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## NEURORADIOLOGICAL AND NEUROPHYSIOLOGICAL EVIDENCE OF BRAIN DEFICITS IN CHRONIC ALCOHOLICS

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The advent of computerized tomography (CT) has greatly facilitated the assessment of brain lesions. In the last few years, CT studies have been conducted to examine the nature of structural aberrations in the brains of alcoholic patients. *Fox et al.* (1976) used the CT-Scan to study hospitalized alcoholic patients. They reported significantly increased ventricular size in alcoholic patients when compared to normal control subjects. These authors report the incidence of ventricular enlargement to occur in 33 percent of their patients. *Carlen et al.* (1976) reported that all of the alcoholic patients they studied demonstrated neuroradiological evidence of cortical atrophy. *Epstein et al.* (1977) conducted CT examinations in a group of 46 alcoholics and found that 61.4 % showed evidence of cortical atrophy.

The presence of cortical atrophy in alcoholic patients has been reported in several countries. In Sweden, *Myrhed et al.* (1976) and *Bergman et al.* (1980) found cortical atrophy in their alcoholic patients. Sixty percent of the patients showed "clear cut" to "high grade" brain damage, while only 8 percent showed none. Ninety five percent had widened parietal sulci, and 69 % of these also had widened sulci in the frontal locations. In agreement with *Fox et al.* (1976), the same percentage of patients (33 %) manifested ventricular enlargement.

In Australia, *Cala et al.* (1978) observed cortical atrophy in 73 % of their sample. They noted that enlargement of cortical sulci was most prominent in frontal and parietal areas. Similar results were found in England by *Ron et al.* (1977). They found that 65 % of their sample of alcoholics showed evidence of brain damage. A high incidence of cortical atrophy among alcoholic patients has also been noted in Canada by *Wilkinson & Carlen* (1980).

Taken together, these neuroradiological findings indicate that the majority of alcoholic patients manifest cortical atrophy in the fronto-parietal regions of the brain. It should be noted that the correlations between structural changes in the brains of alcoholic patients and neuropsychological deficits have yielded very low but significant values which account for a negligible amount of total variance.

While computerized tomography is used most reliably to assess structural aberrations, the functional integrity of the brain can be examined by studying its product (i.e. behavior) or its process (i.e. neurophysiology). The recent

development of computer technology has made it possible to record the event-related potentials which can be used to study various aspects of brain function. The recording of event-related brain potential (ERBP) offers the possibility of bringing under close scrutiny the millisecond by millisecond transformations of sensory information to higher levels of cognitive processing. In the last few years, we have demonstrated the utility of the event-related brain potentials in assessing the functional integrity of the brains of alcoholic patients. *Porjesz & Begleiter (1979)* recorded ERP's from a sample of abstinent alcoholic patients and normal controls while the subjects were engaged in different attentional tasks. They noted that the late ERP components recorded from the alcoholic patients were significantly lower than those recorded from the control subjects.

More recently we have observed electrophysiological deficits in the late positive complex (P3) or P300 component of the event-related potentials recorded from abstinent alcoholic patients. The P300 component is known to index the subjective evaluation of stimulus significance. We have found that alcoholics manifest a P3 component of much lower voltage than that found in normal subjects (*Porjesz et al. 1980*). Alcoholic patients seem to be unable to differentially respond to relevant and irrelevant inputs. This neurophysiological finding reflects the lack of functional integrity in the brains of alcoholic patients indicative of dysfunction in cognitive processes.

It is well known that given a similar experience of chronic alcohol abuse, some individuals are more susceptible than others to develop morphological changes in the brain. At present, we do not know if the absence of morphological aberrations in the brains of alcoholics are also accompanied by the absence of functional deficits. In the present study we studied the functional integrity of the brain with the use of the P300 component of the event-related brain potential. Neuroradiological and neurophysiological studies were conducted in three different groups of subjects: alcoholics with neuroradiological signs of cortical atrophy; matched alcoholics without neuroradiological signs of cortical atrophy, and control subjects.

#### METHODS

We selected two groups of male alcoholic subjects with a mean age of 39 from a large pool of alcoholic patients who had been subjected to computerized tomography scans. All patients had received a CT-Scan consisting of twelve contiguous 10 mm slides starting from the base of the skull to the vertex (CGR Scanner). All CT-Scans were performed on hospitalized alcoholic patients who were abstinent for a minimum of 6 weeks and medication-free for a minimum of 2 weeks. The patients had been drinking heavily for an average of 10 years and a minimum of 8 years. Alcoholic patients with a history of hepatic encephalopathy, a history of head injury, seizures not associated with alcohol withdrawal, and abuse of other psychoactive drugs were not included in the study.

Cortical atrophy was determined by two methods, using the initial films

magnified by a factor of five. The first method consisted of planimetric measurements of the widths of the frontal interhemispheric fissure and the six largest cortical sulci from all of the CT-Scan cuts. In addition to the planimetric method, we also independently used the clinical judgment of the neuroradiologist (MT) ranging from 0: no atrophy, 1: mild atrophy, 2: moderate atrophy, and 3: severe atrophy. A group of 10 alcoholics with well-defined neuroradiological evidence comprised the patient group with positive CT-Scan findings (Pos-CT). Patients selected in this group manifested a high degree of concordance between the two methods used to assess cortical atrophy. The patients included in the Pos-CT group had moderate cortical atrophy ( $\bar{X}$  rating 2.4) at the frontal and parietal cortices. Patients with other types of neuroradiological findings were excluded from this group.

Another group of 10 alcoholics without any neuroradiological evidence of structural aberrations were included in the negative CT-Scan (Neg-CT) group. Patients in the Neg-CT group were matched for age, sex, education and history of alcohol abuse (duration and amount) to those in the Pos-CT group. The control group consisted of 27 medication-free healthy males who were matched to the patients for age and education. None of the control subjects had any history of alcohol abuse.

Event-related brain potentials were recorded from all subjects on the same day as the CT examination. The subject was seated in a sound-attenuated enclosure with his head resting on a chin rest 50 cm from a computer generated display. All stimuli were flashed in the center of the screen for a duration of 20 msec; they occurred one at a time with a random interstimulus interval of 2 to 5 seconds. The stimuli consisted of a square and a triangle and irregular geometric shapes, equated for size and intensity.

The subject was told to minimize all movements including eye movements, and was asked to fixate the center of the CRT at all times. He was instructed to press a button to the target stimulus only (either a square or triangle). When the square was designated the target, the triangle was designated the non-target and vice-versa. The target and non-target stimuli were alternated every block of 96 stimuli. A tone indicated the beginning of a new block which signalled to the subject that the target and non-target stimuli were being switched. A total of four blocks were used in the experiment. In each block, the target and novel (irregular geometric shapes) stimuli occurred infrequently ( $N=8$ , each) while the non-target stimuli occurred frequently ( $N=80$ ). Each novel stimulus was presented only once.

Electrodes were placed at midline occipital (Oz), parietal (Pz), central (Cz), and frontal (Fz) scalp locations in accordance with the 10-20 International System. Monopolar recordings were obtained using the linked ears as reference and the nasion as ground; vertical eye leads were used to rule-out eye movement contamination. The ERP's were amplified by Grass amplifiers (bandwidth 0.3-60 Hz) and were sampled by a PDP 11-40 computer for a 500 msec epoch (200 pts/sec).

Latency measures were calculated as the time of occurrence (in msec) of peaks P1, N1, P2, N2 and P3. Peak-to-peak amplitude measures were obtained

as the voltage difference between successive peaks (P1-N1, N1-P2, P2-N2, and N2-P3). We chose to measure the amplitude of P3 from N2 (N2-P3) as opposed to a baseline to peak measure. It has recently been shown that baseline to peak measurement of P300 is compounded by a slow wave which contaminates baseline determinations. ERP's were sorted and averaged according to stimulus category (target, non-target, and novels). Thus, for the target and non-target categories, ERP's were obtained to the same stimuli (triangle and square) when they served as task-relevant signals or task-irrelevant stimuli. In order to obtain an equal number of ERP's in each stimulus category, ERP's were averaged to all the novels (N), targets (T), and only the non-target stimuli immediately preceding the target stimuli (preceding non-targets or PNT). Only results from a two-way analysis of variance performed on ERP's obtained at the parietal electrode will be presented here.

### RESULTS

The analyses for the latency measures did not yield any statistically significant differences across the three groups of subjects. Analyses of variance comparing the amplitudes of P1-N1 or N1-P2 across the Neg-CT group, Pos-CT group and control subjects did not reach statistical significance. Statistical analysis of the N2-P3 component across the control group, Neg-CT group and Pos-CT yielded significant differences ( $p < 0.01$ ). Individual mean comparisons were performed with the use of t-tests. The N2-P3 component of the ERP's to the

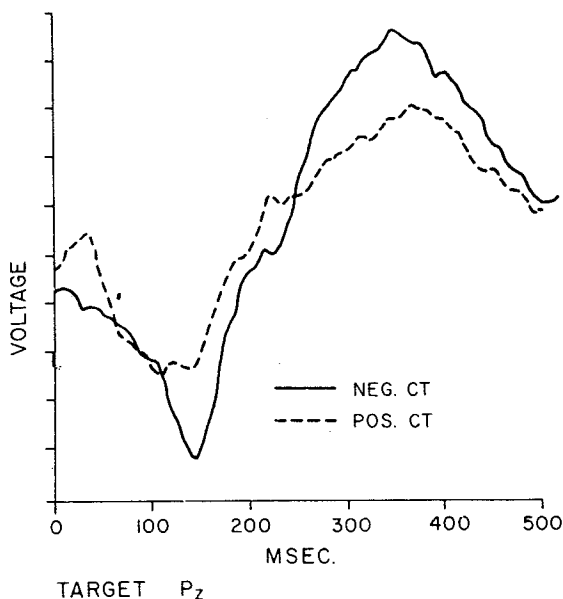


Figure 1. Grand mean ERP to target stimuli recorded at parietal (Pz) for the Pos-CT ( $n=10$ ) and Neg-CT ( $n=10$ ) groups of alcoholic subjects, respectively. (Note that positive voltage is up.)

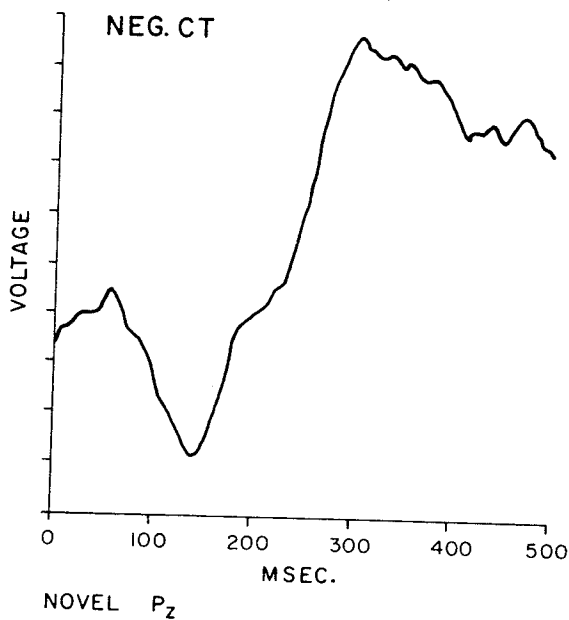


Figure 2. Grand mean ERP to novel stimuli recorded at parietal (Pz) for the Neg-CT ( $n=10$ ) group of alcoholic subjects. (Note that positive voltage is up.)

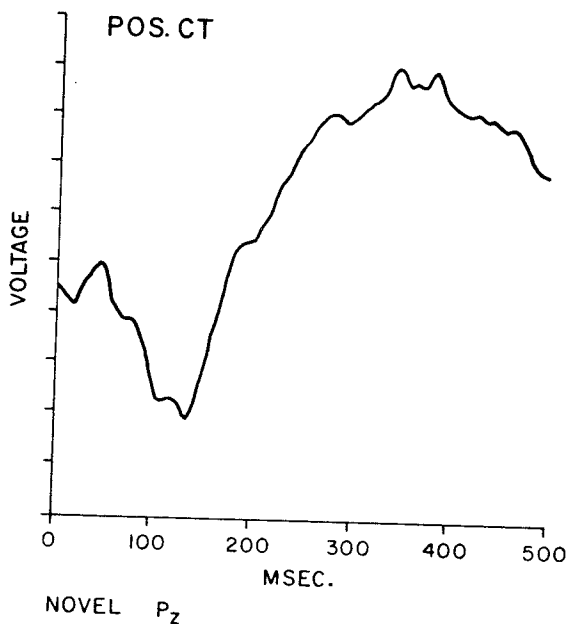


Figure 3. Grand mean ERP to novel stimuli recorded at parietal for the Pos-CT ( $n=10$ ) alcoholic subject group. (Note that positive voltage is up.)

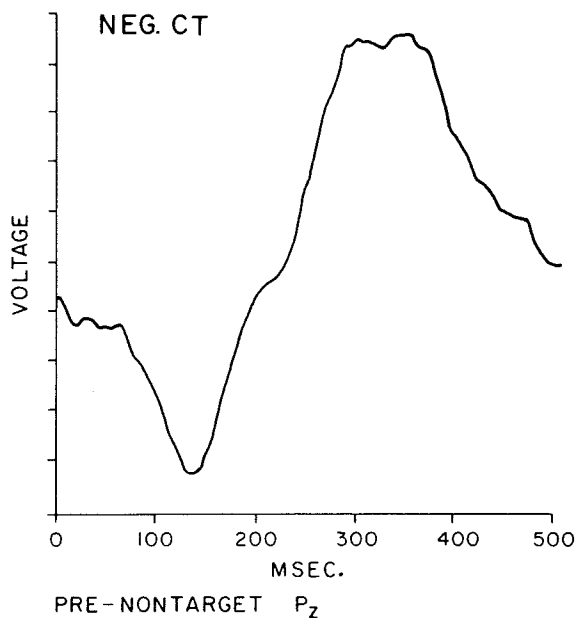


Figure 4. Grand mean ERP to pre-non-target stimuli recorded at parietal (Pz) for the Neg-CT ( $n=10$ ) group of alcoholic subjects. (Note that positive voltage is up.)

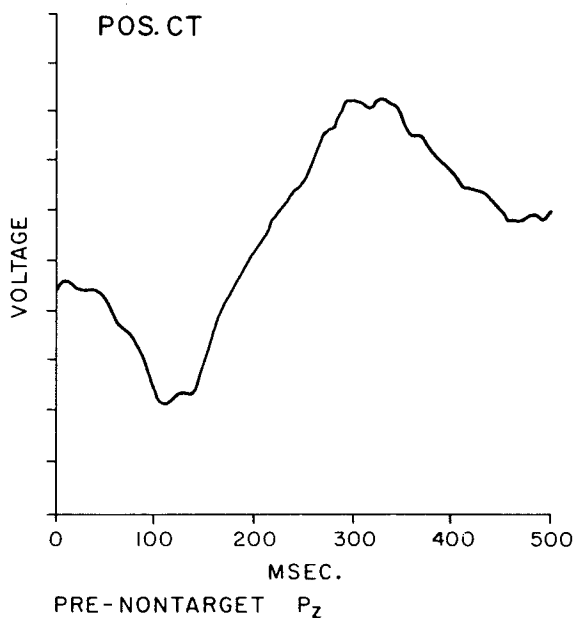


Figure 5. Grand mean ERP to pre-non-targets at parietal for the Pos-CT ( $n=10$ ) group of alcoholics. (Note that positive voltage is up.)

target stimuli differed significantly between the control group and the Pos-CT group ( $p < 0.001$ ) and the control group and the Neg-CT group ( $p < 0.02$ ). The N2-P3 component of the ERP's to the target stimuli were also significantly different between Pos-CT group and Neg-CT group ( $p < 0.01$ ) as illustrated in Fig. 1.

The N2-P3 component obtained to the novel stimuli also differed significantly between control group and Pos-CT group ( $p < 0.01$ ) but not between the control group and Neg-CT. Fig. 2 illustrates the grand mean ERP's of the Neg-CT group obtained to the novel stimuli, while Figure 3 is the grand mean ERP's of the Pos-CT group to the novel stimuli. A comparison of Figures 2 and 3 indicates that the N2-P3 component of the ERP's to the novel stimuli differed between Pos-CT group and Neg-CT group; this was significant at  $p < 0.01$ .

Figure 4 and 5 illustrate the grand averages of the ERP's obtained to the pre-non-target stimuli in the Neg-CT and Pos-CT groups, respectively. As can be seen, the N2-P3 component is significantly larger in the Neg-CT group as compared to the Pos-CT group ( $p < 0.05$ ). The N2-P3 component of the ERP's to non-target stimuli was not significantly different between control group and Pos-CT group ( $p > 0.05$ ) or between control group and Neg-CT group ( $p > 0.05$ ). There was a significant difference in the amplitude of N2-P3 between target and pre-non-target stimuli in the control group only ( $p < 0.001$ ). Neither the Pos-CT or Neg-CT groups displayed a significant difference between target and non-target stimuli ( $p > 0.05$ ).

#### CONCLUDING REMARKS

Our results indicate that the P3 component of the event-related potential recorded from alcoholic patients is significantly lower than that obtained from control subjects. These data are consistent with previous results from our laboratory (Porjesz *et al.* 1980) which also indicated a significant reduction in the P3 component in a different sample of alcoholic patients. It should be noted that in our previous study (Porjesz *et al.* 1980) we selected our alcoholic patients without prior knowledge of the structural integrity of their brains. With the introduction of a noninvasive technique such as the CT-Scan, it has become possible to examine the morphological changes in the brains of alcoholic patients. It is now well established that there is a relatively high incidence of atrophic changes found among alcoholic patients. While these structural deficits are quite frequent, they are nevertheless not invariably present in all alcoholics. Furthermore, these structural deficits provide limited insight concerning the functional integrity of the central nervous system.

Our findings not only demonstrate that the P3 component of the ERP's from alcoholic patients is significantly lower than that of normal controls, but that the same ERP component is significantly different between two groups of alcoholic patients with and without neuroradiological evidence of structural deficits. Alcoholic patients with enlarged cortical sulci (Pos-CT) have a P3

component considerable lower than the one obtained from a matched group of patients without any evidence of cortical atrophy.

It is of interest to note that the electrophysiological event which discriminates best between the three groups of subjects is the P3 component of the event-related brain potential. The P3 component of the ERP recorded in humans is an endogenous neuroelectric event, which is non-modality specific. This component is obtained to stimuli which are relevant or significant to the organism. The P3 component represents an electrophysiological manifestation of the orienting response (*Sokolov 1969*). The orienting response to a significant or novel stimulus requires the use of a comparison process. Each new input stimulus must be compared with previously stored stimuli. This continuous process of comparison between incoming and stored stimuli is necessary for the manifestation of the orienting response. The orienting response is readily distinguishable from a general "arousal reaction" because it is highly selective in character and plays a fundamental role in the organization of behavior.

In recent years a number of studies have indicated that patients with frontal lobe lesions manifest significant electrophysiological deficits in the orienting response (*Pribram & Luria 1973*). *Luria (1973)* postulated that in man, the frontal lobes are involved in the manifestation and expression of the orienting response. Our present findings indicate that the P3 component of the ERP is significantly more impaired in patients with cortical atrophy than in patients without cortical atrophy. Furthermore, it should be noted that both groups of alcoholic subjects elicited similar P3 amplitudes to all classes of stimuli, regardless of their differential task relevance. This suggests a deficit in appropriate attenuation or inhibition of responses to irrelevant events. While the Neg-CT group did not manifest any neuroradiological evidence of cortical atrophy, the P3 component of these patients was significantly impaired compared to the control subjects. The presence of electrophysiological deficits in the absence of apparent structural damage may possibly indicate the occurrence of neurochemical or subtle morphological changes not readily detectable by the CT-Scan. It is interesting to speculate that these electrophysiological deficits might possibly reflect the imminent onset of overt structural changes.

In the last few years it has been reported that many neurons in hippocampus are involved in the orienting response system (*Vinogradova 1970*). These neurons which have no modality specific functions are in fact responsible for "comparing" stimuli, reacting to the appearance of novel or significant stimuli and inhibiting the response during the development of habituation to repeated stimuli. While the P3 component of the ERP is a manifestation of the orienting response, its neural origins are presently unknown. Topographic studies of the scalp distribution of the P3 component indicate that its amplitude is maximal over the parietal area and that it is bilaterally distributed without any apparent hemispheric asymmetry (*Simson et al. 1976, 1977a, 1977b*). A recent study to determine the neural generators of P3 was conducted with implanted electrodes in man (*Wood et al. 1979*). The investigators found that maximal amplitude of the P3 component was obtained at subcortical loci. While those results do not



rule out the contributions of cortical sites, they emphasize the important role of limbic structures in generating the P3 component. It may be suggested that the P3 component of the human ERP is generated in subcortical structures, most likely involving the hippocampus.

A recent animal experiment (Riley & Walker 1978) demonstrated that chronic alcohol intake results in the loss of dendritic spines on neurons in the mouse hippocampus. In our laboratory, we have also demonstrated acute and chronic alcohol effects on evoked potentials recorded in monkey hippocampus (Begleiter *et al.* 1980). Furthermore, recent studies with alcoholic patients have shown memory deficits which also implicate hippocampal aberrations (Birnbaum & Parker 1977).

It is interesting to note that while the Pos-CT group and Neg-CT group had significantly different P3 components from each other, both groups of patients were significantly impaired when compared to the normal control groups. It is reasonable to conclude that cortical atrophy does not appear to be the sole determinant of the amplitude of the P3 component, and possibly may not even be directly related. Our present findings suggest that the significantly impaired P3 component obtained in both groups of alcoholics may possibly reflect both cortical and hippocampal damage. This postulated hippocampal origin of P3 would explain its significant reduction in the Neg-CT group in the absence of cortical atrophy.

The potential involvement of the hippocampal formation in chronic alcohol abuse is further supported by recent work from our laboratory. Porjesz *et al.* (1980) demonstrated that electrophysiologically alcoholics did not differentiate between relevant target and irrelevant non-target stimuli in terms of their P3 components. The present study supports these findings and furthermore indicates that while not significant, the P3 component to target stimuli was somewhat larger than to non-target stimuli. These results suggest that the alcoholics are unable to inhibit responses to irrelevant stimuli. It has been reported that hippocampal structures are critically involved in the mechanisms of inhibition of irrelevant stimuli and thus are part of an active filtering process which participates in selective responses to stimuli of varying significance (Luria 1973). Our present data suggest that in man, chronic alcohol abuse not only results in atrophic changes in cortex but may also involve functional aberrations indicative of possible hippocampal deficits.

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