Decreased Volume of the Brain Reward System in Alcoholism

Nikos Makris, Marlene Oscar-Berman, Sharon Kim Jaffin, Steven M. Hodge, David N. Kennedy, Verne S. Caviness, Ksenija Marinkovic, Hans C. Breiter, Gregory P. Gasic, and Gordon J. Harris

Background: Reinforcement of behavioral responses involves a complex cerebral circuit engaging specific neuronal networks that are modulated by cortical oversight systems affiliated with emotion, memory, judgment, and decision making (collectively referred to in this study as the "extended reward and oversight system" or "reward network"). We examined whether reward-network brain volumes are reduced in alcoholics and how volumes of subcomponents within this system are correlated with memory and drinking history.

Methods: Morphometric analysis was performed on magnetic resonance brain scans in 21 abstinent long-term chronic alcoholic men and 21 healthy control men, group-matched on age, verbal IQ, and education. We derived volumes of total brain and volumes of cortical and subcortical reward-related structures including the dorsolateral-prefrontal, orbitofrontal, cingulate cortices, and the insula, as well as the amygdala, hippocampus, nucleus accumbens septi (NAc), and ventral diencephalon.

Results: Morphometric analyses of reward-related regions revealed decreased total reward-network volume in alcoholic subjects. Volume reduction was most pronounced in right dorsolateral-prefrontal cortex, right anterior insula, and right NAc, as well as left amygdala. In alcoholics, NAc and anterior insula volumes increased with length of abstinence, and total reward-network and amygdala volumes correlated positively with memory scores.

Conclusions: The observation of decreased reward-network volume suggests that alcoholism is associated with alterations in this neural reward system. These structural reward system deficits and their correlation with memory scores elucidate underlying structural-functional relationships between alcoholism and emotional and cognitive processes.

Key Words: Alcoholism, amygdala, dorsolateral-prefrontal cortex, MRI, nucleus accumbens, reward system

Emotional, memory, and motivational abnormalities in alcoholism are associated with changes in the mesocorticolimbic system (1,2), a complex multifunctional network responsive to positive and negative reinforcement. Positive reinforcement (reward) increases the probability of a subsequent response, and drugs of abuse are at least as potent as natural reinforcers (e.g., food) (3). Circuitry involved in the development of reinforced behaviors is a central part of this network (see Figure 1). Principal components of the mesocorticolimbic reward circuit include amygdala, hippocampus, nucleus accumbens (ventral striatum), and ventral diencephalon (including basal forebrain, ventral tegmentum, and hypothalamus), as well as cortical areas with modulating and oversight functions, such as dorsolateral-prefrontal, orbitofrontal, temporal pole, subcallosal, and cingulate cortices, parahippocampal gyri, and the insula (2,4–15). We hypothesized that morphometric abnormalities would present in alcoholic subjects in these subcortical gray-matter limbic and paralimbic regions, which mediate primary reward functions, together with associated cortical centers, which are important for executive functioning, emotional judgment and responses, decision making, and oversight (2,16). Collectively, this cortical/subcortical circuit is referred to in this study as the "extended reward and oversight system" or the "reward network." However, in addition to reward functions, this system is associated with motivation and evaluation, approach and avoidance, impulsivity and inhibition, and reward and punishment.

In alcoholics, brain regions previously studied with magnetic resonance imaging (MRI) include frontal lobes, cingulate cortex, striatum, amygdala, hippocampus, hypothalamus, and cerebellum (17–20). Most studies demonstrated alcoholism-related structural changes, including atrophy and white-matter damage (17,18,21–23). However, no prior study comprehensively assessed the reward network as an interconnected system in its entirety and in its subcomponents. Brain regions that have received relatively little attention in alcoholism include nucleus accumbens septi (NAc) and ventral diencephalon. Studying groups of anatomic regions, which are components of structural and functional circuits, is an important avenue in identifying a biomarker for a disease (15,24).

Using MRI in this study, we analyzed brains of abstinent long-term chronic alcoholic subjects (AL) and group-matched healthy nonalcoholic control subjects (NC) to test the hypothesis that alcoholism is associated with volumetric changes in the reward network. We also explored relationships of volumetric alterations of the reward network with memory, IQ, and drinking history.

Methods and Materials

Subjects

Participants were right-handed men from the Boston area. Handedness was determined by a handedness questionnaire (25) and the Edinburgh Inventory (26). The study included 21 AL

Athinoula A. Martinos Center (NM, SKJ, SMH, DNK, VSC, KM, HCB, GPG), Harvard Medical School Departments of Neurology, Psychiatry, and Radiology Services; Center for Morphometric Analysis (NM, SKJ, SMH, DNK, VSC, KM, HCB, GPG), Massachusetts General Hospital; VA Healthcare System, Boston Campus (NM, MO-B); Departments of Psychiatry, Neurology, and Anatomy & Neurobiology (NM, MOB), Boston University School of Medicine; Radiology Computer Aided Diagnostics Laboratory (SKJ, SMH, GJH), Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts.

Address reprint requests to Marlene Oscar-Berman, Ph.D., Boston University School of Medicine, Suite L-815, 715 Albany Street, Boston, MA 02118; E-mail: oscar@bu.edu.

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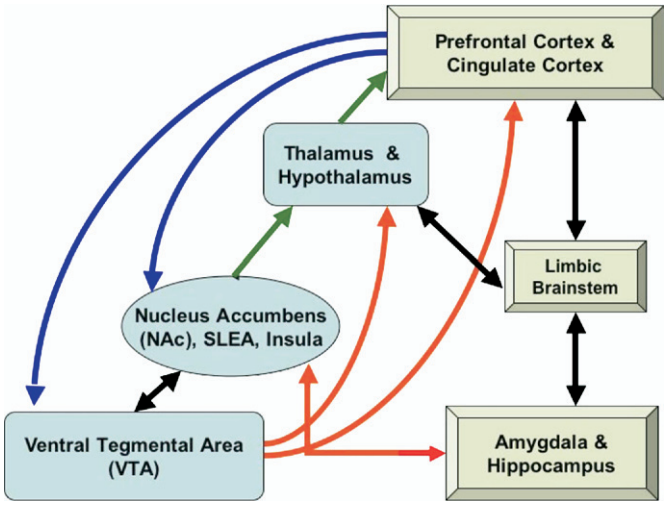

Figure 1. Brain regions involved in the extended reward and oversight system. Prefrontal and cingulate regions connect to the nucleus accumbens (NAc) in the ventral striatum, the midbrain ventral tegmental area (VTA), and reciprocally with other limbic system structures (limbic brainstem, amygdala, and hippocampus). Limbic structures also interconnect with the NAc and to the basal forebrain (substantia innominata, or sublenticular extended amygdala [SLEA]). The VTA projects to the NAc (reciprocally), to the thalamus and hypothalamus, and to prefrontal cortex. The NAc projects to the thalamus, which projects to prefrontal cortex.

individuals, abstinent from alcohol at least 4 weeks, and 21 healthy NC subjects (Table 1). Participants were native English speakers with comparable socioeconomic backgrounds. Groups were comparable with respect to demographic variables.

Participation was solicited from newspaper and Web-based advertisements and from Boston University Medical Center, Boston Veterans Affairs (VA) Healthcare System, and VA aftercare programs. Twenty participants (12 NC, 8 AL) were veterans. This study was approved by the institutional review boards of the participating institutions. Informed consent was obtained from each subject before neuropsychological testing and scanning. Participants were reimbursed for time and travel expenses. Neurobehavioral and psychiatric evaluations typically required from 7 to 9 hours over 2 or more days. Participants had frequent breaks, and sessions were discontinued and rescheduled if a subject indicated fatigue.

Neurobehavioral and Psychiatric Evaluations

Participants underwent medical history interview and vision testing, plus a series of questionnaires (e.g., handedness, alcohol and drug use) to ensure they met inclusion criteria. Participants performed a computer-assisted, shortened version of the Diagnostic Interview Schedule (DIS) (27) that provides lifetime psychiatric diagnoses according to DSM-IV (28) criteria. Participants were excluded if any source (DIS scores, hospital records, referrals, or personal interviews) indicated they had one of the following: history of neurological dysfunction (e.g., major head injury with loss of consciousness greater than 15 min, stroke, epilepsy, or seizures unrelated to alcohol withdrawal); electroconvulsive therapy; major psychiatric disorder (e.g., schizophrenia or primary depression); symptoms of clinical depression within the 6 months before testing; current use of psychoactive medication; history of abuse of drugs besides alcohol; clinical evidence of active hepatic disease; history of serious learning disability or dyslexia; and uncorrected abnormal vision or hearing problem.

Participants received a structured interview regarding their drinking patterns, including length of abstinence and years of heavy drinking. A Quantity Frequency Index (QFI), which factors the amount, type, and frequency of alcoholic usage over the past 6 months (for the nonalcoholic subjects) or over the 6 months preceding cessation of drinking (for the alcoholic subjects) was calculated for each participant (29). Heavy drinking was quantified as greater than 21 drinks per week (one drink: 355 ml beer, 148 ml wine, or 44 ml hard liquor). The AL group had QFI of 11.2 ± 9.4, had heavy drinking for 18.3 ± 8.5 years, and had been sober for 5.9 ± 10.4 years. The NC group had QFI of .4 ± .5. AL participants met DSM-IV (28) criteria for alcohol abuse and dependence for a period of at least 5 years in their lives and had abstained from alcohol for at least 4 weeks before testing.

Tests of intelligence, memory, and affect were administered, including the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III, for Verbal IQ, Performance IQ, and Full-Scale IQ) (30), Wechsler Memory Scale, 3rd edition (WMS-III, for General Memory and Working Memory) (31), Hamilton Depression Scale (32), Profile of Mood States (POMS) (33), and Multiple Affect Adjective Check List (MAACL) (34). Subtests of the WAIS-III that have been reported as sensitive to alcohol-related visuospatial dysfunction are Digit Symbol, Picture Arrangement, Block Design, and Object Assembly (35–37). In addition, subjects underwent the following tests sensitive to frontal brain systems: Trail Making Test versions A and B (38); a computer scored (39) Wisconsin Card Sorting Test (WCST) (40,41); and the Controlled Oral Word Association Test (COWAT) (42).

MRI Acquisition

The MRI scans were obtained at Massachusetts General Hospital (MGH) on a Siemens 3-Tesla Trio scanner (Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania). Image acquisitions included sagittal scout, T2-weighted turbo spin echo (T2-TSE) (to rule out gross pathology), and two T1-weighted magnetization prepared rapid gradient echo (MP-RAGE) series for volumetric analysis (repetition time = 2530 msec, echo time = 3.31 msec, inversion time = 1100 msec, flip angle = 7°, field of view = 256 mm, slice thickness = 1.33 mm, number of slices = 128 contiguous, sagittal images of the entire brain, matrix = 256 × 256, number of excitations = 2). The two MP-RAGE series were averaged, then the averaged series was resliced in a standard coronal three-dimensional brain coordinate system (43). Images were reformatted to standard spatial orientation, but not rescaled in size.

MRI Morphometric Analysis

Image analyses followed semiautomated procedures developed by the Center for Morphometric Analysis at MGH (44–46). Intracranial volumes were segmented on T2-TSE images because cerebrospinal fluid has a bright T2-TSE signal, allowing clear demarcation within the intracranial vault (meninges/dura). Gray matter, white matter, and ventricles were segmented on T1-weighted images using a computer-assisted approach (44). Gray matter was then subdivided into cortical and subcortical components. Neocortex was subdivided further into parcellation units, involving a number of manual and computer-assisted operations (47). Cortical subcomponents of the reward network were derived: dorsolateral-prefrontal (defined as the sum of the dorsolateral superior-frontal and middle-frontal gyri, approximating Brodmann's cytoarchitechtonic areas 8, 9, and 46), insula, subcallosal, orbitofrontal, and cingulate cortices, parahippocampal gyrus, and temporal pole (see Figures 2 and 3). Gray matter

Table 1. Demographic, Clinical, and Neuropsychological Testing Data

	Nonalcoholic Comparison Subjects ($n = 21$)[a]	Subjects with Alcoholism ($n = 21$)[a]	
	Mean ± SD	Mean ± SD	*p* Value
Age at Scan	54.0 ± 11.8	50.7 ± 11.7	.36
Years of Education	14.5 ± 2.0	13.5 ± 2.1	.13
IQ and Memory			
Full Scale IQ[b]	109.2 ± 10.4	103.8 ± 12.0	.13
Verbal IQ	109.3 ± 11.6	106.8 ± 12.0	.50
Performance IQ	107.7 ± 10.7	99.7 ± 12.6	.04
General Memory[c]	103.3 ± 14.2	99.4 ± 11.5	.34
Working Memory	105.6 ± 13.8	109.3 ± 18.1	.46
WAIS-III[b] Performance Subtests			
Digit Symbol	10.4 ± 2.8	8.2 ± 2.3	.01
Block Design	11.1 ± 2.6	10.3 ± 2.9	.35
Picture Arrangement	11.3 ± 2.7	10.4 ± 2.3	.27
Object Assembly	9.9 ± 3.1	10.3 ± 2.9	.69
Executive Functioning			
WCST Perseverative Errors (%)[d]	44.5 ± 33.2	42.4 ± 28.2	.83
COWAT Word Generation (%)[e]	44.5 ± 19.9	39.0 ± 24.5	.44
Time (sec) to Complete Trails A[f]	33.9 ± 12.8	33.8 ± 14.9	.98
Time (sec) to Complete Trails B	87.3 ± 32.0	77.5 ± 36.0	.36
Depression Inventories			
POMS[g]	37.9 ± 4.2	42.4 ± 8.5	.04
MAACL[h]	46.4 ± 5.7	57.2 ± 30.8	.13
Hamilton[i]	1.2 ± 1.2	4.5 ± 5.4	.01
Anxiety Measure			
MAACL	43.4 ± 5.0	48.2 ± 12.3	.11
Drinking History			
QFI[j]	.4 ± .5	11.3 ± 9.4	<.0001
Years of consuming 21+ drinks/week	—	18.3 ± 8.6	
Length of sobriety (years)	—	5.9 ± 10.4	

[a]One control subject did not receive neuropsychological or clinical tests, and one alcoholic subject did not complete the Multiple Affect Adjective Check List.
[b]Wechsler Adult Intelligence Scale, 3rd edition (30).
[c]Wechsler Memory Scale, 3rd edition (31).
[d]Wisconsin Card Sorting Test (40,41).
[e]Controlled Oral Word Association Test (42).
[f]Trail Making Test versions A and B (38).
[g]Profile of Mood States (33).
[h]Multiple Affect Adjective Check List (34).
[i]Hamilton Depression Scale (32).
[j]Quantity-Frequency Index (a drinking severity scale) (29).

subcortical structures in the reward network included NAc (46), amygdala, hippocampus (44,48), and ventral diencephalon (49), which according to our morphometric definition contains the hypothalamus, basal forebrain, and sublenticular extended amygdala (SLEA), as well as a large portion of ventral tegmentum (which is included in our ventral diencephalon region by convention although part of midbrain). For comparisons to reward-network regions, we included analyses of non-reward-related frontal cortex ("frontal pole," defined in each hemisphere as cortex anterior to a coronal plane at the rostral end of the anterior horizontal ramus of the Sylvian fissure [47]), sensory cortex (cuneal cortex), and subcortical (dorsal striatum) regions.

Segmentation and cortical parcellation were carried out by an experienced research assistant (SKJ) with training in neuroanatomy, supervised by our neuroanatomist (NM). Blindness of group assignment was maintained during analysis. High interrater and intrarater reliability of these methods has been established (47–54).

Topological Analyses

Prior studies have indicated atrophic changes in amygdala and hippocampus in alcoholic subjects (21,22,55,56). Therefore, to elucidate further the subregions of the structures potentially affected by alcoholism, we performed topological analyses using methods described in a previous report (54). Skull-stripped T1-weighted scans were registered (FSL/FLIRT: see http://www.fmrib.ox.ac.uk/fsl) to a template scan of a 35-year-old normal male subject (distinct from either group). Hippocampus and amygdala probability for each group was calculated on a voxel-by-voxel basis with the aligned data. Isosurfaces for the .5-probability regions were created for each cohort. These surfaces were visualized in three-dimensional space to look for systematic group differences in topology of hippocampus and amygdala.

Volumetric and Correlation Analyses

Statistical analyses were performed using JMP software (version 5.0.1.2; SAS Institute, Cary, North Carolina). Regions were

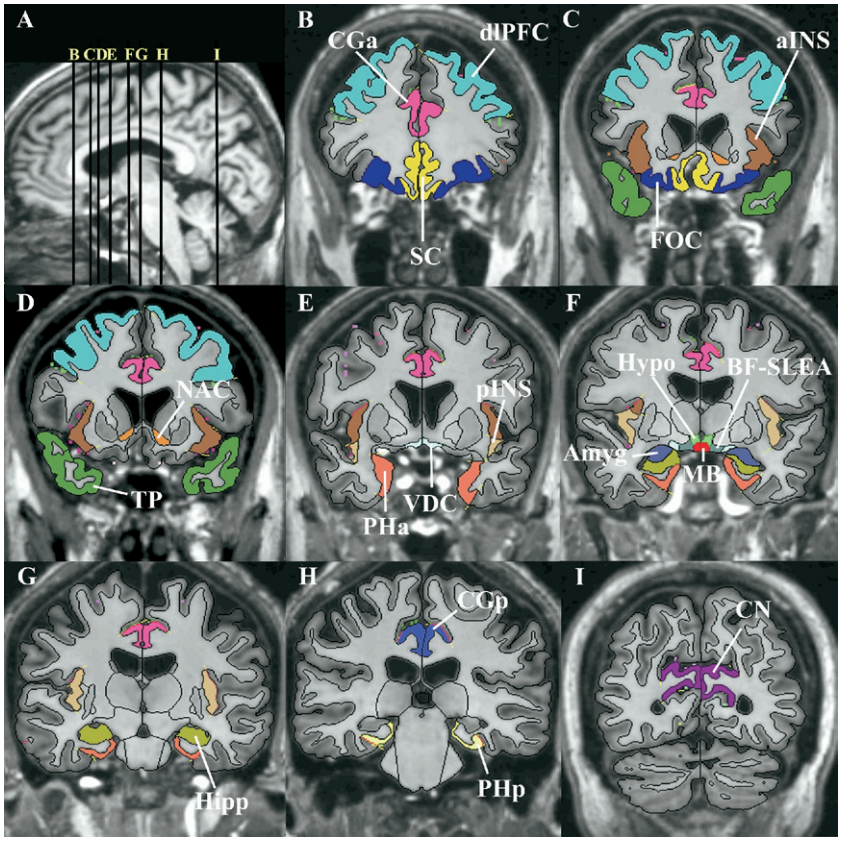

Figure 2. Segmentation method of the cortical and subcortical structures composing the reward system, shown in T1-weighted magnetic resonance images (44,47). Image A shows the midsagittal section on which vertical lines indicate the locations of representative coronal slices of images B–I. aINS, anterior insular lobule; Amyg, amygdala; BF-SLEA, basal forebrain/sublenticular extended amygdala; CGa, anterior cingulate cortex; CGp, posterior cingulate gyrus; CN, cuneal cortex (a cortical control region not included in the reward network); dlPFC, dorsolateral-prefrontal cortex; FOC, orbitofrontal cortex; Hipp, hippocampus; Hypo, hypothalamus; MB, mammilary body; NAC, nucleus accumbens area; PHa, anterior parahippocampal gyrus; PHp, posterior parahippocampal gyrus; pINS, posterior insular lobule; SC, subcallosal cortex; TP, temporal pole; VDC, ventral diencephalon.

defined as raw volumes and as ratios to cerebrum size. Between-group comparisons were made on raw volumes using analysis of covariance (ANCOVA) controlling for age and total cerebral volume (for global brain volume measures, only age was covaried). We applied a multilevel data analysis approach. First, global volumetric brain measures were assessed to determine whether there were global differences in brain, gray matter, white matter, or cerebrospinal fluid volumes between groups. Second, we assessed the reward network as a whole (sum of all reward-network regions), to determine whether the reward network specifically was affected in alcoholism. Third, if total reward-network group differences were observed, we followed the overall reward-network analysis with post hoc assessments of differences within the reward network by using ANCOVA of reward-related subregions. Thus, following the single total reward-network analysis, in the presence of positive findings, we probed which regions were most affected within the reward network, knowing that overall differences existed. Therefore, this final post hoc analysis was exploratory, and multiple comparison corrections were not applied.

Within-group partial correlation analyses, covaried for age and total cerebrum volume, were applied to assess relationships between regional reward-network volumes with memory, IQ, and drinking history. Distribution of drinking history measures such as length of abstinence were highly skewed. Therefore, log values of drinking history measures were used in correlation analyses. Only total reward-network volume and bilateral volumes of those subregions showing post hoc group differences were included in the correlation analyses to limit the number of comparisons.

Results

Subjects

Table 1 provides group comparisons on demographic and neuropsychological test measures. Groups did not differ significantly in age, Full-Scale or Verbal IQ, memory scores, or education, although AL subjects scored significantly lower on Performance IQ. Both groups were in the clinically normal range for depression and anxiety scores, although the AL group's scores were higher than the NC group's. The only significant group differences on neurobehavioral comparisons were decreased Performance IQ (especially Digit Symbol subtest scores) and higher depression scores in AL subjects.

Morphometric Analyses

Morphometric measures of global brain volume (Table 2) showed that intracranial volume and total cerebrum volume were both 4.5% larger in the AL than the NC group ($p = .14$). Although brain size and age were not significantly different between groups, we covaried for these variables in subsequent regional analyses to account for modestly larger brains and younger age in the AL group. Thus, reward-related regions were analyzed by covarying raw volumes for total cerebrum volume and age. Total reward network (sum of all reward regions of interest volumes bilaterally) showed a significant decrease in AL subjects (Table 2). As a second-level analysis, having identified overall reward-network volume decrease in AL, we performed post hoc analyses of reward-network subregions (Table 3). Within the reward network, individual structures that demonstrated significant ($p < .05$) volumetric decrease were right dorsolateral-prefrontal cortex, right anterior insular lobule, and

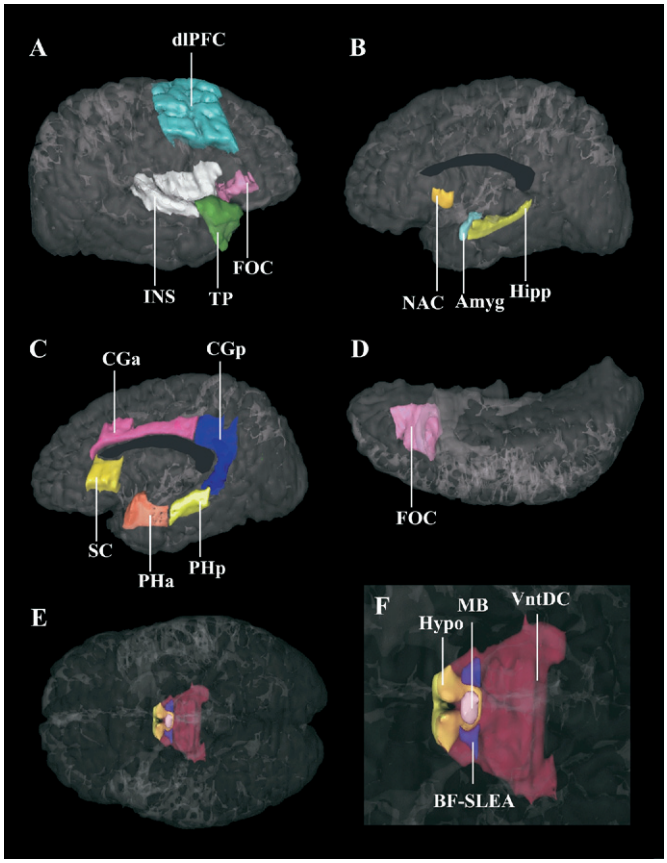

Figure 3. Three-dimensional representation of the cortical and subcortical structures composing the reward system in the human brain. **(A)** Lateral view of the right hemisphere. **(B and C)** Medial view of the right hemisphere. **(D)** Inferior view. **(E and F)** Ventral views of both hemispheres showing the hypothalamus, mammillary bodies, sublenticular extended amygdala, and ventral diencephalon. The latter structures are shown in image F in a zoomed view. Amyg, amygdala; BF-SLEA, basal forebrain/sublenticular extended amygdala; CGa, anterior cingulate cortex; CGp, posterior cingulate gyrus; dlPFC, dorsolateral-prefrontal cortex; FOC, orbitofrontal cortex; Hipp, hippocampus; Hypo, hypothalamus; INS, insula; MB, mammillary body; NAC, nucleus accumbens area; PHa, anterior parahippocampal gyrus; PHp, posterior parahippocampal gyrus; SC, subcallosal cortex; TP, temporal pole; VDC, ventral diencephalon.

right NAc. Left amygdala showed a trend ($p < .07$) toward decreased volume. However, assessed as a ratio to total cerebrum volume covaried for age, left amygdala was significantly decreased in AL subjects ($p < .05$).

Nonreward reference regions included frontal pole as a frontal cortex control region, cuneal cortex as a sensory-cortex control region, and dorsal striatum as a subcortical control region. These regions did not differ between groups.

Topological Analyses

Topological analyses of amygdala and hippocampus showed group differences in topology. Decreased volume in AL was localized in basolateral-central nuclear groups of amygdala and subicular region (Figure 4). This was principally noted in left amygdala, which showed reduced volume in AL.

Correlations Associating Morphometry with Memory, IQ, Age, and Drinking History

In AL subjects, age was significantly correlated with increasing length of abstinence ($r = .59$; $p = .005$) and had trends toward correlation with increasing years of heavy drinking ($r = .42$; $p = .06$), and decreasing QFI ($r = -.36$; $p = .11$). Cerebral cortex volume had positive partial correlation, covarying for age, with length of abstinence ($r = .48$; $p = .03$), and negative partial correlation with years of heavy drinking ($r = -.49$; $p = .03$). Both groups displayed decreasing brain volume and increasing ventricular volume with increasing age. However, these age effects were significant in AL subjects (brain: $r = -.43$; $p = .05$, ventricles: $r = .56$; $p = .01$) but not in NC (brain: $r = -.29$; $p = .2$, ventricles: $r = .24$; $p = .3$).

Total reward-network volume, and specific reward regions showing post hoc morphometric differences (dorsolateral-prefrontal cortex, anterior insula, NAc, and amygdala) were included bilaterally in correlation analyses with memory, IQ, and drinking history. Because the AL group on average was 3.3 years younger with 4.5% larger brains than the NC group and because aging affects morphometry and cognition, partial correlations were applied covarying for age and total cerebrum volume. We restricted analyses to these regions and behavior and demographic measures to limit the number of comparisons.

Although groups were equivalent on Full-Scale IQ and memory test scores, they differed with respect to correlations between memory scores and volumes of reward circuit regions (Table 4). In AL subjects but not in NC subjects, total reward-network volume correlated positively with Working Memory scores, and total amygdala volume correlated with General Memory scores. NAc and anterior insula volumes increased with length of sobriety in AL subjects, demonstrating morphometric improvement with length of abstinence. IQ measures did not show significant correlations with reward-network measures in either group.

Discussion

The extended reward and oversight system consists of a network of cortical and subcortical regions that mediate the effects of positive and negative reinforcement (reward and aversion). By virtue of its cortical and subcortical centers and its multiple interconnections (57,58), the reward network is central to such functions as sensory processing, stimulus-reward associations and memory, and determination of mood (58–60). This system is strongly involved in executive functions and decision making (61), inhibition of perseverative behaviors (14), and initiating drug and alcohol abuse or relapse (1). In this study, we used segmentation-based MRI morphometry to measure volumetric brain alterations in abstinent long-term alcoholic men. We tested the hypothesis that the reward network is altered volumetrically in alcoholism. We observed that total reward-network volume was significantly reduced in alcoholic men compared with nonalcoholic control subjects. Reward regions affected included right dorsolateral-prefrontal cortex, right anterior insula, right NAc, and left amygdala. In alcoholic subjects, total reward network volume correlated positively with Working Memory scores, and amygdala volume correlated with General Memory. Furthermore, NAc and anterior insula volumes improved in alcoholic subjects with increasing length-of-abstinence, suggesting some potential recovery of structural deficits. Deficits were specific to the reward network; global brain and gray matter measures did not differ between groups, nor did cortical (frontal pole, cuneal cortex) or subcortical (dorsal striatum) control regions.

Prior structural neuroimaging studies in alcoholism have focused principally on global atrophic changes in cerebral

Table 2. Morphometric Measures of the Total Extended Reward and Oversight System (Total Reward Network) Expressed as Raw Volume (in cubic centimeters) and as a Ratio to Total Cerebrum Volume (%)

Region	Nonalcoholic Comparison Subjects ($n = 21$) Mean ± SD	Subjects with Alcoholism ($n = 21$) Mean ± SD	ANCOVA Group Effect[a] *t* Value
Total Reward Network Measures			
Reward Ratio to Total Cerebrum Volume (%)	12.2 ± 0.6	11.5 ± 1.0	−2.4[b]
Reward Raw Volume (cc)	128.9 ± 13.6	127.6 ± 14.1	−2.2[b]
Global Measures (cc)			
Intracranial Volume	1456.9 ± 112.7	1491.1 ± 121.7	.9
Total Brain	1210.1 ± 124.0	1264.3 ± 110.8	1.2
Total Cerebrum	1061.7 ± 111.2	1109.9 ± 99.4	1.2
Total Cerebral Cortex	524.9 ± 53.5	537.7 ± 64.1	.4
Total Cerebral White Matter	456.1 ± 62.8	492.9 ± 65.0	1.6
Total Ventricular System	29.3 ± 16.4	27.0 ± 9.1	−.2

ANCOVA, analysis of covariance.

Raw volumes (cc) of the global brain regions are presented. Components of the reward network are shown in Table 3.

[a]For total reward network measures, we show the *t* value of the Group effect from the univariate ANCOVA tests on Raw Volumes, covaried for Total Cerebrum Volume ($p < .001$) and for age ($p = .4$) and on Ratio to Total Cerebrum Volume, covaried for age; for the global measures, we show the *t* value of the Group effect from the univariate ANCOVA tests on raw volumes, covaried for Age. There were significant Age effects ($p < .05$) for Total Brain, Cerebrum, Cortex (decreasing volume with age), and Ventricular System (increasing volume with age).

[b]$p < .05$.

cortex, white matter, and cerebellum, plus local effects in hippocampus (62), demonstrating volume reduction (21–23,63). Smaller right amygdalae have been reported in relatives of alcoholics (56). Neuropathologic observations demonstrated alcoholism-related neuronal loss in prefrontal association cortex, hypothalamus, and cerebellum (64,65). Frontal dysfunction in alcoholism has been demonstrated by neuropsychological investigations (66–71) and by metabolic (20), cerebral blood

Table 3. Volumes of Regions Within the Extended Reward and Oversight System (Reward Regions) and Nonreward Control Regions, Expressed as a Ratio to Total Cerebrum Volume (%)

	Left Hemisphere			Right Hemisphere		
Region	Nonalcoholic Comparison Subjects ($n = 21$) Mean ± SD	Subjects with Alcoholism ($n = 21$) Mean ± SD	ANCOVA Group Effect[a] *t* Value	Nonalcoholic Comparison Subjects ($n = 21$) Mean ± SD	Subjects with Alcoholism ($n = 21$) Mean ± SD	ANCOVA Group Effect[a] *t* Value
Subcortical Reward Regions						
Nucleus Accumbens	.054 ± .01	.053 ± .01	−.5	.054 ± .01	.047 ± .01	−2.5[b]
Amygdala	.15 ± .03	.13 ± .02	−1.8[c]	.14 ± .03	.13 ± .02	−1.1
Hippocampus	.33 ± .04	.31 ± .03	−.8	.35 ± .04	.33 ± .03	−1.2
Ventral Diencephalon	.44 ± .07	.41 ± .05	−.9	.43 ± .06	.40 ± .05	−1.1
Cortical Reward Regions						
Insula, Anterior	.42 ± .05	.41 ± .05	.0	.41 ± .03	.38 ± .04	−2.2[b]
DLPFC	1.74 ± .31	1.59 ± .41	−1.5	1.76 ± .30	1.57 ± .31	−2.2[b]
Insula, Posterior	.21 ± .04	.19 ± .03	−1.8[d]	.21 ± .02	.21 ± .03	−.1
Orbitofrontal Cortex	.44 ± .08	.45 ± .12	.8	.46 ± .09	.42 ± .08	−1.5
Cingulate Cortex	.99 ± .15	.96 ± .19	−.4	1.04 ± .17	1.05 ± .15	.6
Subcallosal Cortex	.21 ± .03	.20 ± .04	−.7	.20 ± .03	.20 ± .03	−.9
Parahippocampal Gyrus	.37 ± .05	.35 ± .07	−.5	.35 ± .06	.33 ± .07	−.5
Temporal Pole	.72 ± .09	.71 ± .12	−.3	.69 ± .09	.69 ± .09	.3
Nonreward Control Regions						
Dorsal Striatum	.93 ± .07	.91 ± .09	−.7	.96 ± .06	.93 ± .08	−1.3
Frontal Pole	3.65 ± .78	3.55 ± .53	−.3	3.85 ± .86	3.57 ± .58	−.8
Cuneal Cortex (sensory)	.50 ± .09	.51 ± .11	.7	.55 ± .09	.58 ± .12	.7

ANCOVA, analysis of covariance; DLPFC, dorsolateral prefrontal cortex.

[a]We show the *t* value of the Group effect from the univariate ANCOVA tests on raw volumes, covaried for Total Cerebrum Volume and for Age. The overall ANCOVA (including Group, Age, and Total Cerebrum Volume in the model) is significant for all regions except right amygdala, left ventral diencephalon, left orbitofrontal cortex, left parahippocampal gyrus, left cingulate cortex, and the right frontal pole; Age effects were nonsignificant except for the right accumbens and left amygdala; Total Cerebrum Volume was a significant covariate in all regions except the left orbitofrontal cortex and the parahippocampal gyrus bilaterally.

[b]$p < .05$.

[c]$p = .07$, ratio covaried for age $p < .05$.

[d]$p = .08$, ratio covaried for age $p = .2$.

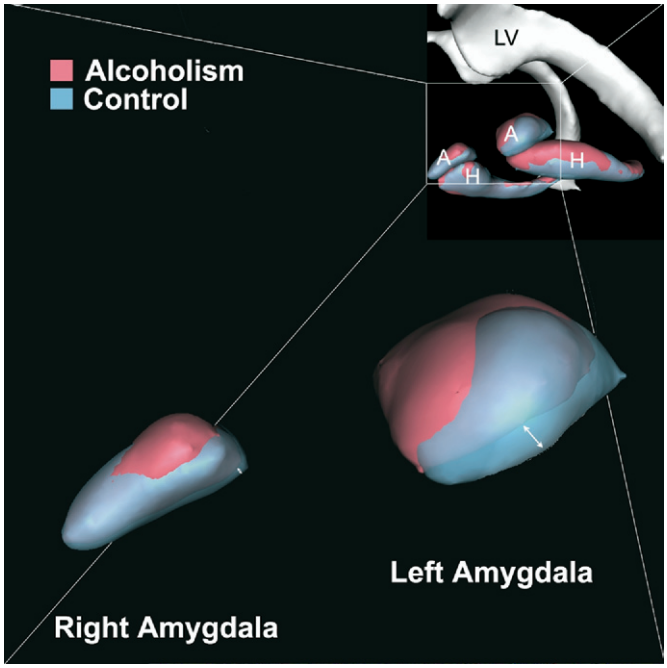

Figure 4. The hippocampus and amygdala shown as three-dimensional isosurfaces. The average shape of the hippocampus and amygdala of control subjects is coregistered and superimposed on the average shape of these structures in the subjects with alcoholism. This figure indicates that the volumetric reductions are bilateral but more pronounced in the left basolateral amygdala (see arrow) as well as bilaterally at the subiculum. These data suggest a topological specificity to volume reductions in amygdala-hippocampal structures in alcoholism. A, amygdala; H, hippocampus; LV, lateral ventricle.

flow (72,73), and functional MRI (74) studies. Brain structural changes become more prominent with aging (17,21,35), and alcoholism can exaggerate age-related volumetric reductions (75,76).

Regarding overall brain volumes, studies comparing alcoholics and nonalcoholic control subjects have yielded variable results. One factor contributing to this variability is length of abstinence. In one study (77), alcoholics showed improvement in cortical gray matter, sulcal, and lateral ventricular volumes early in abstinence (up to 1 month), as well as improvement in third ventricular volume with continued abstinence (up to 1 year). A recent report noted baseline atrophy in abstinent alcoholics, which improved with 8 months of abstinence (78). Another study followed alcoholics and control subjects over a 5-year period (79): age-related changes were observed in both groups, but alcoholics showed a greater rate of gray matter volume loss than did control subjects, a result similar to the age-related brain changes observed in our study. However, measures of ventricular enlargement in alcoholics who maintained sobriety were comparable to those of control subjects, and the authors concluded that continued alcohol abuse results in progressive brain tissue volume shrinkage. In our study, the length of abstinence of the AL group was 5.9 years (± 10.4 years), and this may account for the similarity of the AL and NC groups in overall brain volume. Furthermore, we observed negative correlation between cerebral cortex volume and years of heavy drinking, whereas length of abstinence correlated positively with volume in cerebral cortex and in some of the affected reward subregions (NAc, anterior insula), thereby confirming both the deleterious cerebral effects of chronic alcoholism and the potential for improvement in brain structural deficits with abstinence.

Frontolimbic Relationships Within the Reward Network

Dorsolateral-prefrontal cortex is richly interconnected with many reward network structures (80,81) enabling it to assess reward-aversion information, enhance rewarded behaviors, and modify the probability of subsequent responses (4). Moreover,

Table 4. Partial Correlations (*Pr*) Between Behavioral Data and Volumes of Subcomponents of the Reward Circuitry, Controlled for Effects of Age and Total Cerebrum Volume

		Nonalcoholic Comparison Subjects ($n = 20$)[a]		Subjects with Alcoholism ($n = 21$)	
Region	Test	*Pr*	*p* Value	*Pr*	*p* Value
Total Reward	Length of Sobriety	—	—	.26	.3
Total Amygdala	Length of Sobriety	—	—	−.32	.2
Total Anterior Insula	Length of Sobriety	—	—	.60	.007
Total Dorsolateral Prefrontal Cortex	Length of Sobriety	—	—	.11	.7
Total Nucleus Accumbens	Length of Sobriety			.47	.04
Total Reward	General Memory	−.01	.9	−.32	.2
Total Amygdala	General Memory	−.07	.8	.61	.006
Total Anterior Insula	General Memory	−.50	.03	−.37	.12
Total Dorsolateral Prefrontal Cortex	General Memory	.06	.8	−.28	.2
Total Nucleus Accumbens	General Memory	−.11	.7	−.22	.4
Total Reward	Working Memory	−.03	.9	.57	.01
Total Amygdala	Working Memory	.13	.6	.21	.4
Total Anterior Insula	Working Memory	−.25	.3	.27	.3
Total Dorsolateral Prefrontal Cortex	Working Memory	−.23	.4	.34	.2
Total Nucleus Accumbens	Working Memory	.10	.7	.06	.8

Only regions with significant group effects were included in correlation analyses. No significant correlations were observed for IQ or for other drinking history measures.

[a]Memory scores were not obtained for one control subject.

the role of dorsolateral-prefrontal cortex in oversight of limbic-paralimbic centers within the reward circuitry is crucial for normal cognitive and emotional functioning (80,82,83). Furthermore, there is extensive connectivity among the amygdala and adjacent structures within the basal forebrain and NAc, structures considered to be part of the same neural system (84–87). These centers are involved in establishing associations between stimulus cues and reward and for evaluating effectiveness of reinforcing stimuli. Largely through these associations, sensory inputs get transformed into powerful motivational and emotional representations (81). Therefore, structural alterations in dorsolateral-prefrontal cortex, anterior insula, NAc, and amygdala would disrupt the reward processing stream and disorganize these integrative functions.

The reward network may be an integral part of the neurobiology of drug addiction in general, and alcohol dependence in particular (88). Structural malfunction in this system may increase risk for drug-seeking behaviors and reward deficiency syndrome (1,89). These abnormalities may reflect a genetically influenced alteration in alcoholism (90). Recent neuroimaging positron emission tomography (PET) reports have identified higher levels of dopamine D_2 receptors in ventral striatum (NAc) in nonalcoholic members of alcoholic families, suggesting that higher levels of dopamine in the reward system may have a protective effect (91). Striatal D_2 receptor availability in nonalcoholic family members correlated with positive emotionality and with metabolism in orbitofrontal, anterior cingulate, and prefrontal cortex, demonstrating a connection among behavior, subcortical D_2 neuroreceptors, and cortical function in reward-network regions. A related PET study found that alcohol craving in detoxified alcoholic men correlated with lower levels of striatal dopamine receptors and corresponded to a greater relapse risk on follow-up (92). This circuitry may be crucial to alterations in hedonic set points related to development of drug use and dependence (88,93,94).

Processing of emotions engages the two hemispheres differentially, with negative emotional processing predominantly in right hemisphere and positive emotional processing primarily in the left hemisphere (35,95,96). In this report, the localization of right dorsolateral-prefrontal cortex, right anterior insula, and right NAc deficits supports the right hemisphere and frontal hypotheses of deficits in alcoholism (16,35). What is currently known regarding cerebral dominance and lateralization of the reward function is limited, however. Structural brain asymmetry and lateralization of functional dominance may result from molecular regulation, neural connections, and plasticity (97). Although genetic factors connecting cerebral asymmetry and functional dominance are supported, molecular correlates of cerebral asymmetry have yet to be identified (98,99).

Topological Analyses in Amygdala and Hippocampus

Our topological analysis of hippocampus and amygdala indicated that volumetric decrease in alcoholics was localized in the basolateral nuclear group of left amygdala and the subiculum. Remarkably, connections of amygdala with other structures within the reward network, such as dorsolateral-prefrontal cortex, anterior insula, hippocampus, and NAc, are through its basolateral nuclear group. Whereas the central nucleus is associated with autonomic behavior modulating the general motivational influence of reward-related events, the basolateral nuclear group is thought to be part of the frontotemporal association system mediating outcome-specific incentive processes (100,101). In our study, AL subjects displayed correlation between Working Memory and reward-network volume and between amygdala volumes and General Memory. Left amygdala volumetric decrease may account for deficits in performance related to analytical aspects of memory, as well as verbal memory (14,102). Hippocampal and amygdala volume reductions have been previously reported in alcoholics (22,55,56), and reduced amygdala volume was present in adolescents of high-risk alcoholism families, indicating a possible neurodevelopmental component (56). However, no prior studies evaluated particular subportions of these structures.

Limitations

First, we studied only men, whereas effects of alcoholism may be even more devastating in women (103,104). However, we selected men to avoid interactions of gender effects. In an ongoing companion study, we are examining female alcoholic and control subjects to determine whether these effects are seen in alcoholic women as well. Second, we did not include highly sensitive behavioral or functional MRI measures of brain asymmetry in this study; these findings will be detailed in a separate report. Third, we did not selectively recruit our AL subjects from families with a high prevalence of alcoholism, and the volumetric abnormalities we observed may be better defined in alcoholics with a strong positive family history. Fourth, we applied a multilevel analysis approach to identify whether the reward network overall was affected in alcoholism, followed by post hoc analyses of reward subregions. We did not apply multiple comparison corrections, because these post hoc regional analyses were performed to explore which reward-related subregions were most influential in the presence of an overall reward-network group effect. However, our findings should be replicated in a larger sample. In addition, the effect sizes we observed were modest, and although the overall reward network demonstrated group differences, only a few regions within the network displayed significant effects. Finally, the morphometric analysis framework samples relatively large regions; small structures such as ventral tegmentum or SLEA may have regional differences that are undetectable with these methods. In addition, we do not have a parcellation unit defined for ventral putamen, even though this region may be related to NAc. However, we chose neuroanatomically specific and highly reliable regional parcellation methods over other, more automated methods to assess specific morphometry of reward-network regions a priori. There are advantages and disadvantages of the methods employed in this study compared with more automated methods such as FreeSurfer (105,106) or voxel-based morphometry (107). FreeSurfer was validated using the methods described herein (105,106). Voxel-based morphometry is not well suited to testing hypotheses regarding an a priori, specifically defined, extensive neuroanatomic network. The advantages of FreeSurfer or voxel-based morphometry are automation, speed, and low cost. However, automated methods are more prone to coregistration artifacts and atlasing misalignment (108). Although automated methods are preferable for some studies and are less time-consuming, our methods are the gold standard for anatomic accuracy, and they ensure precision in measuring regional neuroanotomic networks.

Conclusions

Abstinent long-term chronic alcoholics have volumetric deficits in the brain's extended reward and oversight system. Deficits were most pronounced in right dorsolateral-prefrontal cortex, right anterior insula, right NAc, and left amygdala. This study differs from prior investigations in two principal aspects. First,

structures related to processing reward information were considered to be an interconnected and interrelated system, which was treated as a unique group of regions in statistical analyses. Second, correlations associating reward-network morphometry with behavioral tests and drinking history were performed. Memory correlated positively with reward-network volume—particularly the amygdala—and length of abstinence correlated with increased volumes in NAc and anterior insula. The circuitry overseeing reward and aversion is fundamental for normal emotional functioning and its malfunction. The finding that the reward system is altered in alcoholism and is correlated with memory and drinking history argues that a condition predisposes individuals to alcohol dependence, perhaps as a result of a genetic deficit in reward circuitry; that long-term alcoholism damages parts of the brain involved in reward processing and may lead to a cycle of accelerating dependence on alcohol; or both.

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