ORIGINAL INVESTIGATION

Glutamate, N-acetyl aspartate and psychotic symptoms in chronic ketamine users

**James M. Stone · Fiona Pepper · Johnson Fam ·
Hannah Furby · Emer Hughes · Celia Morgan ·
Oliver D. Howes**

Abstract

Rationale Ketamine, a non-competitive NMDA receptor antagonist, induces acute effects resembling the positive, negative and cognitive symptoms of schizophrenia. Chronic use has been suggested to lead to persistent schizophrenia-like neurobiological changes.

Objectives This study aims to test the hypothesis that chronic ketamine users have changes in brain neurochemistry and increased subthreshold psychotic symptoms compared to matched poly-drug users.

Methods Fifteen ketamine users and 13 poly-drug users were included in the study. Psychopathology was assessed using the Comprehensive Assessment of At-Risk Mental State. Creatine-scaled glutamate (Glu/Cr), glutamate+glutamine (Glu+Gln/Cr) and *N*-acetyl aspartate (NAA/Cr) were measured in three brain regions—anterior cingulate, left thalamus and left medial temporal cortex using proton magnetic resonance spectroscopy.

Results Chronic ketamine users had higher levels of subthreshold psychotic symptoms ($p < 0.005$, Cohen's $d = 1.48$) and lower thalamic NAA/Cr ($p < 0.01$, $d = 1.17$) compared to non-users. There were no differences in medial temporal cortex or anterior cingulate NAA/Cr or in Glu/Cr or Glu+Gln/Cr in any brain region between the two groups. In chronic ketamine users, CAARMS severity of abnormal perceptions was directly correlated with anterior cingulate Glu/Cr ($p < 0.05$, $r = 0.61$—uncorrected), but NAA/Cr was not related to any measures of psychopathology.

Conclusions The finding of lower thalamic NAA/Cr in chronic ketamine users may be secondary to the effects of ketamine use compared to other drugs of abuse and resembles previous reports in individuals at genetic or clinical risk of schizophrenia.

Celia Morgan and Oliver D. Howes contributed equally to this work.

J. M. Stone · J. Fam · O. D. Howes
Department of Experimental Medicine, Imperial College London, London, UK

F. Pepper · H. Furby · C. Morgan
Clinical Psychopharmacology Unit, University College London, London, UK

E. Hughes
Robert Steiner MRI Unit, Imaging Sciences Unit, Hammersmith Hospital, Imperial College London, London, UK

F. Pepper · O. D. Howes
MRC Clinical Sciences Centre, Hammersmith Hospital, Imperial College London, London, UK

J. M. Stone · O. D. Howes
Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, UK

J. M. Stone (✉)
Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London, London, UK
e-mail: james.m.stone@kcl.ac.uk

Introduction

Ketamine, a dissociative anaesthetic agent and non-competitive NMDA receptor antagonist, induces acute effects

at subanaesthetic doses that resemble the positive, negative and cognitive symptoms of schizophrenia (Krystal et al. 1994). When administered to patients with stable schizophrenia, ketamine may lead to a relapse of symptoms indistinguishable from the idiopathic disease (Lahti et al. 1995).

Despite considerable interest in the NMDA receptor antagonist model of psychosis, acute ketamine administration has been suggested to be somewhat unlike idiopathic psychoses because of its relatively short-lived effects (Tsai and Coyle. 2002). In contrast, chronic ketamine administration may be more representative of the long-term NMDA receptor dysfunction hypothesised to occur in schizophrenia (Tsai and Coyle. 2002). In rats, repeated administration of ketamine has been reported to lead to neurodegenerative changes in brain regions resembling those affected in schizophrenia (Keilhoff et al. 2004). Reductions in brain N-acetyl aspartate (NAA), suggested to be a marker of neuronal integrity and, possibly, of glutamatergic neuronal function (Reynolds and Harte. 2007), have been reported in rats administered the NMDA receptor antagonist phencyclidine (Reynolds et al. 2005). NAA reductions measured using proton magnetic resonance spectroscopy (1H-MRS) are also a consistent finding in patients with schizophrenia, becoming more marked and affecting more regions with disease progression (Steen et al. 2005; Brugger et al. 2011). NAA reductions in thalamus have been reported in individuals at high clinical and genetic risk of psychosis, whilst more widespread reductions, including temporal cortex and frontal cortex, have been reported in patients with chronic schizophrenia (Brugger et al. 2011). These findings suggest that reduced thalamic NAA may be an indicator of early pathophysiological changes linked to the risk for psychosis.

In terms of brain glutamate levels, 1H-MRS findings have been mixed. In individuals at risk of psychosis, and in patients with first-episode psychosis, elevations in medial prefrontal glutamine or glutamate+glutamine levels have been reported (Bartha et al. 1997; Théberge et al. 2002; Tibbo et al. 2004; Stone et al. 2009; Marsman et al. 2013), but others have not found any evidence of difference in brain glutamate metabolites in these groups (Wood et al. 2007; Yoo et al. 2009). In contrast, in patients with chronic schizophrenia, brain glutamate levels have generally been reported as being normal or low (Szulc et al. 2013; Marsman et al. 2013), although this may be an effect of medication as a recent study demonstrated elevated medial prefrontal glutamate+glutamine levels in unmedicated patients with chronic schizophrenia (Kegeles et al. 2012).

To date there have been three reports of glutamate metabolite estimation with 1H-MRS following acute ketamine administration in humans. One reported increased anterior cingulate glutamine (Rowland et al. 2005), one reported increased anterior cingulate glutamate (Stone et al. 2012), and one reported no change in anterior cingulate glutamate+glutamine levels (Taylor et al. 2011), although the latter study was potentially underpowered, utilising a between-subject analysis with a sample size of nine subjects receiving placebo and eight receiving ketamine. No human studies of the effects of chronic ketamine use on brain glutamate have been reported, but in rats elevations in brain glutamate measured using 1H-MRS have been reported (Kim et al. 2011).

Although chronic NMDA receptor blockade is an established preclinical model of schizophrenia, it is not known if chronic NMDA receptor blockade in humans is associated with reductions in levels of brain NAA and increases in glutamate seen in preclinical models and in people with early symptoms of psychosis. It would not be ethical to administer daily ketamine to healthy volunteers over an extended period of months or years, but an alternative method to study chronic NMDA receptor hypofunction in humans is to study people who choose to take ketamine regularly. Ketamine users have been reported to have increased prefrontal dopamine D1 receptors (Narendran et al. 2005) as well as reduced gray matter volume in anterior cingulate cortex (Liao et al. 2011). In this study, we tested the hypothesis that compared to non-ketamine-using poly-drug users, individuals with chronic ketamine use have greater levels of subthreshold psychotic symptoms, elevations in creatine-scaled anterior cingulate glutamate (Glu/Cr) and glutamate+glutamine (Glu+Gln/Cr) and reductions in creatine-scaled thalamic, medial temporal cortex and anterior cingulate N-acetyl aspartate (NAA/Cr).

Methods

The study was approved by Imperial College London Research Ethics Committee, UK. Fifteen ketamine users (age range 20–29 years old, with a history of using ketamine at least three times per week for the last year) and 13 poly-drug-using controls (matched for age, sex and education level but who had no history of regular ketamine use) were included in the study. All participants completed information about their level and history of substance use including ketamine. Levels of subthreshold psychotic symptoms were assessed using the Comprehensive Assessment of At-Risk Mental State (CAARMS)—abnormalities of thought content (bizarre+non-bizarre), abnormalities of perceptions and abnormalities of speech production subscales (Yung et al. 2005), with participants describing their experiences when drug-free.

All participants then underwent MRI imaging on a Philips 3-T Intera magnetic resonance system, software release 2.1.3. An initial localizer scan was performed followed by acquisition of a whole-brain 3D-MPRAGE (TR=9.6 ms, TE= 4.5 ms, flip angle 8°, slice thickness=1.2 mm, 0.94 mm× 0.94 mm in plane resolution, 150 slices). PRESS (Point RESolved Spectroscopy) data were then acquired (TE= 35 ms; TR=3,000 ms; 64 averages for anterior cingulate, 96 averages for medial temporal cortex and thalamus), utilising

the default "Excite" water suppression routine. Auto-shimming was performed using second-order pencil beam shim. The 3D MPRAGE was used to place regions of interest for the PRESS analysis. The anterior cingulate region of interest (ROI) was prescribed from the midline sagittal slice, and the centre of the 20 mm×20 mm×20 mm ROI was placed 13 mm above the anterior section of the genu of corpus callosum at 90° to the AC-PC line (Fig. 1). The centre of the thalamus ROI (20 mm×15 mm×20 mm) was defined at the point in the axial slices where the thalamus was widest, using sagittal and axial planes, and rotating the ROI to ensure that it was clear of CSF (Fig. 2). The centre of the medial temporal cortex ROI (20 mm×20 mm×15 mm) was positioned superior to the anterior edge of the cerebellum and angled in line with the body of the hippocampus (Fig. 3).

PRESS spectra (Fig. 4) were analyzed using LCModel version 6.3. The raw spectral data were read into LCMgui, the graphical user interface for LCModel. A standard basis set of 16 metabolites (L-alanine, aspartate, creatine, phosphocreatine, GABA, glucose, glutamine, glutamate, glycerophosphocholine, glycine, myo-inositol, L-lactate, N-acetyl aspartate, N-acetylaspartylglutamate, phosphocholine, taurine), included as part of LCModel and acquired with the same field strength (3 T), localization sequence (PRESS) and echo time (35 msec) as our study was used. Model metabolites and concentrations employed in the basis set are fully detailed in the LCModel manual (http://s-provencher.com/pages/lcm-manual.shtml). For all metabolites, we used the recommended cutoff of Cramer-Rao Lower Bounds (CRLB) of 20 % to exclude poorly fitted metabolite peaks. As absolute quantification is not possible at field strengths above 1.5 T due to the breakdown of the law of reciprocity (Jansen et al. 2006) and

due to the fact that we did not have access to unsuppressed PRESS spectra for water scaling, we quantified all metabolites as a ratio to creatine.

Group differences in demographic, drug use, rating and metabolite data were assessed with Welch's two-sample t-test and the chi-square test was implemented in R version 2.14.1 (Ihaka and Gentleman. 1996). Correlations between metabolite levels and CAARMS severity of abnormal thought content, abnormal perceptions or speech production were investigated in ketamine users using Pearson's correlation.

Results

Ketamine users did not differ from controls in demographic or other substance use variables, except for amount of amphetamine used per month (Table 1). Ketamine users had significantly greater severity of CAARMS—abnormalities of thought content (mean score=2.3 vs. 0.54; t=3.36; p=0.003, Cohen's d=1.48), with six of the ketamine users and 0 controls reaching formal criteria for an at-risk mental state (Table 1) (Yung et al. 2005).

1H-MRS spectra were of reasonable quality in anterior cingulate and left thalamus, with a mean (SD) signal-to-noise ratio reported by LCModel of 16.9 (3.4) and 11.75 (3), respectively, and of passable quality in left medial temporal cortex with a mean (SD) signal-to-noise ratio of 8.1 (3.4). Line widths reported by LCModel followed a similar pattern with mean (SD) of 5.4 (0.97) Hz in anterior cingulate, 6.4 (1.4) Hz in left thalamus and 8.3 (3.3) Hz in left medial temporal cortex. Signal-to-noise ratio did not differ in any region between controls and ketamine users, but the line width in
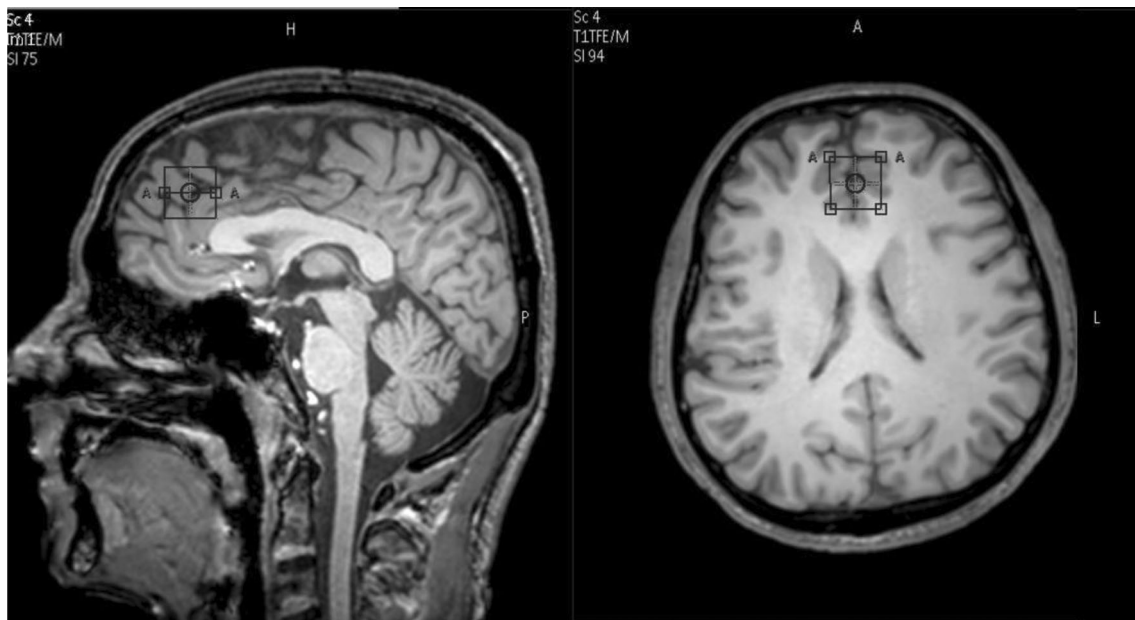

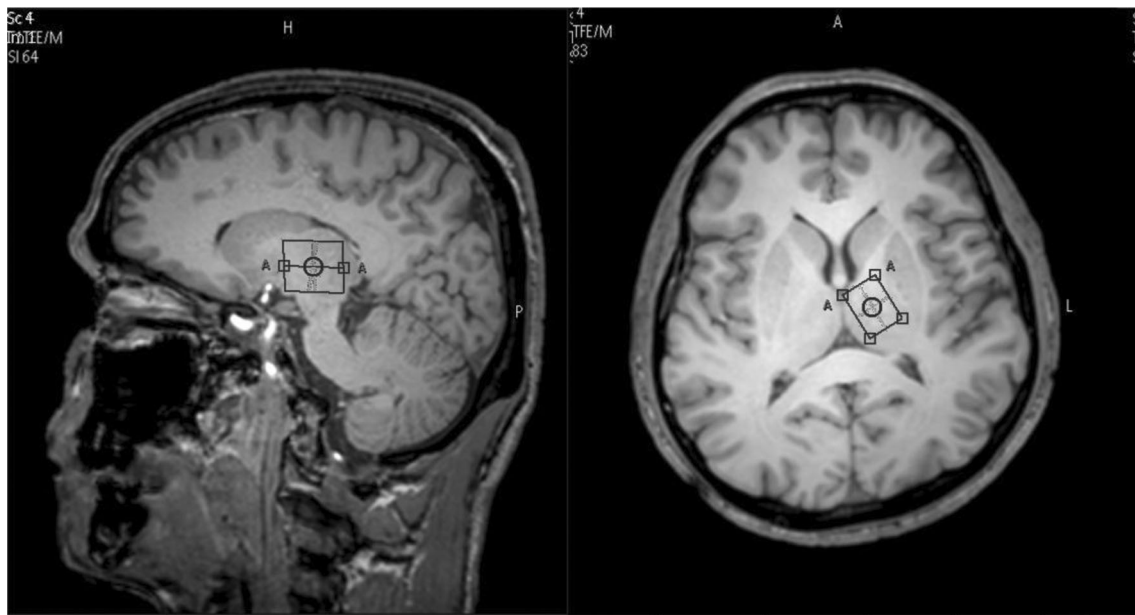**Fig. 1** Placement of anterior cingulate ROI

Fig. 2 Placement of left thalamus ROI

thalamus was wider in ketamine users (mean=5.9 Hz, 7.0 Hz; $p=0.03$). Glu+Gln/Cr was not measureable at CRLB<20 % in thalamus in one ketamine user or in medial temporal cortex in two ketamine users and two controls. Medial temporal cortex NAA/Cr was not measureable at CRLB<20 % in one ketamine user.

Ketamine users had significantly lower NAA/Cr in thalamus than controls (mean level=1.17 vs 1.24; $t=2.84$; $p<0.01$, Cohen's $d=1.17$). This did not appear to be due to differences in scan quality between ketamine users and controls as there

was no relationship between LCModel-reported line width and NAA/Cr in thalamus ($p=0.2$). There were no differences in medial temporal cortex or anterior cingulate NAA/Cr or in Glu+Gln/Cr or Glu/Cr in any brain region between the two groups ($p>0.05$; Table 2).

In ketamine users, there was a significant relationship between anterior cingulate Glu/Cr levels and CAARMS severity of abnormal perceptions ($p=0.02$, $r=0.61$; Fig. 5). A similar trend relationship was seen between anterior cingulate Glu+Gln/Cr and CAARMS severity of abnormal perceptions
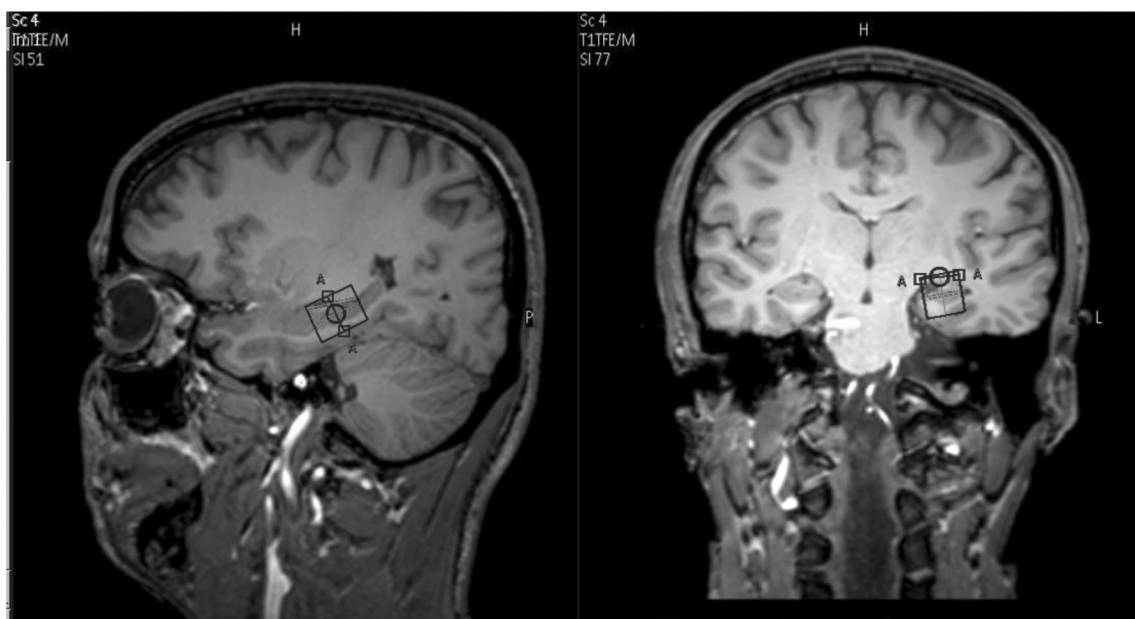

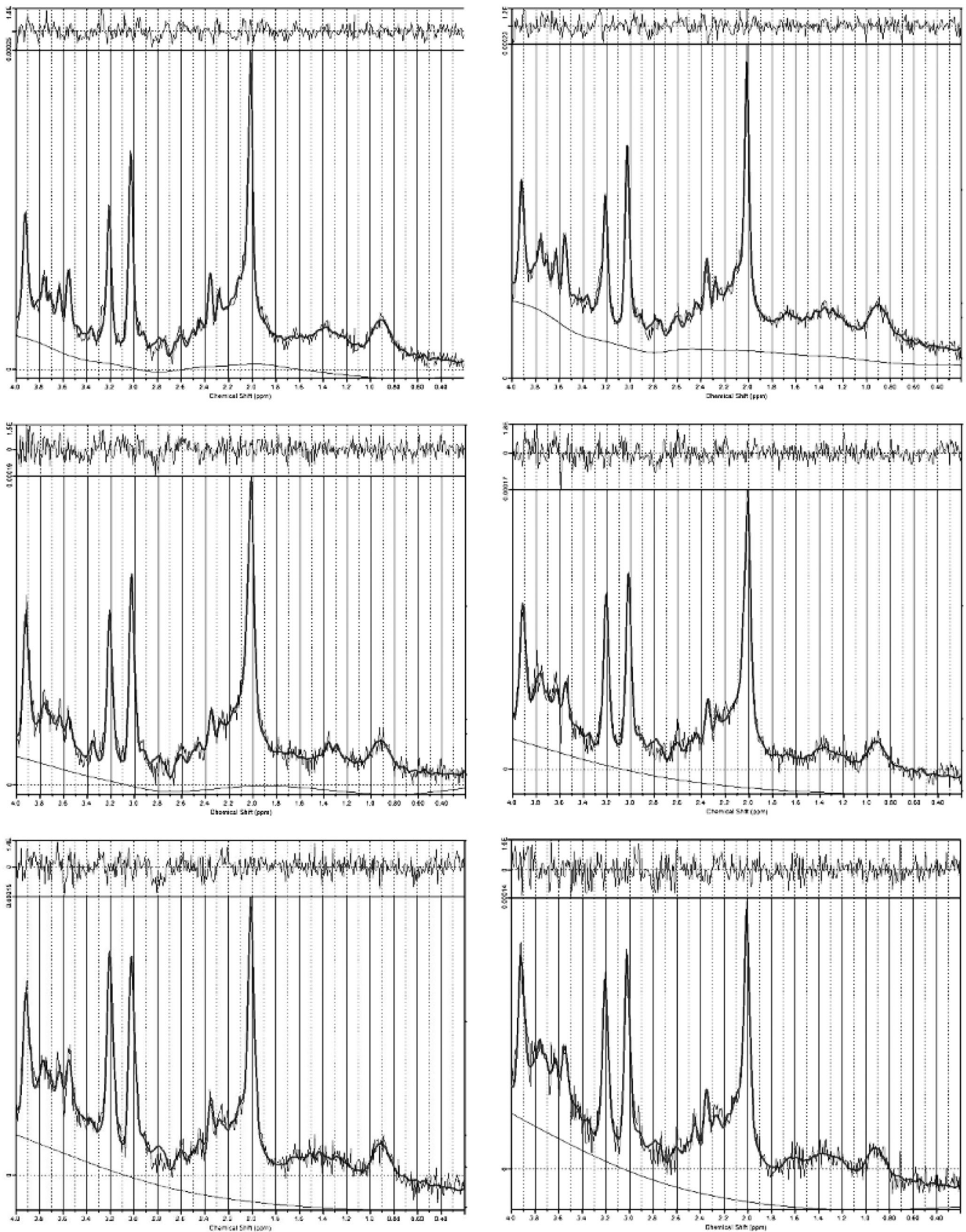**Fig. 3** Placement of left medial temporal cortex ROI

Fig. 4 Sample 1H-MRS spectra (LCModel output) from anterior cingulate, thalamus, and medial temporal cortex ROIs (control—*left*, ketamine—*right*)

Table 1 Participant demographics, self-reported drug use, and clinician-rated psychotic-like symptoms

	Ketamine users ($n=15$)	Controls ($n=13$)	Statistical significance analysis
Age mean (SD)	25.7 (2.1)	24.5 (2.6)	$t=1.3$; $p=0.2$
Sex (M/F)	9/6	11/2	$\chi^2=1.03$; $p=0.30$
Years of education, mean (SD)	14.9 (3.9)	17.3 (4.1)	$t=1.6$; $p=0.12$
Smoker (Y/N)	9/6	6/7	$\chi^2=0.12$; $p=0.72$
History of alcohol use (Y/N)	15/0	13/0	$\chi^2=$N/A; $p=1$
Alcohol units per week, mean (SD)	54.3 (80.2)	12.1 (9.2)	$t=1.8$; $p=0.08$
History of cannabis (Y/N)	15/0	13/0	$\chi^2=$N/A; $p=1$
Level of cannabis use—days taken to smoke 1/8 oz cannabis (SD)	9 (17.2)	341 (838)	$t=1.19$; $p=0.27$
History of MDMA (Y/N)	14/1	9/4	$\chi^2=1.36$; $p=0.24$
MDMA mg per month, mean (SD)	2,218 (5,103)	178 (549)	$t=1.54$; $p=0.15$
History of cocaine (Y/N)	15/0	10/3	$\chi^2=1.84$; $p=0.18$
Cocaine (grams per month), mean (SD)	6.3 (8.8)	1.78 (5.7)	$t=1.57$; $p=0.13$
History of amphetamine use (Y/N)	13/2	8/5	$\chi^2=1.20$; $p=0.27$
Amphetamine (grams per month), mean (SD)	0.6 (0.75)	0	$t=2.77$; $p=0.02$*
History of ketamine (Y/N)	15/0	5/8	$\chi^2=10.1$; $p=0.001$***
Ketamine (grams per month), mean (SD)	100 (114)	0 (0)	$t=3.34$; $p=0.005$**
CAARMS—severity of abnormalities of thought content, mean (SD)	0.53 (0.88)	2.33 (1.84)	$t=3.37$; $p=0.003$***
CAARMS—severity of perceptual abnormalities, mean(SD)	1.69 (2.01)	2.26 (1.67)	$t=0.81$; $p=0.42$
CAARMS—severity of abnormalities of speech production, mean(SD)	1.38 (1.76)	2.07 (1.79)	$t=1.01$; $p=0.32$

CAARMS Comprehensive Assessment of At-Risk Mental State

*$p<0.05$; **$p<0.01$; ***$p<0.005$

in ketamine users ($p=0.06$, $r=0.48$). However, these relationships were not corrected for multiple comparisons (18 tests in total) and were not present in the total sample (poly-drug controls plus ketamine users). There was no relationship between thalamic NAA levels and CAARMS severity of abnormal thought content, abnormal perceptions or speech production in ketamine users or controls.

Table 2 Creatine-scaled metabolite levels as reported by LCModel

|		Ketamine users, mean (SD)	Poly-drug controls, mean (SD)	Statistical significance
Anterior cingulate				
	Glutamate/creatine	1.55 (0.15); $n=15$	1.52 (0.24); $n=13$	$t=0.34$; $p=0.74$
	Glutamate+glutamine/creatine	2.15 (0.32); $n=15$	2.11 (0.36); $n=13$	$t=0.32$; $p=0.75$
	N-Acetyl aspartate/creatine	1.16 (0.09); $n=15$	1.11 (0.11); $n=13$	$t=1.59$; $p=0.12$
	Myoinositol/creatine	0.72 (0.11); $n=15$	0.72 (0.05); $n=13$	$t=0.15$; $p=0.88$
	GPC/creatine	0.25 (0.027); $n=15$	0.25 (0.029); $n=13$	$t=0.35$; $p=0.73$
Thalamus				
	Glutamate/creatine	1.27 (0.12); $n=12$	1.30 (0.15); $n=13$	$t=0.57$; $p=0.57$
	Glutamate+glutamine/creatine	1.77 (0.37); $n=14$	1.86 (0.33); $n=13$	$t=0.65$; $p=0.52$
	N-Acetyl aspartate/creatine	1.17 (0.06); $n=15$	1.24 (0.07); $n=13$	$t=2.84$; $p=0.009$**
	Myoinositol/creatine	0.57 (0.10); $n=14$	0.57 (0.17); $n=13$	$t=0.028$; $p=0.98$
	GPC/creatine	0.30 (0.02); $n=13$	0.30 (0.02); $n=12$	$t=0.16$; $p=0.87$
Medial temporal cortex				
	Glutamate/creatine	1.37 (0.26); $n=13$	1.32 (0.24); $n=9$	$t=0.41$; $p=0.69$
	Glutamate+glutamine/creatine	1.73 (0.54); $n=13$	1.94 (0.52); $n=11$	$t=0.91$; $p=0.37$
	N-Acetyl aspartate/creatine	1.04 (0.22); $n=14$	1.05 (0.11); $n=12$	$t=0.15$; $p=0.88$
	Myoinositol/creatine	0.99 (0.30); $n=12$	0.90 (0.32); $n=12$	$t=0.72$; $p=0.48$
	GPC/creatine	0.33 (0.04); $n=13$	0.33 (0.03); $n=11$	$t=0.17$; $p=0.87$

GPC glycerophosphocholine

**$p<0.01$
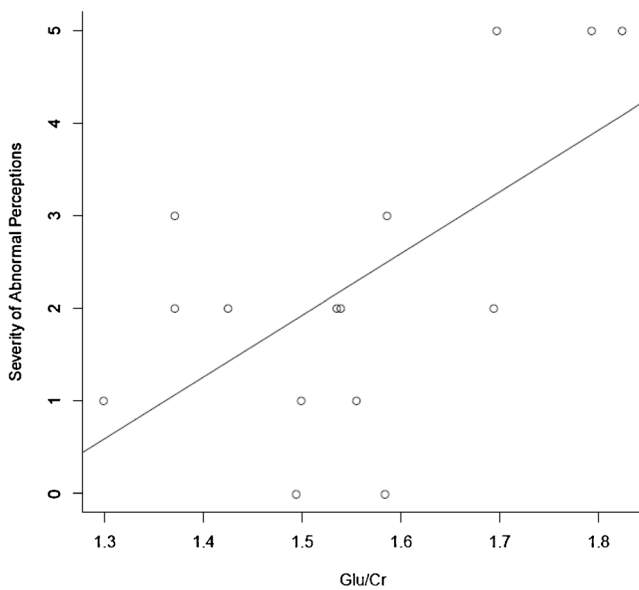
Fig. 5 Relationship between Glu/Cr in anterior cingulate and CAARMS severity of abnormal perceptions in ketamine users

Discussion

This is the first study, to our knowledge, to report brain 1H-MRS findings in chronic ketamine users. The finding that ketamine users have subthreshold psychotic symptoms as well as reduced levels of thalamic NAA/Cr reflects previous reports of reduced thalamic NAA in individuals at clinical and generic risk of schizophrenia as well as in patients with first episode and chronic schizophrenia (Brugger et al. 2011). It suggests that adding chronic ketamine use to poly-drug use is associated with psychotic symptoms and brain alterations in the thalamus similar to those seen during the development of schizophrenia. This is of relevance in the treatment of people with chronic ketamine abuse as it suggests that they may be at increased risk of developing psychosis compared to poly-drug users.

The thalamus is thought to play a key role in the filtering of sensory information, integrating internal and external perceptions. Abnormalities of thalamic function have been hypothesised to be central to the development of psychotic symptoms (Carlsson and Carlsson. 1990; Vollenweider and Geyer. 2001; Clinton and Meador-Woodruff. 2004; Behrendt. 2006). Recent studies support this mechanism: the neurotoxic effects of ketamine in rodents appears to occur through action in the thalamus as opposed to direct effects on cortical brain regions (Sharp et al. 2001); reductions in thalamic blood flow have been shown to occur following administration of the serotonergic hallucinogen psilocybin (Carhart-Harris et al. 2012), and several case reports of patients with thalamic infarct describe the sudden onset of a schizophrenia-like psychosis (Arikan et al. 2009; Mittal and Khan. 2010; Crail-Melendez et al. 2012).

Current evidence suggests that alterations in thalamic structure and function may be one of the earliest detectable changes in the development of schizophrenia. Volumetric reductions in thalamus are a consistent finding in patients with schizophrenia, with a recent meta-analysis reporting that these reductions were more marked in unmedicated patients than those on antipsychotic treatment (Haijma et al. 2012). An MRI study of individuals at genetic high risk of developing schizophrenia has also reported reductions in thalamic volume (Lawrie et al. 1999).

Reductions in NAA, suggested to represent changes in neuronal integrity, are present at all stages of illness and in multiple brain regions, but the thalamus is the only region that has been reported to show NAA reductions in individuals with prodromal symptoms or at genetic risk of schizophrenia (Brugger et al. 2011). Thalamic NAA has been reported to be negatively correlated with duration of untreated psychosis (Jakary et al. 2005) and with length of prodrome (Theberge et al. 2004), while antipsychotic treatment is associated with an increase in thalamic NAA (Szulc et al. 2013). Reductions in thalamic NAA levels also appear to be related to other biological endophenotypes of schizhophrenia: we have reported that reductions in thalamic NAA in individuals with prodromal psychosis correlated with deficits in frontal P300 (Stone et al. 2010) as well as with reductions in cortical grey matter volume (Stone et al. 2009). The significance of the reductions in thalamic volume and NAA level in ARMS individuals and patients with psychosis is unclear, but in post-mortem studies on patients with chronic schizophrenia, reductions in thalamic neuron density have been found (Clinton and Meador-Woodruff. 2004), possibly due to loss of glutamatergic thalamocortical projection neurons (Danos et al. 1998).

The finding that chronic ketamine users did not differ from poly-drug-using controls in terms of brain Glu/Cr or Glu+ Gln/Cr levels, although unexpected, is not altogether surprising. In patients with schizophrenia and first episode psychosis, there has been a great deal of heterogeneity in studies on brain glutamate levels. From a meta-analysis of the literature, we would predict that ketamine users, if they resemble patients with first episode psychosis, would have elevated glutamine levels in anterior cingulate (Marsman et al. 2013). Unfortunately, we were unable to reliably separate glutamine from glutamate in this study. Our finding of a relationship between the level of anterior cingulate Glu/Cr and perceptual distortions in ketamine users should be viewed with caution as it is uncorrected for multiple comparisons. We previously reported a relationship between anterior cingulate glutamate levels and positive psychotic symptoms following acute ketamine administration (Stone et al. 2012). Furthermore, we found elevated Glu/Cr in patients with first episode psychosis who remain symptomatic following antipsychotic treatment (Egerton et al. 2012). Thus, it is possible that ketamine users with more marked psychotic symptoms may have higher Glu/

Cr levels in anterior cingulate, but the present study is not sufficiently powered to address this question.

The findings from this study are broadly in keeping with the literature on patients with schizophrenia and first episode psychosis in which NAA reductions are more robustly associated with illness trait but are not closely related to symptomatology (Brugger et al. 2011), whereas elevated anterior cingulate Glu levels, although less strongly associated with illness trait (Marsman et al. 2013), may be related to the severity of psychotic symptoms (Egerton et al. 2012; de la Fuente-Sandoval et al. 2013; Demjaha et al. 2013).

The study has a number of limitations:

(1) Most notable is that ketamine users had taken a variety of other drugs. In particular, ketamine users had a significantly higher monthly intake of amphetamine than polydrug-using controls. There was also a large amount of variance in level of use in the ketamine users group, and ketamine users generally had a higher mean level of all substances than controls. At present, although there is no evidence that other drugs affect thalamic NAA levels, cannabis, cocaine, methamphetamine and MDMA use has been associated with reduced NAA in frontal cortex (Chang et al. 1999; Reneman et al. 2002; Nordahl et al. 2005; Hermann et al. 2007; Salo et al. 2007; Cowan et al. 2009), and alcohol dependence has been reported to be associated with reduced thalamic grey matter volume and reduced temporal and parietal NAA levels (Gazdzinski et al. 2008). Another group reported that chronic cocaine use was associated with reduced anterior cingulate glutamate levels (Yang et al. 2009). It is thus not possible to be completely sure that the reported reductions in thalamic NAA/Cr were due to ketamine exposure rather than to amphetamine or other substances;

(2) An associated limitation is due to the fact that the control group was poly-drug users. As drugs of abuse have been reported to have effects on reducing 1H-NAA levels (primarily in frontal cortex), as described earlier, the effect of ketamine may have been masked to a certain extent by these effects. The lack of a drug-free control group may make generalisation of the model to schizophrenia more problematic;

(3) A third limitation is that the spectroscopy data were scaled to creatine rather than water. This approach has an advantage of not requiring correction for the amount of CSF in the ROI as brain metabolites such as Cr and NAA are present in brain tissue and not in CSF. On the other hand, scaling to creatine means that we cannot exclude the possibility that the differences in NAA/Cr were driven by group differences in creatine. The fact that there were no differences in other creatine-scaled metabolites between the two groups makes this unlikely, however;

(4) Lastly, reverse causality is a possibility—individuals with an At-Risk Mental State, or with low thalamic NAA, may have been at a higher probability of becoming regular ketamine users. However, given that ketamine worsens psychotic symptoms (Lahti et al. 1995), it seems unlikely that individuals with subthreshold psychotic symptoms would recreationally abuse a drug that worsened their symptoms. Longitudinal studies are required to investigate this possibility.

In summary, this study suggests that chronic ketamine use, a naturalistic model of chronic NMDA receptor dysfunction, is associated with symptoms and neurochemical changes that have also been reported in individuals at high risk of developing schizophrenia. It supports the hypothesis that abnormalities of NMDA receptor function may drive symptoms and brain pathology in the early stages of the illness. Further work in our laboratory will seek to determine whether this is a unique effect of ketamine or whether other drugs of abuse, such as cannabis, are also associated with reductions in thalamic NAA.

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