Frontal white matter abnormalities following chronic ketamine use: a diffusion tensor imaging study

Yanhui Liao,1,* Jinsong Tang,1,* Mingdong Ma,2 Zhimei Wu,3 Mei Yang,3 Xuyi Wang,1 Tieqiao Liu,1 Xiaogang Chen,1 Paul C. Fletcher4 and Wei Hao1

1 Mental Health Institute, Second Xiangya Hospital, Central South University, 139 Renmin (M) Road, Changsha, Hunan, 410011, People’s Republic of China
2 Kangda Voluntary Drug Rehabilitation Centre, 280 Chengnan Road, Changsha, Hunan, 410007, People’s Republic of China
3 Department of Addiction Medicine, Hunan Brain Hospital, 94 Chiling Road, Changsha, Hunan, 410011, People’s Republic of China
4 University of Cambridge, Department of Psychiatry, Addenbrooke’s Hospital, Hills Road, Cambridge, CB2 2QQ, UK

*These authors contributed equally to this work.

Correspondence to: Dr Wei Hao,
Mental Health Institute,
Second Xiangya Hospital,
Central South University,
139 Renmin (M) Road,
Changsha, Hunan, 410011,
People’s Republic of China
E-mail: weihaochangsha@googlemail.com

Correspondence may also be addressed to: Dr Paul C. Fletcher,
University of Cambridge,
Department of Psychiatry,
Addenbrooke’s Hospital,
Hills Road, Cambridge,
CB2 2QQ, UK
E-mail: pcf22@cam.ac.uk

Ketamine abuse has been shown to have a deleterious impact on brain function. However, the precise mechanisms of ketamine dependence-induced pathological change remain poorly understood. Although there is evidence for white matter changes in drug abuse, the presence of white matter abnormalities in chronic ketamine users has not been studied. White matter volumes were measured using in vivo diffusion tensor magnetic resonance imaging data in 41 ketamine-dependent subjects and 44 drug-free healthy volunteers. White matter changes associated with chronic ketamine use were found in bilateral frontal and left temporoparietal cortices. There was also evidence that frontal white matter fractional anisotropy correlated with the severity of drug use (as measured by estimated total ketamine consumption). We provide direct evidence for dose-dependent abnormalities of white matter in bilateral frontal and left temporoparietal regions following chronic ketamine use. The findings suggest a microstructural basis for the changes in cognition and experience observed with prolonged ketamine use. Moreover,
the similarities of these changes to those observed in chronic schizophrenia have implications for the glutamate model of this illness.

**Keywords:** ketamine dependence; voxel-based morphometry; diffusion tensor imaging; fractional anisotropy; frontal white matter

**Abbreviations:** NMDA = N-methyl-D-aspartic acid; SPM = Statistical Parametric Mapping

### Introduction

Ketamine is a dissociative anaesthetic drug (Domino et al., 1965) that induces psychedelic effects (Wolff and Winstock, 2006). While it continues to be used as an anaesthetic in humans and animals due to its remarkable safety profile, its use in adult humans is nevertheless greatly limited by its psychotogenic properties. These properties, together with its dissociative and euphoria-inducing effects have made it an increasingly popular drug of abuse (Ahmed and Petchkovsky, 1980). In the past decade the use of ketamine as a club drug has increased dramatically. For example, in Taiwan, its use has been reported as being as high as 47% among rave party participants (Lua et al., 2003), and more recently its popularity has continued to rise among young people, including students, in Taiwan (Leung et al., 2008), Hong Kong (Joe-Laidler and Hunt, 2008) and mainland China (Fang et al., 2006). With its increasing use, reports of adverse effects have emerged, including bladder dysfunction (Chu et al., 2007; Tsai et al., 2009), cognitive impairments (Morgan et al., 2010) and ketamine-related deaths (Gill and Stajic 2000; Schifano et al., 2010).

There is evidence that a single dose of ketamine does not have lasting consequences (Krystal et al., 1994). However, while controlled studies of ketamine administration have provided a detailed profile of the cognitive and subjective symptoms induced by acute use, and naturalistic studies examining repeat users in a leisure (night club) setting have established cognitive changes persisting for up to three days after acute usage, the full, particularly neurological, impact of ketamine’s chronic use has yet to be elucidated. There is evidence from animal studies that chronic ketamine use produces changes in associative and sensory processing (Maxwell et al., 2006; Amann et al., 2009). Moreover, excitotoxicity-induced brain changes are reported to be widespread (Ellison, 1995). Ketamine’s comparability to the non-competitive N-methyl-D-aspartic acid (NMDA) antagonist dizocilpine (MK-801) (Tsukada et al., 2005), prompted Narendran and colleagues (2005) to examine whether chronic ketamine use produced the prefrontal hypodopaminergic state reported following repeated administration of MK-801. They assessed binding of a selective D1 receptor ligand (11C NNC 112) in individuals with a history of significant repeated use of ketamine for at least 2 years (rising to at least 200–300 mg per week) (Narendran et al., 2005). They showed increased D1 receptor availability in chronic ketamine users with the increase relating to average weekly dose (although it may also relate to route of administration, with highest users favouring an intra-muscular route). This finding was compatible with their prediction that chronic NMDA antagonism would lead to D1 up-regulation via reduced dopamine levels. Narendran et al. (2005) pointed out that their findings in ketamine users were relevant to schizophrenia, a condition in which chronic NMDA receptor hypofunction has been hypothesized, and in which they had shown a comparable prefrontal D1 receptor availability increase (bi-Dargham et al., 2002). The status of acute ketamine use as a model for schizophrenia is of course relevant to this, but whether chronic ketamine use mimics schizophrenia has been less fully explored. It is certainly the case that chronic use produces persistent psychotic symptoms (Morgan et al., 2004) and may model cognitive impairments such as memory impairment more fully (Jansen, 1990). Recently, Morgan et al. (2009) assessed cognitive and oculomotor function in individuals who repeatedly used ketamine for at least a year. Compared to matched patients with schizophrenia, they made comparable antisaccade errors but were otherwise distinct from these patients in terms of other oculomotor and cognitive functions (Morgan et al., 2009).

Clearly, an important question is whether chronic ketamine use has a lasting impact on brain structure and function. The functional evidence so far suggests that there may well be important functional changes, particularly frontally-related ones; but evidence of structural changes in humans has not been reported. Given the suggestions that chronic NMDA blockade may exert an effect on synaptic plasticity, an evaluation of connectivity-related changes may well prove useful. White matter organization and integrity can be evaluated with diffusion tensor imaging, a novel, non-invasive magnetic resonance technique capable of providing quantitative investigation of the microstructural organization of white matter based on patterns of water diffusion in neural tissue (Le et al., 2001). White matter integrity can be studied by examining the degree of fractional anisotropy; this is a measure that quantifies the restriction (anisotropy) of water diffusion by tissue microstructure in each image voxel. High fractional anisotropy indicates a non-spherical tensor with preferential orientation in a particular direction, while a reduced fractional anisotropy indicates more isotropic diffusion, which has been found to be characteristic of disrupted or damaged white matter (Beaulieu, 2002). Recently, it has been shown that these measures can sensitively detect behaviour-dependent changes in brain connectivity (Scholz et al., 2009). Moreover, they have been used to identify and quantify white matter abnormalities in schizophrenia (Kyriakopoulos et al., 2008), even in early stage of the illness (Kyriakopoulos and Frangou, 2009). Although the finding of white matter abnormalities is not completely consistent, frontal white matter seems to be more commonly affected (Kyriakopoulos et al., 2008). For example, Jeong et al. (2009) reported white matter abnormalities of left inferior frontal gyrus in schizophrenia. Camchong et al. (2009) found that frontal white
matter structures have reduced fractional anisotropy in relatives of schizophrenia, which suggested that reduced white matter integrity in frontal regions might be associated with the genetic liability to schizophrenia. Pomarol-Clotet et al. (2010) have more recently shown convincing evidence that medial frontal white matter changes characterize schizophrenia.

Given these observations, the current study was set up to determine whether chronic ketamine use was associated with white matter changes, and whether there was any relationship between such changes and the amount of drug used, as well as its effects on cognition and psychopathology. In particular, we were interested in whether there were any frontal white matter changes, given ketamine’s status as model for schizophrenia.

Materials and methods

Subjects

The study sample comprised 41 ketamine-dependent subjects and 44 age-matched healthy volunteers.

Ketamine-dependent volunteers were recruited from two drug rehabilitation centres: the Kangda Voluntary Drug Rehabilitation Centre in Hunan Province and the Department of Addiction Medicine, Hunan Brain Hospital. All these subjects met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria for lifetime ketamine dependence determined from the Structured Clinical Interview (Spitzer et al., 1992). Subjects were excluded if they met criteria for other substance dependence (excluding nicotine) at any time. Subjects were also excluded if they reported solvent abuse, major medical or psychiatric disorders, current use of psychotropic medications, use of intravenous drugs, pregnancy or contraindications for MRI. Subjects were required to abstain from ketamine for at least 48 h and nicotine for at least 12 h before scanning, and from other psychoactive substances for at least 2 weeks. Nicotine patches were provided as needed.

Control subjects were recruited through a combination of targeted site sampling, advertisement and snowball sampling referrals. Participants were excluded if they (i) were minority rather than Han Chinese; (ii) had suffered learning disabilities or central nervous system disease or condition; (iii) had a medical condition or disease with likely significant central nervous system effects; (iv) had a history of head injury with skull fracture or loss of consciousness of greater than 10 min; (v) had a physical problem that would render study measures difficult or impossible; (vi) had any current or previous psychiatric disorder; (vii) had a family history of psychotic disorder; (viii) had undergone current or previous use of electroconvulsive therapy; or (ix) used psychotropic medications. Participants were additionally excluded for a positive pregnancy test. A licensed psychiatrist, at MD level, conducted all clinical interviews. The Central South University Review Boards approved all procedures used. Subjects were fully informed about the measurement and MRI scanning in the study. Written informed consent was given by all subjects.

Diffusion tensor imaging data acquisition

Diffusion tensor imaging was performed on a 3 T Siemens scanner (Allegra; Siemens Medical System) at the Magnetic Resonance Centre of Hunan Provincial People’s Hospital. A standard birdcage head coil was used, along with restraining foam pads to minimize head motion and to diminish the sounds of the scanner. Image sequences were acquired by means of diffusion weighted imaging with single-shot echo planar imaging in alignment with the anterior–posterior commissural plane. Integral parallel acquisition technique was used with an acceleration factor of 2. The diffusion sensitizing gradients were applied along 30 non-linear directions \((b = 1000 \text{s/mm}^2)\), together with an acquisition without diffusion weighting \((b = 0 \text{s/mm}^2)\). The imaging parameters were 45 continuous axial slices with a slice thickness of 3 mm and no gap, field of view \(= 240 \times 240 \text{mm}^2\), repetition time \(= 6046/93 \text{ms}\), acquisition matrix \(= 128 \times 128\). To provide a high resolution anatomical reference for normalization, axial 3D T1-weighted images were obtained with a spoiled gradient recall sequence and the following parameters: slice thickness \(= 1 \text{mm}\), gap \(= 0 \text{mm}\), repetition time \(= 2000 \text{ms}\), echo time \(= 3.7 \text{ms}\), field of view \(= 256 \times 256 \text{cm}\), flip angle \(= 8^\circ\), matrix size \(= 256 \times 256\) slices \(= 144\).

Magnetic resonance imaging data analysis

Diffusion tensor images were pre-processed with previously published methods as followed. The diffusion data set was pre-aligned to correct for head motion, and the effects of gradient coil eddy currents using software tools from the FMRIB software library (FSL; http://www.fmrib.ox.ac.uk/fsl). After these steps, the diffusion tensor at each voxel was calculated using the FMRIB diffusion toolbox in FSL. The resulting fractional anisotropy images were transformed into Montreal Neurological Institute standard space with Statistical Parametric Mapping (SPM5) (Wellcome Department of Cognitive Neurology, London, UK) by means of the following steps: the \(b = 0 \text{s/mm}^2\) images were coregistered with the structural T1 image for that individual, the same coregistration parameters were applied to the fractional anisotropy maps (in the same space as the \(b = 0 \text{s/mm}^2\) images), each individual’s T1 image was then normalized to the SPM T1 template (in Montreal Neurological Institute standard space), and the same normalization parameters were then applied to the coregistered fractional anisotropy images. Finally, fractional anisotropy images were smoothed with an 8 mm full-width at half-maximum Gaussian kernel. Then, all images were re-sampled with a final voxel size of \(2 \times 2 \times 2 \text{mm}^3\). Furthermore, each fractional anisotropy image was spatially smoothed with an 8 mm full-width at half the maximum Gaussian kernel in order to decrease spatial noise and compensate for the inexact nature of normalization.

Statistical analysis

Between-group tests were performed on diffusion tensor images of fractional anisotropy using a parametric two sample t-test on a voxel-by-voxel basis using SPM5 software. A white matter mask was used to restrict the search volume for analysis. This white matter mask was defined by binarizing the SPM5 a priori white matter template to a binary mask through thresholding each voxel at 50% white matter to define white matter regions for analysis. An initial threshold of 100 voxels or greater, surviving an uncorrected threshold of \(P < 0.001\) was set. However, given the multiple comparisons inherent in such an analysis, we focus only on regional differences that survived a false discovery rate threshold of \(P < 0.05\), which takes into account the number of comparisons made (Genovese et al., 2002). For visualization of regions showing significantly different fractional anisotropy values between the two groups, the significant clusters were superimposed onto SPM5’s spatially normalized template brain.
In order to investigate the clinical association of significant clusters further, region of interest analyses were performed additionally. MarsBar 0.41 (http://marsbar.sourceforge.net/) was used to extract regions of interest containing all the voxels classified as white matter from spatially normalized and smoothed fractional anisotropy images. Then mean fractional anisotropy values from the regions of interest were calculated using log_roi_batch v2.0 (http://www.aimfeld.ch/). Masking threshold for fractional anisotropy values of 0.20 was set for excluding voxels containing partial volume of white matter and other tissues. Finally, the average fractional anisotropy values of individual clusters were calculated for each subject. Correlational analysis of fractional anisotropy values with clinical factors including age at which ketamine use started, total lifetime ketamine consumption, years of ketamine abuse, ketamine-associated symptoms, age and years of education were examined using bivariate correlation analysis ($P<0.01$). A t-test was carried out to determine any effects of gender on fractional anisotropy, though we are cautious in interpreting this, given that the sample contained very few female volunteers.

**Results**

**Demographic data**

The overall sample was characterized typically by middle–upper class socioeconomic status. Demographic data from the study subjects did not differ significantly between groups. The ketamine dependent subjects consumed ketamine only by snorting the powder. Detailed demographic and drug use characteristics of patients with ketamine dependence and control subjects are shown in Table 1. The most frequent self-reported symptoms of ketamine use were slurring of speech (92.68%), hallucinations (82.93%), memory damage (82.93%), blurring of vision (80.49%), insomnia (78.05%), floating sensation and dissociation (75.61%), dizziness (75.61%), stimulation (73.17%), unpleasant imagery (73.17%), irritability (73.17%) and euphoria (70.73%); detailed symptoms have been presented in a separate paper.

**Diffusion tensor imaging of ketamine dependent patients**

Analysis of white matter anisotropy revealed bilateral frontal and left temporoparietal reductions in fractional anisotropy in patients with ketamine dependence in relation to control subjects (Fig. 1 and Table 2).

**Correlation between ketamine related variables and diffusion tensor imaging indices in regions of interest**

Pearson correlations were used to examine the relationships between diffusion tensor imaging indices (fractional anisotropy) in regions of interest and age at which ketamine use started, total lifetime ketamine consumption, years of ketamine abuse, age and years of education. Analyses revealed that fractional anisotropy values in the left ($P=0.015$, Pearson correlation $-0.379$, Fig. 2) and right ($P=0.003$, Pearson correlation $-0.447$, Fig. 3) frontal white matter, but not the left temporoparietal white matter, negatively correlated with the total lifetime ketamine consumption (g). However, we failed to find a correlation between fractional anisotropy values and the age at which ketamine use started or years of ketamine abuse. Also, we did not find any correlation between fractional anisotropy in white matter and age or education level. Given the non-independence of the correlated variables, we have attempted to deal with the multiple comparisons problem inherent in running several correlations for each region by correcting for the false discovery rate for each region (Benjamini and Hochberg, 1995). Taking into account the three key correlations for each region, the two reported correlations survive a False Discovery Rate correction ($P<0.05$).

**Correlations between the ketamine-associated symptoms and reduced fractional anisotropy values in the regions of interest**

Among ketamine users, there was no significant correlation between reduced fractional anisotropy values in the regions of interest and Table 1.

**Table 1** Demographic and drug use characteristics of patients with ketamine dependence and control subjects

<table>
<thead>
<tr>
<th>Demographic and drug variable</th>
<th>Ketamine dependent (n=41)</th>
<th>Control subjects (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, years</td>
<td>26.9±4.87</td>
<td>26.3±5.84</td>
</tr>
<tr>
<td>Range, years</td>
<td>19–39</td>
<td>19–38</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>8 (19.5)</td>
<td>10 (22.7)</td>
</tr>
<tr>
<td>Education, mean ± SD, years</td>
<td>11.9±2.8</td>
<td>15.0±2.6*a</td>
</tr>
<tr>
<td>Han Chinese, n (%)</td>
<td>41 (100)</td>
<td>44 (100)</td>
</tr>
<tr>
<td>Right-handed, n (%)</td>
<td>40 (97.6)</td>
<td>43 (97.7)</td>
</tr>
<tr>
<td>Married, n (%)</td>
<td>24 (60)</td>
<td>29 (65.9)</td>
</tr>
<tr>
<td><strong>Ketamine use variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of first use, mean ± SD, years</td>
<td>23.10±5.21</td>
<td></td>
</tr>
<tr>
<td>Range, years</td>
<td>14–36</td>
<td></td>
</tr>
<tr>
<td>Duration, mean ± SD, months</td>
<td>41.2±21.53</td>
<td></td>
</tr>
<tr>
<td>Range, months</td>
<td>12–126</td>
<td></td>
</tr>
<tr>
<td>Smoking variables, n (%)</td>
<td>41 (100)</td>
<td></td>
</tr>
<tr>
<td>Age at start of smoking, mean ± SD, years</td>
<td>15.4±3.65</td>
<td></td>
</tr>
<tr>
<td>Range, years</td>
<td>10–30</td>
<td></td>
</tr>
<tr>
<td>Duration, mean ± SD, years</td>
<td>11.39±4.89</td>
<td></td>
</tr>
<tr>
<td>Range, years</td>
<td>1.5–21</td>
<td></td>
</tr>
<tr>
<td><strong>Other drug use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol*, n (%)</td>
<td>30 (73.17)</td>
<td>9 (20.45)</td>
</tr>
<tr>
<td>Ecstasy, n (%)</td>
<td>28 (68.29)</td>
<td></td>
</tr>
<tr>
<td>'Ma Gu' (amphetamine and caffeine), n (%)</td>
<td>27 (65.85)</td>
<td></td>
</tr>
<tr>
<td>Methamphetamine, n (%)</td>
<td>23 (56.10)</td>
<td></td>
</tr>
<tr>
<td>Marijuana, n (%)</td>
<td>8 (19.51)</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine (only diazepam), n (%)</td>
<td>6 (14.63)</td>
<td></td>
</tr>
<tr>
<td>Heroin, n (%)</td>
<td>1 (2.44)</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

a Significantly different from control group, $P<0.01$.
b Each person could have tried more than one drug.
c Four ketamine dependent subjects reported drinking more than once a week, no control subjects reported drinking more than once a week.
interest and ketamine-associated symptoms (such as negative and positive hallucinations, vivid dreams, unpleasant imagery, separation of state, schizophrenia-like symptoms or dreaming experience during wake up) (Table 3).

Effects of gender on reduced white matter fractional anisotropy values in regions of interest

There were no significant statistical differences between males and females for reduced fractional anisotropy values in left and right frontal cortex. However, left temporoparietal white matter did show a gender difference (being relatively more affected in males) of reduced fractional anisotropy values (Table 4).

Discussion

Our data demonstrate white matter changes in bilateral frontal and left temporoparietal cortices associated with chronic ketamine use. Furthermore, we observed a correlation between the severity of drug use (as measured by estimated total ketamine consumption) and the extent of white matter change in bilateral frontal cortex. The medial frontal changes reported here are remarkably consistent with those recently shown by Pomarol-Clotet et al. (2010) in schizophrenia. This striking overlap is complemented by the pattern of symptoms in the ketamine user group, which included perceptual changes and hallucinations. Given that acute ketamine administration is widely used as a model for schizophrenia (Vollenweider and Geyer, 2001; Krystal et al., 2005), the current findings are interesting. They suggest that, with more chronic ketamine use, there is a compelling similarity of brain change, at least in terms of white matter, with this illness.

Ketamine’s status, when acutely administered, as a model of schizophrenia, emerges from a range of studies showing that it can induce experiences and cognitive changes that are redolent of a range of psychotic symptoms (Vollenweider and Geyer, 2001).
It is also noteworthy that bilateral frontal white matter abnormalities may characterize other forms of chronic drug use (Goldstein and Volkow, 2002). For example, such abnormalities have been frequently observed in drug, alcohol (Rosenbloom et al., 2003; Pfefferbaum et al., 2009), amphetamine (Thompson et al., 2004; Salo et al., 2009), methamphetamine (Alicata et al., 2009) (including abstinent methamphetamine abusers, Chung et al., 2007), cocaine (Moeller et al., 2005), cannabis (Arnone et al., 2008; Alicata et al., 2009) and heroin dependence (Liu et al., 2008) as well as in smokers (Wang et al., 2009).

A growing number of brain imaging studies have shown evidence to support the hypothesis of cortical ‘hypofrontality’ (reduced baseline activity of several regions of frontal cortex) in patients with chronic drug dependence (Nestler, 2005). These comparable results across several different forms of drug use are also consistent with the view of ‘hypofrontality’ as a fundamental change in addiction. We should, of course, raise the question of whether the observations here are caused by chronic ketamine use or rather reflect a predisposing factor. Our essentially observational study does not allow us to distinguish between these two possibilities, but the intimate relationship between the fractional anisotropy abnormalities and the estimated total amount of ketamine consumed is perhaps suggestive that the changes are, at least in part, a consequence of drug consumption. Comparable dose-related effects have been reported in other addiction studies. For example, greater lifetime alcohol consumption is predictive of greater degradation of fibre bundles in alcoholism (Pfefferbaum et al., 2009); dose-dependent effects have also been indicated in a positron emission tomography study of ‘ecstasy’ users (McCann et al., 1998). It is noteworthy that we did not find a correlation between fractional anisotropy values and age at which ketamine use started or the duration of ketamine use. This suggests that the reported white matter changes reflect cumulative lifetime ketamine consumption. Perhaps, therefore, the long-term use of the drug therapeutically, for example in the treatment of alcoholism (Petrakis et al., 2004) or as an adjunct in treatment-resistant depression (aan het Rot et al., 2010), will not necessarily lead to such white matter changes if doses used are low. Clearly, however, our results suggest that caution must be used in the repeated administration of the drug.

The study also showed that there was a small but statistically significant reduction in fractional anisotropy in left middle temporal region and subgyral parietal region (temporoparietal junction region) of white matter in patients with ketamine dependence. Although an abnormality of this region has not previously been noted in association with drug use, it has been widely reported in patients with Alzheimer’s disease (Hess, 2009). Perhaps this is noteworthy given the memory impairment associated with ketamine.

There are, of course, a number of limitations to our study. First of all, the direction of the causal relationship between white matter changes and chronic ketamine use cannot be fully determined within the current design although, as above, the correlation with duration of use perhaps suggests that chronic ketamine use causes the white matter change rather than the reverse. Second, education levels were not well-matched between the two groups. However, when we explicitly explored the impact

---

**Table 3** Correlation between ketamine-associated symptoms and reduced fractional anisotropy values in regions of interest

<table>
<thead>
<tr>
<th>Anatomical region</th>
<th>Ketamine-associated symptoms</th>
<th>Pearson correlation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right frontal cortex</td>
<td>-0.10</td>
<td>0.521</td>
<td></td>
</tr>
<tr>
<td>Left frontal cortex</td>
<td>0.03</td>
<td>0.851</td>
<td></td>
</tr>
<tr>
<td>Left temporoparietal cortex</td>
<td>0.04</td>
<td>0.813</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4** Gender differences of mean fractional anisotropy in regions of interest

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>Gender</th>
<th>n</th>
<th>Mean ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left frontal cortex</td>
<td>Male</td>
<td>33</td>
<td>0.38 ± 0.03</td>
<td>0.701</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>8</td>
<td>0.37 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>Right frontal cortex</td>
<td>Male</td>
<td>33</td>
<td>0.37 ± 0.04</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>8</td>
<td>0.41 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>Left temporoparietal cortex</td>
<td>Male</td>
<td>33</td>
<td>0.33 ± 0.03</td>
<td>0.499</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>8</td>
<td>0.34 ± 0.03</td>
<td></td>
</tr>
</tbody>
</table>

However, it is acknowledged that there are a number of differences between the nature of experiences associated with acute drug administration and the course and pattern of symptoms in schizophrenia. With this in mind, the increasing trend towards chronic ketamine use offers the opportunity to extend the model. In this regard, the current study complements observations of structural and functional changes in chronic ketamine users and suggests a further similarity with schizophrenia, notably in the dose-dependent reduction in fractional anisotropy of frontal white matter. Although the findings of white matter abnormalities in patients with schizophrenia are not completely consistent, frontal white matter is the more commonly affected region (Kyriakopoulos et al., 2008). More recently, Camchong et al. (2009) have shown that medial frontal white matter anomalies may reflect an enhanced risk for schizophrenia.
of duration of education on frontal white matter in the ketamine users group, we saw no significant correlation (P > 0.3). This suggests that our findings cannot simply be explained in terms of this variable. Third, since the proportion of females in the sample was relatively small, we were unable to explore gender differences with confidence. While we did observe a significant difference in temporoparietal white matter associated with gender, the very small proportion of females makes us cautious about drawing any conclusions from this. Fourth, it is always possible that the results could be confounded by the use of other substances in the ketamine user group. Such a confound could arise directly or from interaction between ketamine and other substances. In mitigation of this however, we did exclude patients reporting dependence on other substances (except nicotine), so as far as we are aware this possibility is minimized by the exclusion criteria. Related to this, we did not acquire recent urine or blood toxicology screens (although ketamine users’ test records from the rehabilitation centre were checked to confirm that other drugs were not a major factor). Finally, we excluded psychiatric disorders in this sample. This is a strength in terms of interpreting the findings, however it does mean that major psychiatric illness in the context of ketamine use was not examined here.

Conclusion

In conclusion, using diffusion tensor imaging, we have identified abnormalities in ketamine-dependent patients in bilateral frontal (including corpus callosum and anterior cingulate cortex) and left temporoparietal whiter matter. We also report that fractional anisotropy values negatively correlate with the total lifetime ketamine consumption. Our findings should serve as starting points for further investigations into how white matter changes may relate to the experiences and behaviours that characterise chronic ketamine use. We believe that these findings also have implications for the glutamate model of schizophrenia.

Acknowledgements

The authors thank Dr Yan Zhou and Dr Benwen Deng from Kanda Voluntary Drug Rehabilitation Centers in Hunan Province for their support and Dr Jianbin Liu, Xiaoyun Liu and Feng Huang from Magnetic Resonance Center of Hunan Provincial People’s Hospital for providing expert MRI support.

Funding

National Key Technology R&D Program in the 11th Five-Year Plan of China [2007BA107B01 to W.H.]; National Science Foundation of China [30971050 to W.H., 30870893 to X.G.C., 30900486 to J.S.T.]; National Key Basic Research and Development Program (973) [2006CB500808 to X.G.C., 2007CB512301 to X.G.C.]; Paul C. Fletcher is supported by the Bernard Wolfe Health Neuroscience fund and by the Wellcome Trust. Yanhui Liao is supported by a fellowship from the China Scholarship Council and by Professor Trevor W Robbins to study at University of Cambridge, Behavioural and Clinical Neuroscience Institute.

References

Camchong J, Lim KO, Sponheim SR, Macdonald AW. Frontal white matter integrity as an endophenotype for schizophrenia: diffusion tensor imaging in monozygotic twins and patients’ nonpsychotic relatives. Front Hum Neurosci 2009; 3: 35.


