Decreased frontal white-matter volume in chronic substance abuse

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Abstract

There is quite a body of work assessing functional brain changes in chronic substance abuse, much less is known about structural brain abnormalities in this patient population. In this study we used magnetic resonance imaging (MRI) to determine if structural brain differences exist in patients abusing illicit drugs compared to healthy controls. Sixteen substance abusers who abused heroin, cocaine and cannabis but not alcohol and 16 age-, sex- and race-matched controls were imaged on a MRI scanner. Contiguous, 5-mm-thick axial slices were acquired with simultaneous T2 and proton density sequences. Volumes were estimated for total grey and white matter, frontal grey and white matter, ventricles, and CSF using two different methods: a conventional segmentation and a stereological method based on the Cavalieri principle. Overall brain volume differences were corrected for by expressing the volumes of interest as a percentage of total brain volume. Volume measures obtained with the two methods were highly correlated ($r = 0.65$, $p < 0.001$). Substance abusers had significantly less frontal white-matter volume percentage than controls. There were no significant differences in any of the other brain volumes measured. This difference in frontal lobe white matter might be explained by a direct neurotoxic effect of drug use on white matter, a pre-existing abnormality in the development of the frontal lobe or a combination of both effects. This last explanation might be compelling based on the fact that newer concepts on shared aspects of some neuropsychiatric disorders focus on the promotion and inhibition of the process of myelination throughout brain development and subsequent degeneration.

Introduction

With the advent of structural and functional neuroimaging techniques, the study of substance abuse has turned from a more neuropsychological and physiological assessment of substance abusers to the elucidation of the neurobiological correlates of the chronic and acute effects of abused substances with neuroimaging methods (Lingford-Hughes, 2005). In terms of functional neuroanatomy, it has been demonstrated that chronic cocaine abusers have decreased resting state regional cerebral blood flow (rCBF) compared to healthy subjects (Mena et al., 1990; Tumeh et al., 1991; Volkow et al., 1988; Weber et al., 1990). These decreases in rCBF seem to be especially prominent in the frontal cortex and in the left parietal and left temporal cortex, persisting for weeks after withdrawal (Ernst et al., 2000; Strickland et al., 1993). Acute administration of cocaine also results in decreased brain perfusion, especially in the frontal lobes (Johnson et al., 2005; Pearlson et al., 1993; Wallace et al., 1996). It has also been demonstrated that the acute action of morphine (London et al., 1990) or amphetamine (Wolkin et al., 1987), also result in global decreases of cerebral glucose metabolism.

Although much information about the functional neuroanatomy related to substance abuse has accumulated (Goldstein and Volkow, 2002), there is less information about how such abuse might affect structural neuroanatomy, despite the existence of high-resolution brain-imaging methods. A notable
exception is alcohol abuse. It is a well-established finding that alcoholics have signs of regional brain damage, especially reduced white-matter volume (Harper and Matsumoto, 2005). In morphological brain-imaging studies conducted in subjects with multiple substance abuse (including alcohol), correlations concerning differences in brain structures could only be found with alcohol consumption (Aasly et al., 1993; Cascella et al., 1991; Csernansky, 2001). A volumetric magnetic resonance imaging (MRI) study of ventricle-to-brain ratio (VBR), an index of brain atrophy, failed to show larger VBR or even a tendency towards a relative increase in ventricular volume in substance abusers compared to controls (Liu et al., 1995). However, a computerized tomography (CT) study reported that the brains of habitual cocaine users had a significantly larger atrophy index than those of controls and of first time cocaine users (Pascual-Leone et al., 1991). The CT differences found in these studies may be attributable to the fact that chronic cocaine abuse can lead to frank abnormalities in brain and behaviour, including cerebral haemorrhage (Lichtenfeld et al., 1984), seizure activity (Pascual-Leone et al., 1990), and new onset of multifocal tics (Pascual-Leone and Dhuna, 1990).

This study used MRI, a method providing high resolution, to identify potential structural differences and permit volumetric analysis. We investigated whether substance abusers have observable differences in total brain volume, total grey and white matter and grey and white matter in the frontal lobe compared to well-matched, non-substance-abusing control subjects.

Methods

Thirty-two subjects participated in this study. Written informed consent was obtained, subjects were compensated for their time and the appropriate Institutional Review Board for human research approved the protocol.

All substance abusers (mean age 38.8 ± 6.2 yr) had a history of substance abuse of 7–12 yr (mean 9.2 ± 3.2 yr), in which they met DSM-IV diagnostic criteria for the disorder, as determined by DSM-IV (SCID; Spitzer et al., 1994), all met criteria for substance abuse at the time of the study. Abused substances included intravenous cocaine (14 subjects), metamphetamine (9 subjects) intravenous heroin (15 subjects) and cannabis (16 subjects).

A group of 16 healthy controls, who were not abusing any psychotrophic substance, as assessed by the interview and urine screen, were matched to these subjects on age (38.4 ± 7.4 yr), sex and race. Neither substance abusers nor control subjects were currently abusing alcohol or had any previous history of alcohol abuse or dependence as assessed by the SCID interview; absence of comorbid psychiatric disorder or current medical problems within the 6 months preceding the study was established.

Substance abusers and control subjects did not differ significantly in educational level (13 substance abusers, 12 control subjects had completed high school; 3 substance abusers and 4 control subjects completed college or a professional school. Only male subjects were included to eliminate any confounds associated with sexual dimorphism of the brain (Schlaepfer et al., 1995).

MRI

Magnetic resonance images were acquired on a General Electric (Milwaukee, WI, USA) 1.5 T Signa scanner. Contiguous, 5-mm-thick axial slices were acquired with simultaneous dual echo $T_2$ and proton density sequences to improve grey–white matter contrast. The images extended from the base of the cerebellum to the vertex, parallel to the anterior commissure–posterior commissure (AC–PC) line. Scan parameters were TR = 2500, TE = 20/80. Number of excitations was one (Schlaepfer et al., 1994). Total grey and white matter, frontal grey and white matter, both lateral ventricles, and cerebral spinal fluid (CSF) were measured by raters blinded to the status of the subject. Frontal lobes were delineated using a method previously described by Bilder et al. (1994). Frontal grey matter was defined by excluding from the total brain grey-matter measurement all points at or posterior to the most anterior point on the midline of the corpus callosum, while frontal white matter was measured by excluding from the total brain white-matter measurement all points at or posterior to the most anterior point on the midline of the corpus callosum.

Two different approaches, a segmentation method and a stereological method, were used to assess the described volumes. In order to correct for different total brain volumes across subjects, regional brain volumes were expressed as percentages of total brain volume.

Segmentation

Proton density and $T_2$-weighted images were stripped of all non-brain structures and then filtered with a low-pass filter. Grids were then randomly placed over the brain, and a human rater classified the grid dots into one of five categories: grey matter, white matter, CSF, dura or noise. At least 60 grid dots for each type
of matter were used. Twenty additional dots were used to define dura. Using a computer algorithm similar to the one used by Cline et al. (1990), all voxels in the brain were classified into one (and only one) of the five types of matter (grey, white, CSF, dura and skull). Grey- and white-matter files were manually edited to remove outliers in each area. The edited files were used to generate final grey- and white-matter volumes for the entire brain. We assessed intra-rater and inter-rater reliability by repeating measurements for the five types of brain matter (on the same grids) for 10 patients.

**Stereological volume estimates**

We used the Cavalieri principle of stereological volume measurements (Gundersen, 1988; West and Gundersen, 1990). The Cavalieri principle refers to a method of obtaining an unbiased estimate of the volume of a structure by superimposing a randomly offset 3D grid on the data and counting the number of equally sized cubes within a structure. This principle was incorporated in software developed in our laboratory (Barta et al., 1997). The cubes were defined by the distance between the same points across slices. Each cube had sides of equal length. All points (intersection of grid lines) which fall within the object of interest are selected, and the total number of selected points provides an estimate of the volume of the object.

In order to enhance grey/white matter contrast proton and T2 images were added together. T2 images were subtracted from proton images to enhance CSF to brain contrast (Schlaepfer et al., 1994, 1995). A 3D Cavalieri grid (12 × 12 × 12 voxels) was randomly placed on the image. Each dot, which was placed by the program on a grey-matter pixel, was selected to measure total grey matter, including all brain, cerebellum, and brainstem down to and including the level of the base of the cerebellum. Each white-matter dot in the same area was (in a separate measurement) selected on the same grid to measure total white matter. A smaller (6 × 6 × 1 voxel) grid and the same technique were used to measure grey and white matter in the frontal lobe (Figure 1). A 2 × 2 × 1 voxel Cavalieri grid placed on the difference image was used to measure the lateral ventricles. All grids, which fell on CSF in either lateral ventricle, were selected for this measurement. Choroid plexus was not included in the CSF measurement.

**Statistical analysis**

Measures for total brain, total grey matter, total white matter, frontal grey matter, frontal white matter, and lateral ventricle volumes were measured with both the segmentation and stereological volume estimates methods. Inter- and intra-rater reliability was assessed for all values calculating the intra-class correlation (Shrout and Fleiss, 1979). In order to correct for different brain size the measurements were expressed as percentage of total brain volume (sum of total grey matter, total white matter, and lateral ventricle volumes). These percentages were then compared using the t test. In a confirmatory analysis in order to control for multiple comparisons (six comparisons) a stepwise logistic regression analysis was calculated.

**Results**

Inter-rater reliability was assessed by repeating all measurements of the 10 subjects, selected at random, with the same Cavalieri grids and contrast settings by two blinded raters. The intra-class correlation (Shrout and Fleiss, 1979) of grey–white segmentation values was 0.93, intra-rater reliability was 0.99. Subjects were matched for race, sex, and age (t = −0.168, d.f. = 30, n.s.). Therefore, differences in brain volume could not be attributed to any of these factors.

The two methods of analysis of brain volume (segmentation and stereology) were used to cross-validate observed differences between substance abusers and controls. Both methods yielded comparable results. Figure 2 shows the correlation (r = 0.65, p < 0.001) for the comparison between the two methods.

Substance abusers had significantly less frontal white-matter volume percentage than controls as determined either by the segmentation method (t = 3.38, d.f. = 30, p < 0.005) or by the stereological method.
Volumes for total grey matter, total white matter, frontal grey matter, and lateral ventricles were not significantly different in the two groups (Table 1). The confirmatory stepwise logistic regression revealed the percentage of frontal white-matter volume to be the only significant factor predicting use status ($p < 0.01$).

**Discussion**

This study systematically assessed brain grey- and white-matter volumes in chronic substance abusers and matched controls. We compared results from two different methods to obtain brain volume measurements. Although both stereological and segmentation methods yielded comparable results and were significantly correlated, the stereological method proved to be a more efficient and reliable way to estimate volume in an unbiased way. The underestimation of the stereological method did not pose a problem in this study since percentage of volumes rather than absolute volumes were compared.

Some important limitations in this study need to be addressed. First, because this study is not longitudinal, the putative cause for its findings are purely speculative. Future structural neuroimaging studies of at-risk populations of adolescents and young adults could provide more insight. Second, we assessed only male subjects in order to eliminate any confounds associated with sexual dimorphism of the brain (Schlaepfer et al., 1995), therefore, it is unclear whether the described volume deficits exist in female substance abusers too. Given the small sample size we aimed for maximal homogeneity in the researched population, both in regard to gender and substance abuse activities. Third, in order to keep the amount of measuring for the stereological assessment within practical limits, we acquired in this study 5-mm-thick axial magnetic resonance images only. This relatively thick slice volume decreases the resolution of the data. However, the fact that we found highly significant differences in frontal white-matter volumes in a small number of subjects at this lower resolution points to the robustness of our data and the assessment techniques used.

In our study sample substance abusers had significantly less frontal lobe white-matter volume relative to matched controls. These findings converge with results obtained from functional neuroimaging studies.
of frontal cortical differences in substance abusers relative to non-substance-abusing subjects (Bolla et al., 2003; Ernst et al., 2000; Gerra et al., 1998; Lim et al., 2002; Little et al., 1996; London et al., 2000; Semple et al., 1996).

Previous studies assessing structural differences focused mainly on indices of ventricle size or total brain as potentially contrasting between substance abusers and controls (Cascella et al., 1991; Liu et al., 1995; Pascual-Leone et al., 1991). Similar to prior reports (Liu et al., 1995) we also found no difference in volumes of lateral ventricles between the group of substance abusers and control subjects. A recent study on MRI assessed structural changes in metamphetamine users found in addition to large grey-matter volume deficits in a broad region encompassing the cingulate cortex a surprising hypertrophy of white-matter volume in regions of the brain adjacent to the ones where the grey-matter volume deficits were found (Thompson et al., 2004). The authors explained this finding as a typical structural pattern found in neurodegenerative disorders.

There are only a few studies reporting on anatomical cerebral changes induced by substances of abuse such as cannabis, cocaine, heroin and metamphetamine, the substances taken by our patient population. Most of our subjects consumed all four substances. Therefore, it is not possible to attribute the observed effect to only one substance. Regarding heroin, Koussa et al. (2001) reported on myelin damage in both cerebellar hemispheres of a patient who inhaled heroin for at least 5 yr. Two years after cessation of the abuse he improved clinically and the lesions visible on the MRI regressed partially. In another case report, on fatal development in an intravenous heroin abuser, neuropathological spongy myelin with diffuse reactive astrogliosis and microglial proliferation without hypoxic necrotic lesions was demonstrated (Rizzuto et al., 1997). Regarding cocaine, it has been recently reported that cocaine dependence may arrest normal white-matter maturation in frontal regions of addicts who continue using cocaine (Bartzokis et al., 2002). This factor could contribute to the findings because the mean age of our studied subjects and their long drug use history increase the possibility that toxic effects could be detected, since normal males continue the process of myelination well into their mid 40s (Bartzokis et al., 2001). A very recent study reported on the gene expression profile of the nucleus accumbens and surrounding white matter in a human post-mortem study. The authors concluded that their data suggest a dysregulation of myelin synthesis in human cocaine abusers (Albertson et al., 2004).

White-matter abnormalities in drug abuse

White-matter deficits have been described in other psychiatric disorders, which have a substantial comorbidity of substance disorder, such as hyperactivity (ADHD) (Biederman et al., 1997, 1998; Horner and Scheibe, 1997; Semrud-Clikeman et al., 2000), bipolar disorder (Lopez-Larson et al., 2002) and schizophrenia (Szeszko et al., 2005). This could be an indication, that an abnormality in development of the frontal lobe might predispose to impairment in judgement (Bechara et al., 1994; Damasio et al., 1994), a pre-existing condition, which might lead individuals to substance misuse and consecutive abuse. However, drug addiction is a complex brain disorder with multiple causes, which might be different for different substances.

While the data reported in this paper certainly do not substantiate pre-existing white-matter abnormalities to be a causative factor for the development of substance abuse disorders, this hypothesis could foster further studies looking at the time-course of brain development in children at risk for later substance abuse. If such an interaction between some neuropsychiatric disorders and substance abuse is confirmed, it might lead to preventive and early intervention strategies aimed at reducing the risk for substance abuse.

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Statement of Interest

None.

References


