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Deep grey matter iron accumulation in alcohol use disorder

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ABSTRACT

Purpose: Evaluate brain iron accumulation in alcohol use disorder (AUD) patients compared to controls using quantitative susceptibility mapping (QSM).
Methods: QSM was performed retrospectively by using phase images from resting state functional magnetic resonance imaging (fMRI). 20 male AUD patients and 15 matched healthy controls were examined. Susceptibility values were manually traced in deep grey matter regions including caudate nucleus, combined putamen and globus pallidus, combined substantia nigra and red nucleus, dentate nucleus, and a reference white matter region in the internal capsule. Average susceptibility values from each region were compared between the patients and controls. The relationship between age and susceptibility was also explored.
Results: The AUD group exhibited increased susceptibility in caudate nucleus (+8.5%, p=0.034), combined putamen and globus pallidus (+10.8%, p=0.006), and dentate nucleus (+14.9%, p=0.022). Susceptibility increased with age in two of the four measured regions - combined putamen and globus pallidus (p=0.013) and combined substantia nigra and red nucleus (p=0.041). AUD did not significantly modulate the rate of susceptibility increase with age in our data.
Conclusion: Retrospective QSM computed from standard fMRI datasets provides new opportunities for brain iron studies in psychiatry. Substantially elevated brain iron was found in AUD subjects in the basal ganglia and dentate nucleus. This was the first human AUD brain iron study and the first retrospective clinical fMRI QSM study.

1. Introduction

Alcohol use disorder (AUD) is a chronic relapsing disease characterized by recurrent compulsive alcohol abuse despite significant alcohol-related behavioural, cognitive, physiological, and social problems (American Psychiatric Association, 2013). AUD can be considered the world's biggest addiction problem. Harmful use of alcohol is estimated to lead to 5.9% of all deaths, 5.1% of the global burden of disease, and has been demonstrated to have a causal relationship with over 200 adverse health conditions (World Health Organization, 2014). This makes AUD one of the most damaging preventable causes of illness in the world. When considering the total harm of AUD including its societal costs, alcohol is by a wide margin the most harmful drug in the western world (Nutt et al., 2010). Neurobiological mechanisms driving adaptive changes during alcohol abuse and subsequent recovery are not fully understood and continue to be of scientific interest (Fein and Cardenas, 2015; Seo and Sinha, 2015). Previous evidence suggests that chronic alcohol abuse can lead to abnormally high systemic iron levels (Duane et al., 1992; Kohgo et al., 2005; Milman and Kirchhoff, 1996; Whitfield et al., 2001) which might be associated

Abbreviations: AUD, alcohol use disorder; QSM, quantitative susceptibility mapping; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; rs-fMRI, resting-state functional magnetic resonance imaging; EPI, echo-planar imaging; DSM, Diagnostic and Statistical Manual of Mental Disorders; SCID-I, Structured Clinical Interview for the DSM-IV-TR; AUDIT, Alcohol Use Disorders Identification Test; ADS, Alcohol Dependence Scale; MPRAGE, magnetization-prepared rapid acquisition echo; FSL, FMRIB software library; FMRIB, Oxford Centre for Functional MRI of the Brain; RESHARP, Regularization Enabled Sophisticated Harmonic Artifact Reduction for Phase data; ppm, parts-per-million; FLIRT, FMRIB's Linear Registration; ROI, region of interest; FDR, false discovery rate; ADHD, attention-deficit hyperactivity; 3D, three dimensional; CTL, control

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with increased brain iron concentration (Nordmann et al., 1987; Rouach et al., 1994, 1997b; Rouach et al., 1990). A wide range of neural disorders is associated with brain iron abnormalities (Zecca et al., 2004), thus increased brain iron may contribute to commonly observed brain damage and atrophy in AUD.

Quantitative susceptibility mapping (QSM) is an emerging magnetic resonance imaging (MRI) technique developed for quantifying tissue magnetic susceptibility (Haacke et al., 2015; Liu et al., 2015; Wang and Liu, 2015). QSM can be used to measure iron content in deep grey matter brain structures and has been extensively validated to be able to identify altered deep grey matter iron in normal aging as well as many neurological disorders (Bartzokis et al., 1999; Bilgic et al., 2012; Haacke et al., 2015; Li et al., 2014; Liu et al., 2015; Stuber et al., 2016). Our team has recently developed a means to extract QSM from previously acquired echo planar imaging (EPI) scans (Sun and Wilman, 2015), as well as traditional functional MRI (fMRI) studies (Sun et al., 2016). Provided the phase or raw signal is available, this method enables retrospective examination of brain iron from existing fMRI studies. Here, using an existing AUD resting state fMRI dataset, we applied this unique QSM method to examine brain iron deposition in clinical cases with AUD to test the hypothesis whether AUD is associated with increased deep grey matter iron concentration. To the best of our knowledge this is the first AUD QSM study and the first clinical study to use retrospective QSM from functional MRI. Our findings provide important technological advances in MRI application that allow us to examine novel aspects of brain tissue alterations, and may be useful for developing highly needed biomarkers for neurological and psychiatric disorders at various stages of progression and treatment.

2. Methods and materials

2.1. Subjects

Twenty recently detoxified male alcohol dependent patients (DSM-IV-TR criteria) (American Psychitric Association, 2000) and 15 matched healthy non-alcohol abusing men were recruited for the AUD and control groups, respectively. The DSM-IV-TR diagnostic investigations were carried out by a psychiatrist, using the Structured Clinical Interview for the DSM-IV-TR (SCID-I) (First et al., 2002). The demographic and clinical overview of the participants is summarized in Table 1. The alcohol dependent participants were recruited from a pool of patients referred to a supervised residential treatment program from all addiction treatment facilities in the Edmonton area between 2012 and 2015 as part of the international TRANSALC project. The patients were consistent, steady, heavy drinkers (mean duration of alcohol dependence of 16.0+/-2.7 years, standard error of mean). All of the patients met the highest Zone IV cut-off score on the Alcohol Use Disorders Identification Test (AUDIT) with average score of 30 out of 40 (Saunders et al., 1993). The AUD patients exhibited on average a substantial level of alcohol dependence (third quartile) according to the Alcohol Dependence Scale (ADS) with the average score of 25.5 out of 47 (Skinner and Allen, 1982). The patients did not abuse non-beverage ethanol or other substances except nicotine. The patients were recruited between 6 to 12 days of abstinence. Abstinence at the time of scanning was verified in all participants by an alcohol breathalyser (BACtrack S50 Personal Breathalyzer, Portable Breath Alcohol Tester) and a urine drug screen (nal von minden GmbH Drug-Screen® Diptest, Version 1.0). The patients were not provided with any prescription medications including adjuvant pharmacotherapy for prevention of relapse such as Naltrexone or Disulfiram during this time. Controls were recruited concurrently to match the patients' general demographic profile (including sex, age, handedness, general occupation/education background). The controls had no history of alcohol or drug addiction and consumed alcohol below the Canada's Low-Risk Alcohol Drinking Guidelines (Butt, 2011). Participants in both arms were excluded if they had any history of serious medical (including psychiatric or neurological) complications, brain injury, use of psychotropic medications (other than during the detoxification process), or did not meet magnetic resonance safety criteria for our imaging facility. The study was approved by the University of Alberta Health Research Ethics Board (study ID: Pro00019424).

2.2. MRI acquisition

Neuroimaging data were acquired using 4.7 T Varian Inova whole-body MRI scanner, located at the University of Alberta. The scanning protocol included anatomic imaging using T1-weighted magnetization-prepared rapid acquisition echo (MPRAGE) and resting state functional MRI (rs-fMRI) using single-shot, T2*-weighted echo planar imaging (EPI). During rs-fMRI participants were asked to remain still, close their eyes, not fall asleep, and not to think of anything in particular. The acquisition parameters for MPRAGE were: TR 1505.9 ms, inversion time 300.0 ms, relaxation delay time (after readout prior to inversion) 300.0 ms, linear phase encoding, TE 3.71 ms, matrix 240×192×128, field of view 240×192×192 mm^3, 1.0×1.0×1.5 mm^3 voxels, whole brain coverage. The acquisition parameters for EPI were: TR 1500 ms, TE 19 ms, matrix 72×68×36, field of view 216×204×126 mm^3, 3×3×3.5 mm^3 voxels, whole brain coverage, and with 320 volumes.

The anatomical scans were visually reviewed by two independent neuroimaging experts for gross abnormalities. None of the subjects exhibited any clinically significant structural abnormalities other than what may be expected from normal aging or prolonged alcohol abuse.

Table 1
Demographic and clinical profile of subjects.

	AUD patients (n=20)				Controls (n=15)				
	Average	Std. error[b]	Min.	Max.	Average	Std. error[b]	Min.	Max.	p-value
Age	43.05	2.38	23.98	60.88	44.61	2.72	29.79	58.60	0.667
Years of education	12.85	0.55	9.00	18.00	12.13	0.48	9.00	16.00	0.351
Edinburgh handedness inventory (Oldfield, 1971)	0.56	0.15	0.00	1.00	0.43	0.13	0.09	1.00	0.516
AUDIT[a] score (Saunders et al., 1993)	30.00	1.03	20.00	37.00	1.67	0.36	0.00	6.00	0.000*
ADS[c] score (Skinner and Allen, 1982)	25.50	1.95	6.00	38.00	0.87	0.32	0.00	4.00	0.000*
Standard drinks per day[d]	21.72	2.50	9.88	54.89	0.22	0.06	0.00	0.81	0.000*
Days of abstinence	9.11	0.46	6.00	12.00	N/A	N/A	N/A	N/A	N/A

[a] Alcohol Use Disorders Identification Test.
[b] Standard Error of Mean.
[*] Significant at *a priori* α level of P < 0.05.
[c] Alcohol Dependence Scale.
[d] Canadian standard drink constitutes of 17.24 mL or 13.6 g of ethanol.