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Structural connectivity and response to ketamine therapy in major depression: A preliminary study

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Abstract

Background—Ketamine elicits an acute antidepressant effect in patients with major depressive disorder (MDD). Here, we used diffusion imaging to explore whether regional differences in white matter microstructure prior to treatment may predict clinical response 24 hours following ketamine infusion in 10 MDD patients.

Methods—FSL's Tract-Based Spatial Statistics (TBSS) established voxel-level differences in fractional anisotropy (FA) between responders (patients showing >50% improvement in symptoms 24 hours post-infusion) and non-responders in major white matter pathways. Follow-up regions-of-interest (ROI) analyses examined differences in FA and radial (RD), axial (AD) and mean diffusivity (MD) between responders and non-responders and 15 age- and sex-matched controls, with groups compared pairwise.

Results—Whole brain TBSS ($p<0.05$, corrected) and confirmatory tract-based regions-of-interest analyses showed larger FA values in the cingulum and forceps minor in responders compared to non-responders; complementary decreases in RD occurred in the cingulum ($p<0.05$). Only non-responders differed from controls showing decreased FA in the forceps minor, increased RD in the cingulum and forceps minor, and increased MD in the forceps minor ($p<0.05$).

Limitations—Non-responders showed an earlier age of onset and longer current depressive episode than responders. Though these factors did not interact with diffusion metrics, results may be impacted by the limited sample size.

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We have no conflicts of interest to declare.

Conclusions—Though findings are considered preliminary, significant differences in FA, RD and MD shown in non-responders compared to responders and controls in fronto-limbic and ventral striatal pathways suggest that the structural architecture of specific functional networks mediating emotion may predict ketamine response in MDD.

Keywords

Diffusion Tensor Imaging (DTI); fractional anisotropy (FA); treatment response; biomarkers; glutamate

Introduction

Individuals with major depressive disorder (MDD) are often exposed to multiple and lengthy antidepressant trials. Less than 50% of patients respond to 3-months of treatment with antidepressant medication (Trivedi et al., 2006) while 10–30% remain unresponsive to two or more pharmacotherapies and are characterized as treatment-resistant (Mrazek et al., 2014). The development of faster-acting treatments optimized for particular patients is thus a critical goal of translational research in depression.

Recently, ketamine, an NMDA-antagonist targeting glutamatergic neurotransmission (Sanacora et al., 2008), has been shown to elicit a fast-acting antidepressant response in 60–70% of treatment-resistant patients (Sanacora et al., 2008; Zarate et al., 2006). Though the clinical benefits of a single ketamine infusion are transient, depressive symptoms can continue to improve over hours to days suggesting that neuroplasticity in pathways mediating mood and emotion play a downstream role in therapeutic response (Zarate et al., 2006). Several studies show remission of depressive symptoms lasting 1-week post-ketamine treatment (Zarate et al., 2006; Niciu et al., 2014), while one study showed antidepressant effects lasting 4-weeks in 27% of patients (Ibrahim et al., 2012). Though preclinical studies have shown an increase in glutamate post-ketamine, the mechanisms of antidepressant action remain elusive. Presently there are no objective pretreatment criteria with which to determine which patients will respond.

MDD involves disruptions in structural and functional connectivity and interacting neurotransmitter systems where a large body of imaging research points to abnormalities in brain network components including the dorsal and subgenual anterior cingulate cortex (ACC), and the subcortical amygdala, hippocampus and ventral striatum (Phillips et al., 2015; Price and Drevets, 2012). Here, functional connections between basal and medial prefrontal regions are repeatedly implicated and point to under-reactive prefrontal-limbic networks linked with mood-regulation and over-reactive subcortical limbic networks linked with emotional and visceral responses (Mayberg, 2003; Drevets et al., 2008; Koenigs and Grafman, 2009). Antidepressant treatments are further suggested to impact functional connectivity within these circuits (Korgaonkar et al., 2014a; Hamilton, 2013). Altered structural connectivity, typically measured using the diffusion tensor imaging (DTI) metric of fractional anisotropy (FA) reflecting white matter (WM) integrity, are similarly shown in fronto-limbic networks in prior MDD studies (Sexton et al., 2009; Murphy and Frodl, 2011; Gotlib and Hamilton, 2008). Recent evidence also shows changes in structural connectivity

with antidepressant medication treatments (Korgaonkar et al., 2014b) and we have demonstrated that fronto-limbic changes in FA associate with therapeutic response to electroconvulsive therapy, which like ketamine, elicits a rapid antidepressant response (Lyden et al., 2014). However, no studies have yet addressed whether characteristics of WM microstructure impact response to ketamine.

To better understand the biological basis of rapid clinical response, in this preliminary study we examined if regional differences in WM connectivity in fronto-limbic and fronto-striatal circuits most implicated in prior investigations have the potential to dissociate ketamine responders from non-responders and if these subgroups differ from controls. Our focus was on examining whole brain voxel-level differences in FA between groups. To further describe WM neuroplasticity, secondary measures of radial (RD), axial (AD) and mean diffusivity (MD) were also explored and voxel-level effects were additionally confirmed by comparing groups using anatomically defined tracts.

Methods

Participants

Ten MDD patients, for whom ketamine-infusion was independently deemed as beneficial by clinical evaluation and 15 age- and sex-matched controls, who did not receive treatment, provided informed consent for participation as approved by the University of California, Los Angeles Institutional Review Board. Recurrent MDD was diagnosed using Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. Study inclusion required absence of neurological/physical/developmental disorders, substance abuse/dependence history, psychotic features, and contraindication to ketamine and/or MRI. Controls, recruited locally, received Mini International Neuropsychiatric Interview screening to exclude any history of depression. The Montgomery–Åsberg Rating Scale administered 1 week before and 24 hours post infusion, determined the magnitude of antidepressant response in MDD patients. For subjective response, patients also completed the Quick Inventory of Depressive Symptomology scale (QIDS). Nine patients were receiving concurrent antidepressant therapy at the time of infusion. Clinical, demographic and drug information is provided in Table 1.

Treatment included a single subanesthetic dose (0.5 mg/kg) of ketamine diluted in 60cc of saline administered over 40 minutes via IV infusion with continuous clinical and hemodynamic monitoring (Zarate et al., 2006; Niciu et al., 2014; Ibrahim et al., 2012).

Clinical response to ketamine was defined as a 50% decrease in MADRS ratings from pretreatment to 24 hours post-ketamine infusion. Patients who showed less than a 50% symptom improvement were defined as non-responders.

Image Acquisition and Analysis

MRI scanning occurred within a week of the ketamine infusion. DTI data included 61 non-collinear directions, 10 b0 images and 55 axial slices (TR/TE: 7300/95 ms, b=0, 1000 s/mm^2, 2.5 mm isotropic voxel size) collected on a Siemens 3T Allegra MRI system using a spin-echo echo-planar imaging (EPI) sequence. Images were inspected for motion and

combined nonlinear 2-dimensional and 3-dimensional rigid body registrations corrected for slice prescription, eddy current distortions and any residual motion artifacts (Woods et al., 1998a; Woods et al., 1998b). A linear least squares method was utilized to compute the diffusion tensor at each voxel (Basser et al., 1994). The resultant eigenvalues were then used to compute FA representing the degree of anisotropic diffusion. To augment these analyses, AD ($\lambda 1$, diffusivity along the principal axis), RD ($(\lambda 2+\lambda 3)/2$), diffusivity along the two minor axes) and MD (overall diffusivity) were examined as secondary measures. Diffusion images were scalp-edited using masks generated from the co-registered b0 images (Smith et al., 2004).

FSL's Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/) established voxel-level differences in FA between responders, non-responders, and controls in major WM pathways throughout the brain. In brief, using well-validated TBSS workflows (Lyden et al., 2014), FA images were aligned across subjects and then to standard MNI152 space using combined nonlinear and affine registrations. A mean FA image was subsequently created and thinned by identifying the center most voxels with maximal FA values. This procedure creates a mean FA skeleton representing the centers of all tracts common to the sample. Each subject's aligned FA, MD, RD and AD data was then projected onto this skeleton in a common image space and the resulting data fed into voxelwise cross-subject statistics.

To confirm voxel-based findings at the level of individual anatomically-defined tracts, follow-up region-of-interest (ROI) analyses examined group differences and relationships with change in mood symptoms in diffusion metrics averaged across tracts including the cingulum, forceps minor/major and fronto-striatal tract extracted from the Johns Hopkins University WM atlas (Wakana et al., 2004). Diffusion values from the cingulum and fronto-striatal tracts were combined across hemisphere.

Statistical Analysis

FSL's Randomise tool (http://www.fmrib.ox.ac.uk/fsl/randomise/index.html) was used for voxel-based analysis of FA using t-tests to establish differences between responders and non-responders and controls, with the 3 groups examined pairwise. FSL's threshold-free cluster enhancement methods corrected for multiple statistical testing using 5000 randomly generated permutations. TBSS analysis controlled for variations in sex and age. Using anatomical ROIs, in follow-up analyses, FA values were subsequently averaged, plotted and compared within the cingulum, forceps minor/major, and fronto-striatal tracts in 4 separate ANOVAs, again controlling for sex and age, where an uncorrected two-tailed alpha level of 0.05 determined significance. Since AD, RD and MD may provide additional information regarding WM fiber coherence and myelination, these metrics were additionally explored to help interpret FA findings in the 4 tracts of interest. Associations between diffusion metrics showing significant group differences with MADRS and QIDS ratings were examined in post-hoc analyses.

Results

Patients and normal controls did not differ significantly in age or sex (both $p>0.05$). Six MDD patients showed a positive response to ketamine while four showed no response (Table 1).

Whole brain TBSS [Fig. 1, $p<0.05$, cluster corrected] and follow-up tract-based ROI analyses showed larger FA values in the cingulum and forceps minor ($t(8)=-2.7$, $p=0.03$ and $t(8)=-2.5$, $p=0.04$, respectively) in ketamine responders compared to non-responders; complementary decreases in RD occurred in the forceps ($t(8)=2.5$, $p=0.04$). AD and MD values showed no significant difference between the two MDD groups.

Only non-responders showed significant differences in tract-based diffusion metrics compared to controls. Specifically, non-responders showed reduced FA in the forceps minor ($F(2,22)= 3.8$, $p=0.04$) and increased RD in the cingulum ($F(2,22)= 4.1$, $p=0.02$) and forceps minor ($F(2,22)= 5.3$, $p=0.03$), and reduced MD in the forceps minor ($F(2,22)= 3.9$, $p=0.04$).

Though differences were observed in response groups dichotomized according to improvements in MADRS ratings, when change in mood was examined as a continuous measure, only improvements in QIDS ratings from baseline to 24 hours after ketamine infusion showed significant associations with increased FA in the cingulum ($p=0.05$), decreased MD ($p=0.03$) and RD ($p=0.04$) in the forceps minor, and decreased RD in the striatum ($p=0.03$) (Figure 3).

Discussion

Alterations in neural circuitry, particularly in pathways connecting basal and medial forebrain, limbic and ventral striatal regions are widely implicated in the pathophysiology of MDD (Phillips et al., 2015; Price and Drevets, 2012). Therefore, microstructural properties of particular WM pathways may influence treatment response and subsequent clinical outcome. By leveraging in vivo diffusion imaging methods, the current study explored whether regional WM structural connectivity, measured prior to ketamine treatment, relates to positive clinical response. Improvements in depressive symptoms 24 hours post-ketamine infusion correlated with greater FA in the cingulum, decreased MD and RD in the forceps minor, and decreased RD in the fronto-striatal tract in groups separated by the extent of clinical response. These results, though preliminary, suggest that variations in FA and in other diffusion metrics including RD and MD in fronto-limbic pathways linking brain regions associated with mood regulation and emotion may distinguish treatment ketamine responders from non-responders.

Only a few studies using functional or volumetric neuroimaging methods have addressed potential imaging correlates of response to ketamine therapy in MDD (Abdallah et al., 2015; Murrough et al., 2015; Salvadore et al., 2009; Salvadore et al., 2010; Carlson et al., 2013; Ortiz et al., 2014; Haile et al., 2014). Until now, no published diffusion imaging study has yet examined structural plasticity in the context of ketamine treatment. In MDD, the majority of cross-sectional DTI studies have focused on measuring and reporting changes in FA in frontal and temporal regions (Murphy and Frodl, 2011). More detailed information

regarding altered tissue microstructure may be achieved by examining other scalar diffusion metrics. Specifically, increases in RD may signify decreased myelination and decreases in AD may imply axonal damage (Concha et al., 2006). Larger MD may point to decreased cellular density or myelin breakdown (Song et al., 2003). In this study, greater FA and lower RD in the cingulum, connecting prefrontal and ventral limbic structures, and greater FA in the forceps minor projecting to lateral and medial PFC through the anterior callosum were observed in ketamine responders. Decreased FA with increased RD in non-responders thus suggests that altered structural connectivity in the cingulum and forceps, potentially attributable to myelination, may affect an individual's predisposition for rapid clinical response to ketamine therapy. In further support of this, only non-responders showed significantly decreased FA within the forceps and corresponding increases in RD (forceps and cingulum) and MD (forceps) compared to controls.

Reduced FA in fronto-limbic pathways appear the most reproducible findings from prior DTI studies of MDD (Sexton et al., 2009; Murphy and Frodl, 2011). We have also recently shown that significant increases of FA, together with decreased RD, in dorsal fronto-limbic circuits encompassing the anterior cingulum and forceps minor are modulated by ECT and relate to therapeutic response, suggesting a key role of these pathways in treatment outcome (Lyden et al., 2014). The cingulum, encompassing fibers from the ACC with other medial and ventral prefrontal regions, the dorsolateral prefrontal cortex (PFC) and limbic structures, is involved in emotional and pain processing. Connections to the amygdala, insula, and hippocampus, in particular, link the cingulate to avoidance learning, salience monitoring, and emotional recall (Vogt, 2005; Phan et al., 2002). The striatum is also connected with the PFC as well as with mesolimbic brainstem regions. Here, dorsal striatal-frontal connections may modulate affective-emotional processing and cognitive flexibility (van Schouwenburg et al., 2012), while ventral glutamatergic, GABA-ergic and dopaminergic pathways play a role in motivation, pleasure, and reward. The forceps minor with widespread connections to the PFC is also a part of the fronto-limbic system and thus disturbances may reflect processes of mood regulation and control (Johnstone et al., 2007).

Though no comparable diffusion study exists, results from this pilot investigation are in line with volumetric, fMRI, magnetoencphalography (MEG), and PET findings that suggest neuroimaging measures relate to and may predict ketamine treatment outcome. For example, left hippocampal volume was shown to negatively correlate with the antidepressant effects of ketamine at 24-hour follow-up (Abdallah et al., 2015). Using fMRI, increased task-related activity to positive and neutral faces in the right caudate and greater functional connectivity was also reported in association with decline in depressive symptoms at 24-hour follow-up (Murrough et al., 2015). Further, an MEG study showed increased reactivity to fearful faces in the ACC with increased antidepressant response to ketamine (Salvadore et al., 2009), while another MEG study reported that imaging correlates of working memory might predict ketamine therapeutic response (Salvadore et al., 2010). Finally, a PET study reported decreased metabolism in the ventrolateral and dorsolateral PFC post-ketamine (Carlson et al., 2013). Molecular studies have shown complementary results when studying antidepressant response to ketamine. For example, higher baseline Shank3 levels have been reported to predict antidepressant response (Ortiz et al., 2014) and brain-derived neurotrophic factor (BDNF) levels are shown as increased in responders compared to non-

responders 240 minutes post-infusion (Haile et al., 2014). Though using a different treatment modality, the current findings are in line with those from a recent study showing DTI measures within fronto-limbic tracts predict overall response to antidepressant medication (Korgaonkar et al., 2014b) and with reports showing the remission of depressive symptoms after sertraline treatment are associated with lower frontal FA values (Taylor et al., 2008). These studies together with the current results, suggest the feasibility of diffusion structural connectivity measures as a biomarker for potential response in MDD.

This study had several limitations. Though using acquisition with 61 diffusion gradients and well-validated analysis tools, due to limitations inherent to the tensor model, changes in tensor-derived measurements should be interpreted with caution in areas where fibers are crossing. In spite of significant findings, the small sample size employed here, may have hindered the detection of more subtle changes in diffusion parameters and also did not allow for further exploration of potential confounding effects such as age of depression onset, and length of current depressive episode and other clinical characteristics. However, we note that at least for this study, while non-responders had an earlier age of onset and a longer current depressive episode compared to responders, these differences did not reach significance perhaps due to high variance. Despite these limitations, this study provides the first evidence that diffusion characteristics at baseline may predict which patients are most likely to benefit from ketamine therapy. Further investigation with a larger cohort is needed to validate the differences in structural connectivity observed between non-responders and responders. Overall, these preliminary results suggest that fiber coherence and/or myelination in fronto-limbic and striatal pathways may distinguish treatment non-responders from both responders and controls and facilitate the antidepressant effects of ketamine in MDD.

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Highlights

- Ketamine elicits a fast-acting antidepressant response in 60–70% of patients with treatment-resistant depression.
- We report diffusion tensor imaging (DTI) data at baseline was able to predict ketamine response in our study sample.
- We report only significant differences in DTI data were found between non-responders to ketamine treatment compared to normal controls.
- We report that improvements in the Quick Inventory of Depressive Symptomatology (QIDS) from pre- to 24 hours post-infusion correlated with the DTI data.

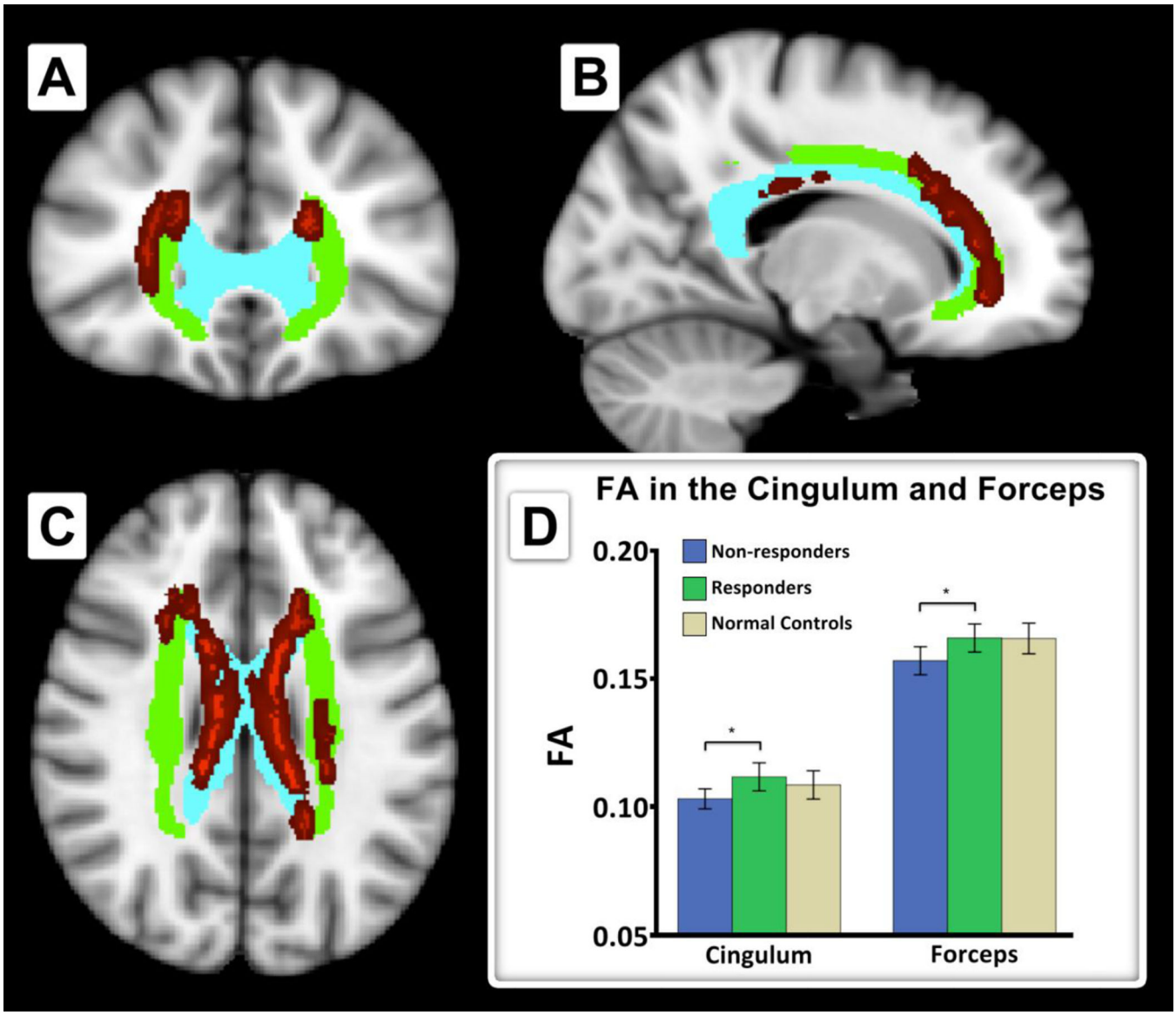

Figure 1.

Fractional anisotropy (FA) in the forceps and cingulum. Figures A, B, and C show a significant decrease in FA in ketamine non-responders compared to responders in the forceps (blue) and cingulum (green). The anatomical masks in blue and green were extracted from the Johns Hopkins University White Matter atlas. Figure D shows the mean FA ± standard deviation within the two regions for responders, non-responders, and normal controls.

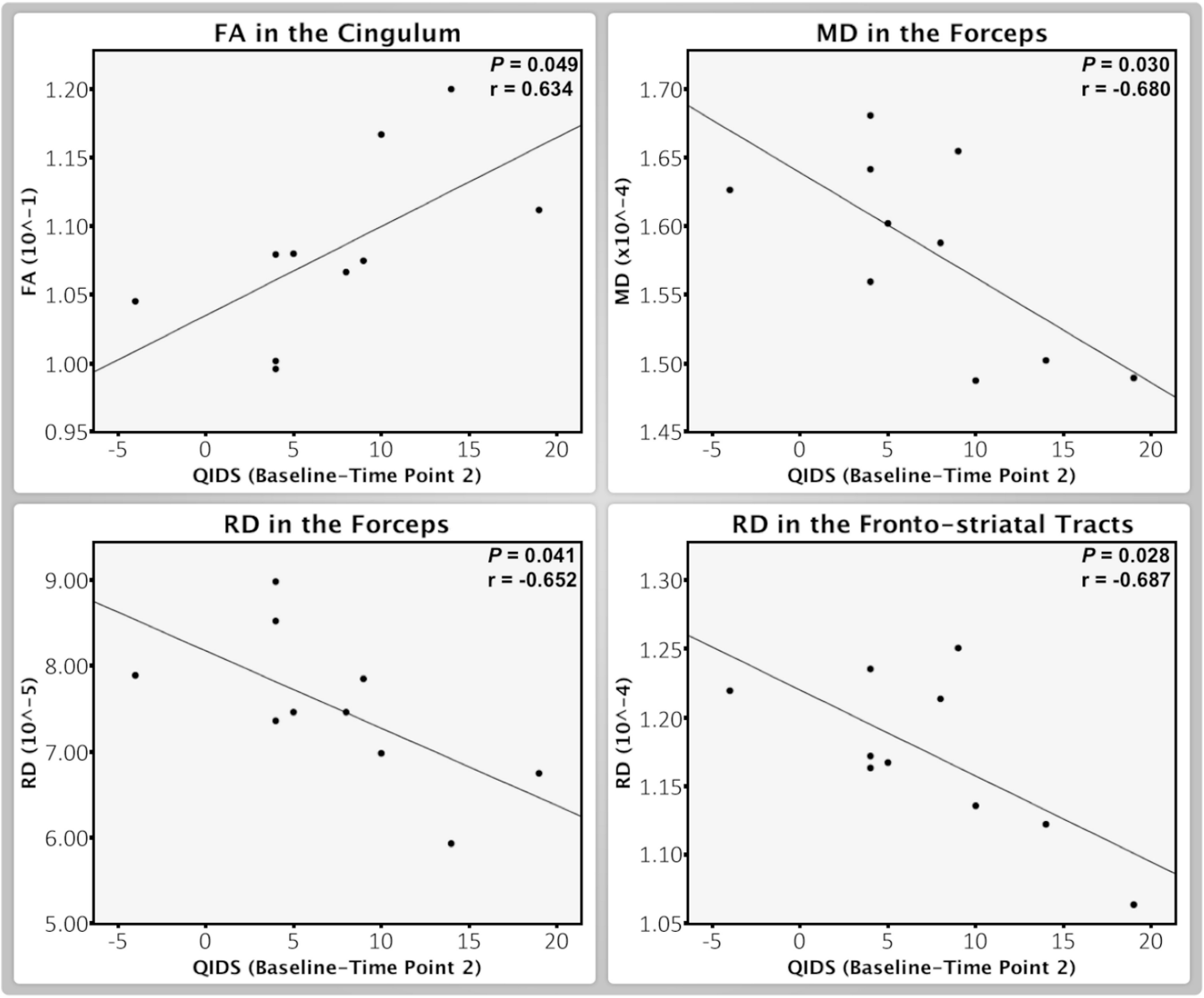

Figure 2.

Relationships between change in the Quick Inventory of Depressive Symptomology scale (QIDS) and FA in the cingulum, MD in the forceps, and RD in the forceps and striatum. As scores on the QIDS improve, FA in the cingulum increases, MD in the forceps decreases, and RD in the forceps and striatum decreases.

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Table 1

Demographic and Clinical Characteristics

	Patients[a]		Controls
	Non-responders (n = 4)	**Responders (n = 6)**	**Normal Controls (n = 15)**
Age, yrs.	50.7 (12.4)	45.7 (12.2)	45.7 (11.0)
Male/female	4/0	4/2	10/5
Age of onset, yrs.	16.7 (3.3)	22.5 (8.2)	--
Current episode, yrs[b]	18.5 (20.0)	9.8 (11.3)	--
Change in MADRS (%)	19.7 (16.7)	79.4 (19.5)	--

Diffusion metrics averaged within tract ROIs

	Forceps	**Cing**	**Striatum**	**Forceps**	**Cing**	**Striatum**	**Forceps**	**Cing**	**Striatum**
FA	0.157[c, d] (0.0055)	0.103[c] (0.0039)	0.133 (0.0028)	0.166 (0.0055)	0.112 (0.0055)	0.137 (0.0059)	0.165 (0.0060)	0.108 (0.0056)	0.133 (0.0050)
RD*	0.819[d] (0.071)	1.07[c, d] (0.056)	1.20[d] (0.035)	0.707 (0.068)	1.00 (0.072)	1.16 (0.067)	0.696 (0.070)	0.97 (0.059)	1.13 (0.054)
AD*	3.24 (0.041)	2.38 (0.046)	2.9 (0.060)	3.25 (0.13)	2.44 (0.093)	2.91 (0.13)	3.22 (0.12)	2.37 (0.061)	2.85 (0.064)
MD*	1.63[d] (0.050)	1.50 (0.053)	1.76[d] (0.038)	1.55 (0.070)	1.48 (0.073)	1.74 (0.075)	1.54 (0.055)	1.44 (0.048)	1.7 (0.046)

All non-responders and five of the six responders were receiving standard and stable (unchanged for at least 6 months) antidepressant treatment at the time of ketamine infusion (monoamine oxidase inhibitors (MOAs): n=1; selective serotonin reuptake inhibitors (SSRIs): n=3; serotonin and norepinephrine reuptake inhibitors (SNRIs): n=2; norepinephrine and dopamine reuptake inhibitors (NDRIs): n=2; serotonin antagonists and reuptake inhibitors (SARIs): n=1; lithium: n=1). All patients were tapered off benzodiazepines if needed for a period of 72-24 hours prior to infusion. All values with the exception of sex distributions represent means and standard deviations (SD); MADRS, Montgomery–Åsberg Rating Scale; FA, fractional anisotropy; RD, radial diffusivity; AD, axial diffusivity; MD, mean diffusivity; Forceps: Forceps minor and major; Cing: Cingulum, Striatum: tracts at the level of the ventral striatum.

Age of onset (years) and [a]duration of current episode (years), which was unavailable for one subject, was obtained from patient self-report. Neither of these measured differed significantly between responders and non-responders (P = 0.30 for duration of current episode and P = 0.08 for age of onset).

*RD, AD, and MD values have been multiplied by 10,000.

[c]P < 0.05 for comparisons between responders and non-responders,

[d]P < 0.05 for comparisons between non-responders and normal controls.