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Neuropsychological Disturbance in Schizophrenia: A Diffusion Tensor Imaging Study

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Abstract

Patients with schizophrenia and healthy control subjects underwent both neuropsychological evaluation and magnetic resonance diffusion tensor imaging, during which the cingulum bundle (CB) and the uncinate fasciculus (UF) were defined with fiber tractography and their integrity was quantified. On the basis of prior findings, it was hypothesized that neuropsychological disturbance in schizophrenia may be characterized, in part, by 2 dissociable functional neuroanatomical relationships: (a) executive functioning–CB integrity and (b) episodic memory–UF integrity. In support of the hypothesis, hierarchical regression results indicated that reduced white matter of the CB and the UF differentially and specifically predicted deficits in executive functioning and memory, respectively. Neuropsychological correlates of the CB also extended to lower generalized intelligence, as well as to reduced visual memory that may be related to failures of contextual monitoring of to-be-remembered scenes. Reduced white matter of the CB and the UF may each make distinct contributions to neuropsychological disturbance in schizophrenia.

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Keywords

diffusion tensor imaging; memory; executive functioning; neuropsychology; schizophrenia

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Deficits in executive functioning and in declarative episodic memory represent two distinct facets of the neuropsychological impairment of schizophrenia (e.g., Aleman, Hijman, de Haan, & Kahn, 1999; Heinrichs, 2005; Heinrichs & Zakzanis, 1998; McKenna, 1991; O'Carroll, 2000; Saykin et al., 1994; Weinberger, Berman, & Zec, 1986). Although typically occurring against a backdrop of generalized cognitive impairment, disease-related deficits in episodic memory for events encoded in time and place can be dissociated from disruptions in executive functions that serve to guide action and thought (Nestor et al., 2004). These neuropsychological deficits may also each involve different pathophysiology, as twin studies have strongly implicated genetic factors in executive dysfunction, whereas nongenetic influences may preferentially impact memory disturbance (Cannon et al., 2000).

As the "primary expression of the schizophrenic brain" (Heinrichs, 2005, p. 229), neuropsychological disturbances of memory and executive functions have increasingly been theorized to reflect sequelae not of focal brain abnormalities but of pathological connectivity among brain regions (Andreasen et al., 1999; McGlashan & Hoffman, 2000; Nestor et al., 1998, 2004; Stephan, Baldeweg, & Friston, 2006; Weinberger, Berman, Suddath, & Torrey, 1992; Winterer, Coppola, Egan, Goldberg, & Weinberger, 2003). Wernicke (1906) first ascribed a central role in the expression of schizophrenia to anatomical abnormalities of association fiber tracts traveling between frontal and temporal lobes. More recently, neuroimaging findings that showed abnormal functional connectivity in schizophrenia have echoed Wernicke's seminal, generative idea of disease-related disruption in the functional integration of neural systems as a core element of the pathophysiology of the schizophrenic brain (see Friston, 1998; Stephan et al., 2006).

Magnetic resonance diffusion tensor imaging (DTI) provides a noninvasive method for assessing the integrity of specific white matter tracts that functionally connect distinct networks of segregated areas across the brain. As such, the long-standing question of abnormal connectivity in schizophrenia can be assessed by examining DTI of particular white matter tracts in the human brain. The theory of DTI focuses on the diffusion of water in brain tissue, with the pivotal assumption that the motion of water reflects the integrity of the medium in which it travels (Kubicki et al., in press). In brain tissue, water movement can be restricted at many levels, as, for example, by interaction with different tissue components, such as cell membranes, macromolecules, fibers, myelin sheaths, and fiber tracts. Thus, within white matter, the mobility of water is restricted in directions that are parallel to the fiber tracts, and the degree to which water diffuses in a discernible, coherent direction along imaged tracts can be calculated by fractional anisotropy (FA; see, e.g., Basser, Mattiello, & LeBihan, 1994; Cheng et al., 2006; Kubicki et al., in press). DTI assumes that, as myelin sheath of white matter increases, as reflected by the density and coherence of such local tissue components as cell membranes, axons, and organelles, so too does the orderly movement of water molecules along the main pathways of fiber tracts of the brain. Higher FA values reflect greater orderly water movement along imaged fiber tracts (Basser et al., 1994; Basser & Pierpaoli, 1996; Papadakis et al., 1999) due to increased microstructural white matter integrity—a key characteristic of both brain and cognitive development that is essential for long-range axonal communication among widespread networks of brain regions (see Andreasen et al., 1999; Gaffan, 2005).

By correlating DTI-derived FA with neuropsychological performance, researchers can empirically test the relationship of microstructural integrity of particular white matter tracts with specific facets of cognitive functioning in schizophrenia. For example, we (Nestor et al.,

2004) examined neuropsychological correlates of two important white matter tracts, the cingulum bundle (CB) and the uncinate fasciculus (UF), in patients with chronic schizophrenia. The results pointed to a statistical double dissociation between low executive functioning, as measured by the Wisconsin Card Sorting Test (WCST), and reduced FA of the CB versus poor declarative episodic memory, as measured by the Wechsler Memory Scale—Third Edition (WMS–III), and reduced FA of the UF. That is, reduced microstructural integrity of the CB—considered the most prominent white matter tract in the limbic system, it furnishes both input and output to the dopaminergic-rich anterior cingulate cortex and lateral frontal sites, as well as to the amygdala, nucleus accumbens, and medial dorsal thalamus (Goldman-Rakic, Selemon, & Schwartz, 1984; Pandya & Seltzer, 1982; Vogt, Rosene, & Pandya, 1979)—correlated with poor executive functioning but not with deficits in episodic memory. By contrast, poor memory but not executive functioning correlated with reduced microstructural integrity of the UF. The UF is considered the major fiber tract reciprocally connecting inferior frontal and anterior temporal areas (Ebeling & von Cramon, 1992; Highley, Walker, Esiri, Crow, & Harrison, 2002; Petrides & Pandya, 1988; Ungerleider, Gaffan, & Pelak, 1989) into a network that serves an important role in binding stimuli into specific episodes that can be retrieved and consciously recollected (Squire & Zola-Morgan, 1991).

Two principal aims guided the current study. The first was to examine whether the double dissociation of CB–executive functioning and UF–episodic memory shown by neuropsychological measures and by DTI could be replicated in a new and larger sample of patients with schizophrenia. The second was to examine how deficits in CB–executive functioning and UF–episodic memory might interact in the neuropsychological expression of the disorder. Although statistically dissociable, memory and executive functions are mutually dependent processes, and the encoding and retrieval of certain kinds of memory may impose differential demands on particular executive functioning processes. In particular, we tested the hypothesis that remembering visual scenes that depicted various actions of characters, as assessed by the WMS–III subtest Family Pictures, involves the coordination of both CB monitoring and UF mnemonic processes. We therefore predicted that remembering these family scenes would reflect mnemonic as well as executive monitoring processes; thus, scores on this test were predicted to correlate with both UF and CB.

Method

Subjects

All subjects were right-handed males between 17 and 55 years of age. They were native speakers of English without histories of electroconvulsive therapy, neurological illness, or alcohol or drug abuse in the past 5 years, as assessed by the Addiction Severity Index (McClellan et al., 1992). All subjects gave informed consent prior to their participation in the study. Diagnoses were ascertained by the Structured Clinical Interview for *DSM–III–R* Axis I Disorders—Patient Edition (Spitzer, Williams, Gibson, & First, 1990a), along with chart review. All patients were part of an ongoing comprehensive, longitudinal study of schizophrenia, and all were receiving neuroleptic medication; the mean chlorpromazine-equivalent daily dose was 453.94 mg ($SD = 343.07$). The mean duration of illness was 16.2 years ($SD = 10.05$). Healthy control subjects, recruited by newspaper advertisement, underwent the Structured Clinical Interview for *DSM–III–R* Axis I Disorders—Nonpatient Edition (Spitzer, Williams, Gibson, & First, 1990b) and were equated with patients on the basis of age, sex, handedness, and parental socioeconomic status. Mean age did not differ significantly, $t(58) = 1.005$, $p = .319$, between the patient group (39.1 years, $SD = 9.11$) and the control group (41.4 years, $SD = 8.67$). After the study was described to them, all subjects provided written informed consent. A sample of 28 control subjects and 25 patients with schizophrenia

underwent both magnetic resonance DTI (Kubicki et al., in press) and neuropsychological studies.

Procedure

Neuropsychological assessment—The neuropsychological assessment included the WMS–III and the WCST, along with the Wechsler Adult Intelligence Test—Third Edition (WAIS–III; Wechsler, 1997). The WAIS–III yielded composite measures of intelligence (full-scale IQ, verbal IQ, performance IQ) and index scores of verbal comprehension, perceptual organization, working memory, and processing speed. The WMS–III provided index scores of auditory immediate memory, visual immediate memory, immediate memory, auditory delayed memory, visual delayed memory, general–delayed memory, auditory recognition delayed memory, and working memory. Subjects also completed a computerized version of the WCST, a well-known test of executive functions of planning, self-monitoring, and response regulation (Heaton, 1981). Three sorting principles (color, form, number) were tested twice and formed a total of six categories, each of which required 10 consecutive responses for criterion. The WCST-dependent measures are the number of categories achieved (0–6), perseverative errors, and nonperseverative errors.

Diffusion tensor imaging—As described elsewhere in detail (Kubicki et al., 2002), we applied line-scan-diffusion imaging to obtain FA maps in order to measure the integrity of fibers within the UF and the CB. Magnetic resonance scans used a quadrature head coil on a 1.5.-Tesla GE Echospeed system (General Electric Medical Systems, Milwaukee, WI), which permits maximum gradient amplitudes of 40 mT/m. Three orthogonal Time 1 weighted images were used as localizers (sagittal, axial oblique aligned to the anterior commissure [AC–PC] line, and another sagittal oblique aligned to the interhemispheric fissure). For each session, six images were collected with high (1000 s/mm^2) diffusion weighting along six noncollinear directions. For low (5 s/mm^2) diffusion weighting, two images were collected, an adequate sample in that diffusion-related changes were minimal. Scan parameters were rectangular field of view, 220×165 mm; 128×128 scan matrix (256×256 image matrix); slice thickness 4 mm; interslice distance 1 mm; receiver bandwidth $+/-4$ kHz; echo time 64 ms; repetition time (TR) 81 ms; (effective TR 2,592 ms); scan time 60 s/section. The number of coronal slices acquired to cover the entire brain ranged from 31 to 35 slices, depending upon brain size. After reconstruction, the diffusion-weighted images were transferred to a UNIX workstation for calculation of eigenvalue, eigenvector, and FA maps of diffusion.

We extracted CB and UF in several steps, using DoDTI software (available from http://neuroimage.yonsei.ac.kr/~dodti; Park et al., 2004). First, we used out-of-plane diffusion maps and then the segmentation method (Kubicki et al., 2002, 2003; Nakamura et al., 2005; Nestor et al., 2004) to define the UF region of interest (ROI) on a single coronal slice and the CB ROI on eight consecutive slices perpendicular to the main fiber bundles (see Figure 1). We used these ROIs to guide fiber tractography and to extract bundles of interest. To extract CB, we used first and last slice ROIs for each side and case, whereas for the UF, we drew the additional ROIs within the anterior temporal lobe. Next, we used fiber tractography, a postprocessing method for propagating streamline points by following the local fiber orientation, as defined by the diffusion tensor field (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Mori, Crain, Chacko, & van Zijl, 1999), to extract entire tracts.

Instead of tracking fiber bundles starting from seed points of an ROI, a method that is more prone to partial volume effects and that can limit the number of fiber tracts included in the analysis (Mori & van Zijl, 2002), we first reconstructed entire white matter fiber bundles from seed points assigned to all voxels inside the white matter segmentation of B0 images (scans without diffusion weighting). Stopping criteria for fiber tracking included a low FA (0.15) and

a rapid change of direction (20° per 1 mm; used in Jones et al., 2005). The next step included fiber extraction, which was done with previously defined ROIs. After the algorithm automatically excluded fibers that did not travel through two ROIs, mean FA averaged over all the voxels belonging to the CB and the UF fiber bundles was calculated separately for the left and right sides and was subjected to correlational analysis. In addition, mean fiber length, mean angular change for each tract, and total number of fibers for each tract were calculated and compared between groups. No group differences were shown.

Statistical Analyses

A mixed analysis of covariance with education as the covariate was used for group comparisons of the DTI measures and the neuropsychological composite measures. We computed neuropsychological–DTI correlations for each group separately using Pearson product–moment correlation and then used parametric, hierarchical regression to partition the total variance of the dependent variable, neuropsychological test score, among the independent variables, DTI measures of UF and CB. To examine the unique contribution of DTI measures of CB and UF to neuropsychological test performance, we computed partial (r_p) and semipartial (r_{sp}) correlations in a series of hierarchical regression analyses, which permitted the evaluation of significant univariate relationships by partitioning total variance of the dependent variable (neuropsychological test score) among the independent variables (DTI measures of UF and CB).

The partial correlation squared (r_p^2) is the proportion of variance of a particular neuropsychological test score shared by a specific DTI-derived brain region (e.g., left UF), after the effects of the other DTI-derived brain regions (e.g., left CB) have been removed from both the neuropsychological and the DTI measures (Cohen & Cohen, 1975). This statistic answers the question "What proportion of the remaining neuropsychological variance (i.e., that which is not estimated by the other independent variables in the equation) is uniquely estimated by this DTI measure?" In contrast, the square of the semipartial correlation (r_{sp}^2) estimates the amount of neuropsychological variance that is uniquely shared with a particular DTI measure after the effects of all other DTI measures on that particular DTI measure have been removed (Cohen & Cohen, 1975). It is semipartial because the effects of the other independent variables have been removed from the independent variable but not from the dependent variable. In conjunction with other linear regression statistics, partial and semipartial correlations provide a comprehensive picture of how DTI measures of the UF and the CB relate to neuropsychological test scores when collinearity is controlled. For all regression analyses, the *F*-to-enter probability was 0.05 and the *F*-to-exclude probability was 0.1. Significance levels are two-tailed.

Results

To make sure that the fiber tractography threshold criteria did not introduce any systematic bias toward one of the groups, we ran *t* tests comparing the number of fibers, mean length, and mean angle for four fiber tracts (i.e., left UF, right UF, left CB, and right CB). No differences in variables were observed for any of these fiber tracts.

The FA values presented in Table 1 were submitted to a mixed analysis of covariance, with group (patient, control) as a between-subjects factor and white matter tract (UF, CB) and side (left, right) as within-subject factors. The group main effect, $F(1, 53) = 7.29$, $p < .01$, partial $\eta^2 = .121$, revealed overall reduced FA in patients in comparison with control subjects. Most striking, though, was the significant interaction of group and white matter tract, $F(1, 53) = 7.16$, $p = .01$, partial $\eta^2 = .119$, which reflected reductions, bilaterally, in the CB, but not in the UF, for patients in comparison with control subjects. This replicates our previous findings,

which were obtained with a different analytic method and a nonoverlapping group of subjects (Kubicki et al., 2003).

Table 2 presents scores for the neuropsychological composite measures for both groups. The WAIS–III analysis of verbal and performance intelligence scales revealed significantly lower scores for both scales for the patients in comparison with control subjects, $F(1, 50) = 4.97$, $p < .05$, partial $\eta^2 = .09$. In addition, scale interacted with group, $F(1, 50) = 12.28$, $p = .001$, partial $\eta^2 = .197$, as the patients showed disproportionately lower scores for performance intelligence. For the WMS–III, the patient group scored significantly lower than did the control group for immediate and delayed memory, $F(1, 47) = 6.29$, $p < .05$, partial $\eta^2 = .118$, with similarly depressed scores across auditory and visual modalities, $F(1, 47) = 5.61$, $p < .05$, partial $\eta^2 = .107$. For the WCST, after controlling for education, the patients did not differ from control subjects in overall performance, nor did the groups show different patterns of scores across the three dependent measures of categories completed, perseverative errors, and nonperseverative errors. The interaction of group and dependent measure did, however, approach significance, $F(1, 96) = 2.50$, $p = .09$. The patient group completed fewer categories than did the control group, $t(50) = 2.08$, $p < .05$, and made more perseverative errors, $t(50) = 2.416$, $p < .05$.

We next examined Pearson correlations of DTI and neuropsychological measures for the patient and control groups. As shown in Table 3, for patients with schizophrenia, as predicted, the univariate correlations pointed to significant associations between reduced FA of left UF and lower general–delayed memory ($r = .456$, $p = .033$), between right UF and auditory delayed memory ($r = .479$, $p = .024$), and between increased nonperseverative WCST errors and reduced FA for left CB ($r = −.408$, $p = .043$) and right CB ($r = −.459$, $p = .021$). Also of interest is the significant correlation between lower scores on delayed recall of WMS–III Family Pictures and reduced FA for UF ($r = .421$, $p = .05$) and both left CB ($r = .498$, $p = .022$) and right CB ($r = .719$, $p < .001$). Thus, for patients, DTI-derived measures of the UF and the CB correlated with performance on different neuropsychological measures. Scatterplots of these significant correlations are presented in Figure 2.

For patients, correlational analyses also indicated a bilateral relationship of reduced FA values for CB and lower scores across all WAIS–III composite measures, with the exception of processing speed. That is, lower FA values for left CB correlated significantly with lower scores on verbal IQ ($r = .413$, $p = .045$), performance IQ ($r = .547$, $p = .006$), verbal comprehension ($r = .409$, $p = .047$), perceptual organization ($r = .546$, $p = .006$), and working memory ($r = .447$, $p = .029$). Likewise, lower FA values for right CB correlated significantly with lower scores on verbal IQ ($r = .622$, $p = .001$), performance IQ ($r = .624$, $p = .001$), verbal comprehension ($r = .562$, $p = .004$), perceptual organization ($r = .613$, $p = .001$), and working memory ($r = .598$, $p = .002$).

Neither subject socioeconomic status nor parental socioeconomic status correlated significantly with either UF or CB, and the DTI measures did not correlate with medication level for the patient group. However, for the patient group, older age correlated very significantly with lower FA values for right UF ($r = −.641$, $p < .001$), right CB ($r = −527$, $p = .006$), and left CB ($r = −.596$, $p = .001$). Longer illness duration correlated significantly with lower FA values for right UF ($r = −.578$, $p = .002$), right CB ($r = −.437$, $p = .033$), and left CB ($r = −.470$, $p = .021$).

For control subjects, FA values for left UF and right UF did not correlate significantly with scores on the WMS–III or the WCST. However, similar to the patient group, reduced FA values for left CB correlated with increased nonperseverative WCST errors ($r = −.426$, $p = .03$). In addition, the control group showed unexpected inverse correlations of reduced FA values for left CB and higher scores for auditory delayed memory ($r = −.534$, $p = .005$), verbal

comprehension ($r = -.413$, $p = .032$), and delayed auditory recognition ($r = -.524$, $p = .006$), which also correlated with reduced FA values for right CB ($r = -.454$, $p = .02$).

To compare the specific and joint contributions of FA of the UF and the CB to neuropsychological performance on the WCST and the WMS–III, we entered both brain regions as predictors into a hierarchical regression, first with WMS–III Auditory Delayed Memory index, and then with WCST nonperseverative errors, as the dependent variable. As predicted, in the patient group, for WMS–III Auditory Delayed Memory index, right UF produced a significant R^2 change of .292, $F(1, 19) = 7.85$, $p = .01$, in contrast with a nonsignificant R^2 change of .004, $F(1, 18) = .113$, $p = .741$, accounted for by right CB. Right UF and WMS–III Auditory Delayed Memory index revealed an (r_p^2) value of .507 and an (r_{sp}^2) value of .494, compared with values of .079 and .066 for right CB and WMS–III Auditory Delayed Memory index. These values indicated that right UF uniquely accounted for 26% and 24% of the variance in scores on the WMS–III Auditory Delayed Memory index. Further analyses also demonstrated that only right UF (standardized $\beta = .519$, $t = 2.50$, $p = .022$) contributed significantly to variance in scores on the WMS–III Auditory Delayed Memory index.

By contrast, for the WCST nonperseverative errors, in the patient group, right CB produced a significant R^2 change of .211, $F(1, 23) = 6.148$, $p = .021$, in contrast to a nonsignificant R^2 change of .069, $F(1, 11) < 1.0$, $p > .35$, accounted for by right UF. Right CB and WCST nonperseverative errors revealed a partial correlation value of $-.513$ and a semipartial value of $-.511$, in comparison with values of .270 and .240 for right UF and WCST nonperseverative errors. As predicted, these values indicated that right CB uniquely accounted for 26% of the variance in scores for WCST nonperseverative errors. Likewise, right CB (standardized $\beta = -.539$, $t = -2.81$, $p = .010$) but not right UF contributed significantly to WCST nonperseverative errors. For control subjects, these hierarchical regression models did not demonstrate the same significant patterns of association that were seen in the patient group.

Discussion

In this study, we integrated neuropsychological and neuroimaging measures to examine cognitive disturbance in schizophrenia. The white matter integrity of two key brain pathways, the UF and the CB, was examined in relation to schizophrenic impairment in executive functioning and in declarative memory. The results indicated that for the patient sample, bilateral reductions of the UF but not of the CB correlated with deficits in memory but not with deficits in executive functioning. By contrast, bilateral reductions of the CB but not of the UF correlated with deficits in executive functioning but not in memory. This rather selective pattern of correlations occurred against the backdrop of overall reduced neuropsychological scores for the patient sample, as well as of lower FA values overall for left and right CB in comparison with those values for control subjects. These cognitive and neuroanatomical differences were independent of the lower education level of the patient sample.

The neuropsychological tests discussed here are best viewed as quantitative summary measures of overall performance in overlapping, interacting cognitive domains, such as declarative memory, executive functioning, and intelligence. Although not especially well suited for disentangling underlying information processes, mechanisms, or operations, these tests, in conjunction with DTI measures, reliably dissociated deficits in memory and in executive functions in this sample of patients with schizophrenia. Indeed, the hierarchical regression results arguably offered the strongest statistical evidence in support of a schizophrenic double dissociation of reduced memory and UF integrity, on one hand, and of reduced executive functioning and CB integrity, on the other hand. In so doing, these results replicate our previous

study (Nestor et al., 2004). They provide further evidence linking distinct aspects of neuropsychological disturbance in schizophrenia to reduced integrity in long-range axonal communication among widespread networks of brain regions that are functionally connected by either the CB or the UF (see Andreasen et al., 1999; Gaffan, 2005).

In the current study, the UF correlated only with memory, whereas the CB correlated not only with executive functioning but with measures of intelligence and visual memory. These more extensive neuropsychological correlations would be in keeping with the functional neuroanatomy of the CB as a key subcortical white matter tract carrying axons to and from the anterior cingulate cortex. The CB connections of the anterior cingulate cortex with both the limbic and motor systems may help to serve the key cognitive function of monitoring the consequences of voluntary actions and internally generated decisions for the essential purpose of assessing the value of selected responses and guiding future choices (Carter, McDonald, Ross, & Stenger, 2001; Paus, 2001; Walton, Devlin, & Rushworth, 2004).

Such a broad and ubiquitous function as monitoring is likely recruited by a variety of neuropsychological tasks. Perhaps not surprisingly, then, the current findings indicate rather strong correlates of reduced CB white matter and of lower scores on several aspects of generalized intelligence for the patient group. The neural underpinnings of generalized intelligence, which has long been considered primarily, if not exclusively, a psychometric abstraction, have only recently begun to be elucidated. These data, with healthy subjects (Duncan et al., 2000; Gray, Chabris, & Braver, 2003) as well as from animal studies (Matzel et al., 2003), generally comport with the current CB correlates, with all pointing to the importance of lateral and medial prefrontal involvement in generalized intelligence. For patients with schizophrenia, functional neuroimaging studies have linked reduced activity of the anterior cingulate cortex to monitoring failures elicited by Stroop conflict stimuli (Carter et al., 2001). Such failures, which might very well influence both IQ and performance on the WCST, perhaps stem from a common disruption of an error-correcting learning mechanism, supported by anterior cingulate cortex, that has been established as fundamental for both human and animal cognition (Gehring, Goss, Coles, Meyer, & Donchin, 1993; Hayden & Platt, 2006).

A recent study by Kennerley, Walton, Behrens, Buckley, and Rushworth (2006) of monkeys with lesions in the anterior cingulate cortex sheds additional light on the nature of this error-corrected learning mechanism. Monkeys were trained with reinforcement on a two-choice task similar to the WCST, in which one of two actions, lifting or turning a handle, was rewarded. For example, a lifting action received reward for 25 consecutive trials, following which the rewarded action switched to turning. The results indicated that monkeys with anterior cingulate cortex lesions responded normally to reduced rewards or to errors. In other words, the lesions did not impair monkeys' performance immediately after incorrect, unrewarded actions. However, the monkeys with anterior cingulate lesions failed to sustain rewarded responses. Kennerley et al. concluded that the anterior cingulate cortex does not function simply as an error detector but rather as an integrator of past reward experiences, "guiding voluntary choices based on the history of actions and outcomes" (Kennerley et al., 2006, p. 940). Such an account certainly resonates beyond the disease-related neuropsychological disturbance and perhaps may illuminate the real-life difficulties that persons with schizophrenia face in using recent information about actions and their consequences to make sound decisions (Hayden & Platt, 2006).

As predicted, the reduced white matter integrity of the CB also correlated with lower scores on visual memory. This correlation appeared to be driven primarily by the remarkably strong relationship of the right CB and the Family Pictures subtest. A new subtest to both the WMS–III and to clinical practice, Family Pictures depicts a family (grandmother, grandfather, mother,

father, son, daughter, and the dog) interacting in four different scenes (picnic, department store, yard, meal); the examinee is asked to recall scene characters, character activity, and character location (Tulsky, Zhu, & Ledbetter, 1997). Recall requires monitoring information retrieved from episodic memory, so that the proper roles, locations, and actions of the various family members depicted in each event or scene can be selected (see Burgess & Shallice, 1996). Using functional imaging of healthy volunteers, Henson, Shallice, and Dolan (1999) found such retrieval-related contextual monitoring to be specifically related to the midlateral region of the right prefrontal cortex, an area through which the right CB travels. More recently, in patients with chronic schizophrenia, Weiss et al. (2006) used functional magnetic resonance imaging to demonstrate prefrontal abnormalities on an explicit memory task that required access to contextual information needed to distinguish previously studied words from novel words. For the patient group of this study, then, the right CB may signify degraded contextual monitoring of to-be-remembered scenes, as might be involved in eyewitness memory. This degraded monitoring may be complemented by UF-based disruption in the more formal mnemonic properties of storage and access.

The current DTI and neuropsychological correlates may be viewed as support for the idea that cognitive disturbance in schizophrenia reflects, in part, abnormal structural connectivity in white matter fiber tracts of the brain. In fact, the results provided empirical support for the hypotheses that neuropsychological disturbance in schizophrenia may be characterized, in part, by two dissociable functional neuroanatomical relationships: (a) executive functioning–CB integrity and (b) episodic memory–UF integrity. In addition, the data supported the hypothesis that disturbances in the CB executive function of monitoring interacted with those disturbances related to UF mnemonic processes, with both contributing to low scores in remembering visual scenes among patients with schizophrenia. The results thus provided support for integration of structural imaging and neuropsychological measures to partition functional neuroanatomical relationships in schizophrenia.

However, several limitations of the study are important to keep in mind. First, patients with schizophrenia differed from control subjects on a number of variables that likely influenced both neuropsychological and DTI results. And though, for example, analyses of covariance helped to control for the influence of education on the group differences demonstrated by DTI and by neuropsychological measures, one should always be cautious about attributing cognitive and neuroanatomical changes, such as those demonstrated here, to intrinsic versus extrinsic factors of schizophrenia. In a similar vein, the extent to which the current findings may be generalized to other samples of patients with schizophrenia is unclear. Indeed, the well-known heterogeneity of the expression of schizophrenia always poses challenges when one considers whether sample findings generalize to a broader population of patients. In addition, a finding somewhat atypical for the current results was the absence of significant differences in WCST measures of executive functioning when controlling for education. Although this absence may be due to the peculiarities of the control sample, whose average categories completed fell below the norm of six, the absence of a significant deficit on the WCST for the patient sample may limit the generalizability of the current findings. Also surprising was the absence of a significant relationship among age, white matter, and processing speed in this sample, given that older age correlated with reduced FA for the CB and the UF, for both control and patient groups, and that mental slowing is a robust correlate of aging.

Among the interpretive ambiguities related to the current results is that the precise structural processes that are captured by DTI-derived FA have yet to be completely established. Various distinct properties, such as density of axons or number of glial cells, particularly the oligodendrocytes that form myelin sheaths around axons, could all contribute to FA values. An additional limitation to this study is that FA values for the CB correlated inversely with some of the memory and intelligence measures for the control sample. The basis for these

unexpected correlations is unclear, but they nonetheless underscore the need for caution and further study of the relation of FA and cognition. This caution may be especially important, given that in the current study, the patient and control groups also overlapped on some of the critical variables of interest. For example, even though lower FA values for the UF correlated with poorer memory scores in the patient but not the control sample, the groups did not differ significantly in FA values for the UF. In addition, also important to bear in mind is that despite hypothesis-driven tests of specific functional anatomical relationships, the data analyses entailed many statistical comparisons performed on a relatively small number of subjects, which might have inflated Type I error. Finally, although lower FA values and poorer neuropsychological performance in the patient sample may signify less efficient communication among areas functionally connected by the UF and the CB, the nature of these computations and their neural circuitry cannot be elucidated on the basis of these findings and requires computer simulation and functional imaging studies.

Acknowledgments

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Figure 1.
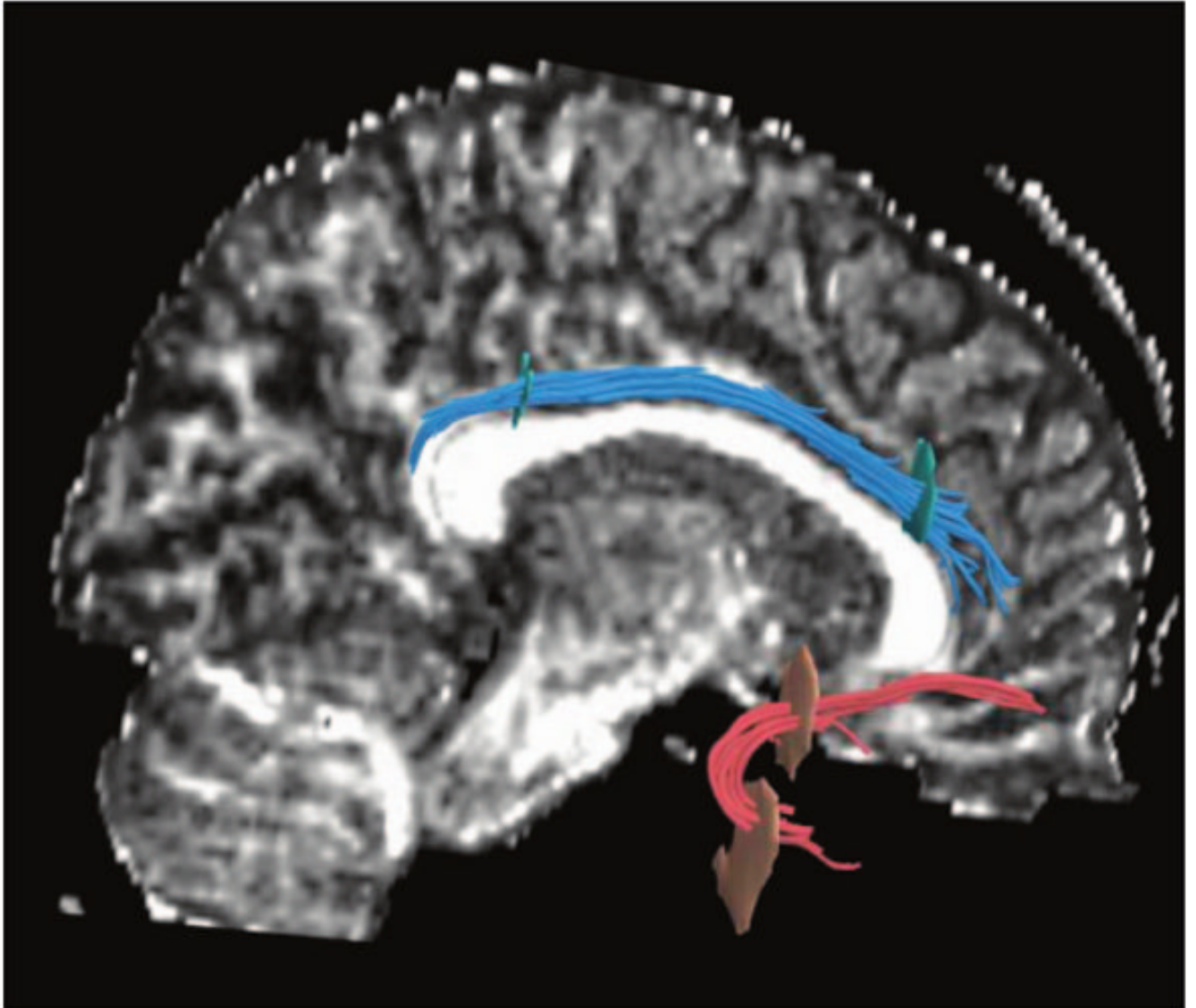Right cingulum bundle (blue) and right uncinate fasciculus (red) fiber bundles generated using fiber tractography and the two regions of interest method, overlayed on sagittal fractional anisotropy map.
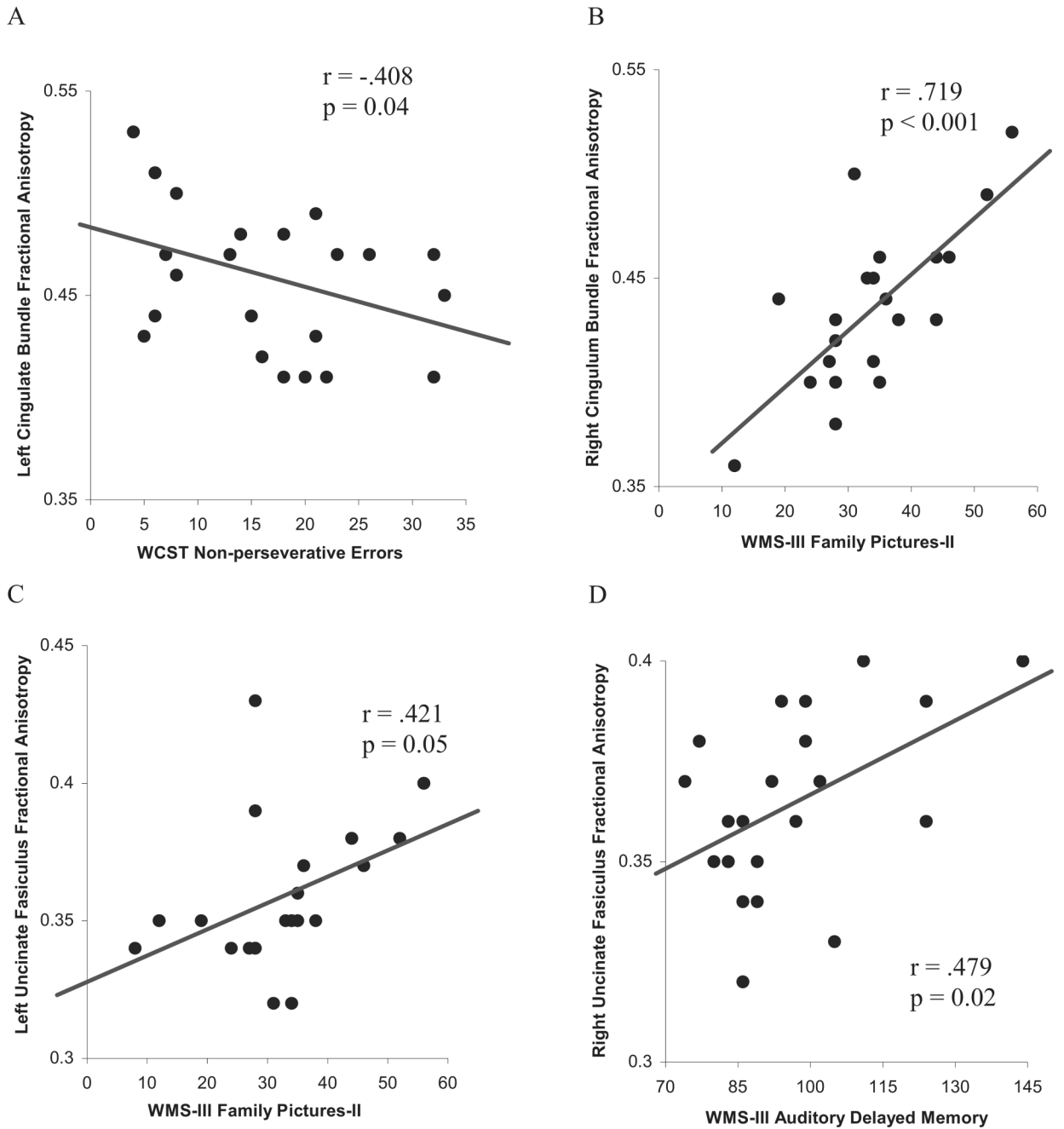
Figure 2.
Scatterplots of fractional anisotropy values and neuropsychological test scores for patients with schizophrenia. WCST = Wisconsin Card Sorting Test; WMS–III = Wechsler Memory Scale —Third Edition.

Table 1

Fractional Anisotropy Values for the Uncinate Fasciculus and Cingulum Bundle for Patient and Control Groups

Within-subject factor	Patient group	Control group
Uncinate fasciculus		
Left	.3596 ± .02630	.3607 ± .02490
Right	.3608 ± .02208	.3640 ± .02372
Cingulum bundle		
Left	.4604 ± .03412	.4783 ± .03696[**]
Right	.4346 ± .03669	.4507 ± .03841[**]

Note. Values are means plus or minus standard deviations.

[**] $p < .01$ (covarying for education differences between patient and control groups).

Table 2

Neuropsychological Summary Scores for Patients With Schizophrenia and Control Subjects

Variable	Patient	Control subject
	Demographic information	
Age	39.11 ± 9.11	41.42 ± 8.67
Education	12.89 ± 1.99	15.34 ± 2.16 [**]
SES	3.89 ± 1.09	2.39 ± 1.17
Parental SES	3.13 ± 0.99	2.63 ± 1.26
	Measure	
WAIS–III IQ		
Full scale	92.36 ± 14.31	109.25 ± 13.79 [*]
Verbal	97.20 ± 15.55	109.21 ± 12.77 [*]
Performance	87.56 ± 12.16	108.14 ± 15.50 [*]
WAIS–III index		
Verbal Comprehension	101.00 ± 17.08	107.78 ± 12.60
Perceptual Organization	93.04 ± 15.98	109.70 ± 14.92 [**]
Working Memory	94.60 ± 12.90	108.93 ± 12.20 [**]
Processing Speed	81.04 ± 9.93	102.48 ± 14.40 [**]
WMS–III memory quotient		
Immediate	84.68 ± 15.12	102.32 ± 15.72 [*]
General	88.77 ± 12.74	105.07 ± 14.79 [*]
WMS–III index		
Auditory Immediate Memory	90.41 ± 17.55	104.68 ± 14.04 [*]
Visual Immediate Memory	84.09 ± 10.44	98.36 ± 14.95 [*]
Auditory Delayed Memory	95.77 ± 17.26	106.93 ± 10.79 [*]
Visual Delayed Memory	87.41 ± 11.68	102.71 ± 16.34 [*]
WCST		
Categories completed	4.08 ± 2.10	5.12 ± 1.61
Perseverative errors	20.84 ± 16.06	12.85 ± 7.57
Nonperseverative errors	16.56 ± 9.60	17.62 ± 17.38

Note. Values are means plus or minus standard deviations. SES = socioeconomic status; WAIS–III = Wechsler Adult Intelligence Scale—Third Edition; WMS–III = Wechsler Memory Scale—Third Edition; WCST = Wisconsin Card Sorting Test.

[*]
$p < .05.$

[**]
$p < .01$ (covarying for education differences between patient and control groups).

Table 3

Pearson Correlations of Neuropsychological Scores and Fractional Anisotropy of the Uncinate Fasciculus and the Cingulum Bundle for Patients With Schizophrenia

Measure	Uncinate fasiculus		Cingulum bundle	
	Left	Right	Left	Right
WMS–III memory quotient				
Immediate	.372	.279	.205	.125
General–delayed	.456[*]	.194	.055	.290
WMS–III index				
Auditory Immediate	.380	.295	.082	.166
Visual Immediate	.210	−.102	.346	.663[**]
Auditory Delayed	.279	.479[*]	.125	.230
Visual Delayed	.388	−.056	.115	.412
WCST				
Categories completed	.189	−.059	.366	.341
Perseverative errors	−.103	.098	−.163	−.165
Nonperseverative errors	−.170	.083	−.408[*]	−.459[*]
WAIS–III				
Verbal IQ	.304	.205	.413[*]	.622[**]
Processing IQ	.159	.033	.547[**]	.624[**]
WAIS–III index				
Verbal Comprehension	.273	.231	.409[*]	.562[**]
Perceptual Organization	.177	.084	.546[**]	.613[**]
Working Memory	.219	−.053	.447[*]	.598[**]
Processing Speed	.126	.163	.140	.069

Note. WMS–III = Wechsler Memory Scale—Third Edition; WCST = Wisconsin Card Sorting Test; WAIS–III = Wechsler Adult Intelligence Scale—Third Edition.

[*] $p < .05$.

[**] $p < .01$.