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Hypoperfusion of the Cerebellum and Aging Effects on Cerebral Cortex Blood Flow in Abstinent Alcoholics: A SPECT Study

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Abstract

Background—This study evaluated hypotheses concerning alcoholism, aging, and the relationship between cerebral hypoperfusion and residual deficits in the functioning of cerebellar and neocortical brain systems.

Methods—The participants were 10 healthy abstinent alcoholics (9 men, 1 woman) and 12 nonalcoholic controls (10 men, 2 women) ranging in age from 35 to 67 years. Cerebral blood flow was observed through the use of regionally specific computer-derived quantitative analysis of single photon emission computed tomography (SPECT) perfusion images. Cerebellar perfusion was measured and compared with cerebral cortex perfusion in age-equivalent subgroups of alcoholics and controls (under 55 years; 55 years and over).

Results—In abstinent alcoholics under age 55, cerebellar perfusion ratios were significantly reduced compared with the controls. In alcoholics and nonalcoholic controls 55 years old and older, this relationship was reversed, probably as a result of diminished cortical perfusion with aging in the alcoholics and of cerebellar decline in the controls.

Conclusions—The findings support hypotheses that the residual effects of alcoholism include cerebellar brain abnormalities and that aging combined with long-term alcoholism leads to cerebral cortical decline.

Keywords

Alcoholism; Abstinence; SPECT; Regional Cerebral Blood Flow; Cerebellum

Prolonged Alcoholism Has been associated with widespread brain abnormalities and corresponding changes in mental functioning (Pfefferbaum and Rosenbloom, 1993; Rourke and Loberg, 1996). Observations of structural brain images obtained by techniques such as magnetic resonance imaging (MRI) and computerized tomography (CT) generally support evidence of a relationship between prolonged alcohol consumption and structural brain atrophy, observed as brain shrinkage, widening of the cortical sulci, and enlargement of the brain's ventricles (Jernigan et al., 1991; Pfefferbaum et al., 1992). Functional neuroimaging studies with positron emission or single photon emission computed tomography (PET or SPECT) have documented global cerebral metabolic or perfusion deficits in recently detoxified alcoholics, (Adams et al., 1993; Erbas et al., 1992; Gilman et al., 1990; Melgaard et al., 1990; Volkow et al., 1992; Wang et al., 1993), although both structural (Pfefferbaum et al., 1995) and functional (Pfefferbaum et al., 1995; Nicolás et al., 1993; Volkow et al., 1994) imaging studies have reported partial brain recovery with prolonged abstinence.

Alcoholism-related brain abnormalities become more pronounced as people age, and individuals over age 50 may have increased vulnerability to the synergistically deleterious effects of alcoholism and aging (Pfefferbaum et al., 1992; Oscar-Berman and Schendan, 1999; Ellis and Oscar-Berman, 1989; Oscar-Berman et al., 1993; NIAAA, 1997). In part, this is because older people have a decreased ability to metabolize alcohol, and they may have concomitant medical problems as well (NIAAA, 1997). From the observed similarities in the brains of alcoholic and aging individuals came a search for parallels in structural and functional decline associated with alcoholism and aging. The premature aging hypothesis has been put forth in two versions (Oscar-Berman and Schendan, 1999; Ellis and Oscar-Berman, 1989). According to the first version, the “accelerated aging” (or “cumulative effects”) model, alcoholism is accompanied by the precocious onset of neuroanatomical and behavioral changes typically associated with advancing age; alcoholics become old before their time. The second version places the timing of the changes somewhat differently. In this view, which has been labeled the “increased vulnerability” interpretation, the aging brain is more vulnerable to the deleterious influences of toxic substances, including ethanol, than is the brain of a younger person. Therefore, beginning in the fifth decade of life, alcoholism provides added momentum for the effects of normal chronological aging. Taken together, most of the evidence from neuropathological and neuroradiological investigations supports the view of a link between alcoholism and premature aging. Furthermore, studies favoring the increased vulnerability model are more common than those supporting the accelerated aging model; i.e., older alcoholics are especially vulnerable to the effects of alcoholism (Oscar-Berman and Schendan, 1999).

As predicted by the increased vulnerability model, certain brain structures have been shown to exhibit greater reduction in size in older alcoholics than in younger alcoholics. These include the cerebral cortex (Nicolás et al., 1997), the corpus callosum (Pfefferbaum et al., 1996), and medial temporal lobe structures (Sullivan et al., 1995). Alcoholics also show a stronger association between age and ventricular dilation than do nonalcoholic controls (Pfefferbaum et al., 1997; Di Sclafani et al., 1995). Pfefferbaum et al. (1997) conducted regional MRI analyses of cortical integrity and found evidence that the frontal lobes were especially vulnerable to chronic alcoholism across a wide age range, but the effects were

exacerbated in elderly people, and temporoparietal tissue loss occurred mainly in aged alcoholics.

The cerebellum is another ethanol-sensitive region of the brain (Pentney, 1993), and analogous age-related declines have been reported for the cerebellar hemispheres of alcoholics (Sullivan et al., 1996, 1998a,b). Cerebellar atrophy and degeneration have commonly been observed in neuropathological analyses of the brains of alcoholics (Pentney, 1993; Torvik and Torp, 1986; Victor et al., 1959). Although alterations in the structure of the cerebellum after long-term alcohol consumption have been noted, the means by which this occurs is not known (Pentney, 1993). Some investigators have suggested that alcoholic cerebellar degeneration results from thiamine deficiency and represents the same disease as Wernicke's encephalopathy, an acute, transient stage of alcohol-related neurological problems which include confusion and abnormalities in oculomotor and gross muscle control (Cook et al., 1998; Reuler et al., 1985; Victor, 1992). Cerebellar damage produces problems with movement (mainly gait, balance, and coordination). However, cerebellar atrophy can be present in alcoholics without significant movement abnormalities (Sullivan et al., 1995).

In the current study, SPECT imaging was used to study regional cerebral blood flow (rCBF) in the cerebellum and cerebral cortex of abstinent alcoholics and age-matched nonalcoholic controls across a wide age range (35-67 years). There were two main goals: to document the synergistic effects of chronic alcoholism and aging on brain functioning in long-term abstinent alcoholics and to examine the residual effects of chronic alcoholism on the functioning of the cerebellum. SPECT measurements were made of the cerebellum and of the cerebral cortex. Ratio measures were computed between these two measures as the index variables (i.e., cortex/cerebellum and cerebellum/ cortex ratios). One limitation of this approach is that we cannot determine absolute changes in each measure, only relative changes between them. However, we made assumptions that guided our interpretation of the results. Namely, we assumed that the cortex and the cerebellum measures would each decline (or at best not increase) with advancing age and with alcoholism, albeit at varying severities. Thus a decline in a ratio measure would be interpreted as a greater decrease in the numerator relative to the denominator, whereas a rise in a ratio measure would be interpreted as a greater decline in the denominator than in the numerator (rather than as an increase in the numerator). We expected to find less functional activity in older than in younger participants. Furthermore, in support of the increased vulnerability model of the premature aging hypothesis, we expected the greatest perfusion deficits from the older alcoholic participants.

METHODS

Participants

The experimental group in this study consisted of 10 abstinent long-term alcoholics (nine men, one woman; age mean $\pm$ SD, 56.8 ± 9.3 years). Demographic and neuropsychological information are provided in Table 1. The alcoholic participants were subdivided into "Young" and "Older" subgroups by a median split on age (greater than vs. less than 55 years); the alcoholic subgroups did not differ statistically on any of the measures in Table 1

except Age and Age-at -Last-Drink. The participants were recruited from the Department of Veterans Affairs Medical Center, from alcohol treatment programs in the Boston area, and from advertisements in local newspapers and billboards. Informed consent for participation in the research was obtained before testing.

The alcoholics were right-handed, had 20/20 vision (normal or corrected), and had been abstinent from alcohol for at least 4 weeks before testing. They met DSM-III-R criteria (Spitzer and Williams, 1987) for alcoholism as assessed by the Diagnostic Interview Schedule (DIS) Version III-Revised (Robins et al., 1989). All had histories of heavy drinking (≥ 21 drinks/week) for an average of 23 ± 9 years, and an average sobriety period of 6.1 ± 6.7 years (range: 4 months to 22 years). The alcoholics were given a structured interview in which they were questioned about the 6 months prior to abstinence (Cahalan et al., 1969). A Quantity Frequency Index was obtained by summing the amount of absolute alcohol for wine, beer, and liquor consumed and multiplying this by the frequency of consumption. The participants indicated how long they had been abstinent, the number of years of heavy drinking (more than 21 drinks/week), and the age of onset of heavy drinking. They also were given a medical history interview, the Beck Depression Inventory (Beck, 1987), and nine sections of the DIS (Demographics; Generalized Anxiety; Depression; Mania; Schizophrenia; Alcohol Abuse and Dependence; Drug Abuse and Dependence; Antisocial Personality Disorder; and Organic Brain Syndrome). Alcoholics were excluded from the study if DIS scores or hospital records, referral sources, or personal interviews indicated that they had a history of neurological disease (including epilepsy or head injury with loss of consciousness greater than 15 min), major psychiatric disorder (e.g., schizophrenia), depression, or anxiety disorder within the past 6 months, or electroconvulsive therapy, polydrug abuse, or clinical evidence of active hepatic disease.

The Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981) and the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987) were administered to the alcoholic participants to estimate general level of intellectual functioning and to obtain traditional measures of perceptual-motor and memory abilities. Visuospatial deficits were evaluated as the difference between WAIS-R Verbal IQ and WAIS-R Performance IQ scores (VIQ-PIQ difference scores). Memory deficits were calculated as the difference between WAIS-R Verbal IQ and WMS-R General Memory scores (VIQ-GM difference scores), according to convention (Oscar-Berman et al., 1993).

Twelve nonalcoholic controls were included in this study as a comparison group. Data for the nonalcoholic controls were taken from the Nuclear Medicine registry at New England Medical Center where the head SPECT procedures were performed. The first 12 people (without mass lesion on CT or MRI scan) were selected who matched the alcoholics on age (mean, $\pm$ SD: 49 ± 11 years; $t[20] = 1.79$; $p = 0.09$) and gender (10 men, two women), and who had no clinical history of alcoholism, psychotic disorder, or structural brain lesion (e.g., from stroke, tumor, or head trauma). The control group also was subdivided by age into Young and Older subgroups according to the criteria used for the alcoholic group (greater than vs. less than 55 years old). The control subgroups were equivalent to the alcoholic subgroups with respect to age, gender, and handedness. The young control subgroup included nine subjects (seven men, two women) aged 43.7 ± 7.7 years ($t[\text{sqbl}2] = 1.35$; $p =$

0.20 compared to the young alcoholic subgroup), and the older control subgroup consisted of three individuals (all men), aged 64.0 ± 3.6 years ($t[6] = 0.26$; $p = 0.80$ compared to the older alcoholic subgroup). Ten of the controls were right-handed and two were left-handed. Whereas the reasons for scans varied (e.g., headache, suspicion of supranuclear palsy, etc.), the SPECTs of all control subjects were regarded as normal by nuclear medicine attending physicians.

Head SPECT

Head SPECTs of the 10 alcoholics were compared with those of the 12 nonalcoholic controls. Each participant received an intravenous injection of 20–25 mCi (740–925 MBq) Tc-99m HMPAO, a lipophilic agent which accumulates within functioning brain parenchyma in proportion to rCBF. Injection was given in a quiet, darkened room to minimize extraneous visual and auditory stimuli. SPECT imaging was begun 30 min later, with a single-head γ camera (Siemens Rota, Hoffman Estates, IL) fitted with a low-energy, high-resolution, parallel-hole collimator. Sixty projections, 30–45 sec each (depending upon count rate), were acquired over a 360° circular rotation using a 64×64 matrix. Data were processed with standard filtered back-projection reconstruction techniques, with transaxial 6.2-mm isotropic voxel size (e.g., 6.2 mm a side in all three dimensions), and were reviewed interactively on a computer system as well as on hard copy.

rCBF Method

For each subject, the SPECT image was selected that (by visual inspection) best passed through the middle of the cerebellum. The cerebellum was outlined by an automated edge-detection algorithm, and the mean SPECT value from this region was used as the relative measure of cerebellar rCBF.

The semiquantitative analysis of rCBF in cerebral cortex used highly reliable, semiautomated software developed by our group (Harris et al., 1991). To summarize the method, the cortex was delineated as a ring extending from the outer brain edge inward for a fixed distance (based on each brain diameter) toward the brain centroid. Analyses were performed on the image that best passed through the inferior frontal lobes, defined as the most inferior image that had complete, unbroken frontal lobes without visually apparent partial volume tissue loss, and on the next superior slice. The mean cortical value averaged across the cortical ring regions in these two slices was used as the index measure of relative cerebral cortex perfusion. Thus, the cortical ring included samples of cerebral cortex from frontal, temporal, parietal, and occipital lobes, providing a broad-based measure of overall cerebral cortical perfusion. This cortical/cerebellar perfusion ratio was then subdivided by cortical hemisphere for comparison with neuropsychological measures.

Because SPECT measures are not in absolute blood flow units, it is necessary to normalize analysis regions to a reference region to compare measures across subjects. The mean cerebral cortex and mean cerebellum SPECT values were compared to each other by computing the ratio of the index region mean image value, divided by the reference region mean value $\times 100$. The cerebellum measures and cortical measures were thus computed as ratios relative to each other. The cerebellum/cortex ratio would be low if the cerebellum was

hypoperfused or if the cortex was hyperperfused. Likewise, the cortex/cerebellum ratio would decline, either from a decrease in cortical perfusion or from an increase in cerebellar perfusion. Thus, in interpreting changes and group differences in these relative measures, assumptions must be made regarding the likelihood of relative decreased or increased perfusion in the index and reference regions. Regional analyses in this study were hypothesis driven and limited to cerebellum and cerebral cortex regions, to avoid multiple comparison problems.

Statistical Analyses

Linear and binomial regressions were applied so we might examine the relationship in each group between aging (Age and Age-at-Last-Drink) and perfusion ratios as dependent variables. Comparisons also were made between the cortex/cerebellum perfusion ratio and duration and severity of drinking, duration of sobriety, and neuropsychological measures. Regressions were not additionally computed between drinking/neuropsychological measures and cerebellum/cortex ratios, because cerebellum/cortex ratios have inverse statistical correlations of the same magnitude as do cortex/cerebellum ratios, one being an inverse measure of the other. Furthermore, we assumed that the cortex was the more appropriate numerator, because it is more likely directly related to cognitive functioning.

Neuropsychological measures of visuospatial and memory functions, i.e., VIQ-PIQ and VIQ-GM difference scores, were calculated and evaluated by one-sample t-tests to assess for significant deficits relative to a stable measure (VIQ) of cognitive functioning in alcoholics. A median split of the alcoholic group was then performed based on age (greater than vs. less than 55 years), and these subgroups were compared to one another with two-tailed t-tests, and against nonalcoholic controls also split into subgroups based on the same age cutoff as the alcoholics.

It should be noted that because relative perfusion ratios were used, with cerebellar and cortical perfusion measured relative to each other, a change in these ratios could result from either an increase in one measure or a decrease in the other, e.g., a decline in the cortical/cerebellar ratio with age could result from a decrease in the cortical measure, an increase in the cerebellar measure, or some combination of the two. Therefore, it was necessary to interpret the results based on the most likely interpretation of the relative changes. The assumptions made in the discussions to follow were that it is unlikely that chronic effects of alcoholism and effects of aging resulted in cerebral perfusion increases in either the cortex or cerebellum. It is more likely that cerebellum and cortex both had declines to varying degrees at different age points. Thus, it was assumed that the older alcoholics had decreased cortical perfusion rather than increased cerebellar functioning, and that the older controls had decreased cerebellar perfusion rather than increased cortical functioning.

RESULTS

Cortical Perfusion and Neuropsychological Measures

Alcoholic subjects ($n = 10$) were divided into two subgroups based on a median split on age ($n = 5$). The demographics, drinking histories, and neuropsychological scores for the overall

group and the subgroups are presented in Table 1. Other than group differences in Age and Age-at-Last-Drink (age-years sober), the subgroups did not significantly differ on other measures. However, there were some neuropsychological deficits in the alcoholics, as well as significant correlations among imaging measures and neuropsychological variables.

A deficit in visuospatial functioning (VIQ-PIQ difference score) was observed in the overall alcoholic group ($t[9] = 3.35; p < 0.01$) and in the younger subgroup ($t[4] = 3.37; p < 0.03$); however, the deficits did not reach significance in the older subgroup ($t[4] = 1.56; p = 0.19$). In addition, performance IQ scores were significantly correlated with cortex/cerebellar ratios in the younger subgroup ($r[4] = 0.96; p < 0.005$). These correlations were somewhat stronger with the right hemisphere cortex/cerebellar ratio ($r[4] = 0.98; p = 0.002$) than with the left hemisphere measure ($r[4] = 0.91; p = 0.03$).

A significant memory deficit (VIQ-GM difference score) was observed in the older alcoholic subjects ($t[4] = 2.92; p < 0.05$) but not in the younger subgroup ($t[4] = 0.61; p = 0.57$) or in the overall alcoholic group ($t[9] = 1.90; p = 0.09$), although there was a trend in the overall group. No significant correlations were observed in the older alcoholic subgroup between imaging variables and neuropsychological scores. The neuropsychological tests were not administered to the control subjects.

Cortical Perfusion, Aging, and Drinking History

Linear regression analysis revealed a steep and significant decline in cortical/cerebellar perfusion ratio with aging in the alcoholics ($r[9] = -0.79; p = 0.006$), as can be seen in Fig. 1. The correlation was even stronger between cortical/cerebellar perfusion ratio and Age-at-Last-Drink ($r[9] = -0.90; p < 0.0001$). There were no significant correlations between cortical/cerebellar perfusion ratio and years drinking, years sober, or the quantity-frequency index of drinking severity.

The nonalcoholic controls did not show a significant linear trend ($r[11] = 0.34; p = 0.28$). However, the controls demonstrated a U-shaped relationship between aging and cortical/cerebellar perfusion ratios, resulting in two age-overlapping subgroups with significant linear regression slopes. The cortical/cerebellar ratio showed a significant linear decline in the younger control subjects between the mid-30s and mid-50s (ages 35–54) ($r[8] = -0.70; p = 0.03$), and it increased in the older control subjects between their mid-40s and mid-60s (ages 45–67) ($r[7] = 0.76; p = 0.03$). This U-shaped effect, with a minimum at about age 50, resulted in a significant second-order (binomial) regression coefficient in the controls ($t[11] = 2.84; p = 0.02$) that was not seen in the alcoholics ($t[9] = -1.17; p = 0.28$). Whereas there was a significant second-order (binomial) correlation between the cortical/cerebellar ratio and Age in control subjects, this is only a general description of the curve shape and does not imply an exact second-order relationship. The sample size in this study is too small to enable one to draw conclusions about the exact shape of such a curve.

Cerebellar Perfusion Deficits

Cerebellar deficits were then examined based on the cerebellar/cortical perfusion ratio (the inverse of the cortical/cerebellar ratio). The alcoholic participants who were 55 and younger

had significantly reduced cerebellar/cortical perfusion ratios compared with the young subgroup of controls (Table 2 and Figure 2). In participants over age 55, this pattern was reversed, with the controls demonstrating lower perfusion ratios than the alcoholics. Furthermore, the young subgroup of alcoholics had significantly lower cerebellar/cortical ratios than did the older alcoholics, whereas the older controls had significantly reduced cerebellar/cortical ratios than the younger controls.

The cerebellar/cortical perfusion ratio provided a strong discriminating variable among the subgroups. All of the alcoholics 55 years old and younger (5/5) and all of the older controls (3/3) had cerebellar/cortical perfusion ratios below 97%, whereas all but one younger control (8/9) and all of the older alcoholics (5/5) had perfusion ratios above 100%. Thus, 21 of 22 participants in the study (95%) were correctly classifiable by cerebellar/cortical perfusion ratios based on the age and diagnosis subgroupings.

DISCUSSION

In interpreting the results of the current study, some necessary assumptions were made, as noted in “Methods.” That is, we assumed that the older alcoholics had decreased cortical perfusion rather than increased cerebellar functioning and that the older controls had decreased cerebellar perfusion rather than increased cortical functioning. The discussion to follow is based upon these assumptions.

Effects of Chronic Alcoholism

Cerebellar Deficits—In the present study, the subgroup of alcoholics under the age of 55 years demonstrated clear cerebellar abnormalities evidenced by decreased cerebellar/cortical perfusion ratios. A prior PET study also reported decreased cerebellar glucose metabolism in alcoholics with clinical signs of cerebellar degeneration; the severity of cerebellar hypometabolism correlated with clinical signs of neurological impairment (Gilman et al., 1990). Cerebellar hypoperfusion or hypometabolism is consistent with cerebellar effects of long-term alcohol abuse (Sullivan et al., 1998a). Long-term alcoholics tend to exhibit broad-based gait and loss of muscular coordination and power, causing lurching and staggering, generally associated with cerebellar damage (Pentney, 1993; Sullivan et al., 1996, 1998a,b; Neiman et al., 1990). However, cerebellar atrophy can be present in alcoholics without significant movement abnormalities (Sullivan et al., 1995). Cerebellar atrophy and degeneration is commonly observed in neuropathology of alcoholics, with a severe decline in the numbers of Purkinje cells (Torvik and Torp, 1986; Victor et al., 1959). In studies of rodents, cerebellum appears to be one of the most ethanol-sensitive regions of the brain, with a large decline both in Purkinje cell numbers and in the area of Purkinje cell dendritic networks as a result of ethanol toxicity (Pentney, 1993; Walker et al., 1980, 1981). As a result, the circuitry of the cerebellum may be altered by long-term alcoholism in unpredictable ways. In keeping with our initial assumptions, we interpret the rise in cerebellar/cortical perfusion ratio in our older subgroup of alcoholics as the probable result of more severe cortical decline with aging in alcoholism, rather than of an improvement of cerebellar function.

Cortical Decline With Aging—Among the alcoholics in the present study, the cortical/cerebellar perfusion ratio decreased strongly with aging in a fashion that differed dramatically from that observed in controls. Correlations between cortical/cerebellar perfusion ratio and Age-at-Last-Drink were even stronger than the correlations with Age. These observations of age-related decline in cortical function are consistent with observations of accelerated brain atrophy and increased vulnerability in older alcoholic subjects (Pfefferbaum et al., 1992).

Alcoholism has been associated with premature aging of the brain, although there are differences of opinion about the time period in the lives of alcoholics during which premature aging begins (Ellis and Oscar-Berman, 1989; Oscar-Berman and Schendan, 1999). According to one view, aging is accelerated at whatever age problem drinking commences. This is the accelerated aging version of the premature aging hypothesis. It predicts that young alcoholics will become old before their time and that neurobehavioral and brain changes in alcoholics should mimic those found in chronologically older nonalcoholics. According to the other view, vulnerability to alcohol-related brain damage is hastened only in people over age 50, in whom the normal manifestations of aging already have begun (Oscar-Berman et al., 1993). The second view is the increased vulnerability version of the premature aging hypothesis. This view suggests that older alcoholics will suffer more age-related symptoms and be more impaired than younger alcoholics and their nonalcoholic peers because of the increased vulnerability of an aged brain. The findings in the current study—that there is a strong relation between cortical dysfunction and Age-at-Last-Drink—strengthens the suggested link between alcoholism and increased vulnerability to premature aging. Evidence for and against both versions of the premature aging hypothesis has come from studies of brain neuropathology (Courville, 1955), neuro-imaging (Pfefferbaum et al., 1992; Wilkinson and Carlen, 1982), and neurobehavior (Ellis, 1990). Results from the present study provide support for both versions of the premature aging hypothesis. That is, cerebellar perfusion ratios were significantly reduced in alcoholics age 55 and younger, whereas alcoholics over age 55 showed diminished cortical perfusion.

The premature aging hypothesis evolved from early observations of structural brain changes in alcoholics. Courville (1955) characterized the postmortem appearance of brains of alcoholics as being reduced in size and shriveled compared with the brains of age-equivalent peers, and likened these attributes to the shrinkage that is associated with normal chronological aging. Other researchers, using neuroimaging techniques, have reported similar findings. Wilkinson and Carlen (1982) compared CT brain scans of alcoholics ranging in age from 20 to 70 years old with those of patients who had medical conditions unrelated to alcoholism (Wilkinson and Carlen, 1982). The researchers found similar degrees of atrophy in the brains of alcoholics and chronologically older nonalcoholics. A recent CT scan study has provided evidence to support the view that aging increases one's vulnerability to alcoholism-related brain damage; older alcoholics displayed more brain tissue loss than younger alcoholics (Kato et al., 1991). Corroborating evidence also has come from several laboratories using MRI imaging techniques (Hayakawa et al., 1992; Pfefferbaum et al., 1992), as well as from a study of brain event-related potentials in alcoholics across a wide age span (Cadaveira et al., 1992). In addition, elderly alcoholics

have an increased risk of accidents, side effects, and overt toxicity resulting from alcohol intake, inasmuch as they may have concomitant medical problems, and they have a decreased ability to metabolize alcohol. Taken together, most of the evidence supports a possible link between alcoholism and premature aging. The present findings also are consistent with a controversial neuropsychological literature on alcoholism suggesting that brain pathology may be present in young alcoholics without clear behavioral dysfunction (Evert and Oscar-Berman, 1995; NIAAA, 1997).

Aging in Nonalcoholic Controls

Cerebellar Changes With Aging. Compared with the younger nonalcoholic controls, the older subgroup of nonalcoholics, 55 years and over, displayed a significant reduction in cerebellar/cortical perfusion ratio. A decline in cerebellar functioning in this age group is consistent with reports of increased falls among the elderly. Falls make up the largest percentage of accidents among the elderly population, and overall, falling is the second leading cause of accidental death in the United States (Apple and Hayes, 1993). It is possible that decreased cerebellar function, as observed in the current study, influences the balance and gait problems often experienced by older individuals and may contribute to their increased likelihood of suffering injurious falls (Sullivan et al., 1995).

Cortical/Cerebellar Perfusion Ratio and Aging—The pattern of cortical/cerebellar perfusion ratio change with aging was very different in the nonalcoholic controls from that of the alcoholics. In the control group, there was a U-shaped relationship between cortical/cerebellar perfusion ratio and age, with the ratio declining in individuals under 55 years of age and then rising in the older subjects; the minimum ratio occurred at approximately age 50. However, in this small sample, it is not possible to specify the exact curve shape with confidence, and the description here is meant as a general reporting of the relationship between cortical/cerebellar perfusion ratio and age in the control subjects.

This SPECT rCBF age effect in controls is strikingly similar to that reported for normal aging effects on structural gray/white matter volumetric ratios in human brains measured in vivo with MRI (Harris et al., 1994) and measured postmortem by neuropathology (Miller et al., 1980). In both of these previous reports, the gray/white ratio declined between ages 20 and 50 (from about 1.3 to about 1.1) and then rose in elderly subjects (to about 1.4 after age 70). Such a rise in gray/white ratio in the elderly would result from accelerated white matter loss in those subjects, as confirmed by a recent MRI segmentation study (Guttmann et al., 1998). In the current study, the cerebellar decline (and thus the cortical/cerebellar ratio increase) after age 50 closely parallels that observed for white matter in the gray/white studies (Guttmann et al., 1998; Harris et al., 1994; Miller et al., 1980). Thus, it appears that both gray matter volume and cortical rCBF measures undergo a gradual decline through adulthood to about age 50, after which the declines in white matter volume and cerebellar perfusion become more severe and are the more dominant factors in the normal elderly population, leading to relative increases in the gray/white volumetric and cortical/cerebellar perfusion ratios.

Miller et al. (1980) suggested that the gray/white ratio findings “might imply that two separate processes are at work, one predominantly before, and the other after middle age.” In fact, a CT study observed that white matter lesions showed a steady increase after age 50 (Go to et al., 1981), an MRI report demonstrated accelerated white matter loss after age 60 (Guttmann et al., 1998), and a neuropathological report observed more severe loss of capillary density in white matter than gray matter in the elderly (Meier-Ruge et al., 1992). Because the volume of a nerve cell body is much smaller than that of its myelinated fiber, loss of neurons in later life should be reflected by greater white matter loss and an increase in gray/white ratio.

Thus, the findings from the current study of decline in cortical/cerebellar perfusion ratio until age 50–55, followed by an increase in this ratio in older subjects, are consistent with data from other structural neuroimaging and neuropathology reports showing similar patterns in gray and white matter changes. The data are consistent with a roughly linear loss of cortical gray matter throughout adult life, with an accelerated decline in white matter and cerebellum after age 50–55.

Relationship of Imaging and Neuropsychological Measures in Alcoholic Participants

A positive relationship was observed between cortical/ cerebellar perfusion ratio and PIQ in the younger alcoholic subgroup, who also displayed significantly lower VIQ-PIQ difference scores. The correlation between cortical/cerebellar hypoperfusion and lower PIQ was slightly stronger in the right hemisphere than in the left hemisphere. These findings are consonant with a model of alcoholism-related brain impairment that suggests right hemispheric vulnerability (Rourke and Loberg, 1996). The Right Hemisphere hypothesis posits that the right half of the brain is more susceptible to the effects of alcoholism (or to the effects of aging) than the left half of the brain (Bates and Convit, 1999; Oscar-Berman and Schendan, 1999; Parsons, 1987; Rourke and Loberg, 1996). In other words, a disproportionate decline in nonverbal, visuospatial functions has been attributed to a greater sensitivity of the right hemisphere to the neurobiological consequences of alcoholism or aging. Studies of right hemisphere contributions to cognitive (visuospatial and perceptual) functions in alcoholism and aging have provided only equivocal support for the hypothesis that alcoholism and aging —alone or together —differentially affect the functioning of the two cerebral hemispheres (Ellis and Oscar-Berman, 1989; Oscar-Berman and Schendan, 1999; Parsons and Nixon, 1993; Parsons, 1993; Rourke and Loberg, 1996). Affirmative findings from the present study may reflect the fact that SPECT measures are more sensitive to brain abnormalities than a variety of neuropsychological tests (Lezak, 1995). Given the small sample size of the present investigation, however, the above speculations are interpreted as suggestive rather than confirmatory.

No significant correlations were observed between imaging and neuropsychological measures in the older alcoholic subgroup. The older alcoholic subgroup demonstrated a relative memory impairment (VIQ-GM difference score), which was not evident in the younger subjects. However, we cannot discern whether these memory deficits result from normal aging or from an interaction of aging and alcoholism, inasmuch as we do not have these neuropsychological data for the control subjects.

This study has several limitations that must be discussed in interpreting these data. Several explanations are possible for the limited relationships observed among imaging and neuropsychological measures. Speculation is offered here that the time of evaluation may impact the findings: IQ and memory functions may be particularly sensitive to the acute stages of alcohol withdrawal and for a relatively short period thereafter, with resolution occurring given long-term sobriety (Gansler et al., 1999). It follows that with an average of 6 years of sobriety in the subjects from the present study, neuropsychological improvement may have occurred during sobriety. Furthermore, the dependent variable is a relative imaging measure, the cortex/cerebellar perfusion ratio, or its inverse. Changes in such a relative measure can result from changes in the numerator, the denominator, or a combination of the two measures. Therefore, linear regression analyses may not be as sensitive to changes in this ratio, which may change in complex ways due to interactions between the numerator and denominator measures. Unfortunately, there is not a known reliable “normal” brain region in alcoholism to use as the reference region. Alternatively, it is possible that SPECT measures are independent of overt neurobehavioral measures (Dupont et al., 1996; Gansler et al., 1999). However, given the small sample size of the present investigation, particularly subgroup comparisons, the above interpretations are suggestive rather than confirmatory.

Conclusions

In the alcoholic sample of the present study, the SPECT-derived cortical/cerebellar rCBF perfusion ratios showed a steady decline with age. By contrast, in the sample of nonalcoholic controls, the cortical/cerebellar perfusion ratios were U-shaped, declining with age before 55 years and increasing after age 55. Cerebellar/cortical perfusion ratios in the subgroups of young alcoholics and older nonalcoholic controls were diminished, compared with young controls and older alcoholics. Taken together, these findings are consistent with results of other studies showing that cerebellar brain abnormalities are present in abstinent alcoholics, and with hypotheses positing that aging combined with long-term alcoholism leads to cerebral cortical decline. The findings also suggest that cerebellar perfusion decreases with normal chronological aging.

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Fig. 1.

Cortical/cerebellar ratios subdivided by diagnostic group. The cortical/cerebellar ratios declined significantly with age in the alcoholics and was U-shaped in the nonalcoholic controls, declining with age before 55 years and increasing in the older controls.

Fig. 2.

Cerebellar/cortical perfusion ratios by diagnostic groups subdivided into age subgroups. Overall, across both groups, 95% of the subjects could be classified on the basis of their cerebellar/cortical perfusion ratio and their age and diagnostic grouping. Young alcoholics and older controls had diminished cerebellar/cortical ratios relative to young controls and older alcoholics.

Table 1

Demographic Information Regarding the Alcoholic Research Participants

	Alcoholic participants	Median split on age	
		Young (<55 yr)	Older (>55 yr)
No.	10	5	5
Age (yr)	56.8 ± 9.3	49.0 ± 5.7	64.6 ± 2.9
Age at last drink	50.7 ± 9.8	43.5 ± 5.4	57.9 ± 7.5
Gender (M/F)	9/1	4/1	5/0
Education	15.5 ± 1.8	15.6 ± 2.6	15.4 ± 0.9
Yr drinking	23.1 ± 9.4	20.0 ± 7.9	26.1 ± 10.6
Yr sober	6.1 ± 6.7	5.5 ± 4.9	6.7 ± 8.7
Quant, freq. index	11.3 ± 4.7	11.7 ± 6.3	10.7 ± 2.3
Full-scale IQ	124 ± 15	121 ± 12	127 ± 18
Performance IQ	115 ± 14	111 ± 8	118 ± 19
Verbal IQ (VIQ)	126 ± 14	126 ± 14	127 ± 15
VIQ-PIQ diff.	11.8 ± 11.1	14.8 ± 9.8	8.8 ± 12.6
Gen. mem. (GM)	119 ± 12	122 ± 11	117 ± 13
VIQ-GM diff.	7.1 ± 11.8	4.2 ± 15.3	10.0 ± 7.6
Beck score	4.8 ± 5.3	2.4 ± 3.4	7.2 ± 6.2

Note: The two alcoholic subgroups (median split by age into young or older) were statistically similar (all $t < 1.53$; $p > 0.16$) on all variables except for Age and Age at Last Drink. Significant visuospatial deficits (VIQ-PIQ) were observed in the overall group and in the young subjects ($t > 3.35$; $p < 0.03$). Memory deficits (VIQ-GM) were observed only in the older subgroup ($t = 2.92$; $p < 0.05$). The comparison group consisted of 12 nonalcoholic controls who were group- matched to the alcoholics on age, gender, and handedness. The control group was split into young ($n = 9$) and older subgroups ($n = 3$) based on the same age breaks as the alcoholics. The control subgroups were also equivalent to the respective alcoholic subgroups on age, gender, and handedness.

Table 2

Cerebellum/Cortical Perfusion Ratios in the Alcoholic and Control Groups Subdivided by Age (cutoff 55 yr)

	Alcoholics	Controls	(<i>t</i> -value (df))	<i>p</i> -value
Young (<55 yr)	94.1 ± 3.1 (<i>n</i> = 5)	102.8 ± 3.5 (<i>n</i> = 9)	4.59 (12)	0.0006
Older (>55 yr)	106.2 ± 4.4 (<i>n</i> = 5)	95.1 ± 1.7 (<i>n</i> = 3)	4.10(6)	0.006
(<i>t</i> -value (df))	5.07 (8)	3.54 (10)		
<i>p</i> -value	0.001	0.005		