NeuroImage: Clinical 2 (2013) 469–476

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Deficits in cortical, diencephalic and midbrain gray matter in alcoholism measured by VBM: Effects of co-morbid substance abuse ☆☆,★

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ARTICLE INFO

Article history:
Received 24 August 2012
Received in revised form 15 March 2013
Accepted 21 March 2013
Available online 1 April 2013

Keywords:
Voxel-based morphometry
Alcoholism
Polysubstance use
Gray matter structure

ABSTRACT

Objective: Alcoholism has been associated with a widespread pattern of gray matter atrophy. This study sought to investigate the spectrum of volume alterations in a population of alcoholics with only alcohol dependence, polysubstance abusing alcoholics, and a comparison population of healthy controls.
Method: Thirty-seven 'pure' alcoholics, 93 polysubstance abusing alcoholics, and 69 healthy controls underwent structural T1 MRI scans. Voxel-based morphometry was performed to investigate gray matter alterations.
Results: Alcoholic dependent inpatients (both with and without a history of DSM-IV substance abuse/dependence diagnosis) displayed significant gray matter differences in the mesial region of the frontal lobe and right temporal lobe. 'Pure' alcoholics exhibited a pattern of subcortical changes similar to that seen in Wernicke–Korsakoff Syndrome when compared to polysubstance abusing alcoholics. 'Pure' alcoholics and polysubstance abusing alcoholics did not differ significantly in measures of cortical gray matter, liver function, or nutrition.
Conclusions: These findings reinforce the accepted literature in regards to frontal lobe gray matter atrophy in alcohol dependence. This study calls for additional research in order to investigate the spectrum from uncomplicated alcoholism to Wernicke–Korsakoff Syndrome. Further research is needed to elucidate the exact cause of this pattern of differences and to determine what factors are responsible for the patterns of gray matter reduction or difference in 'pure' and polysubstance abusing alcoholics.

1. Introduction

It has been established that the heavy consumption of alcohol due to alcohol dependence causes gray matter loss (Bjork et al., 2003; Fein et al., 2002; Jernigan et al., 1991). Postmortem studies have demonstrated a lower mean weight in the brains of alcoholics without any other neurological disease (Harper and Blumbergs, 1982), as well as brain tissue loss in chronic alcoholics (Harper and Kril, 1985). Several studies have found that alcohol dependent individuals have specific regional volume loss, particularly in the frontal lobe (Harper and Matsumoto, 2005; Moselhy et al., 2001; Pfefferbaum et al., 1997).

Many magnetic resonance imaging studies of alcoholism have focused primarily on the cerebrum and to a lesser extent, the cerebellum. Recently investigators have begun using voxel-based morphometry (VBM) (Ashburner and Friston, 2000) to evaluate gray matter differences. This procedure also allows for the global analysis of brain structures, including the diencephalon and midbrain, as well as the cerebrum. VBM has been used successfully in the investigation of schizophrenia (Salgado-Pineda et al., 2011), aging (Good et al., 2001), and Alzheimer's disease (Derflinger et al., 2011).

VBM has also been used to investigate brain morphometrical differences in alcoholics relative to healthy controls. (Mechtcheriakov et al., 2007; Rando et al., 2011). One study investigated both white and gray matter loss in 22 alcohol dependent patients and in age and sex matched healthy controls. The alcoholic patients displayed an overall decrease in the gray matter volume in the thalamus, posterior hippocampus, and frontal cortical areas, as well as white matter atrophy in the pons and the cerebellum. The other study compared the gray matter volumes of 45 abstinent alcohol-dependent patients and 50 healthy control subjects. The alcohol dependent patients displayed gray matter volume loss in the lateral prefrontal cortex, the medial frontal cortex, and the posterior cingulate gyrus.

Gray matter alterations have also been investigated in other populations of substance abusers, including cocaine dependent patients (Franklin et al., 2002), heavy cannabis users (Cousijn et al., 2012), methamphetamine abusers (Schwartz et al., 2010), and heroin dependent subjects (Liu et al., 2009). Very few studies have examined

☆☆ Disclosures: All authors report no competing interests.
★ This research was sponsored by the intramural research funds from the National Institute on Alcohol Abuse and Alcoholism.
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2213-1582
http://dx.doi.org/10.1016/j.nicl.2013.03.013

morphometrical alterations in polysubstance abusers (Liu et al., 1998; Reid et al., 2008; Tanabe et al., 2009). Liu and colleagues found that polysubstance abusers had smaller prefrontal lobes bilaterally relative to healthy controls. This volume loss was found only in gray matter. Tanabe and colleagues also found reduced gray matter volume in the frontal lobe of substance dependent individuals, specifically in the medial orbital frontal cortex.

Several years ago we compared forebrain volumes among inpatients at the National Institutes of Health (NIH) Clinical Center alcoholism treatment unit with or without co-morbid abuse of substances in addition to alcohol (Bjork et al., 2003). We found very little difference in brain volume between alcoholic subjects with or without co-morbid substance abuse. However, this study only measured overall forebrain volumes of gray and white matter and did not investigate diencephalon or midbrain alterations, regions which have been noted to be affected in alcoholism (Zuccoli et al., 2007). In addition, regional differences in brain volume were not examined in our earlier study.

In this report we used a VBM approach to compare regional brain volume differences between individuals with alcohol dependence and controls. We hypothesized that the alcohol dependent population would display less gray matter in the frontal lobes, as well as in the cerebellar cortex. Additionally we sought to investigate, we believe for the first time, regional differences between polysubstance abusing alcoholics and alcoholics with only alcohol dependence. Since our previous work comparing overall gray matter forebrain volumes in these groups did not find a significant difference (Bjork et al., 2003), we tested the hypothesis that the groups would differ in regional gray matter volume, but made no specific hypothesis about the direction of the difference.

2. Method

All recruitment and testing procedures were reviewed and approved by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Institutional Review Board. After complete detoxification and withdrawal, experimental procedures (psychometric interviews and magnetic resonance imaging) were explained, and all patients provided written informed consent to participate.

2.1. Subjects

Subjects with alcohol dependence (N = 130: 93 Caucasian, 34 African American, 1 Hispanic, 1 Asian, 1 Other; 47 Female), ages 20–64, were admitted for an inpatient alcoholism treatment program. Community-recruited subjects (N = 69: 47 Caucasian, 12 African American, 4 Hispanic, 4 Asian, 2 East Indian; 22 Female), ages 19–63, with no history of significant medical illness or psychiatric disorders were also included for comparison. Alcohol-dependent patients whose estimated IQ was below 80, who had neurological abnormalities, who had a history of psychotic symptoms, or who were not eligible for an MRI scan were not included in the sample. All subjects were assessed with the Structured Clinical Interview for DSM-IV, which determined that each inpatient met criteria for alcohol dependence and that the comparison subjects did not meet DSM-IV criteria for current axis I disorders. A urine sample was collected to verify drug abstinence. All participants received a physical examination to ensure good general physical and neurological health. A social worker administered a semi-structured lifetime drinking history interview to each subject. Alcohol use history was divided into epochs of various use patterns according to each respondent's history, and from these epochs we calculated three drinking history parameters: 1) age at onset of heavy drinking, defined a priori as the age at which the subject reported first consuming the equivalent of 90 drinks in a 1-month period; 2) years of heavy drinking, defined as the cumulative total contiguous or noncontiguous months during which the subject drank 90 drinks per month (note: since subjects often maintain this high a level of alcohol use for at least 12 consecutive months, months are summed into years); and 3) estimated lifetime alcohol consumption (in kg), which is a summation of all alcohol ingestion, including during periods where ingestion did not reach 90 drinks per month. Age, average years of heavy drinking, years of education, lifetime alcohol consumption, age of onset of alcoholism, past Axis I diagnoses, BMI, gray matter, and intracranial volumes can be found in Table 1.

2.2. Cognitive tests

A selective reminding task used in the current study has been described previously (Weingartner et al., 1996). In short, a list of 12 words is read to the patient and the patient is asked to recall as much as possible. Then the patient is reminded of the words they did not remember. This procedure is repeated 8 times. This procedure, the Buschke selective reminding task (Buschke and Fuld, 1974), has been widely used to measure memory impairments in dementia, head injury, aging, child development, drugs and therapies (for a review, see (Kraemer et al., 1983)). We used total trials required to learn the word list as a measure of episodic memory function.

Intelligence was estimated by two subtests of the Wechsler Adult Intelligence Scale—Revised (WAIS-R; (Wechsler, 1981)), Vocabulary

Table 1
Demographics.

Characteristic of participants	'Pure' alcoholics N = 37		Polysubstance abusing alcoholics N = 93		Healthy controls N = 69	
	Mean	SD	Mean	SD	Mean	SD
Male/female	21/16	–	62/31	–	47/22	–
Age at admission	40.2	9.2	38.1	7.1	36.6	1.1
Years of education[a]	14.5	2.6	13.2	2.3	16.8	0.3
Years of heavy drinking	10.3	7.5	11.9	7.1	–	–
Lifetime alcohol consumption (kg)[a]	467.0	470.6	583.0	458.3	10.1	16.1
Age of alcoholism onset	25.3	9.5	22.7	6.9	–	–
BMI	26.9	4.4	25.8	4.5	27.49	1.3
Intracranial volume (ml)	1323.6	119.7	1307.6	150.9	1353.5	146.5
Gray matter (ml)[a]	553.2	57.4	560.3	63.3	587.3	55.6
Drug abuse/dependence						
Cocaine dependence	0	–	50	–	0	–
Cocaine abuse	0	–	16	–	0	–
Cannabis dependence	0	–	50	–	0	–
Cannabis abuse	0	–	13	–	0	–
Opioid dependence	0	–	14	–	0	–
Opioid abuse	0	–	6	–	0	–
Sedative dependence	0	–	14	–	0	–
Sedative abuse	0	–	7	–	0	–
Amphetamine dependence	0	–	10	–	0	–
Amphetamine abuse	0	–	4	–	0	–
Hallucinogen/PCP dependence	0	–	17	–	0	–
Hallucinogen/PCP abuse	0	–	18	–	0	–
"Other" substance abuse	0	–	2	–	0	–
Past Axis I disorders						
Major depression	25	–	70	–	0	–
Mood disorder	25	–	72	–	0	–
Anxiety disorder	15	–	54	–	0	–
Eating disorder	1	–	6	–	0	–
Post-traumatic stress disorder	12	–	33	–	1	–
Attention deficit hyperactive disorder	5	–	28	–	1	–
Obsessive compulsive disorder	10	–	36	–	0	–
Conduct disorder	6	–	29	–	0	–

Because most polysubstance abusing alcoholics used more than one substance in addition to alcohol the total diagnoses add up to more than 93.

[a] Significant difference between all alcoholics and controls at $p < 0.05$.