14	-.02	-.02	-.27
3			1.00	.61	.07	-.02	-.12	.13	-.23	.22	-.02	.01	.02	-.07	-.11
4				1.00	-.04	.05	-.25	.04	-.07	.30	.02	.19	-.14	.18	-.10
5					1.00	.51	.11	.00	.01	.16	-.43	-.22	.23	-.18	.26
6						1.00	-.04	.28	-.04	-.06	-.20	.10	-.08	-.09	-.03
7							1.00	.30	.26	-.02	-.32	-.42	-.04	.06	.16
8								1.00	.06	.03	-.22	.04	-.05	-.13	-.20
9									1.00	.22	.21	.05	-.02	.29	.27
10										1.00	-.03	-.16	-.09	-.10	.44
11											1.00	.59	.04	-.19	-.13
12												1.00	-.09	-.12	-.16
13													1.00	.01	.18
14														1.00	.01
15															1.00

S5, Low Dose, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.44	.32	-.04	.00	.22	-.12	.10	.08	-.17	.19	-.07	.13	.12	.93
2		1.00	.04	.03	-.19	.01	.08	-.22	.24	-.12	.24	-.02	.14	.21	.40
3			1.00	.19	.28	.43	-.32	-.07	-.25	.01	.09	.18	.12	.12	.33
4				1.00	-.18	.02	-.40	-.19	.06	-.15	.18	.05	.02	-.03	.02
5					1.00	.24	.04	.03	-.20	.00	-.49	-.24	-.33	-.06	.01
6						1.00	-.18	.09	-.16	.09	.02	.23	.07	.25	.12
7							1.00	.19	-.13	.11	-.47	-.31	-.18	-.17	-.09
8								1.00	-.16	.13	-.18	.06	.14	-.06	.06
9									1.00	.01	.22	.06	.01	-.05	.09
10										1.00	-.10	.19	.02	-.16	-.24
11											1.00	.43	.38	.17	.18
12												1.00	.09	.05	-.07
13													1.00	.41	.06
14														1.00	.00
15															1.00

S5, High Dose, P2

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	-.01	.25	-.04	-.09	-.06	-.14	.25	-.16	-.21	.05	.01	.11	-.37	.90
2		1.00	.08	.11	.22	.27	-.06	.08	.00	.20	-.07	.04	-.10	-.28	-.02
3			1.00	.08	.09	.10	.04	-.19	-.48	-.14	-.16	-.24	-.33	-.28	-.25
4				1.00	-.03	.46	.10	.08	-.02	.21	.17	.20	.05	-.09	.03
5					1.00	.49	.12	-.06	.19	.03	-.43	.04	-.01	-.08	.00
6						1.00	.15	.01	.16	.32	-.15	.34	-.08	-.10	-.01
7							1.00	.02	.14	.07	-.61	-.15	-.29	.08	-.05
8								1.00	.11	-.06	-.05	.24	-.07	-.15	.25
9									1.00	.23	.07	.22	.02	.44	-.21
10										1.00	.11	.33	-.13	.33	-.29
11											1.00	.37	.28	.03	-.07
12												1.00	.11	.07	-.05
13													1.00	.04	.10
14														1.00	-.47
15															1.00

APPENDIX 2

CORRELATION MATRICIES FOR EEG AND ER VARIABLES

S1, Placebo, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.17	-.26	-.22	-.03	.21	-.29	.00	.23	.02	.23	.04	.54	.05	.95
2		1.00	-.29	-.03	.03	.21	.12	.13	-.41	.04	-.13	.11	.20	.33	.18
3			1.00	.48	.32	-.05	-.09	-.04	.19	.08	-.01	.08	-.32	-.18	-.22
4				1.00	.04	-.24	-.11	-.21	.04	-.01	.07	.07	-.14	-.13	-.24
5					1.00	.51	.26	.13	.08	.10	-.48	-.04	-.09	-.06	-.01
6						1.00	.01	.08	-.13	.16	-.21	.18	.12	.01	.29
7							1.00	.59	-.20	.00	-.45	-.10	-.12	-.02	-.29
8								1.00	-.17	-.07	-.27	-.19	-.14	-.10	.01
9									1.00	.19	.36	-.07	.01	-.29	.21
10										1.00	-.08	.24	-.04	-.12	.02
11											1.00	.06	.01	-.06	.22
12												1.00	-.09	-.23	.05
13													1.00	.55	.51
14														1.00	.03
15															1.00

S1, Low Dose, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.55	-.06	-.04	.01	-.02	-.13	.20	.15	.09	-.17	-.02	.15	-.32	.85
2		1.00	.08	-.11	-.15	-.21	.09	.36	-.14	.17	-.11	-.07	-.04	-.23	.26
3			1.00	.50	.33	.25	.01	.26	.05	-.15	.13	-.01	-.21	-.01	-.21
4				1.00	.45	.36	-.07	-.03	.28	.02	-.11	-.10	-.22	-.11	-.05
5					1.00	.43	-.22	-.31	-.03	.03	-.09	-.15	-.32	-.09	-.04
6						1.00	.00	-.20	.23	.05	-.02	-.04	-.10	.03	-.04
7							1.00	.49	-.09	.08	-.27	.05	.25	.14	-.23
8								1.00	-.02	-.06	-.02	.22	.18	.10	-.02
9									1.00	.01	.11	-.26	.17	-.13	.24
10										1.00	-.17	-.21	.08	.12	.07
11											1.00	.22	-.11	.26	-.13
12												1.00	.24	-.02	.10
13													1.00	.17	.25
14														1.00	-.44
15															1.00

S1, High Dose, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.40	.10	.21	-.07	.00	-.22	.08	.04	-.21	.26	.17	-.06	-.29	.84
2		1.00	.10	.08	.09	-.22	.15	.04	.12	.03	.09	.10	-.15	.01	.20
3			1.00	.40	.40	.25	.31	.03	-.33	.06	-.04	.01	.40	-.07	.08
4				1.00	.08	.31	-.08	-.04	-.08	-.20	.10	.31	.20	.06	.16
5					1.00	.20	.29	-.01	-.17	.20	-.56	-.17	.45	.23	-.02
6						1.00	.03	.12	.01	.10	.03	.26	.17	.05	.03
7							1.00	.45	-.29	.28	-.36	-.20	.29	.04	-.11
8								1.00	-.13	-.03	.08	.20	.03	-.36	.13
9									1.00	.09	.10	.19	-.24	-.18	.10
10										1.00	-.03	-.25	-.01	.27	-.07
11											1.00	.47	-.30	-.18	.09
12												1.00	-.20	-.07	.05
13													1.00	.15	-.04
14														1.00	-.50
15															1.00

S2, Placebo, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.27	.06	.09	.21	.06	.20	-.07	-.08	-.08	-.28	.06	.21	-.19	.96
2		1.00	.37	-.19	-.11	-.04	.16	-.22	-.15	.11	-.13	.19	-.02	.09	.19
3			1.00	.41	.00	.20	.30	.06	-.17	.17	-.14	.02	-.14	-.21	.09
4				1.00	-.22	-.02	.03	.11	-.17	.23	.13	-.05	.25	-.03	.13
5					1.00	.57	.19	.01	.19	-.04	-.50	.02	-.17	-.24	.23
6						1.00	-.09	-.19	.28	-.03	-.05	.08	-.19	-.32	.12
7							1.00	.46	.10	.20	-.54	-.06	-.15	.04	.11
8								1.00	.07	.17	-.25	-.28	-.03	-.21	-.01
9									1.00	.07	-.15	-.40	-.44	-.09	.02
10										1.00	-.04	-.27	.02	.27	-.12
11											1.00	.16	.29	.22	-.29
12												1.00	.18	.15	-.01
13													1.00	.46	.11
14														1.00	-.36
15															1.00

S2, Low Dose, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.52	.55	.45	.11	.22	.31	.24	-.21	.17	-.08	-.29	-.03	-.10	.94
2		1.00	.19	.09	.17	.03	.15	-.02	-.07	-.21	-.06	-.08	-.17	-.01	.43
3			1.00	.49	.17	.28	.42	.09	-.10	.12	-.18	-.06	.00	-.12	.49
4				1.00	.02	-.02	.24	.05	-.25	.26	-.13	-.30	.06	-.18	.41
5					1.00	.12	.28	-.07	-.15	-.05	-.55	-.34	-.24	-.02	.11
6						1.00	.32	.27	-.01	-.23	-.24	.28	-.14	-.12	.31
7							1.00	.26	-.17	-.14	-.43	-.10	-.39	.07	.31
8								1.00	-.12	-.18	-.07	.13	.02	.04	.32
9									1.00	.10	.29	.26	-.11	.28	-.19
10										1.00	.12	-.34	.41	.11	.13
11											1.00	.15	.26	.16	-.07
12												1.00	-.04	.01	-.22
13													1.00	.13	-.06
14														1.00	-.24
15															1.00

S2, High Dose, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.43	.35	.09	-.04	-.34	.04	.10	.23	.24	.21	-.14	-.11	-.15	.89
2		1.00	.21	.12	-.16	-.03	-.15	.16	.51	.20	.25	.19	-.08	.06	.22
3			1.00	.12	.08	-.14	.15	.10	.08	.22	.42	-.01	-.23	.01	.37
4				1.00	.07	-.05	-.06	.27	.14	.04	-.07	.04	-.21	-.05	.00
5					1.00	.37	.09	.06	-.16	.23	-.39	-.04	-.03	.01	.06
6						1.00	.27	.11	-.06	-.07	-.38	.18	-.04	.23	-.34
7							1.00	.40	-.21	.06	-.40	-.01	-.02	.19	.06
8								1.00	.26	.35	.14	.08	.03	-.02	.06
9									1.00	.19	.25	.20	-.07	-.18	.13
10										1.00	.21	-.10	.06	-.32	.28
11											1.00	.10	-.10	-.20	.11
12												1.00	-.14	.22	-.20
13													1.00	-.39	.08
14														1.00	-.37
15															1.00

S3, Placebo, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.18	.06	-.27	-.19	-.25	.05	-.05	.07	.06	.00	-.09	-.12	-.13	.90
2		1.00	.32	-.04	.10	.07	-.12	-.09	.04	.16	-.10	.04	-.20	.28	.07
3			1.00	.22	.22	.25	.06	.05	.03	-.17	-.29	-.29	-.17	.11	.01
4				1.00	.08	.33	.20	.34	-.17	.00	.04	.24	-.04	-.02	-.33
5					1.00	.37	-.29	-.19	.39	.04	-.29	.19	-.12	-.02	-.10
6						1.00	-.38	-.18	.08	-.02	-.12	-.08	.15	-.29	-.17
7							1.00	.47	.09	.11	.13	-.04	-.05	.09	-.05
8								1.00	-.07	-.27	.29	.27	-.02	.10	-.03
9									1.00	.39	-.13	.02	.18	-.06	.07
10										1.00	-.02	.08	.06	.07	-.07
11											1.00	.51	.33	-.04	.06
12												1.00	.32	-.16	-.02
13													1.00	-.59	.12
14														1.00	-.43
15															1.00

S3, Low Dose, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.02	.09	.34	.08	-.01	-.07	.14	-.13	.14	.00	-.17	.10	-.43	.84
2		1.00	-.28	.23	-.07	.02	-.07	-.01	.13	.01	-.15	.17	.13	.31	-.13
3			1.00	.28	.44	.11	.14	.01	.32	.13	.01	-.21	.04	-.05	-.02
4				1.00	.19	.48	-.11	-.20	-.14	-.01	-.09	-.16	-.18	-.11	.20
5					1.00	.15	-.08	-.18	-.10	.04	-.45	-.36	-.16	-.02	.13
6						1.00	-.17	-.12	-.30	-.02	-.02	-.09	.05	-.24	.06
7							1.00	.44	.31	.05	-.10	.02	-.10	-.03	.07
8								1.00	.09	-.01	-.02	.07	.20	.30	.27
9									1.00	.11	.17	.07	.06	.14	-.18
10										1.00	-.04	-.16	-.07	.09	.05
11											1.00	.55	.38	-.15	-.08
12												1.00	.31	-.03	-.31
13													1.00	-.29	.10
14														1.00	-.63
15															1.00

S3, High Dose, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.46	.13	.34	.22	-.21	.07	-.11	-.18	.06	-.33	-.33	-.02	-.45	.92
2		1.00	.15	.48	.12	-.14	.12	.18	-.04	-.09	-.12	.06	-.03	-.03	.44
3			1.00	.10	.30	-.21	.00	.21	-.19	.11	-.30	-.22	.22	.03	.07
4				1.00	.02	.07	.08	.15	.06	.06	-.04	.06	.24	.10	.21
5					1.00	.27	.05	.21	-.11	.48	-.43	-.03	.11	-.05	.19
6						1.00	.03	.00	.21	.03	.27	.51	-.08	-.05	-.17
7							1.00	.16	.00	.05	.12	-.17	-.12	.18	.04
8								1.00	-.03	.09	-.21	.02	-.07	.19	-.18
9									1.00	.07	.24	.44	.08	.12	-.22
10										1.00	-.17	.07	.09	.26	-.10
11											1.00	.53	.02	.07	-.30
12												1.00	-.12	.08	-.29
13													1.00	-.04	-.04
14														1.00	-.58
15															1.00

S4, Placebo, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.43	.14	.01	-.04	.09	-.10	-.01	.30	.19	.05	.07	.05	.00	.90
2		1.00	.23	.17	.04	.14	.08	.12	.27	.18	-.06	.02	-.01	-.02	.42
3			1.00	.22	.25	.18	.27	.25	.01	.13	-.16	-.06	-.04	.08	-.04
4				1.00	-.03	-.16	-.02	.16	.18	.14	-.05	-.18	.06	.09	.03
5					1.00	.43	-.03	-.24	-.17	.04	-.25	.27	.07	-.01	-.13
6						1.00	.03	.03	.07	.23	.13	.13	.08	-.07	.02
7							1.00	.23	.03	.22	-.23	-.15	-.04	.11	-.16
8								1.00	-.06	.10	.17	.13	.10	-.25	.06
9									1.00	.22	.00	-.06	.19	.07	.26
10										1.00	-.21	.04	-.17	.21	.15
11											1.00	.35	.11	-.32	.17
12												1.00	.34	-.32	.13
13													1.00	-.58	.07
14														1.00	-.25
15															1.00

S4, Low Dose, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.43	.40	-.14	-.11	-.21	.02	.00	.43	.08	.01	.05	.25	-.18	.90
2		1.00	.44	-.15	-.10	-.16	.03	.07	.20	.16	-.01	-.13	.16	.04	.35
3			1.00	.19	.12	-.20	.05	.04	.50	.29	-.22	-.17	.21	.25	.25
4				1.00	.06	.11	-.07	-.03	.05	.27	-.02	-.03	-.06	.00	-.18
5					1.00	.29	-.20	.21	-.25	.06	-.22	-.03	-.41	.05	-.13
6						1.00	-.17	-.14	-.10	.09	.01	-.06	-.22	.11	-.23
7							1.00	.58	.23	.20	-.34	-.18	-.10	.32	-.15
8								1.00	.02	.43	-.25	.10	-.28	.24	-.13
9									1.00	.32	-.20	-.02	.24	.22	.37
10										1.00	-.28	.05	-.09	.05	.05
11											1.00	.40	.10	-.17	.14
12												1.00	-.06	-.21	.17
13													1.00	-.20	.36
14														1.00	-.38
15															1.00

S4, High Dose, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.45	-.05	-.32	.16	.32	.00	.02	-.21	.09	.01	-.08	.05	-.25	.88
2		1.00	-.05	-.07	.07	-.09	.12	.04	.11	.14	-.23	-.37	-.26	-.14	.41
3			1.00	.55	.48	-.07	-.09	.02	.05	.37	-.03	-.01	.08	.45	-.21
4				1.00	.21	-.03	-.16	-.12	.03	.10	.01	-.14	-.28	.19	-.34
5					1.00	.28	-.08	.17	-.10	-.03	-.12	-.24	-.01	.13	.15
6						1.00	-.07	.04	-.17	-.32	-.10	-.09	-.07	.02	.28
7							1.00	.32	.02	-.15	-.32	.24	.20	-.02	.02
8								1.00	.06	.00	.07	.01	.06	.06	.04
9									1.00	.52	-.15	-.15	.04	.14	-.07
10										1.00	-.04	-.20	.03	-.05	.12
11											1.00	.18	-.19	-.05	.04
12												1.00	.18	.05	-.07
13													1.00	.00	.02
14														1.00	-.51
15															1.00

S5, Placebo, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.01	-.13	.07	.15	.09	.07	-.26	.14	.17	-.27	-.10	-.08	-.33	.94
2		1.00	-.42	-.35	-.27	-.12	.07	.01	-.13	-.20	-.16	-.01	.29	.19	.04
3			1.00	.61	.07	-.02	-.12	.13	-.21	.22	-.02	.01	-.08	.04	-.06
4				1.00	-.04	.05	-.25	.04	-.07	.30	.02	.19	-.28	-.06	.06
5					1.00	.51	.11	.00	.01	.16	-.43	-.22	-.13	-.10	.16
6						1.00	-.04	.28	-.04	-.06	-.20	.10	-.16	-.03	.04
7							1.00	.30	.26	-.02	-.32	-.42	-.02	-.19	.13
8								1.00	.06	.03	-.22	.04	-.13	.05	-.24
9									1.00	.22	.21	.05	.00	-.11	.15
10										1.00	-.03	-.16	-.08	-.08	.22
11											1.00	.59	.00	.16	-.30
12												1.00	-.12	.08	-.15
13													1.00	.34	-.12
14														1.00	-.50
15															1.00

S5, Low Dose, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.68	.29	-.13	.15	.10	-.19	-.06	.03	-.18	.10	-.08	.10	-.09	.96
2		1.00	.01	-.01	-.13	-.08	-.13	.07	.03	-.19	.07	-.07	.19	.07	.60
3			1.00	.19	.28	.43	-.32	-.07	-.25	.01	.09	.18	.05	-.18	.33
4				1.00	-.18	.02	-.40	-.19	.06	-.15	.19	.05	.06	.19	-.04
5					1.00	.24	.04	.03	-.20	.00	-.49	-.24	-.06	-.22	.15
6						1.00	-.18	.02	-.16	.09	.02	.23	.00	-.08	.13
7							1.00	.19	-.13	.11	-.47	-.31	-.24	-.20	-.21
8								1.00	-.16	.13	-.18	.06	.07	-.23	-.06
9									1.00	.01	.22	.06	-.19	.45	-.03
10										1.00	-.10	.19	.02	.19	-.20
11											1.00	.43	.22	.18	.08
12												1.00	-.09	.33	-.12
13													1.00	-.24	.10
14														1.00	-.23
15															1.00

S5, High Dose, N1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1.00	.37	.13	-.26	-.05	-.12	-.08	.28	-.03	-.17	-.02	-.01	.07	.07	.90
2		1.00	.24	-.14	.32	.10	-.13	.10	-.18	-.10	-.07	-.06	-.24	.49	.35
3			1.00	.08	.09	.10	.04	-.19	-.48	-.14	-.16	-.24	-.33	.44	.10
4				1.00	-.03	.46	.10	.08	-.02	.21	.17	.20	.11	-.09	-.16
5					1.00	.49	.12	-.06	.19	-.03	-.43	.04	-.24	.30	-.05
6						1.00	.15	.01	.16	.32	-.15	.34	-.17	.16	-.06
7							1.00	.02	.14	.07	-.61	-.15	-.08	-.08	.00
8								1.00	.11	-.06	-.05	.24	.10	.01	.30
9									1.00	.23	.07	.22	.13	-.04	.00
10										1.00	.11	.33	.02	-.03	-.20
11											1.00	.37	.08	-.10	.00
12												1.00	.22	-.24	-.07
13													1.00	-.48	.02
14														1.00	.04
15															1.00

APPENDIX 3

SUMMARY OF MULTIPLE REGRESSION ANALYSIS
WITH P2 AS THE CRITERION

S1, Placebo, P2

Step number	Variable entered	Multiple R	RSQ	Increase in RSQ	F Value
1	1	.8597	.7391	.7391	107.62
2	14	.8787	.7721	.0330	5.36
3	13	.8838	.7811	.0090	1.48
4	5	.8874	.7875	.0065	1.07
5	9	.8912	.7942	.0067	1.10
6	2	.8969	.8044	.0102	1.17
7	7	.9007	.8112	.0069	1.16
8	8	.9047	.8185	.0073	1.25

Summary Table

S1, Low Dose, P2

Step number	Variable entered	Multiple R	RSQ	Increase in RSQ	F Value
1	1	.9179	.8425	.8425	203.33
2	3	.9269	.8592	.0167	4.38
3	14	.9313	.8674	.0082	2.22
4	4	.9341	.8725	.0051	1.39
5	10	.9355	.8752	.0027	.75
6	12	.9366	.8772	.0029	.54
7	9	.9381	.8801	.0005	.76
8	6	.9384	.8806	.0009	.12

Summary Table

S1, High Dose, P2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.8770	.7692	.7692	126.64
2	14	.8958	.8024	.0332	6.22
3	8	.9046	.8183	.0159	3.15
4	11	.9070	.8227	.0043	.85
5	13	.9105	.8290	.0064	1.27
6	4	.9128	.8332	.0042	.83
7	10	.9157	.8385	.0052	1.04
8	2	.9183	.8433	.0049	.96

Summary Table

S2, Placebo, P2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.8774	.7699	.7699	127.15
2	13	.9131	.8337	.0638	14.19
3	11	.9263	.8580	.0243	6.17
4	7	.9354	.8749	.0169	4.72
5	14	.9367	.8774	.0025	.70
6	6	.9380	.8798	.0024	.66
7	8	.9397	.8830	.0031	.85
8	2	.9415	.8865	.0035	.96

Summary Table

S2, Low Dose, P2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.9118	.8314	.8314	187.45
2	4	.9206	.8476	.0161	3.91
3	7	.9266	.8585	.0109	2.78
4	14	.9285	.8621	.0036	.91
5	9	.9300	.8650	.0029	.73
6	11	.9327	.8699	.0049	1.24
7	8	.9344	.8732	.0033	.84
8	5	.9354	.8749	.0017	.42

Summary Table

S2, High Dose, P2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.8690	.7551	.7551	117.19
2	12	.8869	.7867	.0315	5.47
3	6	.8990	.8081	.0215	3.85
4	11	.9095	.8271	.0190	2.87
5	14	.9168	.8406	.0135	2.88
6	5	.9238	.8534	.0128	1.59
7	2	.9276	.8604	.0070	.90
8	13	.9297	.8443	.0039	.66

Summary Table

S3, Placebo, P2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.8286	.6866	.6866	83.26
2	3	.8477	.7186	.0320	4.21
3	8	.8625	.7439	.0253	3.56
4	10	.8839	.7813	.0374	5.98
5	13	.8909	.7936	.0123	2.03
6	9	.8949	.8008	.0072	1.19
7	6	.8979	.8062	.0054	.88
8	12	.9008	.8115	.0053	.87

Summary Table

S3, Low Dose, P2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.7718	.5958	.5958	56.00
2	13	.8621	.7432	.1475	21.25
3	7	.8756	.7666	.0234	3.60
4	8	.8861	.7851	.0185	3.02
5	3	.8919	.7954	.0103	1.70
6	4	.8949	.8008	.0054	.89
7	2	.8958	.8024	.0016	.26
8	6	.8965	.8038	.0013	.20

Summary Table

S3, High Dose, P2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.9458	.8945	.8945	322.11
2	8	.9489	.9005	.0060	2.23
3	6	.9516	.9055	.0050	1.90
4	10	.9525	.9072	.0018	.67
5	2	.9531	.9084	.0012	.44
6	11	.9534	.9091	.0006	.23
7	5	.9542	.9105	.0014	.52
8	14	.9548	.9117	.0012	.42

Summary Table

S4, Placebo, P2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.9383	.8803	.8803	279.54
2	14	.9512	.9047	.0244	9.46
3	3	.9592	.9200	.0153	6.88
4	2	.9663	.9337	.0137	7.24
5	12	.9724	.9445	.0118	7.34
6	9	.9736	.9470	.0024	1.50
7	8	.9743	.9493	.0014	.90
8	7	.9753	.9512	.0020	1.24

Summary Table

S4, Low Dose, P2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.7512	.5643	.5643	49.22
2	14	.8144	.6033	.0990	10.88
3	4	.8501	.7226	.0593	7.69
4	7	.8783	.7714	.0488	7.47
5	6	.8973	.8051	.0336	5.87
6	13	.9096	.8274	.0223	4.26
7	8	.9196	.8456	.0182	3.78
8	11	.9277	.8607	.0151	3.35

Summary Table

S4, High Dose, P2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.8403	.7061	.7061	91.32
2	3	.8979	.8063	.1002	19.13
3	5	.9101	.8283	.0220	4.62
4	6	.9167	.8403	.0120	2.63
5	8	.9199	.8461	.0058	1.28
6	11	.9217	.8495	.0034	.74
7	7	.9247	.8550	.0055	1.22
8	4	.9262	.8578	.0028	.61

Summary Table

S5, Placebo, P2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.9312	.8671	.8671	247.98
2	2	.9371	.8782	.0111	3.38
3	5	.9420	.8874	.0091	2.92
4	14	.9438	.8907	.0034	1.07
5	8	.9451	.8932	.0025	.80
6	3	.9459	.8947	.0015	.46
7	4	.9466	.8967	.0013	.40
8	12	.9477	.8781	.0021	.64

Summary Table

S5, Low Dose, P2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.9270	.8594	.8594	232.40
2	14	.9346	.8734	.0141	4.11
3	10	.9402	.8838	.0104	3.21
4	3	.9415	.8864	.0026	.80
5	6	.9437	.8906	.0042	1.30
6	4	.9441	.8914	.0008	.24
7	7	.9449	.8929	.0015	.45
8	12	.9456	.8941	.0012	.35

Summary Table

S5, High Dose, P2

Step number	Variable entered	Multiple R	RSQ	Increase in RSQ	F Value
1	1	.8955	.8019	.8019	153.87
2	14	.9074	.8233	.0214	4.48
3	11	.9128	.8332	.0099	2.14
4	4	.9151	.8374	.0041	1.89
5	10	.9179	.8425	.0052	1.12
6	2	.9192	.8429	.0024	.51
7	5	.9197	.8459	.0009	.19
8	3	.9202	.8468	.0009	.18

APPENDIX 4

SUMMARY OF THE MULTIPLE REGRESSION ANALYSIS
WITH N1 AS THE CRITERION

S1, Placebo, N1

Step number	Variable entered	Multiple R	RSQ	Increase in RSQ	F Value
1	1	.9463	.8954	.8954	325.37
2	6	.9507	.9039	.0084	3.24
3	5	.9517	.9057	.0018	.69
4	3	.9537	.9096	.0039	1.53
5	4	.9545	.9111	.0015	.57
6	2	.9549	.9119	.0008	.30
7	10	.9551	.9122	.0004	.13
8	14	.9553	.9127	.0004	.15

Summary Table

S1, Low Dose, N1

Step number	Variable entered	Multiple R	RSQ	Increase in RSQ	F Value
1	1	.8498	.7221	.7221	98.73
2	2	.8860	.7849	.0629	10.81
3	14	.9066	.8220	.0370	7.49
4	13	.9165	.8400	.0180	3.94
5	8	.9232	.8522	.0123	2.82
6	5	.9285	.8611	.0100	2.39
7	12	.9320	.8685	.0063	1.54
8	10	.9337	.8719	.0033	.80

Summary Table

S1, High Dose, N1

Step number	Variable entered	Multiple R	RSQ	Increase in RSQ	F Value
1	1	.8435	.7114	.7114	93.69
2	14	.8871	.7870	.0756	13.13
3	10	.9039	.8171	.0301	5.92
4	11	.9209	.8480	.0310	7.13
5	2	.9298	.8645	.0165	4.14
6	4	.9323	.8691	.0046	1.16
7	3	.9354	.8749	.0058	1.48
8	8	.9362	.8764	.0015	.37

Summary Table

S2, Placebo, N1

Step number	Variable entered	Multiple R	RSQ	Increase in RSQ	F Value
1	1	.9558	.9136	.9136	401.63
2	14	.9718	.9444	.0308	20.50
3	7	.9739	.9485	.0041	2.86
4	8	.9756	.9517	.0032	2.35
5	9	.9766	.9537	.0019	1.42
6	3	.9774	.9553	.0017	1.24
7	2	.9780	.9565	.0012	.86
8	11	.9784	.9572	.0007	.53

Summary Table

S2, Low Dose, N2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.9393	.8823	.8823	284.78
2	14	.9510	.9045	.0222	8.59
3	8	.9572	.9163	.0118	5.09
4	4	.9592	.9201	.0038	1.68
5	3	.9607	.9230	.0029	1.27
6	9	.9621	.9255	.0025	1.13
7	2	.9630	.9274	.0019	.83
8	5	.9636	.9286	.0012	.51

Summary Table

S2, High Dose, N2

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.8890	.7903	.7903	143.25
2	14	.9222	.8505	.0602	14.89
3	2	.9332	.8708	.0203	5.66
4	13	.9381	.8800	.0092	2.68
5	3	.9443	.8917	.0117	3.67
6	11	.9468	.8965	.0048	1.52
7	4	.9497	.9019	.0054	1.75
8	5	.9506	.9036	.0018	.57

Summary Table

S3, Placebo, N1

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.8966	.8039	.8039	155.80
2	14	.9508	.9040	.1001	38.55
3	4	.9568	.9155	.0115	9.91
4	10	.9617	.9248	.0093	4.35
5	5	.9641	.9294	.0046	2.21
6	8	.9676	.9363	.0069	3.57
7	11	.9692	.9393	.0030	1.56
8	7	.9703	.9415	.0022	1.17

Summary Table

S3, Low Dose, N1

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.8368	.7003	.7003	88.78
2	14	.8898	.7917	.0914	16.23
3	12	.9120	.8317	.0400	8.56
4	3	.9229	.8517	.0800	4.72
5	7	.9319	.8684	.0168	4.33
6	5	.9353	.8749	.0164	1.70
7	11	.9371	.8782	.0033	.87
8	8	.9388	.8813	.0031	.81

Summary Table

S3, High Dose, N1

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.9241	.8539	.8539	222.10
2	14	.9422	.8877	.0338	11.12
3	10	.9473	.8974	.0097	3.42
4	4	.9499	.9023	.0049	1.77
5	2	.9521	.9065	.0042	1.51
6	8	.9536	.9093	.0028	1.04
7	5	.9545	.9111	.0017	.63
8	3	.9551	.9122	.0011	.40

Summary Table

S4, Placebo, N1

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.9003	.8105	.8105	162.57
2	14	.9343	.8730	.0624	18.18
3	13	.9463	.8954	.0225	7.74
4	3	.9565	.9148	.0194	7.96
5	4	.9613	.9241	.0092	4.73
6	2	.9621	.9256	.0015	.67
7	5	.9629	.9271	.0016	.69
8	12	.9639	.9291	.0020	.86

Summary Table

S4, Low Dose, N1

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.8957	.8024	.8024	154.26
2	14	.9222	.8505	.0481	11.91
3	13	.9278	.8608	.0103	2.67
4	12	.9324	.8694	.0085	2.28
5	7	.9354	.8750	.0057	1.54
6	4	.9375	.8788	.0038	1.04
7	9	.9395	.8826	.0038	1.02
8	3	.9417	.8866	.0040	1.08

Summary Table

S4, High Dose, N1

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.8800	.7744	.7744	130.45
2	14	.9295	.8641	.0896	24.40
3	9	.9397	.8831	.0190	5.87
4	5	.9429	.8890	.0059	1.87
5	3	.9464	.8957	.0066	2.15
6	12	.9485	.8997	.0040	1.33
7	11	.9498	.9021	.0024	.79
8	7	.9500	.9024	.0003	.09

Summary Table

S5, Placebo, N1

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.9436	.8903	.8903	308.47
2	14	.9643	.9299	.0396	20.92
3	3	.9663	.9338	.0039	2.11
4	4	.9684	.9378	.0040	2.26
5	10	.9696	.9401	.0023	1.30
6	6	.9704	.9416	.0015	.84
7	11	.9706	.9411	.0005	.28

Summary Table

S5, Low Dose, N1

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.9546	.9112	.9112	390.14
2	14	.9657	.9326	.0214	11.74
3	4	.9726	.9460	.0134	8.92
4	2	.9739	.9485	.0025	1.68
5	13	.9747	.9500	.0015	1.03
6	5	.9750	.9507	.0007	.46
7	10	.9753	.9513	.0006	.39
8	3	.9756	.9519	.0006	.38

Summary Table

S5, High Dose, N1

Step number	Variable entered	Multiple R	Multiple RSQ	Increase in RSQ	F Value
1	1	.8995	.8091	.8091	161.05
2	7	.9021	.8138	.0047	.94
3	11	.9047	.8184	.0046	.90
4	12	.9076	.8238	.0054	1.07
5	6	.9116	.8311	.0073	1.47
6	8	.9148	.8369	.0058	1.17
7	10	.9162	.8394	.0025	.51
8	14	.9173	.8414	.0020	.39

APPENDIX V

THE MEANING OF EVOKED RESPONSE COMPONENTS

The changes seen in the evoked response waveform following drug administration bear directly upon theories regarding the underlying neural substrate. The finding that the functional capacity of the RF is maintained while the postsynaptic components of the VEP show marked attenuation verifies the action of alcohol on the responsivity of cortical neurons (Nakai, et al., 1969). These data, coupled with our description of the diminishing late components of the human scalp response, seriously question the supposition that long latency potentials are conveyed cephalad via extralemniscal and reticular relays. With particular reference to the surface vertex response there is a growing literature from neuropathology which undermines the validity of the dual projection hypothesis alluded to earlier (see introduction Experiment I). Liberson (1966) and Liberson and Scott (1964) recording bilaterally from aphasic patients found that somatosensory evoked responses (SER's) when absent or reduced on the damaged side were similarly depressed on the normal side. They also noticed that when responses to shock stimuli were attenuated, visual or auditory stimulation could still evoke long latency responses at the same locus of the affected hemisphere. Liberson (1966) concluded that his results were incompatible with the notion that the late components were representative of a dif-

fuse bilateral projection and that ipsilateral responses were most likely initiated by interhemispheric transfer in the corpus callosum or other commissural structures. Further, Williamson, Goff and Allison (1970), studying patients with unilateral parietal lesions accompanied by severe sensory loss, were unable to detect evoked activity over either hemisphere when the affected side was stimulated. They maintain that lemniscal activity reaching the primary cortex is the major source of most components of the mass evoked response. Support for this view comes from the work of Domino, Matsuoka, Waltz and Cooper (1965). These investigators used cryogenic lesions of selected thalamic nuclei to relieve dyskinesic patients of incapacitating motor symptoms. Cortical ER's were recorded both epidurally and from the scalp over the somatosensory area prior to and during the cooling procedure. Lesions confined to the nucleus ventralis (VL) had no effect on the ER. However, freezing of the VL with encroachment on the nucleus ventralis posteriolateralis (VPL) did produce a slight decrease of evoked activity. Only after a massive assault of VPL involving the ventral posteriormedial nucleus (VPM) and possibly some centre median nucleus (CM) was a sharp reduction of all ER components observed. Since the VPL nuclear group is the final destination of lemniscal and spinothalamic afferents these results may be taken to mean that most SER components are transmitted in classical sensory pathways.

Even though an extralemniscal route does not appear critical for the genesis of some long latency components, Goff (1970) reminds us that Domino, et al. (1965), analyzed only the first 125 msec. of the response. Several other components, including the vertex spike, have

latencies in excess of 125 msec. What then are the neural elements that give rise to these late occurring potentials? Recently Stohr and Goldring (1969) had the occasion to excise the sensory hand area of three patients suffering from intractable epileptic seizures. They recorded SER's both before and up to 18 months after surgery. Post-operative vertex potentials, for that matter all evoked activity to median nerve stimulation, was virtually abolished. Stimulation of either peroneal nerve, however, elicited the typical response, the leg area being intact. The authors emphasize the necessity of the primary somatic cortex for the generation of all ER components. Vaughn (1968) has also obtained evidence suggesting that vertex potentials, regardless of the modality stimulated, arise secondarily to cellular discharge in the appropriate sensory receiving area. Based on principles of volume conduction and known physioanatomical properties of the brain and its coverings, Vaughn was able to predict the distribution of intracranial sources of the slow (P200) response. His estimates conformed favorably to empirically derived current field maps. Comparisons between trans-cortical and referential recordings also indicate that remote pick-up is often nonpropagated activity (Kelly, Goldring and O'Leary, 1965). Nevertheless, the origin of many long latency components cannot easily be reconciled by models formed solely on principles of volume conduction. First, mention should be made of the fact that the multimodal vertex potential is considerably larger in amplitude than the corresponding primary cortical response. From volume conduction theory an exponential decay with increasing distance from the active locus would be expected. The apparent potentiation of the auditory vertex response,

according to Vaughn, results from bilateral cochlear representation following binaural stimulation. However, since there is little or no ipsilateral input to unilateral somatic stimulation, such an assumption seems unwarranted. Moreover, volume conductor theory encounters great difficulty in attempting to explain such phenomena as the disappearance of the late components following drug administration, when the presumed source (primary cortex) remains fully operational. Also, the magnitude of the single vertex potentials (see Figure 12) reliably recorded in experiment IV clearly rules out the possibility of volume conduction. Finally, Williamson, et al. (1970), have observed a latency discrepancy between the contralateral and ipsilateral vertex positivity, the latter being about five msec. longer. This was true of both somesthetic and auditory ER's and is indicative of a short latency transfer of inter-hemispheric information.

Input-Output Relationships

Implicit in the foregoing discussion is the idea that the late scalp recorded components evince as a consequence of sensory registration in primary cortical receiving areas. The ineffectiveness of alcohol for the modification of the early components attests to the soundness of the lemniscal system and primary cortex at moderate BAC's. It has been known for some time (Cajal, 1911) that the terminals of specific thalamic afferents ramify to form a dense plexus in the fourth cortical layer (granule). Here they make synaptic contact with interclated Golgi type II neurons which in turn make numerous connections with local stellate cells. The discharge of the later cell group excites many small and medium size pyramids in layers II and III, the arbors of which run

parallel with the apical dendrites of the large pyramids of the fifth layer. This circuit, however, is not exclusive for the reception of sensory signals upon apical shafts. Following the destruction of relevant corticopetal afferent systems (e.g., geniculocalcarine radiations) the Scheibels (Scheibel and Scheibel, 1970) have observed degeneration of spines (gemules) along the dendrites of the deep pyramids. The loss of spines revealed a definite pattern with respect to the input source. Spine counts showed that presynaptic termini of specific radiations were concentrated in the middle two-thirds (near the soma) of the apical dendrites. Projections from the axial brain stem and nonspecific thalamus ended along the entire span of the apical shaft. The oblique branches received commissural input whereas the recurrent collaterals of the pyramids synapsed on the horizontally situated baselar dendrites.

Based on intracellular synaptic activity recorded simultaneously with the surface ER to electrical stimulation of the thalamus, Creutzfeldt, Watanabe and Lux (1966) and Creutzfeldt and Kuhnt (1967) have advanced a model of ER electrogenesis. They sought to relate the various deflections of the surface ER to cellular activation and potential spread across the soma-dendritic membrane. It was shown that epicortical positivity corresponded to primary excitation (the EPSP). This obtains when a synchronous volley ascending in specific afferent fibers arrives at or near the soma membrane. A secondary EPSP arising from activation of nonspecific afferents terminating more superficially on the dendritic shaft subserves the initial surface negative peak. During this phase an IPSP due to activity in recurrent collaterals develops at the soma. Associated with the IPSP and resulting cell polarization is

the second cortical positive wave. Oscillatory asynchronous depolarization of the whole neuronal membrane and cessation of afferent input with the return of the resting potential was postulated as the electromotive force underlying the after-discharge as well as spontaneous spindle waves.

The hypothetical potential distribution put forth by Creutzfeldt and his associates (Creutzfeldt, et al., 1967) satisfactorily accounts for components arising from thalamic input to vertically oriented cortical elements (pyramidal cells). It does not consider components of intracortical origin. The axons of pyramidal cells, which constitute the chief outflow from the sensory cortex, can be subdivided into those that 1) enter the underlying white matter, 2) course upwards and may reach the molecular layer, and 3) branch profusely in the vicinity of the parent cell. All are characterized by extensive recurrent collaterals (c.f. Crosby, Humphrey and Lauer, 1962). Of the first group the larger cells give rise to A) association, B) commissural and C) projection fibers.

Association Fibers

Short association bundles may interconnect adjoining gyri within the same area or may pass from one lobe to another within the same hemisphere. Although parasensory areas integrate activity relayed from adjacent primary fields, it is probably only polysensory association regions that mediate certain long latency components (vertex spike). In this regard Jones and Powell (1970) have shown that from each of the main sensory areas there is an outward stepwise progression directed toward the frontal and parietotemporal cortices. It is here where the

three modalities (auditory, visual, somatosensory) ultimately converge. It is conceivable that such a system participates in the elaboration of some late components. Fascicles from long association bundles which interrelate vastly separated regions of the cortex might also serve this purpose.

Commissural Fibers

Interhemispheric communication via commissural transfer has already been implicated as subserving the late vertex response (Goff, 1969). Callosal fibers take their origin from cells of almost all cortical layers but predominantly from the short pyramids of the third, fifth and sixth laminae (for a review, see Comming, 1970). In addition, callosal fibers arise as collaterals from long association and projection tracts. It is through these fibers that heterologous points of the opposite hemisphere become connected. Such a meshwork provides for the interlocking of discrete sensory systems and for interhemispherical association. Curtis (1940a, 1940b) was able to show that stimulation localized to one side could produce wide spread potentials on the contralateral hemisphere. Degenerating terminals following total section of the corpus callosum, and anterior and hippocampal commissures have been identified in premotor cortex and inferior parietal lobule as well as visual and somasthetic association areas (McCulloch and Garol, 1941; Jacobson and Marcus, 1970). The density of terminal degeneration was greatest in layer IV of the primate neocortex whereas intracortical association axons find their way to supragranular layers.

Projection Fibers

Cortical output to remote nuclear sites, like association and commissural pathways, is far too extensive to make more than brief mention of those projections that conceivably take part in the mediation of evoked slow activity. A massive descending system which originates along the sensorimotor strip but elongates to include adjacent cortical fields terminates extensively in medullopontine and mesencephalic tegmental nuclei. From these structures a dorsal leaf ascending into the intralaminar thalamic feltwork and a ventral leaf projecting through the subthalamus and ventrolateral hypothalamus form two powerful cortico-reticular-cortical loops (Brodal, 1969; Scheibel and Scheibel, 1967). While the final relays between nonspecific thalamus and cortex remain elusive, the inferior thalamic peduncle is known to provide a potent reciprocal pathway between the ventral anterior thalamic nucleus (VA) and the orbital cortex. The demonstration by Skinner and Lindsley (1967) that lesions or local freezing of the nucleus VA, inferior thalamic peduncle or orbital cortex led to the abolition of recruiting responses indicates that the VA may serve as the last link. This may not be the only route though; the Scheibels (Scheibel, et al., 1967) refer us to the complexity of nonspecific-specific thalamic interactions. The pathways involved in dispersing potentials from orbitofrontal regions to the remainder of the cortex have yet to be determined but cortico-cortical associations, as already described, might be indicated.

Comment

With all afferent (corticopetal) channels apparently intact following alcohol loading, the output of cortical pyramidal cells is

briefly explored for possible clues relating to the depression of the late components and the pathways underlying them. Whether direct or indirect cortico-cortical connections, interhemispheric exchange, cortical-subcortical loops or combinations of these constitute the crucial circuitry can, at the moment, only be speculated.

An electrode superficially placed over the saggittal fissure would seem ideally situated to monitor interhemispheric crosstalk. The amplitude distribution of the vertex positivity corresponds well to the points of maximum projection of the different modalities across the midline (Sunderland, 1940), the visual evoked response having a more posterior gradient (Goff, 1969). This might help explain the striking similarity between auditory and somatosensory vertex potentials, which differ slightly from the waveform evoked by light stimuli and at the same time circumvent the issue of convergence altogether. Goff (1969) points out that classical vertex potentials can only be recorded from man and possibly some primates and that the size of the corpus callosum parallels the phylogenetic development of the neopallium. This argument, of course, holds for the expansion of association cortices as well. The long latencies and delicate sensitivity of certain of these long latency components indeed suggest a plurisynaptic associational system. Simple sensory or perceptual capabilities as measured by a variety of psychological tests have been found to be quite resistant to alcohol showing detrimental effects only at fairly high BAC's (see Wallgren, 1970 for a review). However, tests that require sensory-motor coordination, even highly practiced skills such as ocular-motor responses, are extremely sensitive to alcohol. Generally speaking per-

formance worsens with increasing task difficulty and increasing BAC.

A decline in ER amplitude to a highly synchronized afferent volley (median nerve shock) could signify a reduction in the number of units firing, a change in the interspike interval or a weakening of the repetitive discharge. The result would be to limit the transcortical spread of information (Robson, 1967). Association, commissural or projection elements or any combination of the three may be involved. The diminished output of one cell group could be confounded with direct blockage of input to subsequent neuronal stations. Whether the effect of alcohol is to actually decrease excitatory activity or to increase inhibitory drive or both, cannot be said.

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