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# T2 relaxation time alterations underlying neurocognitive deficits in alcohol-use disorders (AUD) in an Indian population: A combined conventional ROI and voxel-based relaxometry analysis

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ABSTRACT

Long-term heavy alcohol consumption has traditionally been associated with impaired cognitive abilities, such as deficits in abstract reasoning, problem solving, verbal fluency, memory, attention, and visuospatial processing. The present study aimed at exploring these neuropsychological deficits in alcohol-use disorders (AUD) in an Indian population using the Postgraduate Institute Battery of Brain Dysfunction (PGIBBD) and their possible correlation with alterations in T2 relaxation times (T2-RT), using whole-brain voxel-based relaxometry (VBR) and conventional region of interest (ROI) approach. Multi-echo T2 mapping sequence was performed on 25 subjects with AUD and 25 healthy controls matched for age, education, and socioeconomic status. Whole-brain T2-RT measurements were conducted using VBR and conventional ROI approach. The study was carried out on a 3T whole-body MR scanner. Post processing for VBR and ROI analysis was performed using SPM 8 software and vendor-provided software, respectively. A PGIBBD test battery was conducted on all subjects to assess their cognitive abilities, and the results were reported as raw scores. VBR and ROI results revealed that AUD subjects showed prolonged T2-RTs in cerebellum bilaterally, parahippocampal gyrus bilaterally, right anterior cingulate cortex, left superior temporal gyrus, left middle frontal gyrus, and left calcarine gyrus. A significant correlation was also observed between the neuropsychological test raw scores and alterations in T2-RT in AUD subjects. Our results are consistent with previous studies suggesting tissue disruption or gliosis or demyelination as a possible reason for prolonged T2-RTs. This damage to brain tissue, which is evident as prolonged T2-RT, could possibly be associated with impaired cognitive abilities noticeable in AUD subjects.



## Introduction

Chronic alcohol consumption is known to impair performance in a variety of cognitive functions, as assessed by various neuropsychological studies. Attention, working memory, visuospatial abilities, executive functions, learning skills, and verbal fluency have all been shown to be impaired in alcohol-use disorders (AUD) (Ambrose, Bowden, & Whelan, 2001; Demir, Uluğ, Lay Ergün, & Erbaş, 2002; Fama, Pfefferbaum, & Sullivan, 2004; Oscar-Berman & Marinković, 2007; Stavro, Pelletier, & Potvin, 2013; Uekermann, Daum, Schlebusch, Wiebel, & Trenckmann, 2003). Magnetic resonance imaging (MRI) techniques have contributed significantly to our understanding of the effects of heavy alcohol use on structural, biochemical, and functional changes in the human brain, which might underlie these impaired cognitive abilities. Structural imaging has consistently revealed that AUD individuals have reduced gray and white matter volumes, particularly in the frontal lobe, temporal lobe, hippocampus, and cerebellum (Chanraud et al., 2009; Demirakca et al., 2011; Fein et al., 2006; Mechtcheriakov et al., 2007). Proton magnetic resonance spectroscopy (1H MRS) studies in subjects with AUD have also demonstrated lowered concentrations of N-acetyl-L-aspartate (NAA) and increased concentrations of choline-containing compounds (Cho), most notably in the frontal lobe, temporal lobe, occipital lobe, and cerebellum (Bendszus et al., 2001; Gazdzinski, Durazzo, Weiner, & Meyerhoff, 2008; Modi et al., 2011; Parks et al., 2002; Ross & Bluml, 2001). Diffusion tensor imaging (DTI) studies in subjects with AUD have shown decreased fractional anisotropy (FA) and increased mean

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diffusivity (MD) in the corpus callosum, temporal lobe, cingulum, frontal lobe, hippocampus, occipital lobe, cerebellum, and centrum semiovale, which is suggestive of compromised axonal or myelin integrity (Bagga, Sharma, et al., 2014; Chanraud et al., 2009; Pfefferbaum, Adalsteinsson, & Sullivan, 2006; Trivedi et al., 2013). fMRI results also revealed changes in brain activation pattern (enhanced or diminished activation) in AUD individuals in response to different fMRI tasks, such as abstract reasoning (Bagga, Singh, et al., 2014), semantic judgment (Bagga et al., 2013), working memory (Pfefferbaum et al., 2001), attention (Campanella et al., 2013), and simple decision making (Gilman, Davis, & Hommer, 2010), suggestive of decreased efficiency of relevant brain networks.

Despite a large body of literature demonstrating functional, metabolic, morphological, and microstructural alterations associated with AUD as discussed above, very few studies specifically sought to examine the alterations in associated hemodynamic or paramagnetic properties (as reflected by T2 relaxation times [T2-RT]) in this population. In a study of central pontine T2-RT measurements in patients with alcoholic Korsakoff's syndrome (KS) and asymptomatic alcoholic patients, prolonged T2-RT was observed in KS patients. In asymptomatic alcoholic patients, T2-RT increased significantly with older age (Sullivan & Pfefferbaum, 2001). In another study by Agartz, Sääf, Wahlund, and Wetterberg (1991), conducted at lower field strength, no differences were found in T2-RT in AUD and control subjects. However, this study also found a correlation between atrophy and T1-RT in AUD subjects.

T2 relaxometry is a non-invasive quantitative MR measure that maps T2-RT and has been established as a reliable tool for assessing brain tissue abnormalities in conditions such as temporal lobe epilepsy (Jackson, Connelly, Duncan, Grünewald, & Gadian, 1993; Pell, Briellmann, Pardoe, Abbott, & Jackson, 2008; Pell, Briellmann, Waites, Abbott, & Jackson, 2004), Alzheimer's disease (Laakso et al., 1996), and various mental health disorders (Neema et al., 2009; Oh, Han, Lee, Nelson, & Pelletier, 2007). The technique has been found to be useful for identifying early abnormalities that are not obvious on visual assessment of MRI images (Armspach, Gounot, Rumbach, & Chambron, 1991; Barbosa, Blumhardt, Roberts, Lock, & Edwards, 1994; Grenier et al., 2002; Miller, Johnson, Tofts, MacManus, & McDonald, 1989; Neema et al., 2007; Whittall et al., 2002). These studies have suggested that prolonged T2-RT has been attributed to diffuse abnormality, or pathological processes such as edema, demyelination, and gliosis, or to "small lesions" which are undetected by visual inspection of conventional MR images. The relaxometry studies provide a more detailed characterization of tissues, compared with conventional qualitative imaging approaches (Deoni, 2010) and have shown promise in their ability to detect diffuse damage in various brain regions (Neema et al., 2007). The measurement of the T2 time is commonly achieved by the relatively simple acquisition of multiple spin echo images acquired at a range of echo times. The time constant of the exponential signal decay represents the rate of T2 relaxation. Earlier, analysis of T2 relaxometry data had been carried out by manual placement of regions of interest (ROIs) over predefined areas of anatomy. However, the search space is then obviously limited to those areas chosen for ROI placement. Voxel-based relaxometry (VBR) analysis is a relatively new technique that provides an unbiased and even-handed assessment of major differences in T2-RT throughout the brain, identifying regions of highly significant differences that withstand correction for multiple comparisons (Pell et al., 2004).

Based on the above findings, we hypothesize that we will observe T2-RT alterations in brain regions (frontal, temporal, and parietal lobe) that show changes on structural, metabolic, and functional studies, and that the alterations for various cognitive abilities known to be impaired in AUD subjects.

In the present study, T2 relaxometry was carried out using both voxel-based analysis and ROI analysis with the following objectives: (1) identifying regions of T2-RT alterations in AUD subjects as compared to controls, and (2) identifying the correlation of T2-RT with the neuropsychological test scores of brain dysfunction.

To the best of our knowledge, this is the first VBR-based study to assess the alterations in T2-RT associated with AUD.

## Methods

### *Subjects*

The study included 25 AUD subjects and 25 healthy control subjects. All study participants were men, between 30 and 45 years of age, and all were non-smokers. All the subjects were matched for age, education, and socio-economic status. The AUD subjects were recruited from an army rehabilitation center, and met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for alcohol dependence, and had abstained from drinking alcohol for approximately 2 weeks (median = 17 days). The control subjects were recruited from a local institute. All participants were free of neurological and psychiatric conditions suspected to affect cognition or brain morphology. Control participants were interviewed to confirm that they did not meet the criteria for alcohol dependence or abuse (World Health Organization criteria). Additionally, all subjects were evaluated using the Alcohol Use Disorders Identification Test (AUDIT; Reinert & Allen, 2002; see Table 1).

The inclusion criteria for AUD subjects were detoxification for at least 2 weeks and abstinence as assessed by normal levels of gamma glutamyl transferase (GGT) (Table 1). The GGT test is widely used as a marker for alcohol intake. Elevated levels of GGT indicate excessive alcohol consumption.

All participants were examined to identify the following exclusion criteria: history of non-alcohol substance dependence, CNS trauma (such as loss of consciousness for greater than 30 min, seizures not related to alcohol withdrawal, or degenerative disease), serious medical condition (such as insulin-dependent diabetes or hepatic disorder), or mood disorder. All participants gave written informed consent as per the institutional review board

**Table 1**
Sample characteristics.

| Patient characteristics | AUD subjects ($n = 25$) Mean ± SD | Controls ($n = 25$) Mean ± SD |
|---|---|---|
| Age (years) | 36.5 ± 5 | 35.2 ± 3.7 |
| Body mass index (kg/m$^{2)}$ | 24.5 ± 4.1 | 24.6 ± 3.5 |
| Education (years) | 10.5 ± 1.9 | 10.3 ± 1.7 |
| AUDIT | 30.2 ± 4.6 | 0.2 ± 1.3[a] |
| Alcohol consumption[b] | 153.3 ± 19.2 | |
| Duration of dependence (years) | 4.43 ± 1.3 | |
| Abstinence (days) | 17.47 ± 4.39 | |
| Age (years) at first drinking | 23.7 ± 3.1 | |
| Age (years) at the onset of dependence | 33.2 ± 6.2 | |
| **Biological variables** | **Value** | **Laboratory norms** |
| Gamma-glutamyl transferase | 51.3 ± 2.1 | ≤53 |
| Alanine aminotransferase (U/L) | 26.4 ± 14.1 | ≤38 |
| Aspartate aminotransferase (U/L) | 27.3 ± 16.1 | ≤40 |
| Aspartate aminotransferase/alanine aminotransferase | 1.03 ± 0.27 | ≤2 |

[a] $p$ value (≤0.05) for between-group comparisons performed using 2−sample $t$ test; AUDIT: Alcohol Use Disorders Identification Test.
[b] Consumption was defined as grams of pure alcohol/day during the 3 months preceding detoxification.