

REVIEW

FRONTAL LOBE CHANGES IN ALCOHOLISM: A REVIEW OF THE LITERATURE

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Abstract — Alcohol can induce a wide spectrum of effects on the central nervous system. These effects can be recognized at the neurophysiological, morphological and neuropsychological levels. Several studies of the effect of alcohol on the frontal lobes were identified for review from MedLine, PsychLIT databases and by manual searching. In this review article, the different changes are examined in detail. Computed tomography studies have reported changes of frontal lobe in alcoholism, while magnetic resonance imaging studies supported these findings. Neurophysiological studies with positron emission tomography and single photon emission computed tomography have reported a decreased frontal lobe glucose utilization and reduced cerebral blood flow. There is also evidence from neuropsychological studies that there are specific deficits in alcoholism that suggest frontal lobe dysfunction. Considered together, these studies lend a strong credence to the concept of frontal lobe pathology in alcoholism. However, frontal lobe is not an isolated part of the brain and should be considered with its heavy connections to different cortical and subcortical areas of the brain.

INTRODUCTION

In a number of ways, the study of the frontal lobes might be described as the study of the qualities that differentiate a human being from other animals. In 1928 the American neurologist Tilney suggested that the entire period of human evolutionary existence could be considered the 'age of the frontal lobe'. A great deal of indirect evidence supported such a claim (Stuss and Benson, 1984).

Current literature emphasized a primary hypothesis concerning the nature and extent of frontal lobe involvement in alcoholism. Considerable research has focused on the pattern of anterior brain deficit. Tarter (1975a) has suggested that prolonged alcohol abuse results in effects that are most pronounced in the anterior region of the brain, extending from the frontal lobe through the dorsomedial nucleus of the thalamus and associated basal regions.

This review will cover the current state of knowledge of frontal lobe dysfunction in alcoholism. The frontal lobe dysfunction will be presented with a major focus on changes that occur in adult humans. References to the animal literature will be limited, except for the sections on neuroanatomy and neurophysiology, where non-human data are the basis.

NEUROANATOMICAL CONSIDERATIONS

Anatomically, the frontal lobes are the massive cerebral area anterior to the rolandic fissure and above the sylvian fissure. There are two roughly symmetrical lobes, each of which can be divided into three areas: dorsal–lateral, medial, and basilar–orbital. Actually, the frontal lobe may be divided in any number of different ways (Stuss and Benson, 1984).

Frontal lobes compose the single largest cortical region in the brain. The prefrontal cortex is the most complex and

highly developed of the neocortical regions in the human brain. Functioning as a massive association cortex, it has afferent and efferent connections to all other neocortical regions i.e. parietal, temporal and occipital, as well as to cingulate, limbic, and basal ganglia structures. The thalamus serves as a major junctional complex that modulates input to the prefrontal cortex, and it has been proposed that the prefrontal cortex should be defined on the basis of its anatomical relationship with the medial dorsal thalamic nucleus (Nauta, 1971, 1972).

The importance of the frontal lobes derives from rich connections, both afferent and efferent, with almost all other parts of the central nervous system. Frontal connections with cortical sensory areas, providing information from the external milieu, occur either by direct cortical–cortical afferents or via the thalamus. The occipital, parietal, and temporal sensory association cortices connect to both the anterior temporal and inferior parietal areas; in turn, each of these has direct afferent connections to the frontal cortex. The prefrontal cortex receives projections from olfactory sensation; it is thus the only cortical area interacting with all four sensory modalities. The frontal lobe also has well-developed connections with limbic and subcortical areas that provide monitoring of the internal milieu (Nauta, 1971, 1972).

The prefrontal cortex is the single largest brain region in human beings, having been estimated to constitute 29% of the total cortex (Nauta, 1971; Goldman-Rakic *et al.*, 1984; Fuster, 1986; Stuss and Benson, 1986) (see Figs 1 and 2).

FUNCTIONAL CONSIDERATIONS

The specific functions of the different frontal lobe regions are still in the process of being mapped. Studies of experimental lesions in animals and traumatic or disease-induced lesions in humans have indicated that injury to the prefrontal cortex leads to disorders of categorizing (Andreasen *et al.*, 1986). Furthermore, a decrease in voluntary motor behaviour,

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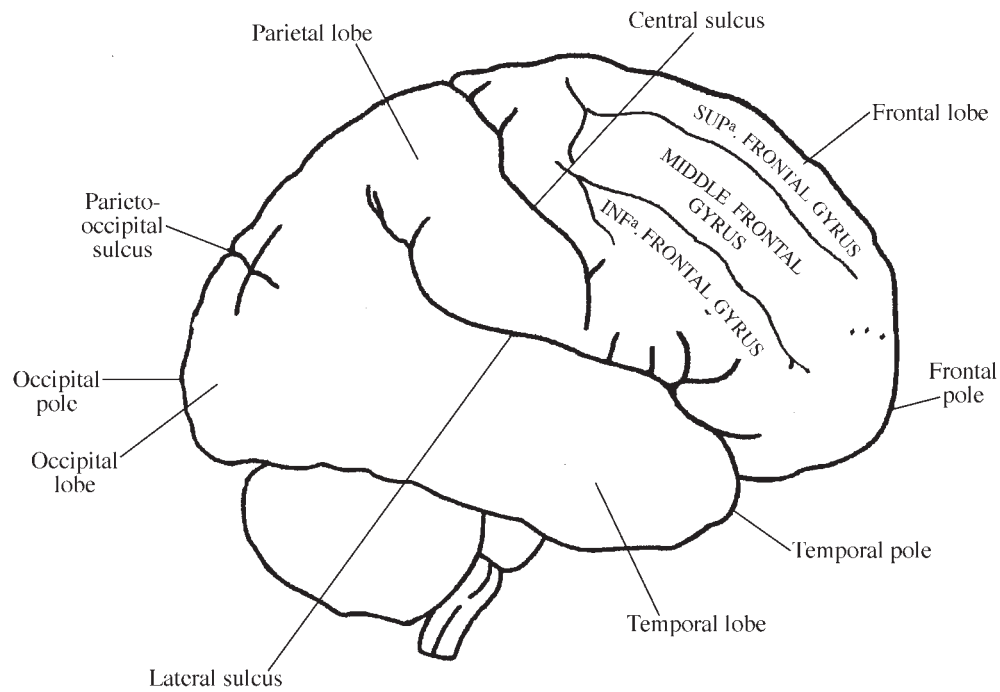


Fig. 1. Cerebral cortex viewed from its right lateral aspect, showing the lobes and large sulci.

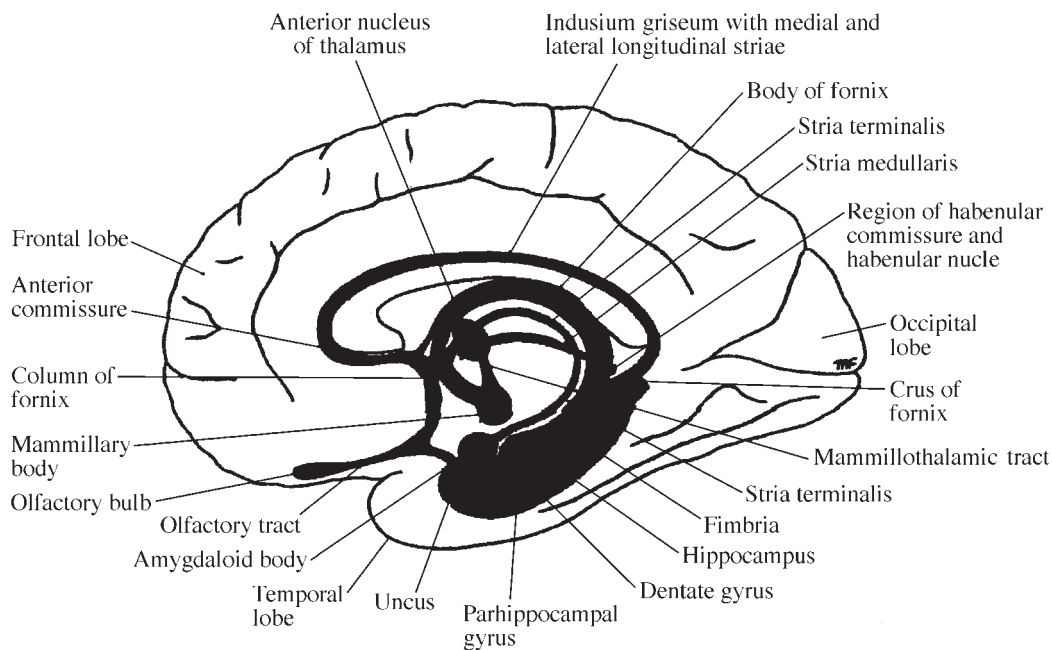


Fig. 2. Medial aspect of right cerebral hemisphere, showing structures that form the limbic system and medial aspect of temporal lobe connects to frontal lobe.

decreased will and energy, a tendency to engage in repetitive or preservative behaviour, difficulty in shifting response set, and abnormalities of affect and emotion, particularly apathy, indifference, and shallowness also occur (Jacobson, 1935; Hebb, 1945; Nauta, 1964, 1971; Drewe, 1975; Damasio, 1979). Other symptoms consistent with dysfunction of the

frontal lobes can include problems with short-term memory, planning, problem solving, impulsivity, disinhibition, and poor motivation (Krans and Maki, 1997). The frontal lobe is involved in functions such as creative thinking, planning of future actions, decision making, artistic expression, aspects of emotional behaviour, as well as spatial working memory,

language and motor control (Miotto *et al.*, 1996; Semendeferi *et al.*, 1997), sustaining attention over time (Rueckert and Grafman, 1996), and smooth pursuit eye movement (Heide *et al.*, 1996).

Efforts have been made to understand frontal lobe deficits in terms of cognitive psychology and artificial intelligence theory (Shallice and Evans, 1978; Shallice, 1982). Shallice (1982) postulated two separate operations in problem solving. Contention scheduling is the term used to describe the fast, efficient, routine use of limited resources. With the introduction of non-routine factors (e.g. a new problem), a general programming, planning, and monitoring system, the supervisory attentional system (SAS) is made operational (Stuss and Benson, 1984). Shallice's theory appears to fit many examples from daily life. For routine tasks, contention scheduling is adequate. Thus a person may drive home and not truly be aware of his behaviour. The SAS can rest or deal with other information, and contention schemas correctly handle the routine behaviours. 'Capture errors' may occur (Norman, 1981). A strong trigger might activate contention scheduling and lead to incorrect response. The SAS, not monitoring the routine behaviour, would be unaware until later (Stuss and Benson, 1986).

PHYSIOLOGICAL DYSFUNCTION OF FRONTAL LOBE IN ALCOHOLISM

Positron emission tomography (PET) studies

Mapping the functional activity of the brain is just one of the current applications of PET. In this context, functional anatomy is described as the relationship between the topography of neural activity and cognitive behavioural or psychomotor tests. The basic principle behind functional mapping is the matching of neuronal activity to motor states, psychological states or pathological states (Dolan, 1992). PET uses as tracers compounds labelled with short-lived positron-emitting isotopes. By tomographically recording their distribution in the body, PET allows the assessment of parameters of tissue function regionally, quantitatively and non-invasively. Two early studies have reported measurements of regional cerebral glucose metabolism in chronic alcoholics. One report found normal absolute values of metabolic rates of glucose in all regions, but a significantly reduced regional distribution index (ratio between regional value and mean cortical value) was found in the medial frontal cortex (Samson *et al.*, 1986). The second study found significantly lower cerebral metabolic rates of glucose in the alcoholic group, than in normal controls; in addition, the alcoholics had fewer significant interregional correlations and also failed to show the normal response of increasing right hemisphere glucose metabolism following a non-verbal auditory stimulus (Sachs *et al.*, 1987).

Later literature revealed decreased local cerebral metabolic rates for glucose bilaterally in the medial-frontal area of the cerebral cortex in alcohol-dependent patients (Gilman *et al.*, 1990; Adams *et al.*, 1993). Also PET has shown decreased glucose utilization in the medial-frontal regions of neurologically unaffected alcoholic patients (Samson *et al.*, 1986). Volkow *et al.* (1993) investigated the effect of lorazepam on regional brain glucose metabolism in 12 normal subjects and 10 alcoholic subjects with the use of PET

and [¹⁸F]fluorodeoxyglucose. They found that lorazepam decreased whole brain glucose metabolism in both the normal subjects (13%) and the alcoholic subjects (10% change), and the response was correlated with the concentration of lorazepam in occipital and cerebellar metabolism; the alcoholic subjects showed significantly less response than the comparison subjects in the thalamus, basal ganglia, and orbitofrontal cortex. The rate of response in the orbitofrontal cortex was significantly correlated with cerebellar metabolism at baseline. Adams *et al.* (1993) examined the behavioural correlates of medial-frontal lobe glucose hypometabolism in 31 chronically alcohol-dependent patients, assessed by PET and neuropsychological correlates [Wisconsin Card Sorting Test (WCST) and Halstead Category Test]. Results suggest that chronic alcohol intakes result in impaired function of cerebral tissue in the medial frontal region, affecting tissue metabolic rates and the behaviour correlates of these rates. Furthermore, Adams *et al.* (1995) investigated the correlation of neuropsychological function using the Wisconsin Card Sorting Test (WCST) and Halstead Category Test (HCT), with the rate of metabolism in subdivisions of the frontal lobes of older alcoholic patients measured with PET. They found that impaired performance on the summary subtest of the HCT was correlated with local cerebral metabolic rate for glucose in all three frontal subdivisions (cingulate, dorsolateral and orbitomedial), whereas the impairment in the summary WCST measure of categories was correlated only with local cerebral metabolic rate in the cingulate region. They suggested that these abnormalities in functioning of the subdivisions of the frontal lobe might contribute to different aspects of the behavioural impairment seen in older alcoholic patients. Additionally, Adams *et al.* (1998) evaluated the possible relationships between family history status and neuropsychological and neuroimaging results using PET. Forty-eight subjects, who had histories of severe chronic alcohol dependence, were divided into two groups: 27 with a first-degree relative with chronic alcoholism and 21 without a first-degree relative with chronic alcoholism. No differences were found between groups on either neuropsychological or neuroimaging tests. These results suggest that a family history of alcoholism does not moderate the damaging effects of severe chronic alcoholism on the functioning of the medial frontal lobe. However, Harden and Pihl (1995), in assessing the profile of cognitive dysfunction drawn from neuropsychological tests designed to assess the functional integrity of the frontal lobes, observed a relationship between high-risk status in sons of male multigenerational alcoholics and their performance on frontal lobe tests. Nevertheless the sample size was small (14 boys with, and 14 without, a positive family history of alcoholism).

Other recent studies (Deckel *et al.*, 1995; Gilman *et al.*, 1996) suggested that severe chronic alcoholism damages neurons containing GABA_A/benzodiazepine receptors in the superior medial aspects of the frontal lobes and that disturbance in integrity of the anterior neocortex may be a risk factor in the development of alcohol-related behaviours.

Single photon emission computed tomography (SPECT) studies

Techniques for measuring cerebral blood flow (CBF) have been available for about five decades. Initially, global CBF

was measured by determining the arteriovenous difference of the inert gas nitrous oxide. Later, the external detection of flow markers labelled with single photon emitting isotopes allowed more regional measurement of CBF. SPECT essentially measures regional cerebral blood flow (rCBF) by following the transport of a single photon-emitting radioisotope tracer to the brain and measuring the resultant activity with detectors. There are three main SPECT tracers for blood flow, ^{133}Xe , $^{99\text{m}}\text{Tc}$ -labelled hexamethylpropylene amine-oxine (HMPAO), and ^{123}I -labelled IMP (iodoamphetamine).

Early studies generally showed reduction in CBF in chronic alcoholics and patients with Korsakoff's syndrome (Meyer *et al.*, 1985; Ishikawa *et al.*, 1986). However, several studies suffered from serious shortcomings: the invasiveness of the procedures, usually involving catheterization of one carotid artery, made it difficult to have really normal control groups; also, patients were often on pharmacotherapy with sedating drugs, while being studied. In several interesting reports, CBF was measured by the non-invasive ^{133}Xe inhalation method in 222 volunteers recruited for a study of the effects of ageing, risks factors for cerebrovascular disease and dementia on CBF. Gray matter CBF significantly inversely correlated with the average alcohol consumption over previous years, which ranged from nil to heavy social drinking. This was regardless of whether or not risk factors for cerebrovascular disease were present (Roger *et al.*, 1983). Flow measurements were reported in patients with Wernicke-Korsakoff syndrome (Meyer *et al.*, 1985) and in chronic alcoholic patients without signs of Wernicke-Korsakoff syndrome (Ishikawa *et al.*, 1986). Both gray and white matter flow were reduced by ~20% in the Wernicke-Korsakoff patients. In chronic alcoholic subjects, values for gray matter flow were normal. Patients were restudied after several weeks of abstinence (and thiamine treatment in the case of the Wernicke-Korsakoff patients). In the compliant subgroups, flow values increased to normal in both sets of patients.

A French study looked at the relation between hepatic pathology and CBF in chronic alcoholics. Reductions in flow were found to correlate with the severity of the hepatic histological abnormalities, though not with the results of the usual biochemical liver function tests (Valmier *et al.*, 1986). These findings are in line with one of the first CBF studies in alcoholism where the results showed the greatest flow reduction in patients with cirrhosis (Shimojo *et al.*, 1967). Additionally, later pathological studies supported the contribution of alcohol, thiamine deficiency and cirrhosis of the liver to cerebral cortical damage in alcoholics (Harper and Kril, 1985; Kril, 1995).

Berglund and Risberg (1981) made serial bilateral measurements of regional rCBF by the ^{133}Xe inhalation method, during 13 withdrawal periods in 12 male alcoholics with pronounced physical dependence. A significant global reduction of rCBF was found during the first two days of withdrawal. Tutus *et al.* (1998) Performed [$^{99\text{m}}\text{Tc}$]HMPAO brain SPECT on the day of admission in non-medicated conditions and again after all the withdrawal symptoms had subsided in the patients. Results indicated that there were significantly reduced left frontal and right frontal, parietal and temporal rCBF values in the patients during alcohol withdrawal compared to those of their remitted state, which were not different from those in the control group.

Nicolas *et al.* (1993) studied the prevalence of central nervous system damage due to ethanol. They evaluated 40 asymptomatic chronic alcoholics and 20 age-matched controls. Studies included neuropsychological testing, brain [$^{99\text{m}}\text{Tc}$]HMPAO SPECT, and morphometric analysis by CT scan. In the quantitative analysis, 30 of the 40 alcoholics showed hypoperfusion areas on the SPECT scan. In the semiquantitative analysis, alcoholics exhibited significant reduction in the rCBF ratio of all brain lobes, compared to controls ($P < 0.001$). The rCBF ratio was specially reduced in frontal lobes (by 65%).

Benson *et al.* (1996) described a case of acute alcoholic-induced Korsakoff amnesia in a 32-year-old female. SPECT showed hypo-perfusion in the orbital and medial-frontal lobe regions and the medial diencephalic area. They repeated the SPECT 4 months later. This showed a return to normal perfusion in the frontal brain areas, but little improvement in the medial diencephalic region. However, it is difficult to generalize from only one case report.

Kuruoglu *et al.* (1996) examined 40 patients with alcohol dependency, including 15 with antisocial personality disorder, as defined in DSM-III-R, and 10 age- and sex-matched healthy controls. The alcoholics were studied after termination of withdrawal symptoms, using high resolution SPECT, CT, and brain stem auditory evoked potentials (BAEP). The authors found a significant reduction in regional cerebral blood flow (rCBF) measurements of the alcoholic patients. Low flow in frontal regions encountered in 67.5% of the patients was associated with the duration of alcohol consumption, whereas no such relationship existed with the amount of daily intake. However, patients with antisocial personality exhibited more marked frontal hypo-perfusion.

Meanwhile, Jagannathan *et al.* (1996) assessed the brain metabolic changes in alcoholism by using localized proton magnetic resonance spectroscopy. They studied the brain metabolic changes in 10 alcoholic patients in the frontal lobe, cerebellum, and thalamus regions. The results obtained were characterized by a reduced *N*-acetyl-aspartate (NAA):choline (Cho) and NAA:total creatine ratios relative to age-matched ($n = 27$) controls. These decreased ratios correspond to depleted concentration of metabolite levels. Reduction of NAA is consistent with neuronal loss, whereas reduction in Cho suggests significant changes in the membrane lipids of alcoholics.

Interestingly, Gansler *et al.* (2000) examined the relationship between cerebral hypo-perfusion and residual deficits in the functioning of frontal brain systems in abstinent alcoholics long-term. CBF was observed through the use of SPECT perfusion images. Results showed a positive relationship between perfusion levels in the left inferior frontal brain region and years of sobriety. Alcoholics with less than 4 years of sobriety had significantly reduced left inferior frontal perfusion, compared with both non-alcoholic controls and alcoholics having longer periods of sobriety. The findings support the hypothesis that frontal brain abnormalities in alcoholics may subside with extended abstinence.

Additionally, both electroencephalographic (EEG) and evoked potential studies support the presence of neurophysiological changes in brains of alcoholics, particularly in the frontal lobe (Pribram and Luria, 1973; Begleiter *et al.*, 1980; Porjesz *et al.*, 1980; Michael *et al.*, 1993; Bauer

et al., 1994; O'Connor *et al.*, 1994; Cohen *et al.*, 1996). These studies led Begleiter *et al.* (1980) to suggest that the presence of electrophysiological deficits even in the absence of apparent structural damage may possibly indicate the occurrence of neurochemical or subtle morphological changes not readily detectable by CT scan. They speculated that these electrophysiological deficits might reflect the imminent onset of overt structural changes.

STRUCTURAL ABNORMALITIES IN THE FRONTAL LOBE SYSTEM IN ALCOHOLISM

Post-mortem studies

Courville (1955), on the basis of neuropathological studies, noted the presence of cortical atrophy, more marked in the frontal lobes, but often widespread, with ventricular enlargement and meningeal thickening. The microscopic picture was one of cell loss, architectural disruption of the cortical laminae, pigmentary degeneration and proliferation of glial elements. In his experience, this picture was sometimes accompanied by marked arteriosclerotic changes. This description was supported by other authors (Warner, 1934; Hecaen and Ajuriaguerra, 1956; Mancall, 1961).

The picture of cortical atrophy, particularly involving the frontal lobes, may occur alone or in combination with other lesions. Victor *et al.* (1971) noted macroscopic cortical atrophy in 27% of their 72 patients, who showed the periventricular gray-matter lesions characteristic of Wernicke-Korsakoff's encephalopathy. Cortical atrophy has also been described in combination with degeneration of the corpus callosum in cases of Marchiafava-Bignami syndrome (Jequier and Wildi, 1955; Delay *et al.*, 1960).

A quantitative neuropathological necropsy study of 22 control and 22 chronic alcoholic subjects showed a statistically significant loss of brain tissue in the chronic alcoholic group. The loss of tissue appeared to be from the white matter of the cerebral hemispheres, rather than the cerebral cortex (Harper *et al.*, 1985). In addition, a quantitative neuropathological necropsy study of the human cerebral cortex showed that the number of cortical neurones in the superior frontal cortex in chronic alcoholic patients is significantly reduced compared with that in controls matched for age and sex (Harper *et al.*, 1987). An analysis of brain weights has demonstrated a decrease of mean values in male alcoholics, when compared with controls. This weight loss occurred independently of the presence of Wernicke's encephalopathy, indicating that alcohol consumption is more important than nutritional deficiency in causing a reduction in brain weight (Harper and Blumbergs, 1982). However, the loss of brain tissue in chronic alcoholic patients was later found to be more severe in those who had nutritional vitamin deficiencies or alcoholic liver damage (Harper and Kril, 1985; Kril, 1995).

It has been suggested that the loss of white matter could be caused by changes in hydration, mainly loss of water (Carlen and Wilkinson, 1980). Such a hypothesis was supported by reports of altered body water balance in relation to the ingestion of alcohol and during the withdrawal phase in alcoholics (Eisenhofer and Johnson, 1982). However, post-mortem studies of the specific gravity and water content of the

white matter negate this hypothesis (Harper *et al.*, 1987, 1988a,b).

The neuropathological lesions encountered in chronic alcoholics are likely to be the end result of a variety of aetiological factors. Post-mortem studies, and perhaps more so those based on forensic autopsies, often suffer from poor ante-mortem documentation. Some of these studies tend to be based on groups of elderly patients who have long drinking histories and may well also suffer from dietary deficiencies. Reporting, inevitably, tends to be selective. The presence of cerebral atrophy in a proportion of these patients is clear, but it is difficult to extrapolate these findings to the alcoholic population as a whole.

Recently, a series of studies of the effect of alcohol on receptors in the frontal cortex has been completed (Volkow *et al.*, 1993; Dodd *et al.*, 1996; Freund and Anderson, 1996; Gilman *et al.*, 1996; Lewohl *et al.*, 1997; Marchesi *et al.*, 1997). These studies concluded that chronic alcoholism leads to moderate increases in the density of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors in the frontal cortex. This up-regulation may represent a stage of alcohol-induced chronic neurotoxicity.

Neuroradiological studies

Until the introduction of CT and MRI scanning, the method required for visualization of cerebral structures was the injection of air in the subarachnoid space (pneumoencephalogram, PEG). As this technique carries a certain morbidity and discomfort, its application is limited to those patients in whom clear clinical indicators are present, such as the need to exclude a space-occupying lesion (Ron, 1977).

Brewer and Perrett (1971) examined 33 alcohol problem patients, using PEG, admitted to a psychiatric hospital. The mean age of the patients was 50 years. It was concluded that cortical atrophy was present in 30 out of 33 patients and that the ventricles were enlarged in 24. Only two patients were regarded as having a normal PEG. Frontal atrophy appeared to be especially common and was noted in 28 patients of the 30 with cortical atrophy.

Numerous other studies have reported PEG changes in chronic alcoholics with cortical and subcortical atrophy, often involving frontal lobes (Tumarkin *et al.*, 1955; Lafon *et al.*, 1956; Lereboullet *et al.*, 1956; Postel and Cossa, 1956; Ledesma Jimeno, 1958; Riboldi and Garavaglia, 1966; Haug, 1968; Carlsson *et al.*, 1970; Ferrer *et al.*, 1970; Iivanainen, 1975).

Some of the difficulties in evaluating PEG studies could be overcome if adequate control groups were available. To find a group of healthy volunteers is practically and ethically impossible. A different approach is to use groups of psychiatric patients as controls (Haug, 1968). Unfortunately, however, it is possible that a number of such patients might have some degree of brain damage and it would be inaccurate to equate their PEG appearance with those of normal controls. Furthermore, deviations from the norm in psychiatric patients may mask or minimize the abnormalities in the group under scrutiny. On the other hand, if the differences between the two groups are clear their significance is probably greater (Ron, 1977).

As the morbidity of PEG has restricted its usage, the advent of CT scanning and MRI has made it possible for the first time to study large and carefully selected groups of alcoholics, to repeat the investigation after a follow-up period, and to examine a normal population for comparison.

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 controls. Carlen *et al.* (1976) reported that all of the alcoholic patients they studied demonstrated neuro-radiological evidence for cortical atrophy. Epstein *et al.* (1977) conducted CT examination in a group of 46 alcoholics and found that 61.4% showed evidence of cortical atrophy. Myrhed *et al.* (1976) and Bergman *et al.* (1980) found cortical atrophy in their alcoholic patients. Sixty per cent of these patients showed 'clear cut' to 'high grade' brain damage, whereas 8% showed none. Ninety five per cent had widened parietal sulci, and 69% of these also had widened sulci in the frontal locations. Cala *et al.* (1978) observed cortical atrophy in 73% of their sample. They noted that enlargement of cortical sulci was most prominent in the frontal and parietal areas. Ron (1977) found that 65% of his sample of alcoholics showed evidence of brain damage. Wilkinson and Carlen (1980) have also noted a high incidence of cortical atrophy among alcoholic patients. Ron *et al.* (1980) performed CT in 100 alcoholics and 41 controls. In their series, radiological abnormalities were detected in a considerable proportion of chronic alcoholics, when compared with normal controls. The radiological abnormalities extended both to cortical structures and to the ventricular system. However, regional variations did not appear to be very obvious. These latter authors suggested that, with the current lack of knowledge of the underlying pathology, it is better to refer to them as 'brain shrinkage' rather than 'brain atrophy', which assumes more specific neuropathological lesions. Rosse *et al.* (1997) suggested that frontal lobe pathology is associated with negative symptoms in patients with chronic alcoholism. The authors examined 19 chronic alcoholic in-patients (aged 18–60 years) in an alcohol treatment unit and found a significant relationship between severity of frontal atrophy measured by CT and negative symptoms, measured by the Scale for the Assessment of Negative Symptoms.

The contribution of gender and drinking history to CT brain changes in alcoholics was studied. CT scan studies of male alcoholics have revealed larger ventricles, and wider cerebral sulci and fissures, compared with control groups (Bergman *et al.*, 1980; Ron, 1983). Similar findings have been demonstrated in a controlled study of female alcoholics, who showed an equivalent pattern of CT brain scan abnormalities, but after a shorter period of excessive drinking and lower estimated peak alcohol consumption than reported in studies with male alcoholics (Jacobson, 1986). Consecutive series of male and female alcoholics, Alcoholic Anonymous (AA) members and controls were examined by interview and with a CT brain scan. The CT scan findings persisted after accounting for body weight and after matching for age and length of drinking history. The CT scan parameters of female AA members approached control values more completely and after briefer abstinence than did those of male AA members. These findings are consistent with sex differences in the vulnerability of the brain to alcohol toxicity, and its recovery with abstinence (Jacobson, 1986).

MRI studies supported the CT scan findings on the effect of alcohol on frontal lobe volume. Pfefferbaum *et al.* (1997) used MRI to quantify the extent and pattern of tissue volume deficit and cerebrospinal fluid volume enlargement in younger,

versus older, chronic alcoholics and relative to normal controls. They divided their group of 62 alcoholic men into a younger group ($n = 33$, mean age 37.5 years, range 26–44) and an older group ($n = 29$, mean age 52.7 years, range 45–63) to examine whether, in addition to extent, the two age groups differed in pattern of tissue type and regional brain volume abnormalities quantified with MRI. The younger group had significant cortical gray, but not white, matter volume deficits and sulcal and ventricular enlargement, relative to age-matched controls. The older group had volume deficits in both cortical gray and white matters and sulcal and ventricular enlargement that significantly exceeded the younger alcoholic group. An analysis of six cortical regions revealed that, although both age groups had gray matter volume deficits throughout the cortex, the older alcoholic group had a selectively more severe deficit in prefrontal gray matter, relative to the younger alcoholic group. Similarly, the cortical white matter volume deficit in the older alcoholics was especially severe in prefrontal and frontal regions. The difference in brain dysmorphology between the two alcoholic groups cannot easily be attributed to potential alcohol history differences typically related to age, because the two groups had similar disease durations and amounts of lifetime alcohol consumption. These results provide evidence that the frontal lobes are especially vulnerable to chronic alcoholism in older men. In another study, Sullivan *et al.* (1996) used MRI to study the relationship between alcohol withdrawal seizures and temporal lobe white matter volume deficits. They examined 11 alcoholics who had experienced one or more alcohol-related seizures and 35 seizure-free alcoholics, relative to controls. Each alcoholic group showed significant bilateral volume deficits of the anterior hippocampus and frontal-parietal and temporal gray matter, relative to controls.

MRI parameters also provide information about brain water. Two studies in chronic alcoholism have produced contradictory results, one describing changes suggestive of decreased free water content during withdrawal (Besson *et al.*, 1981), the other reporting an increase in free water during chronic alcohol consumption with a decrease during withdrawal (Smith *et al.*, 1985). In both reports, patient numbers were small (six and nine patients respectively). Harper *et al.*'s (1988a,b) post-mortem studies of brain water and brain-specific gravity supported the findings of the second of the above two MRI reports.

The conclusion is therefore that the occurrence of morphological abnormalities in brains of chronic alcoholics who appear clinically intact has been recognized. Neuropathological changes have been described, neuroradiological studies have demonstrated abnormalities compatible with cerebral atrophy, and the changes have often been detectable. However, the relative roles of alcohol toxicity, thiamine deficiency and cirrhosis of the liver in the pathogenesis of alcohol-related brain damage are still unclear.

IMPAIRMENT ON NEUROPSYCHOLOGICAL TESTS OF FRONTAL LOBES IN ALCOHOLISM

Although general measures of intelligence, especially those with a large verbal component, do not reveal deficits in performance in alcoholics (Tarter, 1975b, 1980; Parsons,

1987), detailed testing across different cultures has shown deficits in cognitive flexibility, problem solving, verbal and non-verbal abstraction, visuo-motor co-ordination, learning, conditioning, and memory (Jones, 1971; Jones and Parsons, 1972; Parsons, 1975, 1977; Tarter, 1976; Butters *et al.*, 1977; Cala *et al.*, 1978; Jenkins and Parsons, 1979; Tarter, 1980; Bergman, 1985; Miller, 1985; Acker, 1986; Wilkinson, 1987; Nicolas *et al.*, 1993; Beatty *et al.*, 1996; Nixon and Bowlby, 1996).

To detect lesions in the frontal lobes, standard intelligence tests tend to be of limited value. Special psychometric procedures may be more rewarding. Standard intelligence tests have nevertheless been used frequently in surveys of alcoholics, and their main contribution has been to demonstrate that there is no significant difference in IQ between large groups of chronic alcoholics and the normal population (Amark, 1951; Peters, 1956; Bauer and Johnson, 1957).

Attempts have been made to find a typical pattern of performance of chronic alcoholics in the subtests of the Wechsler Adult Intelligence Scale (WAIS). Wechsler (1941) studied a group of 29 chronic alcoholics of normal intelligence, aged from 36 to 55 years, and found that the subtests that offered most difficulty were the Similarities, Digit Symbol, Digit Span and Object Assembly. From this pattern of performance, he concluded that chronic alcoholics were relatively poor at abstract reasoning, perceptual organization, learning and retention. Goldstein and Shelly (1971) made a similar attempt.

More striking results have been obtained when tests especially designed to be sensitive to frontal lobe damage were used. Among these, the Porteus Maze test (PMT; Porteus, 1965) is worthy of mention. The test consists of a number of labyrinths, each increasing in difficulty. The subject must find the most direct route from beginning to end without entering blind alleys or crossing through lines. The subject must not lift the pencil while tracing the route and must keep within the side boundaries. As soon as an error is made, the same labyrinth is presented for a second trial, with a limit of two to four trials, depending on the degree of difficulty of the test. Two types of scores are obtained. A test age compares the particular achievement based on the number of repeated trials with a maximum score of 17, and a qualitative score assesses the type of production errors (e.g. cutting corners, touching the side). The Wisconsin Card Sort Test (WCST; Milner, 1963) requires subjects to learn the correct way to sort cards. On each trial, the subject must generate an attempt, sorting the cards according to the shape, colour, or number of symbols on it. The subject learns by trial and error on the basis of feedback provided by the tester. On this task, the subject does not learn a specific response, but rather a rule that governs their responses. Once they have learned to sort by one rule (such as sorting by shape), the rule is changed and the subject must sort by another rule (such as sorting by colour). When the subject has learned that rule, the rule is again changed, and so on until the subject has sorted all the cards.

The most widely used category identification test is the Halstead Category Test (HCT; Lezak, 1983), which consists of seven subtests, the first six measuring non-verbal abstraction-concept formation in which a series of slides are presented,

each with different figures and patterns. The subject is instructed that something will suggest a number between 1 and 4; he then presses one of the four buttons and receives a feedback tone or buzzer telling him if the answer is correct. At the completion of each group, the examiner states that another group of items will be presented and the main idea may be the same or different. The seventh and final group demands memory of previous stimuli (Stuss and Benson, 1986).

Finally, two new batteries of tests have been prepared from the lifetime experience of the Russian neuropsychologist Luria. A selection of his tests has been translated into English by Christensen (1986), and a second, independent battery (Luria-Nebraska Neuropsychological Battery) designed to conform to current American psychological practices has been developed (Golden, 1986; Golden *et al.*, 1991). Theoretically, with the Luria approach comparatively subtle frontal lobe disturbance can be sought and isolated. In particular, subtests such as rhythm tapping, 'go/no-go', alternating figures, and others are suggested as particularly relevant to frontal lobe malformation.

Fitzhugh *et al.* (1960, 1965) studied a group of 35 alcoholics tested after an average of 12 days of abstinence and compared them with another group of 35 patients with well-documented brain damage and with 35 normal controls. The alcoholics were indistinguishable from the controls in terms of IQ. When the Trail Making test and Halstead Battery tests were used, the alcoholic group performed much worse than the control group and even worse than the patients with brain damage. Several other studies confirmed these findings and found evidence of frontal lobe damage by using the same tests or other frontal lobe tests (Jones and Parsons, 1971; Smith *et al.*, 1973; Long and McLachlan, 1974; Cutting, 1978; Hill, 1980; Goldstein and Shelly, 1982; Parsons, 1987; Sullivan *et al.*, 1993). However, Joice and Robins (1991) found that the impairment of alcoholic non-Korsakoff patients did not appear to be related to frontal lobe dysfunction, compared to Korsakoff patients. Non-Korsakoff patients exhibited fewer impairments that could not be attributed to deficits in either planning or spatial working memory.

Another important area of research was information processing. Previous research has demonstrated an impairment of information processing following alcohol administration (Koelega, 1995). However, it is not known whether this impairment is on all stages of information processing or on the early stages of it.

Studies examined different stages of information processing. The early stages of information processing have been described as those which involve the detection of, and response to, simple stimuli (Koelega, 1995). A task that assesses this function is the inspection time (IT) task, which involves the ability to make an observation/inspection of sensory input on which a discrimination of relative magnitude is based, in contrast to tasks such as reaction time (RT), which generally involve more response-oriented measures of total decision-making time, that constitute total information processing (Tzambazis and Stough, 2000). Several studies on the effect of alcohol on the early stages of information processing have found an impairment of speed of detection (Maylor *et al.*, 1990); attenuated auditory event-related potential (Jaaskelainen *et al.*, 1995); or increased reaction time and impaired stimulus detection (Krull *et al.*, 1994).

On the other hand, there has been considerable research into the effects of alcohol on total information processing, measured by RT, vigilance and attention tasks and tasks assessing cognition ability. Generally, results suggest that, when demands are higher, such as under dual-task conditions, the impairment in performance due to alcohol becomes more significant (Maylor *et al.*, 1990, 1992; Bartl *et al.*, 1996).

Tzambazis and Stough (2000) used IT as a predictor variable in a linear regression analysis to examine whether a disruption of the early stages of information processing accounted for changes in total information processing after alcohol administration. Results indicated that alcohol significantly slowed total information processing, independently of the early stages of information processing.

Acker (1986) assessed the contribution of gender and drinking history to neuropsychological deficits. Alcoholic inpatients were selected for cognitive assessment on a routine consecutive admission basis. The male and female alcoholic groups (72 males and 33 females) performed significantly worse on the cognitive tests than matched controls. The females performed worse on tests of immediate recall, and psychomotor speed. The author concluded that females are more susceptible than males to the harmful effects of prolonged heavy drinking on cognitive performance. Alternatively, it may be that those females who become alcoholic are 'at risk' in some unspecified way, which is reflected in the performance difference.

A large number of neuropsychological studies have examined individuals 'at risk' for developing alcoholism, such as sons of alcoholics (Schaeffer *et al.*, 1984; Drejer *et al.*, 1985; Tarter *et al.*, 1989; Peterson *et al.*, 1992; Knop *et al.*, 1993). They found that sons of alcoholic men exhibited increased impulsivity, decrements in attention, planning ability, and at-risk adolescents differed from low risk ones in Category test, memory tests, tests of abstracting/problem solving, Trail Making test, and significantly more errors on Halstead Category test and the Porteus Maze test. Collectively, these findings suggest that individuals at risk for alcoholism demonstrate a cluster of deficits that may somehow link anterior brain dysfunction to the risk of developing alcoholism.

Recently, it was reported that neuropsychological tests that assess anterior brain functioning are predictive of alcohol-related expectancies (Deckel *et al.*, 1995). Evidence of anterior neocortex involvement in the generation of these expectancies was also found through an examination of electrophysiological and structural data in some of these studies.

As mentioned above, Adams *et al.* (1993) studied the behaviour correlates of medial frontal lobe glucose hypometabolism in chronically alcohol-dependent patients. Thirty-one male patients who were detoxified, medically stable, and free of other central nervous system risk factors for neuropsychological impairment were examined with anatomical imaging (CT or MRI), functional imaging with PET and a battery of neuropsychological tests, including the Wisconsin Card Sorting Test and the Halstead Category Test. The findings suggested that chronic alcohol intake resulted in impaired function of cerebral tissue in the medial frontal region. The impairment pertains both to tissue metabolic rates and behavioural correlates of these rates. These findings have

been supported by other studies (Bergman *et al.*, 1980; Ciesielski *et al.*, 1995; Deckel *et al.*, 1995; Nicolas *et al.*, 1997).

In summary, the impairment of neuropsychological function of the frontal lobe is particularly noticeable in the ability to perform complex psychomotor tasks and in some functions usually attributed to the frontal lobes, such as the ability to solve problems or to manipulate abstract concepts. These studies illustrate the fact that these deficits can be found in subjects whose IQ is average or even above average.

In everyday clinical practice, these tests for frontal lobe damage are seldom used and lesions in this area could easily be overlooked. Behavioural symptoms of frontal lobe impairment could readily be interpreted as part of the 'make-up' of the alcoholic's personality (Ron, 1977).

REVERSIBILITY OF FRONTAL LOBE CHANGES AFTER ABSTINENCE FROM ALCOHOL

The relationship between abstinence and recovery of frontal lobe deficits in chronic alcoholics is only partly understood. Adequate clarification would require following up a group of chronic alcoholics remaining abstinent for long periods, with careful repeat mapping of performance on appropriate investigations.

Page and Linden (1974) tested 20 hospitalized chronic alcoholics during the first week of abstinence. The WAIS, TMT and Benton Visual Retention tests were used. The authors observed an improvement in short-term memory, abstract reasoning, spatial ability, and visuo-motor co-ordination. By comparing successive performances the bulk of the improvement seemed to occur during the first 2 weeks of abstinence. This pattern of improvement was also found by Jonsson *et al.* (1962), Carlsson *et al.* (1973), Templar (1975) and Reed *et al.* (1992).

Clarke and Haughton (1975) studied a group of alcoholics at 2, 6 and 10 weeks after withdrawal: 130 patients were initially seen, but only 55 were tested three times. At psychological assessment, some improvement took place in the first 6 weeks of abstinence, but very little change was recorded thereafter. At 10 weeks, it was still possible to demonstrate impaired performance in psychomotor speed and abstract reasoning. In an attempt to rule out depression as a cause of poor test performance, the patients were asked to complete self-rating scales for depression at regular intervals. By the end of 6 weeks the patients rated themselves as 'normal', while psychological tests continued to show abnormalities.

The brain shrinkage was followed by re-scanning at 6 months to 3 years (Ron *et al.*, 1982; Ron, 1983). In the majority, appearances were unchanged, although some showed worsening, and an important group showed regression of the shrinkage. The factor clearly related to possibilities of improvement was the degree of abstinence achieved during the assessment period. These findings confirmed earlier ones (Carlen *et al.*, 1978; Carlen and Wilkinson, 1980). These findings were further checked in a group of patients drawn from AA (Jacobson, 1986; Lishman *et al.*, 1987). Despite earlier drinking histories, their scans were closer to those of normal controls than to those of current alcoholics; some degree of residual ventricular dilatation was suspected.

In summary, therefore, frontal lobe changes are potentially reversible to some degree with abstinence for several months or years, but even after several years the brain may remain abnormal.

GENERAL CONCLUSIONS

The occurrence of morphological abnormalities in the frontal lobes of chronic alcoholics who appear clinically 'intact' has been recognized. Neuropathological changes have been described, and neuroradiological studies have demonstrated abnormalities compatible with cerebral atrophy. The neuroradiological changes have occasionally been accompanied by cognitive deficits, detectable on careful psychometric testing, and were at least partly reversible.

Several PET and SPECT studies in alcoholics have already been reported and a clearer picture has begun to emerge. However, our understanding of the nature of the frontal lobe changes caused by alcohol, its clinical correlates, and its relation to prolonged drinking or abstinence, remains fragmented.

The possibility that neurophysiological, neuropathological, and neuropsychological changes may antedate the alcoholism is considered, as is the possibility that alcohol may be particularly damaging to the impaired brain. Evidence is accumulating that cognitive deficit is an important predictor of outcome following treatment. In the management of states of frontal lobe changes, attention should be paid to remedying nutritional deficiency and the general principles of rehabilitation should be borne in mind.

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