

White Matter Integrity is Associated with Treatment Outcome Measures in Cocaine Dependence

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Cocaine dependence is associated with white matter impairments that may compromise cognitive function and hence drug users' abilities to engage in and benefit from treatment. The main aim of this study was to assess whether white matter integrity correlates with treatment outcome measures in cocaine dependence. Diffusion tensor imaging (DTI) was used to assess the white matter (WM) of 16 treatment-seeking cocaine-dependent patients before 8 weeks of therapy. The measures for treatment outcome were longest self-reported duration of continuous cocaine abstinence, percent of urine screens negative for cocaine, and duration (weeks) of treatment retention. Correlations between treatment outcome measures and DTI parameters (fractional anisotropy (FA), longitudinal eigenvalue (λ_1), perpendicular eigenvalue (λ_T), and mean diffusivity (MD)) were analyzed. Longest self-reported abstinence from cocaine and percent of cocaine-negative urine samples during treatment positively correlated with FA values and negatively correlated with λ_1 , λ_T , and MD values across extensive brain regions including the corpus callosum, frontal, parietal, temporal, and occipital lobes, and cerebellum. The findings of an association between better WM integrity at treatment onset and longer abstinence suggest that strategies for improving WM integrity warrant consideration in developing new interventions for cocaine dependence.

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INTRODUCTION

Cocaine dependence is a major public health problem for which behavioral therapies presently represent the most widespread and effective treatments (Knapp *et al*, 2007). However, a significant proportion of treatment-seeking cocaine dependent individuals do not achieve long-term abstinence (Ahmadi *et al*, 2006; Carroll, 1997; Dutra *et al*, 2008; Elkashef *et al*, 2007; Knapp *et al*, 2007; Shearer, 2007); thus, there exists a significant need for understanding factors influencing treatment outcome. Cocaine dependence and other substance use disorders (SUDs) are associated with brain function impairment related to diminished self-control, drug craving and drug use (Jentsch and Taylor, 1999; Kalivas and Volkow, 2005; Koob, 2004, 2006; Koob and Le Moal, 2008; Potenza, 2007; Robinson and Berridge, 2008; Weiss, 2005). Impaired neurocognitive performance linked to regional brain function has been implicated in the poor outcome of behavioral therapy for cocaine dependence.

For example, poorer performance on measures of cognitive control and decision-making have been associated with worse treatment outcome in cocaine dependence (Bleiberg *et al*, 1994; Moeller *et al*, 2001; Simpson *et al*, 1999, 2002; Stotts *et al*, 2007; Streeter *et al*, 2008), and activation of the ventral prefrontal cortex (PFC) and putamen during performance of a cognitive control fMRI task before treatment onset was associated with cocaine abstinence, whereas activation of the dorsolateral PFC was associated with treatment retention (ie, weeks participating in treatment; Brewer *et al*, 2008). Together, these findings indicate that specific aspects of brain function are related to specific aspects of treatment outcome for cocaine dependence.

White matter (WM) impairments have been identified in cocaine-dependent individuals, although the relationship between WM integrity and treatment outcome is not well understood. WM mediates communications among different brain regions and its integrity is important for optimal brain function. Cocaine dependence and other SUDs are associated with impaired WM integrity in the frontal lobes and rostral corpus callosum (Bartzokis *et al*, 2002; Lim *et al*, 2002, 2008; Moeller *et al*, 2005, 2007a), and WM impairment has been associated with relevant clinical features. For example, poor WM integrity (ie, lower fractional anisotropy, FA) in the frontal lobes and/or rostral corpus callosum of cocaine or methamphetamine patients has been associated

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with higher levels of impulsivity, as well as poorer cognitive control and mental flexibility (Chung *et al*, 2007; Moeller *et al*, 2005), and these cognitive features have been associated with poor treatment outcome in independent studies (Moeller *et al*, 2001; Streeter *et al*, 2008). However, no study to date has directly investigated how measures of WM integrity relate to treatment outcome for SUDs, and none have used a broad range of WM measures (eg, radial and parallel diffusivity) that may provide additional insight into the nature of how WM integrity might relate to treatment outcome (Moeller *et al*, 2007a; Sidaros *et al*, 2008).

In this report, we present relationships between WM integrity and treatment outcome in cocaine-dependent patients seeking behavioral therapy. We hypothesized that better WM integrity in the frontal lobes and rostral corpus callosum would be associated with better treatment outcome. To test this hypothesis, we used diffusion tensor imaging (DTI) to assess pre-treatment WM integrity of 16 cocaine-dependent patients who received 8 weeks of behavioral therapy alone or in conjunction with disulfiram and analyzed correlations between DTI parameters and measures of treatment outcome.

MATERIALS AND METHODS

Subjects

Participants were treatment-seeking cocaine-dependent adults who met current DSM-IV criteria for cocaine dependence. Exclusion criteria for participating in clinical trials were minimized to facilitate recruitment of a clinically representative, treatment-seeking group. Individuals were excluded if they: (1) did not speak English, (2) had not used cocaine within the past 28 days, (3) had an untreated psychotic disorder which precluded outpatient treatment, or (4) were unlikely to be able to complete 8 weeks of outpatient treatment. Psychiatric diagnoses were obtained through structured clinical interviews (First *et al*, 1996, 1997). Participants from clinical trials were further screened for MRI studies. Subjects who were pregnant, breast feeding, color-blind, left-handed, or had metal in their body were excluded from participating in MRI scans. They provided written informed consent as approved by the Yale School of Medicine Human Investigations Committee. Eighteen participants underwent DTI scanning before treatment, but two participants' scans were excluded from the analysis due to incomplete brain coverage, leaving a final sample of 16 subjects, which were a subgroup of the 20 patients described in an earlier report (Brewer *et al*, 2008).

Clinical Measures and Treatment Outcome Measures

As described previously (Brewer *et al*, 2008), patients were drawn from two randomized clinical trials (RCTs), each involving 8 weeks (56 days) of treatment. The first RCT (RCT1; $n = 7$) compared a standard community-based drug treatment involving access to weekly individual plus group sessions (treatment as usual, TAU) with TAU in addition to twice-weekly access to a multimedia computer-assisted version of cognitive behavioral therapy (CBT) and is described in more detail elsewhere (Carroll *et al*, 2008). In the second RCT (RCT2; $n = 9$), participants received

Table 1 Demographic and Clinical Characteristics, Number of Patients in Each Therapy, and Treatment Outcomes

| <i>Demographic and clinical characteristics</i> | |
|---|-------------|
| Age: mean years (SD) | 38.4 (9.7) |
| Gender, female | 6 |
| Shibley scale IQ score: mean (SD) | 92.4 (12.6) |
| Daily tobacco smoker | 13 |
| Cocaine use, mean days out of 28 day before treatment (SD) | 11.9 (9.3) |
| Lifetime cocaine use, mean years (SD) | 11.2 (8.0) |
| Alcohol use, mean days out of 28 days before treatment (SD) | 5.1 (5.5) |
| Lifetime alcohol use, mean years (SD) | 12.6 (10.1) |
| <i>Number of patients in each treatment</i> | |
| <i>Study one (n = 7)</i> | |
| CBT | 4 |
| Treatment as usual | 3 |
| <i>Study two (n = 9)</i> | |
| CBT+Placebo | 2 |
| CBT+Disulfiram | 3 |
| CBT+CM+Placebo | 3 |
| CBT+CM+Disulfiram | 1 |
| <i>Treatment outcomes (mean (SD))</i> | |
| Maximal days of consecutive abstinence (of 56 days) | 34.3 (20.9) |
| % Cocaine-negative urine samples | 66.7 (43.6) |
| Weeks in treatment | 5.4 (3.2) |

Abbreviations: CBT, cognitive behavioral therapy; CM, contingency management.

weekly individual CBT sessions plus one of four additional treatment components: (1) placebo, (2) disulfiram, (3) contingency management (CM) + placebo, and (4) CM + disulfiram (Table 1).

Participants in both RCTs were similar with regard to age, sex, race, education level, drug use history, employment status, Axis I comorbidity, medication effects, and treatment outcome, and were combined for DTI analyses. Similar combinations of patients from different RCTs were used in previous studies (Brewer *et al*, 2008; Streeter *et al*, 2008). Treatment outcome measures included self-reported longest duration of continuous cocaine abstinence (urine confirmed) during the 56-day active treatment period, percentage of cocaine-negative urine samples, and duration of treatment retention, as used in our previous studies (Brewer *et al*, 2008; Carroll *et al*, 2008). No patients were excluded from analysis because of cocaine use during treatment. The clock for assessing duration of continuous abstinence from cocaine was reset after each use of cocaine during the 56-day treatment period.

Drug Use Assessments

Participants were assessed weekly during treatment and at the 8-week treatment termination point by an independent clinical evaluator. The Substance Abuse Calendar, similar to

the Timeline Follow Back (Fals-Stewart *et al*, 2000; Hersh *et al*, 1999), was administered weekly during treatment to collect detailed day-by-day self-reports of drug and alcohol use throughout the protocol as described previously (Carroll *et al*, 2008). Substance-related problems were assessed at pretreatment and post-treatment using the Addiction Severity Index (ASI) (McLellan *et al*, 1992). Urine samples were collected at every clinical visit, ie, twice and three times weekly in the first (computerized CBT) and second (disulfiram) RCT, respectively, and tested for cocaine, opioids, stimulants, marijuana, and benzodiazepines. Data from all samples collected from each participant were used in the analyses presented, and missing samples were not coded as cocaine-positive.

Scanning Procedures

DTI data were acquired with a 3.0T Siemens Trio scanner at the Yale Magnetic Resonance Research Center before the initiation of treatment. Diffusion sensitizing gradients were applied along 32 non-collinear directions using b -values of 0 (b_0 image) and 1000 s/mm² (TR = 7400, TE = 115, matrix = 128 × 128, FOV = 256 × 256 mm²), and 40 contiguous slices parallel to the AC-PC line were acquired, and each slice was 3.0 mm thick (Wang *et al*, 2008). Two repetitions were acquired for averaging. For each subject, a high resolution T1 image was routinely acquired and examined by a trained neuroradiologist to identify any significant structural anomalies.

Image Processing

Diffusion Toolbox (FDT) and Tract-Based Spatial Statistics (TBSS) from FMRIB's Software Library (FSL, <http://www.fmrib.ox.ac.uk/fsl/>) were used for the DTI analyses. The two image sets from each subject were aligned and averaged to create a set of mean images. This set of mean images was used to construct the diffusion tensor, and to create maps of fractional anisotropy (FA), perpendicular eigenvalue (λ_T), parallel eigenvalue (λ_1), and mean diffusivity (MD) using DTIFIT from FSL. FA and MD are sensitive to the general integrity of WM but do not provide specific information regarding potential cellular impairment (Alexander *et al*, 2007; Bhagat *et al*, 2008; Moeller *et al*, 2007b; Wozniak and Lim, 2006), whereas increased λ_T may suggest demyelination and reduced λ_1 may suggest axonal degeneration (Budde *et al*, 2009; Concha *et al*, 2006; Sidaros *et al*, 2008; Song *et al*, 2002).

TBSS was used to register FA map of each subject into Montreal Neurological Institute (MNI) template space. A mean FA map was created by averaging all subjects' registered FA images, and a mean FA skeleton was created by thinning the mean FA image (commands 'tbss_1_preproc', 'tbss_2_reg', 'tbss_3_postreg', and 'tbss_4_prestats' were executed in sequence (Smith, 2004, 2006, 2007)). The mean skeleton is a pseudo-anatomical representation of the main fiber tracks and represents the center of all tracts common to the group. The aligned FA data of each participant were projected onto the mean skeleton by searching the area around the skeleton in the direction perpendicular to each tract, finding the highest local FA value, and assigning this value to the skeleton. The

transformation matrices created for FA map registration were used to register maps of λ_1 , λ_T , and MD. Skeletons for λ_1 , λ_T , and MD were created using the same procedures for creating the FA skeleton. The correlations between measures of treatment outcome and FA, λ_1 , λ_T , and MD were assessed with FSL 'randomise' program with 5000 permutations, which uses permutation-based non-parametric inferences to perform voxel-wise cross-subject statistics (Nichols and Holmes, 2002). Statistical thresholds for all image analyses were voxel level $t > 1.5$ and cluster $p < 0.05$, corrected for multiple comparisons of the voxel-wise whole brain analysis. Function 'fslmeants' from FSL was used to extract means of FA, λ_1 , λ_T , and MD from all significant clusters surviving correction for multiple comparisons of whole brain analysis. Correlations among non-imaging data, such as participant demographic information, drug use history, and treatment outcomes were analyzed using SPSS 16.

RESULTS

Table 1 presents information on demographics, drug use history, treatment condition, and treatment outcome of participants. Table 2 presents correlations among patient age, Shipley Scale IQ score, histories of cocaine and alcohol use, and measures of treatment outcome. The most robust correlations were observed between number of days of cocaine use within the 28 days before treatment entry and percentage of urine samples testing negative for cocaine during treatment (Table 2). Age, Shipley Scale IQ score, history of cocaine or alcohol use, or treatment retention (weeks) did not show significant correlation with any DTI parameters in any brain regions. DTI parameters and the measures of self-reported and urine-toxicology-based abstinence showed significant correlations surviving whole-brain correction (Table 3, Figure 1), as described below.

Fractional Anisotropy: FA Map

Two clusters showed significant positive correlations with self-reported longest duration of cocaine abstinence. One was located at the superior longitudinal fasciculus (SLF) in the right frontal lobe and extended posteriorly into the parietal lobe. This cluster was adjacent to the superior (SFG), middle (MFG), and inferior frontal gyri (IFG), and pre- and postcentral gyri. It also included the body of corpus callosum and the posterior limb of the internal capsule. The second cluster was in the left cerebellum. Two clusters showed positive correlations with percentage of cocaine-negative urine samples. These clusters were in nearly symmetrical locations in the two hemispheres and included the SLF, body of corpus callosum, external capsule, and regions adjacent to the SFG, MFG, IFG, and pre- and postcentral gyri.

Parallel Diffusivity: λ_1 Map

Three clusters covering extensive brain areas including the frontal, parietal, temporal, and occipital lobes, and rostral midbrain, bilaterally and involving the SLF, corpus callosum, and internal and external capsule correlated negatively with self-reported cocaine abstinence. Three clusters including the corpus callosum, internal capsule,

Table 2 Correlations Among Drug Use History and Measures of Treatment Outcome

| | Pearson's correlation coefficient (r) | | | | | | | |
|--------------------|---------------------------------------|------------------|-------|-------------------|-------|-------------------|--------------------|--------------------|
| | Shipley Scale IQ | Drug use history | | | | Outcome measures | | |
| | | Cocaine | | Alcohol | | Abstinence (days) | Negative urine (%) | Retention (weeks) |
| | | Years | Days | Years | Days | | | |
| Age | 0.17 | 0.26 | 0.19 | 0.51 ^a | 0.03 | 0.07 | -0.19 | 0.18 |
| Shipley scale IQ | | 0.01 | -0.13 | 0.25 | 0.30 | 0.00 | -0.13 | -0.51 ^a |
| Cocaine (years) | | | 0.34 | -0.15 | -0.30 | 0.04 | -0.32 | -0.21 |
| Cocaine (days) | | | | -0.10 | -0.08 | -0.24 | -0.68 ^b | -0.07 |
| Alcohol (years) | | | | | 0.14 | -0.17 | -0.05 | -0.18 |
| Alcohol (days) | | | | | | 0.19 | 0.25 | -0.02 |
| Abstinence (days) | | | | | | | 0.67 ^b | 0.03 |
| Negative urine (%) | | | | | | | | -0.05 |

Abbreviations: Abstinence, maximum duration of contiguous abstinence; days, number of days within 28 days before treatment; years, number of years during life time.

^a $p < 0.05$.

^b $p < 0.01$.

temporal and occipital lobes, and rostral midbrain correlated negatively with percentage of cocaine-negative urine samples.

Radial Diffusivity: λ_T Map

Four clusters correlated negatively with self-reported cocaine abstinence. Two clusters involved the frontal lobes, one in each hemisphere. Both involved the SLF, corpus callosum, and internal and external capsule and were adjacent to the SFG, MFG, IFG, and orbitofrontal cortex. The other two clusters involved the right superior (STG) and middle temporal gyri (MTG), ventral medial temporal lobe, and left cerebellum. One cluster correlated negatively with percentage of cocaine-negative urine samples. This cluster was adjacent to the left MFG, IFG, pre- and postcentral gyri, and external capsule.

Mean Diffusivity: MD Map

Four clusters correlated negatively with self-reported cocaine abstinence. Two clusters were in the left hemisphere, whereas the remaining two were in the right. Together, the four clusters involved extensive brain regions including the frontal, parietal, temporal, and occipital lobes, bilaterally. One cluster correlated negatively with percentage of cocaine-negative urine samples. This cluster involved the left STG, MTG, and bilateral midbrain.

A *post hoc* comparison of FA, λ_1 , λ_T , and MD of patients with long vs short duration of abstinence was conducted using independent two-sample *t*-test analyses. The patients were divided into long ($n = 8$) and short ($n = 8$) duration groups by median-split of the maximal duration of continuous abstinence. As expected, the groups differed on the mean measures of maximal duration of continuous abstinence (long duration: mean = 51.3 days, SD = 8.8; short duration: mean = 17.3 days, SD = 14.1; two sample

t-test, $p < 0.001$, $t = -5.8$, d.f. = 14). The long duration group showed significantly greater FA and smaller λ_1 , λ_T , and MD than did the short duration group in extensive brain regions overlapping significant clusters revealed by the correlation analyses presented in this report.

DISCUSSION

The main finding of this study is that measures of WM integrity were associated with abstinence-related outcome measures in cocaine-dependent individuals. Specifically, multiple DTI measures (eg, FA, MD, λ_1 and λ_T) in extensive brain regions correlated with self-reported and urine toxicology-based measures of abstinence. The identified brain regions included not only the frontal lobes and rostral corpus callosum as hypothesized, but also the parietal, temporal, and occipital lobes, cerebellum, and rostral midbrain. DTI measures were not associated with years of cocaine or alcohol use, number of days of cocaine or alcohol use within the month before treatment, or number of weeks in treatment (ie, treatment retention).

Correlations Between WM Integrity and Treatment Outcome

This is the first study to show that worse WM integrity at treatment onset is associated with poorer abstinence-based outcome in cocaine-dependent patients. One possible explanation for this relationship is that history of cocaine use before treatment correlates with both cocaine abstinence and WM integrity. The current sample showed a significant correlation between number of days using cocaine within a month before treatment and percentage of cocaine-negative urine samples during treatment. Previous studies have reported associations between duration of cocaine abuse and decreased white and gray matter

Table 3 Brain Regions Showing Significant Correlations Between Treatment Outcomes and DTI Parameters

| | L/R | Size Voxels | t-value ^a | MNI coordinates | | |
|---|-----|----------------|----------------------|-----------------|-----|-----|
| | | | | x | y | z |
| <i>FA Map, positive correlation</i> | | | | | | |
| <i>Maximal duration of consecutive abstinence</i> | | | | | | |
| Frontal and parietal lobes and body of CC | R | 2809 | 5.87 | 26 | -10 | 42 |
| Occipital lobe and cerebellum | L | 1977 | 5.50 | -20 | -65 | -25 |
| <i>% Cocaine negative urine samples</i> | | | | | | |
| Frontal and parietal lobes and body of CC | R | 1871 | 5.48 | 39 | -7 | 37 |
| Frontal and parietal lobes and body of CC | L | 1851 | 5.26 | -37 | -8 | 24 |
| <i>λ₁ Map, negative correlation</i> | | | | | | |
| <i>Maximal duration of consecutive abstinence</i> | | | | | | |
| Frontal and parietal lobes and body of CC | L/R | 15144 | 9.21 | 30 | 26 | 22 |
| Parietal and temporal and occipital Lobes | R | 3516 | 6.27 | 39 | -81 | 5 |
| Temporal and occipital lobes and midbrain | L | 2783 | 5.37 | -40 | -7 | 30 |
| <i>% Cocaine negative urine samples</i> | | | | | | |
| Body of CC | L/R | 2566 | 6.84 | -38 | -42 | -1 |
| Temporal lobe and midbrain | R | 1831 | 5.12 | 20 | -11 | 1 |
| Temporal and occipital lobes | L/R | 1796 | 5.46 | 5 | -34 | 18 |
| <i>λ_T Map, negative correlation</i> | | | | | | |
| <i>Maximal days of consecutive abstinence</i> | | | | | | |
| Frontal lobe and body of CC | R | 2186 | 4.78 | 23 | 21 | -13 |
| Frontal lobe and body of CC | L | 2961 | 6.43 | -33 | -11 | 42 |
| Temporal lobe | R | 1145 | 5.66 | 47 | -17 | -1 |
| Cerebellum | L | 1453 | 5.90 | -29 | -45 | -29 |
| <i>% Cocaine negative urine samples</i> | | | | | | |
| Frontal and parietal lobes | L | 1315 | 5.57 | -32 | -10 | 22 |
| <i>MD Map, negative correlation</i> | | | | | | |
| <i>Maximal days of consecutive abstinence</i> | | | | | | |
| Frontal, parietal and temporal lobes | L | 7983 | 7.06 | -16 | 10 | -16 |
| Frontal lobe | R | 1900 | 7.42 | 30 | 26 | 22 |
| Occipital and temporal lobes | L | 2258 | 5.66 | -36 | -83 | -7 |
| Temporal and occipital lobes | R | 1660 | 5.59 | 54 | -28 | -11 |
| <i>% Cocaine negative urine samples</i> | | | | | | |
| Temporal lobe and midbrain | L | 1559 | 4.69 | -24 | -17 | -5 |

Abbreviations: CC, corpus callosum; L, left hemisphere; MNI, Montreal Neurological Institute; R, right hemisphere.

^at-value of a peak voxel.

volumes (Lim *et al*, 2008) and frontal metabolic activity (Volkow *et al*, 1992). These data together suggest that history of cocaine use before treatment might explain correlations between treatment outcomes and DTI parameters. However, this study did not reveal significant associations between drug use history and DTI parameters in any brain regions, and therefore does not provide evidence to support this possibility.

Alternatively, it is possible that WM impairment is related to brain function related to drug use. Findings from several studies are consistent with this possibility. For example, cocaine or methamphetamine-dependent patients have

shown negative correlations between FA values and impulsivity and cognitive control (Lim *et al*, 2008; Moeller *et al*, 2005; Romero *et al*, 2010; Salo *et al*, 2009), and more impulsive patients or those with poor cognitive control have fared worse in treatment (Moeller *et al*, 2001; Patkar *et al*, 2004). We recently reported that abstinence-based treatment outcome measures correlated with pre-treatment Stroop task-related activity in the medial prefrontal cortex, posterior cingulate, and striatum (Brewer *et al*, 2008). All of these brain regions are adjacent to clusters showing significant correlations between DTI parameters and measures of treatment outcome in this study, suggesting

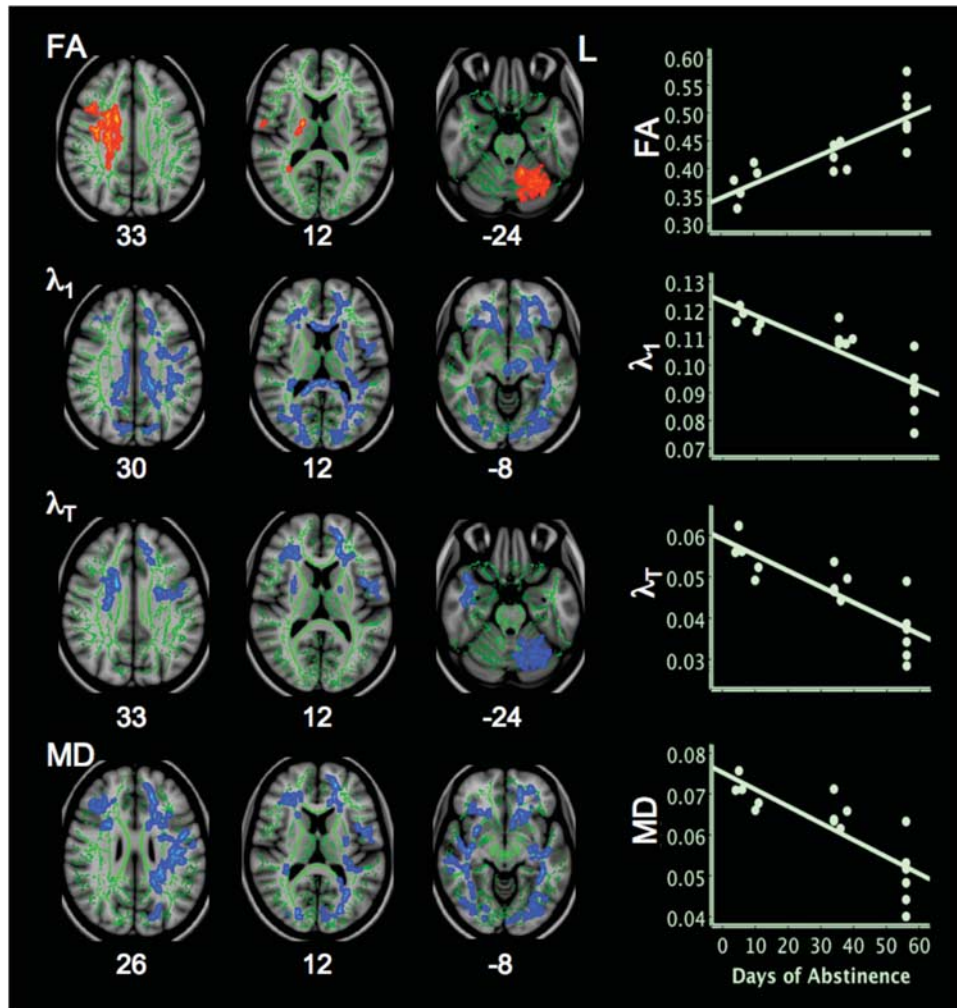


Figure 1 Brain images showing significant positive (red) and negative (blue) correlations between maximal duration (days) of consecutive abstinence from cocaine and FA, λ_1 , λ_T , and MD. MNI (Montreal Neurological Institute) T1 template is used to localize brain regions showing significant correlations, green color on the T1 image shows 'group mean_FA_skeleton', and number below each brain image indicates Z coordinate in MNI space. Only clusters surviving correction for multiple comparisons of voxel-wise whole brain analysis are shown on brain images. Script 'tbss_fill' was used to help visualize the significant clusters. Scatter-plots show correlations between maximal days of consecutive abstinence from cocaine (x axis) and mean values of FA, λ_1 , λ_T , and MD (y axis) calculated from all voxels in clusters showing significant correlation of each patient. L, left.

that WM integrity might have a role in the relationship between Stroop-related brain activity and abstinence-based measures of treatment outcome.

Extent of WM Findings

The significant correlations between abstinence-based measures of treatment outcome and DTI parameters in extensive brain regions suggest that patients with poorer within-treatment outcomes show worse WM integrity in extensive brain regions at baseline relative to patients able to maintain longer abstinence. The brain regions conferring poor prognosis encompass and extend beyond the areas that were shown to be impaired in previous research showing poorer WM integrity (eg, smaller FA or greater λ_T) in the frontal lobe and corpus callosum of cocaine patients relative to healthy controls (Lim *et al*, 2002, 2008; Moeller *et al*, 2005, 2007a), suggesting that more diffuse impairment than that seen in a general sample of cocaine abusers may underlie poorer treatment outcome. Alternatively, metho-

logical differences may contribute to apparent discrepancies across studies, because previous studies typically employed regions of interest analyses (Lim *et al*, 2008; Moeller *et al*, 2005), which may limit the extent of brain areas assessed. Voxel-wise whole brain analysis approaches to DTI data other than TBSS (eg, SPM2) have been employed previously, but may be less sensitive than TBSS (Arnone *et al*, 2008; Smith *et al*, 2006). Nonetheless, results from this study indicated several similarities with respect to previous ones, particularly with WM findings in rostral brain regions (Lim *et al*, 2002, 2008; Moeller *et al*, 2005, 2007a).

Possible Mechanisms Underpinning WM Findings

Demyelination has been associated with increased radial diffusivity (λ_T) without increased parallel diffusivity (λ_1) (Song *et al*, 2002). Parallel diffusivity (λ_1) has been shown to decrease during acute phases of axon degeneration, such as after axotomy or brain injury, and return to normal or to

even greater values during chronic phases of axonal degeneration, possibly due to local accumulation of extracellular fluid (Concha *et al*, 2006; Sidaros *et al*, 2008). Cocaine administration may induce brain vasoconstriction, hypoperfusion, and ischemic stroke, and may lead to demyelination and/or degeneration of axons (Johnson *et al*, 2001; Kaufman *et al*, 1998). Therefore, the increased λ_1 and λ_T showed by patients with worse outcome relative to those with better outcome may reflect both demyelination and chronic axon degeneration. However, this interpretation was countered by lack of a relationship between DTI measures and number of days of cocaine use in the month before treatment or number of years of cocaine use, and a lack of previous evidence indicating that λ_1 increased in cocaine-dependent patients relative to healthy populations (Ma *et al*, 2009; Moeller *et al*, 2007a). Alternate interpretations (eg, pre-existing differences in WM structure) should be considered and investigated in future studies involving larger samples.

Treatments Targeting White Matter Integrity

The link between WM integrity and cocaine abstinence suggests a novel potential target for treatment of cocaine dependent patients, consonant with recent calls to focus on cognitive enhancement among addicted populations (Vocci, 2008). Recent studies have shown that physical or pharmacological treatments may improve WM integrity. Schlaug *et al*, (2009) reported that physical therapy (ie, melodic intonation therapy) for 2–3 months enhanced WM integrity in the right language area and improved speech in aphasic patients with lesions in the left language area. Another study reported that treatment with triiodothyronine (T_3), a thyroid hormone, for 3 weeks improved WM integrity and behavioral symptoms of mice with demyelination induced by chronic cuprizone administration (Harsan *et al*, 2008).

Correlation Between Shipley Scale IQ Scores and Treatment Retention

The patients in this study showed a significant negative correlation between Shipley Scale IQ score and treatment retention. This finding is inconsistent with a previous report of better cognitive function being associated with improved treatment retention in cocaine-dependent patients receiving CBT and medication (ie, gabapentin or venlafaxine; Aharonovich *et al*, 2006). In addition, other studies of substance abusing subjects have not shown associations between IQ score and treatment outcome measures, including treatment retention (Carroll *et al*, in press). Additional research is needed into identifying specific factors related to treatment retention, particularly given challenges clinicians often face with engaging and retaining individuals with drug addictions in treatment settings.

Limitations and Future Directions

Limitations of this preliminary study include a relatively small sample size, the absence of a comparison group to investigate potential differences in cocaine-dependent and

healthy control subjects, absence of post-treatment DTI measures to examine the extent to which WM integrity changes during drug abstinence and treatment, and subjects' receipt of different therapies, precluding the identification of how DTI measures may relate to specific therapies. Futures studies should use larger samples, assess WM integrity more frequently, and examine the relationship between DTI measures and treatment outcomes for specific therapies for cocaine dependence.

Conclusions

Cocaine-dependent patients in this study showed significant correlations between poorer abstinence-based treatment outcomes and impaired WM integrity across extensive regions. These findings provide the first DTI evidence implicating WM integrity in treatment outcome of cocaine-dependent patients, and suggest that WM integrity may serve as a predictor of abstinence or a potential new treatment target.

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