Evoked Brain Potential Deficits in Alcoholism and Aging

Bernice Porges and Henri Begleiter

It has been hypothesized that alcoholism accelerates the aging process. Most evidence for this hypothesis comes from the neuropsychological literature, where similarities in cognitive functioning between young alcoholics and old people have been reported. These neuropsychological studies indicate that alcoholic and geriatric subjects have in common global deficits in abstraction and adaptive abilities, with both groups manifesting perseverative tendencies. However, although alcoholics may exhibit similar behavioral deficits to old people, these behavioral deficits may well reflect the result of different neuronal pathology or may be general enough to be nonspecific.

The evoked potential (EP) techniques provide unique and sensitive indices of brain function, yielding data on the level of sensory, perceptual, and cognitive processing. An EP is obtained by recording the time-locked brain electrical activity following the delivery of a discrete stimulus in any sensory modality. Signal averaging techniques make it possible to extract the time-locked neuromagnetic signal from the background random 'noise.' These time-locked signals ostensibly represent activity at neural generators from the peripheral organ to higher integrative centers of the brain. Thus, with the use of these sophisticated computerized neuropsychological techniques, the functional integrity of various systems in the brain (from the peripheral end organ to the cortex) can be assessed. Therefore, these EP techniques are ideal to assess similarities in brain functioning between alcoholics and old people.

The following chapter will briefly review recent findings of evoked electrical activity in alcoholics and healthy elderly subjects. It will be subdivided according to the EP techniques used to assess brain functioning, namely: brain stem potential (BSP), pattern-evoked potential (PEP), sensory-evoked potential (EP), and event-related potential (ERP). As each of these techniques provides different information about the level of brain functioning, the resultant neurophysiological profiles of alcoholics and the elderly can be compared for underlying pathophysiology.

**Auditory Brain Stem Potentials (BSP)**

The recent development of the Auditory Brain Stem Potential (BSP) technique permits the scalp recording of 'far-field' potentials in the auditory pathway. The BSP consists of seven positive waves, each presumed to reflect activity at different sites along the auditory pathway from the auditory nerve through the lateral geniculate. The time interval between peak I and peak V of the inferior colliculus is taken as a measure of conduction velocity.

Very few studies have investigated the effects of age on the BSP. In general, these studies have found that, with normal aging, slowing in central parts of the auditory pathway does not occur. However, significant effects on the latency of wave V at low intensities have been reported, and have been attributed to cochlear dysfunction rather than increases in central conduction velocities.

Only a few laboratories have examined BSP's in chronic alcoholics. These studies concur that central conduction velocities are delayed in chronic alcoholics. In a study by Stockard et al., two alcoholic patients suspected of central pontine myelinolysis, with quadriplegia and...
multiple cranial nerve deficits, manifested significantly delayed BSP conduction velocities. Chu and Squires\textsuperscript{24} found that alcoholics with histories of alcohol-related neurological disorders (e.g. dementia, gait disturbance, neuropathy, withdrawal seizures, delirium tremors, Wernicke-Korsakoff syndrome and prolonged heavy drinking) also manifested increased central conduction velocity. Recently, in our laboratory, we have recorded BSP’s in neurologically intact chronic alcoholics who were abstinent for 1 month.\textsuperscript{25} We found that they manifested delayed BSP latencies and conduction velocities of peaks II–V. These data are the first systematic demonstration of brain dysfunction in chronic alcoholics in brain areas other than neocortex. It has been suggested that this increase in neural transmission time may represent the pathological process of demyelination that has been suspected in alcoholic patients;\textsuperscript{26} rats alcoholized for long periods of time have been observed to manifest demyelination.\textsuperscript{27} Delays in conduction velocities may also be accounted for by aberrant fluidizing effects of chronic alcohol intake on membranes\textsuperscript{28} which may result in edema. Edema is seen following osmotic stress\textsuperscript{29–31} and has been reported in such demyelinating conditions as central pontine myelinolysis.\textsuperscript{32, 33} Furthermore, edema may in fact cause demyelination.\textsuperscript{34–38}

Thus, the BSP aberrations seen in abstinent alcoholics (delayed central conduction velocities) are quite different from those reported in normal aging (cochlear dysfunction) and indicate very different underlying pathophysiology. BSPs may not change with normal aging, but rather reflect high-frequency hearing loss due to presbycusis. Our findings of delayed BSP latencies in abstinent alcoholics more closely resemble those recently reported in patients with presenile dementia than they resemble healthy aged individuals.\textsuperscript{22}

**VISUAL PATTERN-EVOKED POTENTIALS (PEP)**

Another promising EP technique in diagnosing neurological disorders is the visual 'pattern-reversal' or pattern-evoked potential (PEP) technique. This technique consists of the rapid presentation of two alternating checkerboard patterns, such that the illuminated and nonilluminated areas reverse with successive presentations. The potential evoked with this method consists of a large positive deflection occurring approximately 100 msec after the stimulus (P100). The PEP technique is sensitive in assessing the integrity of the visual system\textsuperscript{39–43} and can detect early stages of neurological disorders such as multiple sclerosis, optic neuritis, compression of the optic nerve, etc.\textsuperscript{39, 40, 43, 44} It has been found to be particularly useful in early diagnosis of demyelinating diseases, where abnormally delayed responses are obtained.\textsuperscript{45}

We have recently concluded a study in which we examined abstinent chronic alcoholics with the use of this visual PEP technique.\textsuperscript{46} Chronic unmedicated alcoholics who are abstinent for 1 month display significantly delayed P100 components. This indicates an increase in transmission time in the visual sensory pathway. Similar findings are also being obtained by Posthuma and Visser\textsuperscript{47} in Holland. We are currently investigating the reversibility of the delays in PEP in the same alcoholics abstinent for 4 months. We find that, while improvement in these responses occurs, they are still delayed with respect to control subjects.

Studies examining PEPs in old people yield conflicting results. Latency of P100 has been reported not to be delayed in subjects younger than 70,\textsuperscript{44, 48} to be delayed in subjects over 50,\textsuperscript{49} and to progressively increase after the second decade.\textsuperscript{50} Shaw and Cant\textsuperscript{41} found that luminance was critical in determining whether age-related slowing was observed; only with low levels of luminance do they report an increase in latency after the fourth decade. Therefore, perhaps methodological differences can account for differences in results, and the importance of standardizing techniques must be emphasized.

The pathophysiology underlying delayed PEPs in elderly individuals is uncertain at the present time. Despite well known changes in visual function with aging (decrease in pupil diameter, increase in lens opacity), the cause of delays in PEP is still uncertain. There is a paucity of studies in the literature reporting changes in the visual pathways with age (e.g., retinal changes, myelin changes in the optic nerves). At present, there are not sufficient data to speculate about underlying pathophysiology in both aging and alcoholism to make a meaningful comparison.
SENSORY-EVOKED POTENTIALS (EP)

Average evoked potentials recorded to repetitive stimuli of any modality elicit a characteristic positive-negative-positive (P1-N1-P2) waveform which occurs between approximately 60 and 250 msec after the stimulus. These waveforms are somewhat arbitrarily divided into ‘early’ components (<100 msec) and ‘late’ components (>100 msec). The early components are more sensitive to physical stimulus characteristics (e.g., intensity) while the later components reflect psychological states (e.g., habituation).

For the last decade, Beck and his colleagues have studied EPs to repetitive flashes in alcoholics and old people. Visual-evoked potentials (VEPs) recorded in abstinent chronic alcoholics manifest reduced late component amplitudes and delayed latencies. The early components, on the other hand, are resistant to alcohol effects. Thus, the waveform has the appearance of increased early components and decreased and delayed late components. Similar waveforms (enhanced early component and decreased late component voltages) have been reported in the elderly to repetitive stimuli for visual, auditory, and for somatosensory modalities.

Increased latencies have been reported with aging in various laboratories. Age-related latency increases are greater for late components (≥50 msec delays) than they are for early components (~25 msec delay). Furthermore, while latency increases in late components occur for all sensory modalities, they do not occur in the auditory modality for early (<100 msec) latency components.

EP studies of the aging process have demonstrated that the early components remain fairly stable until senescence, at which time amplitude increases occur. With aging, the amplitude of the late component of the visual response increases until adolescence and progressively decreases thereafter. Furthermore, latencies of both visual and somatosensory, but not auditory EPs decrease until adolescence and increase through old age. Reduced frontally distributed late component-sustained potentials (SPs) have been reported to auditory stimuli in old people. These investigators hypothesize that this may be due to loss of dendritic mass in frontal areas where SPs originate. It would be tempting to attribute the similarity between late component amplitude decrements in old people and chronic alcoholics to the CT Scan findings that both groups manifest frontal cortical atrophy.

However, despite these gross similarities between EPs in alcoholics and the elderly, closer scrutiny reveals significant differences between groups. While occipitally derived VEPs recorded from alcoholics and old people in Beck’s laboratory are similar to each other, simultaneously recorded centrally derived responses are quite different between the two groups. Furthermore, latencies are significantly longer in the old subjects than the alcoholics. If indeed alcohol accelerates the aging process, it would be difficult to explain why only recording over primary receiving area would manifest this process.

Although most EP studies use only a single stimulus intensity, valuable information can be obtained by including a larger spectrum of intensities. The amplitude intensity gradient (A-I slope) has received a great deal of attention in the EP literature as distinguishing between ‘augmenters’ and ‘reducers’. Alcohols have been reported to be augmenters, manifesting increasing A-I slope with increased stimulus intensity, particularly those with a family history of affective disorder. This positive A-I slope is attributed to an over-responsive to high intensities, which Buchsbaum and Ludwig postulate as representing a lack of cortical inhibition in chronic alcoholics. However, Pfefferbaum et al. failed to find a positive A-I gradient in old people using an auditory EP paradigm. This suggests that old people do not overrespond to sensory stimulation in the same manner as alcoholics and do not manifest the same underlying CNS excitability characteristic of alcoholics.

Thus, while sensory EP studies (with the subject passively attending to repetitive stimuli) indicate some general similarities in waveform between alcoholics and the elderly, they also point to some differences between groups. Until very recently, it was difficult to separate averages depending on the stimulus or response characteristics. Therefore, all the early EP studies which indicated similarities between alcoholics and the elderly were based on averages of all stimuli in a stimulus sequence, regardless of their stimulus characteristics or subjective utility. This could at best yield a gross measure of evoked brain activity, as it leaves many factors
(e.g., attention) uncontrolled. As indicated by the foregoing review, even when separate averages are obtained for more than one intensity of stimulation (A-I gradient), the resultant EP indicates differences between the aging brain and that of the alcoholic. In addition to variations in stimulus parameters, as will become apparent in the next section, changes in task requirements yield valuable information about brain functioning that cannot be obtained with monotonous stimulation.

EVENT-RELATED POTENTIALS (ERP)

The event-related potential (ERP), technique with subjects actively engaged in a task, has proven to be a promising approach in assessing level of brain functioning. ERPs can be obtained in conjunction with behavior or even when no behavioral response is required. They can be obtained to both attended and unattended stimuli. A comparison of responses to attended as opposed to nonattended stimuli can often reveal more information about level of brain functioning than either response alone.

N1

The N1 or N100 component is a negative component occurring at approximately 100 msec after the stimulus. In healthy subjects, it is enhanced to all stimuli in a relevant channel (e.g., stimulus modality), regardless of whether they are the targets or not.

In a recent bimodal (visual and auditory) study in our laboratory, we investigated brain dysfunction in chronic alcoholics by examining the N1 ERP component. Interspersed among frequently occurring randomized single flashes and clicks were rarely occurring double flashes and double clicks. The patient was required to 'shift attentional sets' by counting either the double flashes or double clicks in an otherwise identical stimulus sequence. ERPs were obtained only to the irrelevant frequent single flashes, which were either in the relevant or irrelevant stimulus modality in a given condition; these frequent single flashes elicit N1, but not P3 components, that are normally differentially enhanced in the relevant channel (stimulus modality), and depressed to stimuli in irrelevant channels.

The results indicated that abstinent alcoholics manifested abnormally reduced late component (N1-P2), but not early component amplitudes, particularly over right hemisphere frontal and central scalp loci. Furthermore, less hemispheric asymmetry (right hemisphere amplitudes larger than left) was evident in the alcoholics than in the controls. These ERP results obtained while the subject was actively engaged in a task confirm previous findings with repetitive flashes in chronic alcoholics. Furthermore, we found that alcoholics, in contrast to controls, manifested the same N1 amplitude, regardless of whether the stimulus was in the relevant channel (modality) or not. This suggested to us that perhaps alcoholics have difficulty with 'sensory filtering' processes, being incapable of electrophysiologically differentiating between relevant and irrelevant channels.

In an auditory selective-attention task (target-selection), Ford et al. found that healthy old people exhibited N1 amplitudes that were similar to those obtained in young controls. Ford et al. report that N1 amplitudes are enhanced in the attended channel (ear) and attenuated in the unattended channel (ear) in both young and elderly subjects. Similarly, in a visual target selection task, we found that normal elderly subjects manifested enhanced N1 amplitudes in the attended channel when compared to chronic alcoholics. As in our previous study, we found that alcoholics exhibited reduced N1 amplitudes, comparable to levels obtained in an unattended channel. However, the N1 amplitudes of the elderly subjects in our study were somewhat attenuated when compared to the controls—falling midway between the two groups (and not differing significantly from either of them). Smith et al. report decreased N1 amplitudes in elderly subjects in an active-guessing auditory paradigm. Thus, it seems that the N1 component is more aberrant in alcoholics than it is in elderly subjects in tasks requiring 'sensory filtering.'

P3

The P3 or P300 component is a positive deflection occurring approximately 300 msec after the stimulus. It can only be elicited under specific conditions relating to stimulus significance, namely, task relevance, unpredictability, and infrequency. The P3 component is considered to be 'endogenous' as it is not related to stimulus characteristics and can even be elicited
to an absent but expected stimulus (emitted potential). In terms of scalp topography, the P3 component is not sensory specific, being maximal over parietal scalp loci for all sensory modalities in healthy young subjects.93-95

The most frequently used ERP paradigm to elicit P3 components is the target-selection paradigm, where rarely occurring target signals are embedded in a sequence of frequently occurring non-targets. Studies using this ERP paradigm in normal subjects,97,98,99 find that ERPs recorded to the frequently occurring non-target stimuli consist of N1-P2 components, but no P3, while rare target stimuli elicit both N1-P2 and P3 components. As this is the only P3 experimental design that has been used to investigate brain functioning in both elderly and chronic alcoholic subjects, we will limit our discussion to the target-selection paradigm for the purpose of this review.

In our laboratory, we have investigated brain functioning in healthy elderly subjects and abstinent chronic alcoholics, as well as control subjects using the same visual P3 target-selection paradigm.99 We were interested in comparing ERPs in chronic alcoholics and old people in an effort to ascertain whether, in fact, brain dysfunction in alcoholics supports an accelerated aging hypothesis. A series of frequent and rare geometric shapes were presented, and the subject's task was to selectively press a button to the infrequent target stimulus only. The experimental design required the subject to change sets; stimuli that were relevant in one block were no longer relevant in another block. The experiment was designed to assess whether the subjects could distinguish electrophysiologically between relevant and irrelevant stimuli, and whether they could probability-match stimuli in terms of their frequency of occurrence.

Our results indicated that alcoholics and healthy elderly subjects manifest very different ERP characteristics when challenged with an identical task. Alcoholics were found to exhibit significantly depressed (Fig. 1) or absent P3 components to rarely occurring target stimuli, under conditions optimal for eliciting large P3s.99 Furthermore, as Fig. 1 indicates, while both normal controls and healthy old people manifested differentially enhanced P3 amplitudes to target stimuli, alcoholics maintained the same low amplitude P3s to target and non-target stimuli alike. The striking similarity in P3 amplitudes between healthy young and old people indicates that old people are able to probability-match as well as young people. Thus, it seems that the alcoholics, in contrast to healthy old people, are unable to utilize available information; they seem unable to respond differentially to relevant target stimuli, and attenuate responding to irrelevant stimuli. (Perhaps this indicates a deficit in 'sensory-filtering' in chronic alcoholics.) Thus, the major ERP aberration in the alcoholic subjects is the lack of differentiation between relevant and irrelevant inputs, and the low voltages of their event-related activity.

While we found that the major ERP aberration in the alcoholics was one of voltage, the major ERP dysfunction in the old subjects was found to be one of latency. Although their amplitudes were similar to young healthy controls, the elderly subjects had significantly delayed P3 components both with respect to the alcoholic and control subjects (Fig. 2). Fig. 2 indicates that the latency of P3 did not differ between young alcoholics and controls. The mean P3 latency in the elderly group occurred 80 msec later than the other groups. A delay of this magnitude (80 msec) has been reported in healthy old people in a similar auditory target-selection paradigm.88

Our findings that P3 occurs significantly later
in old people without concomitant amplitude decrements has been recently independently reported in several different laboratories. In one normative P3 study of ERP changes related to age, the rate of delay in latency with age was found to be 0.7 msec/yr for P2, 0.8 msec/yr for N2, and as high as 1.8 msec/yr for P3. Thus, P3 is the ERP component most susceptible to age-related slowing. As P3 latency is often taken to reflect the amount of time necessary to make a decision, the significantly longer P3 latency in the elderly group suggests that old people are slower in deciding whether a stimulus is target. P3 latencies have been found to correlate with reaction time (RT) latencies, and both of these seem to increase with age.

In another study examining P3 latency and age, Squires et al. varied task difficulty of an auditory target-selection paradigm; target stimuli were either easy to discriminate from non-targets (40–60 db) or difficult to discriminate from non-targets (57–60 db). In both conditions, latency of P3 to target stimuli increased with age, but the rate of increase was greater for the more difficult discrimination (0.79 msec/yr for the easy condition and 1.49 msec/yr for the difficult condition). There was a significant interaction between task difficulty and age for P3 latency, indicating that, with increasing age, the more difficult the task, the more susceptible the timing of perceptual processes.

Scalp topographies of P3 in old people have been reported to be more widely distributed than in controls, not displaying any appreciable maximum over parietal areas. This has been reported for visual and auditory target-selection paradigms, as well as for an emitted potential design. In contrast to the equipotential P3 amplitude distributions in the elderly, alcoholics manifest the expected P3 scalp topography with parietal maximum, and do not differ significantly from controls in both visual and auditory target-selection paradigms.

It seems, therefore, that, while both the alcoholic and aged groups manifest electrophysiological brain dysfunction, the nature of this dysfunction may be quite different in the two groups despite behavioral similarities.

The alcoholic's ERPs are similar to infrequent relevant and frequent irrelevant inputs both in terms of amplitude and latency measures. This suggests impaired sensory filtering and probability-matching processes. The elderly subjects, on the other hand, manifest clearly different ERPs to relevant and irrelevant inputs. However, they exhibit impaired stimulus evaluative mechanisms with regard to speed of evaluation, requiring a longer period of time to determine the relevance of a stimulus.

Thus, on the basis of administering the same target-selection ERP experiment to both alcoholic and elderly subjects, it was concluded that, while ERPs in both groups differ from those of young healthy controls, the nature of brain dysfunction is different. Despite behavioral similarities between alcohol-related deficits and those of the aging process, the underlying neurophysiological aberrations are quite different in the two groups, and suggest caution in postulating a common neuropathological mechanism.

CONCLUDING REMARKS

Despite some electrophysiological similarities between aging and alcoholism, the overwhelm-
ing evidence does not support this hypothesis. It
seems that, while both groups manifest aberrant
BSPs, the cause of the aberration has been po-
stulated to be quite different (demyelination ver-
sus cochlear dysfunction). Early evoked activity
(e.g., BSP) has been more clearly delineated in
terms of the origins of neuroelectric signals, and
hence, the underlying pathology can be more
readily identified.

Unfortunately, at the present time the neural
generators and the physiological mechanisms
underlying the more elusive 'late components'
of the ERP have not been clearly defined. Fur-
thermore, the specific nature of the clinical states
accompanying fluctuations in ERP characteristics
has not been elucidated. Therefore, only
inferences can be made about common under-
lying pathophysiology between these clinical
groups. However, once the neural generators of
these late components become better under-
stood, this technique will have significant clini-
cal utility in identifying underlying pathophys-
ology.

Sensory EPs recorded to passively attended
repetitive and insignificant stimuli may have
limited clinical utility. It is only when the brain
is differentially challenged (e.g., responses to
target versus non-target stimuli) that differences
in electrophysiological brain functioning be-
tween clinical groups emerge. Furthermore, for
a complete neurophysiological assessment, it is
necessary to test the same patients under various
experimental paradigms (e.g., BSP, target selec-
tion). Most studies comparing ERPs obtained
from alcoholics to those of old people use find-
ings obtained in similar but not identical experi-
mental designs. However, as the ERP is ex-
tremely sensitive to differences in factors such
as task difficulty, stimulus modality, etc., results
are not always comparable across tasks. There-
fore, in order to identify unequivocal similarities
in evoked activity between alcoholics and el-
derly people, both groups must be tested with
identical paradigms.

Similarities in EP findings, brain morphology
(e.g., widened cortical sulci on CT Scan), and
cognition (e.g., perseveration) between old peo-
ple and alcoholics may only represent gross
superficial CNS changes that do not share a
common pathophysiological mechanism. In an
interesting study examining this issue, Freund
found that, while both alcohol consumption and
aging result in the same behavioral deficits in
mice, aging results in accumulation of lipofus-
cins (aging pigments) while chronic alcohol con-
sumption does not. Moreover, it should be noted
that the content of endogenous norepinephrine
in the brain stem and hypothalamus decreases
with normal aging and increases in alcoholics.114
Another obvious difference between the mecha-
isms underlying brain dysfunction in aging as
opposed to alcoholism is the issue of reversibil-
ity. With abstinence from alcohol, reversibility
of brain dysfunction has been reported in neu-
ropsychological,115-119 neuroradiological,120, 121
and neurophysiological122 measures. Despite sig-
nificant improvements on these measures with
long-term abstinence, alcoholics are still im-
paired with respect to controls.

As the mechanisms underlying both aging
and alcoholism are at present poorly under-
stood, a comparison of the two may have limited
utility. Despite similarities in CT Scan findings
of 'cortical atrophy' in the elderly and alcoholics,
its significance is somewhat questionable, as the
degree of gross atrophy does not seem to corre-
late (or at best weakly correlates) with degree of
intellectual impairment123-125 independent of age.
In fact, cortical atrophy has even been reported
in CT Scans of such disparate diseases as
schizophrenia,126 lupus erythematosus,127 an-
orexia nervosa,128 dementia,129 etc. It seems that
the 'accelerated aging' hypothesis has been ap-
plied to many, if not most diseases, e.g., schizo-
phrenia.130

While alcoholism may have certain electro-
physiological deficits in common with those that
accompany aging, these deficits may not be
sufficiently specific to characterize the disease
entity. In some respects, electrical activity of
alcoholics may resemble activity elicited from
patients with brain damage or dementia more
than they do healthy old people (e.g., BSP); simi-
larly, in other respects they may resemble
responses obtained from healthy old people
(e.g., passive sensory EPs). These electrophys-
iological results support the findings of Williams
et al.5 who investigated this issue with neuropsy-
chological tests (WAIS) and concluded that
mental abilities of chronic alcoholics differ both
from normal mental aging and organicity. In a
later study,131 they found that at all ages alcohol-
ics were shifted more towards organicity,
particularly after the age of 35. Furthermore, it
is difficult to tease out the effects of 'normal aging' per se from those of increased disease with advanced years. It is difficult to find 'healthy' old people, as health is a relative term, and hence, brain changes that accompany the so-called 'normal' aging process may represent accompanying organic deterioration. In conclusion, at the present time the electrophysiological data suggest possible different underlying pathophysiology for alcoholism and aging, casting doubt on the credibility of the 'accelerated aging' hypothesis in alcoholism.

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