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White Matter Integrity and Prediction of Social and Role Functioning in Subjects at Ultra-High Risk for Psychosis

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Abstract

Background—White matter microstructural disruptions have been observed in patients with schizophrenia. However, whether changes exist prior to disease onset or in high-risk individuals is unclear. Here we investigated white matter integrity, as assessed by diffusion tensor imaging (DTI), in individuals at ultra high risk for psychosis (UHR), relative to healthy controls (HC), and the relationship between baseline DTI measures and functional outcome over time.

Methods—Thirty-six UHR participants and 25 HC's completed baseline DTI scans. Subjects also completed clinical follow-up assessments approximately 6 (26 subjects) and 15 months (13 subjects) later. We used a rigorous registration approach (Tract-Based Spatial Statistics (TBSS) to examine fractional anisotropy (FA) in six major white matter tracts.

Results—Relative to the HC group, UHR subjects showed lower baseline FA in the superior longitudinal fasciculus, the major frontal-parietal white matter connection. Cross-sectional analyses demonstrated that UHR youth failed to show the same age-associated increases in FA in the hippocampus and inferior longitudinal fasciculus as HCs. Finally, lower baseline FA in the hippocampus and inferior longitudinal fasciculus predicted deterioration in social and role functioning in UHR participants at 15-month follow-up.

Conclusions—This is the first investigation of white matter microstructural alterations in a clinical high-risk sample. Our findings indicate that white matter development may be altered in youth at risk for psychosis, possibly due to disrupted developmental mechanisms, and further, that white matter integrity may be predictive of functional outcome.

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Keywords

Schizophrenia; prodrome; diffusion tensor imaging; DTI; white matter; social functioning

Introduction

Early detection and prevention strategies for schizophrenia have led to investigations of individuals at the highest level of risk, either due to genetic factors (e.g. first degree relatives of patients with schizophrenia) or due to the exhibition of a constellation of clinical symptoms thought to be characteristic of the "prodromal period" of psychosis during the period when onset of schizophrenia would be expected to occur. Such studies seek to characterize the developmental processes that lead to disturbances of brain structure and function associated with onset of psychosis and to find baseline traits that are predictive of later diagnostic conversion or functional decline.

Disruptions in white matter (WM) integrity have been implicated in disease pathogenesis in schizophrenia (1). Evidence includes neuroimaging studies of first-episode and chronic patients that report WM volume reductions and structural abnormalities (2–4) as well as myelin-related gene abnormalities (5;6). Further, hippocampal and frontal lobe myelination peak during adolescence and early adulthood (7), the time period most associated with psychosis onset. In fact, during normal adolescent brain maturation, gray matter volume decreases, likely due to increased synaptic pruning, while WM volume undergoes a simultaneous increase (8).

How the differences in connectivity observed in schizophrenia develop is of great interest (9). Some behavioral features are observable in patients with schizophrenia years before illness onset (e.g. (10-12)), suggesting that there are neural differences from a very early age that may leave at risk individuals more vulnerable to later insults. One possibility is that this early insult interacts with normal changes that occur later in development (i.e. pruning) thus unveiling the psychotic state in late adolescence (13;14). It is also possible that the changes observable in patients with schizophrenia result from a disruption in the late developmental process itself (15). However, there are also a number of ways that these models may be combined (i.e. an early insult combined with the second hit of an abnormal developmental process), and the ways in which these different phases of development may interact is of great interest (Keshavan, 1994; Lewis, 2002; Waddington, 1998}.

Diffusion tensor imaging (DTI) is a powerful tool for examining WM microstructure in-vivo, based on patterns of water diffusion in neural tissue. The degree of fractional anisotropy (FA) in a voxel indexes WM integrity, potentially reflecting both myelination and tract organization. Previous DTI studies in schizophrenia have shown decreased FA in many major tracts, including the superior longitudinal fasciculus (16–18), cingulate bundle (19–21), uncinate fasciculus (18;22–25), inferior longitudinal fasciculus (26–28) and hippocampus (29;30). Such abnormalities are evident even in the first episode (16;17;31;32). While previous studies of young people at ultra-high risk for developing psychosis (UHR) have utilized structural (e.g. (33;34) and functional neuroimaging methods (e.g. (35;36), WM integrity has been less investigated.

We assessed baseline DTI differences between UHR patients and healthy controls (HC), hypothesizing findings of reduced WM integrity in UHR youth. Additionally, to determine whether WM development is abnormal in UHR individuals, we tested whether age-associated differences in FA differed between UHR youth and HC's as well as whether baseline WM changes were predictive of change in clinical and psychosocial functioning over time. Finally,

in an exploratory analysis, we assessed the relationship of baseline FA with later symptomatology. Longitudinal studies examining conversion to psychosis as the primary outcome can be ambiguous, as conversion may occur subsequent to the final follow up point, and treatment course may ameliorate the natural progression of psychotic-like symptoms. Therefore, our study employed quantitative indices of functional outcome (37;38) previously associated with cognitive change over time to serve as potential proxies for psychosis-related decline (39). We predicted that UHR youth with subsequent functional decline would have greater WM deficits at baseline, reflecting a more compromised system less amenable to improvement with time and treatment.

Methods

Participants

Thirty-six UHR participants and 25 HCs (see Table 1) were enrolled in an ongoing longitudinal study at the University of California, Los Angeles. HCs were recruited from a community sample via advertising, and were age matched to the UHR sample. Baseline measures included clinical and functional assessments and DTI. Subjects completed follow-up assessments of clinical and functional outcome, on average, at 6.11 ± 2.42 (26 subjects) and 15.96 ± 5.76 months (13 subjects, 92.3% of whom also were assessed at the first follow-up time point). UHR participants met criteria for of one of three prodromal syndrome categories, as assessed by the Structured Interview for Prodromal Syndromes (SIPS(40)): (1) attenuated (sub threshold) psychotic symptoms; (2) transient, recent-onset psychotic symptoms; or (3) a substantial drop in social/role functioning in conjunction with Schizotypal personality disorder diagnosis or a first-degree relative with a psychotic disorder. HC youth did not meet DSM-IV criteria for a psychiatric disorder as determined by SCID-I/P or K-SADS interview, have a first-degree family history of a psychotic disorder, or meet criteria for any of the three prodromal states defined above. Additional exclusion criteria for all participants included the presence of a neurological disorder, drug or alcohol abuse or dependence within the past 6 months, insufficient English fluency, and/or IQ below 70. Detailed information regarding SIPS prodromal criteria, reliability and consensus procedures are described elsewhere (41). All participants completed informed consent or assent (parental consent was also obtained for minors) and were compensated for all participation, as approved by the UCLA Institutional Review Board.

Procedures

Social and role functioning were assessed in UHR subjects with the Global Functioning: Social scale (GFS (42)) and the Global Functioning: Role scale (GFR (38)), measures designed to provide global assessments of psychosocial functioning in adolescent and young adult populations (37). These scales rate social and role function on two separate 10-point Likert scales, independent of symptom severity. Functional change over time was determined by calculating the percent change from baseline (either positive or negative) in these scores over the follow-up period. In addition, subjects were assessed using the Global Assessment of Functioning (GAF) and Brief Psychiatric Rating Scale (BPRS).

Scanning Procedures

Subjects were scanned on a 1.5T Siemens Sonata scanner (Siemens, Erlagen, Germany) at the Ahamanson-Lovelace Brain Mapping Center at UCLA. Head motion was restricted using foam padding. DTI data were acquired using a 6-direction EPI sequence with 75 contiguous 2mm AC-PC aligned interleaved slices with no gap (TR=9.5s, TE=77ms, flip angle =90 deg, matrix=128x96, b-value = 1000, FOV 256 mm x 192 mm resulting in 2mm isotropic voxels). Five repetitions were acquired, with a total scan time of 6 minutes 20 seconds.

Data Analysis

Image Processing—The five image acquisitions for each direction were merged, aligned with McFlirt (FMRIB Software Library; FSL (43)), and averaged to create one file each for the 6 directions and the b0 image. Eddy current correction was done using Flirt (FSL), and images were skull stripped using the Brain Extraction Tool. FA images were calculated using DTIFit (FMRIB's Diffusion Toolbox), which fits a diffusion tensor model at each voxel, and then were registered to MNI-152 space using a 12-parameter affine registration with a mutual information cost function implemented in Flirt (FSL). A group map was created using Tract-Based Spatial Statistics (TBSS, (44)). An average FA image was created and the tracts were narrowed to generate an FA "skeleton" representing the center of all tracts common to the entire group. The area around the skeleton in each subjects' aligned FA map was searched and the highest local FA value was assigned to the skeleton. This ensured that each subject's skeleton was in the group space, yet represented the center of that subject's own unique fiber tracts.

Region of Interest Definition—Regions of interest (ROIs) were defined in the anterior thalamic radiation (ATR), cingulate bundle (CB), medial temporal lobe structures (MTL), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF) and uncinate fasciculus (UF). Regions were created by overlying the TBSS generated skeleton (Figure 1) with the John Hopkins University DTI-based probabilistic tractography atlas for the tracts of interest. (45-47). To ensure the validity of the tractography-based ROIs for our TBSS skeleton, in any instance where the skeleton and JHU tract differed, the ROI was edited to incorporate contiguous and inclusive sections of skeleton. Each subjects' FA skeleton was masked using each of the ROIs, and the average FA was calculated for that segment of the skeleton in each region (see Figure 2).

Statistical Analyses

Analysis I, Group-wise Differences at Baseline: Mean FA data were extracted from each ROI. To reduce the number of statistical comparisons, data were collapsed across both hemispheres. A repeated measures within-subjects ANOVA was performed with region (for the 6 ROIs) as a repeated measure, with age and sex as covariates. To decompose the significant effects, an analysis of covariance (ANCOVA), assessed FA by group, covarying for age and sex.

Analysis II, Age Analysis: For the cross-sectional age analysis, a robust regression was performed in Stata (v8) with age predicting FA (for each ROI), covarying for gender. As in the previous analysis, ROI data were collapsed across hemispheres. Data for each individual analysis were tested for outliers, and subjects with high studentized residuals (>2) were excluded from that regression. Group differences in the age-FA relationship were tested using the interaction between the slopes of the regression lines, and tested for significance using a Wald test. To correct for the number of ROIs (six) in this analysis, the p-threshold was set at .05/6=.0083.

Analysis III, Functional Changes: In this robust regression analysis, FA (for each ROI in each hemisphere) was included as a predictor of functional outcome (social and role functioning) in UHR patients, while controlling for age and gender. Twenty-eight UHR subjects completed 6-month follow-up assessments, while 13 UHR subjects completed follow-up at 15-months. The data for each individual regression were again tested for outliers and subjects with high studentized residuals (>2) were excluded. For this analysis, to correct for the number of ROIs (twelve), the p-threshold was .05/12=.0042.

Analysis IV, Exploratory Analysis of Clinical Changes: In a post-hoc exploratory analysis of clinical symptoms we assessed the relationship between baseline FA and negative symptoms, positive symptoms, GAF scores, and indices of dysphoric mood (from the SIPS) and depression (from the BPRS) at 15 months follow up. A robust regression was performed of the clinical measure in question with FA for each of the 12 regions of interest at baseline, covaried for age and gender. Due to the post-hoc nature of the analysis, a p value of .05 was used for all comparisons.

Results

There was no significant difference between UHR participants and controls in age (t(59)=−.86, p=.29)), although there was a significant difference in gender distribution (χ^2=5.44, p=.02), so gender was included as a covariate in all analyses (see Table 1).

Analysis I

In the UHR vs. control FA repeated measures ROI analysis, there was a significant effect of region [F(5,285)=6.801, p<.001], no effect of group [F(1,57)=.100, p=.753], and a significant group by region interaction [F(1,285)=2.452, p=.034]. When this latter effect was decomposed using ANCOVA covarying for age and sex, there was a significant effect of group in the SLF [F(3,57)=4.41, p=.040], with UHR subjects showing reduced FA relative to HCs at baseline. There were no significant differences in the other ROIs examined.

Analysis II

There was a significant group x age interaction in the hippocampus (F(4,53)=6.47, p=.006), and a trend towards an interaction in the ILF (F(4,52)=3.49, p=.022), such that as age increased, FA increased in the control group, but not in the UHR group (see Figure 3). The other ROIs (CB, UF, SLF, and ATR) did not show group x age interactions, although there was a significant main effect of age in the CB (F(4,54)=12.17, p<.001) in the full sample.

Analysis III

The subjects who remained in the study for follow up assessments did not differ from those who were lost to follow up in terms of age [t(34)=1.2070, p=.2358], gender [χ^2=.3612, p=.548], family history [χ^2=.8600, p=.354], baseline GAF [t(34)=1.011, p=.3193], or the SIPS criteria on which their recruitment was based [χ^2=1.273, p=.736]. At 6 month follow-up, no significant associations between baseline FA and change in functioning were observed for UHR individuals, although there were trend associations between lower values of FA in the left ILF (F(3,21)=2.86, p=.033) and right ILF (F(3,21)=2.46, p=.071) and declines in social functioning at 6-months.

However, at the 15-month follow up, lower FA in the right ILF significantly predicted deterioration in role (F(3.7)=14.26, p=.002) and social functioning (F(3.8)=12.39, p<.0001) in the UHR sample. Deterioration in role functioning was also significantly predicted by lower FA in the left hippocampus (F(3.8)=7.78, p=.003) and left ILF (F(3.7)=13.01, p=.004). Furthermore, there were trends towards a relationship of deterioration in social functioning with lower FA in the right hippocampus (F(3,8)=5.83, p=.074) and right ATR (F(3,8)=6.33, p=.073) as well as a trend towards a relationship of deterioration in role functioning with lower FA in the right UF (F(3,8)=1.45, p=.09; See figure 4).

Analysis IV

At 15 months follow up, there were significant relationships between GAF scores and left SLF (p=.029) and right anterior thalamic radiation (p=.040) with trends in the left anterior thalamic

radiation and right hippocampal region. Negative symptoms were significantly associated with the right ILF (p=.045) and with the right hippocampal region (p=.024) with trends in the left SLF and left ILF. Dysphoria was associated with the left SLF (p=.010) with a trend in the right ILF. Depressed mood was associated with right hippocampal region (p=.049). There were no significant relationships between any regions and positive symptoms or conversion status, although there was a trend towards a relationship of conversion and hippocampal FA (p=.0697), and conversion was highly related to functional outcome, particularly social functioning at long-term follow-up (p=.003). (Supplemental Table 1).

Conclusions

Regional FA differed in the UHR and HC groups in the SLF, and cross-sectional analyses indicated differences in the pattern of age-associated change, suggesting an altered developmental trajectory of WM in UHR youth. Further, WM alterations at baseline in the UHR sample were predictive of changes in social and role functioning over the ensuing 15 months, indicating that structural brain changes are detectable before illness onset and may differentiate patients who will and will not deteriorate functionally over time.

Overall, UHR patients had lower baseline FA than controls in the SLF, a fronto-parietal connection, which is consistent with previous findings in first-episode schizophrenia patients (16-18). Previous structural neuroimaging work in UHR subjects has identified gray matter reduction in frontal and temporal lobe structures and the cerebellum (34;48-50). However, findings regarding gray matter abnormalities prior to illness onset in medial temporal structures such as the hippocampus are inconsistent (50;51). A prior study of individuals at clinical high risk revealed differences in callosal shape, supporting the notion that WM alterations may exist prior to illness onset (52). However, UHR samples are highly heterogeneous with regards to age and clinical outcome, which may sometimes obscure group differences and contribute to trend level differences, for instance, a study examining fiber tracking in a smaller sized UHR group also did not find simple group differences when compared to controls (53). Exploration of factors that contribute to such variance, and how they relate to WM alterations, may elucidate differences that are relevant within the UHR samples but that make comparisons between UHR and control samples problematic.

Our results suggest different developmental patterns in temporal lobe WM tracts (MTL and ILF) between UHR youth and healthy controls, such that UHR youth fail to show the expected age-associated increase in FA. This result is consistent with previous longitudinal findings in adolescents with schizophrenia, in which significantly greater gray matter loss over time was seen in patients than controls, suggesting abnormal frontal and temporal development (54). Additionally, hippocampal volume decreases were observed across adolescence in schizophrenia patients but not controls (55), with specific hippocampal subregions showing distinct developmental trajectories, which differed between adolescent schizophrenia patients and healthy controls (56). Moreover, in late adolescence and early adulthood schizophrenia patients show abnormal developmental trajectories in both gray and WM (57), with greater tissue loss seen in patients with poor outcome. While schizophrenia is considered to be a developmental disorder with both early and late developmental influences (58), it is of interest whether the changes seen in adulthood arise as the result of a normal process exerted on a compromised structure or an abnormal developmental process (9;15;59). Our findings indicating that the slope of developmental change differs UHR cases and controls are consistent with the theory that there is a disruption in the developmental process itself.

Finally, lower baseline FA in temporal regions was predictive of a course of declining social and role function in UHR youth. Thus, early microstructural changes may indicate a pervasive neurologically-based deficit, as opposed to a transient symptomatically-based deficit.

Although FA in these regions did not predict conversion to a categorical psychosis diagnosis, we had limited power to examine this question as only 6 subjects converted over the follow-up period. This is a common obstacle for UHR studies examining conversion to psychosis as the primary outcome variable (60). However, conversion was highly correlated with functional outcome, particularly social functioning at long-term follow-up (p=.003). This analysis of social and role functioning, rather than conversion, in relationship to structural brain changes provides a unique contribute to the literature. The results indicate that, while functional outcome and DSM-IV diagnosis are closely related, additional power and information can be gained through use of a continuous variable (i.e., functioning). Our findings further suggest that DTI measures of WM integrity may be a powerful prognostic indicator in at-risk youth. Previous findings in FA and other high risk groups (17;23;26;27;31;32;61–63) support the idea that neural changes are present early in the progression of the illness. However, the use of a longitudinal design in which FA predicts later outcome is novel. That these effects are largely in temporal lobe regions is interesting and consistent with what we know about normal adolescent development- that the temporal lobes are expected to be myelinating during this time and thus have the potential to show changes quite proximal to disease onset. This pattern is also consistent with cognitive findings in the prodrome, in which functions thought to rely on the temporal lobes such as verbal learning and memory are impaired (38).

Our study is limited in part by sample size and heterogeneity. By their nature, UHR groups contain subjects who are experiencing transient changes and patients who are prodromal for other non-psychotic psychiatric disorders in addition to those truly prodromal schizophrenia subjects. Therefore, larger follow-up cohorts may provide additional insight. Additionally, while some UHR participants had been medicated for a relatively brief period of time, none of the FA measures were significantly correlated with antipsychotic use (all p>.05), so there is no evidence that medication use influenced the direction of the results. Although gender distribution differed between groups, gender was included a covariate in all analyses to account for its potential relationship with DTI measures. With only 6 directions in the DTI sequence, our analysis was limited to FA, but future studies in which more directions are measured and in which analyses such as tractography can be performed, will be very informative. Further, due to susceptibility artifacts in the orbitofrontal regions that occur with echo planar imaging scans, the signal for the uncinate should be interpreted with caution. Finally, given the low conversion rate we also must consider other potential explanations, for instance, that WM integrity is predictive of decline across a variety of psychopathologies and not just schizophrenia. However, these subjects did have symptoms consistent with those associated with the prodromal phase of schizophrenia.

In conclusion, our cross-sectional findings suggest a different pattern of WM development in UHR youth relative to healthy controls, particularly in temporal lobe regions, such that UHR youth fail to show the normal progressive increase in FA with age. Further, lower baseline FA in temporal WM tracts predicted deterioration in social and role functioning over follow up. These data thus provide the first evidence that structural brain changes in temporal lobe WM may predict outcome in young people at ultra high risk for psychosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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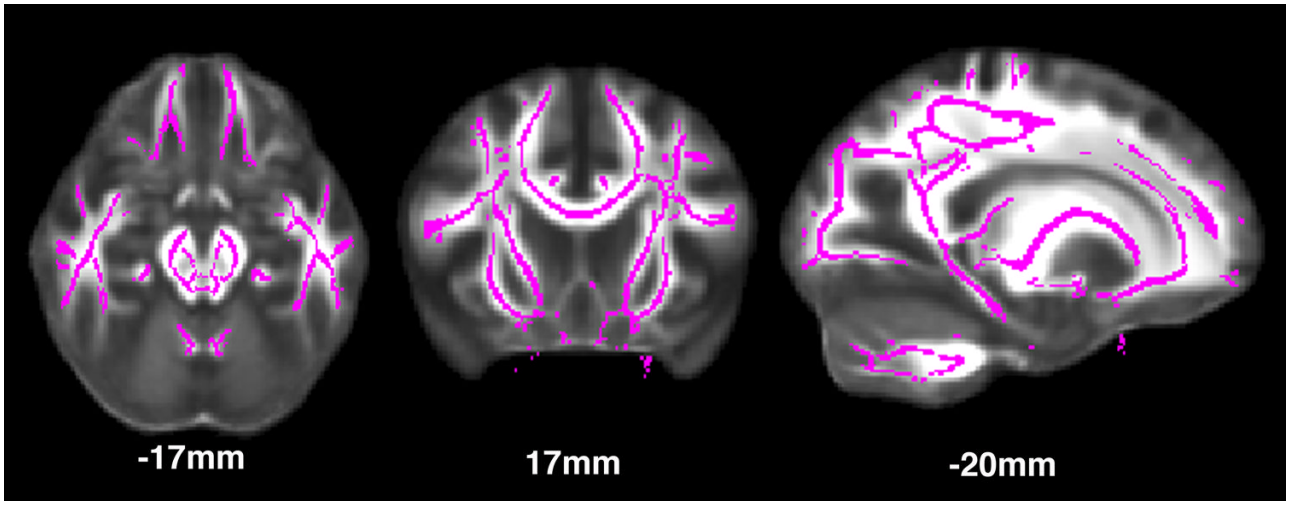

Figure 1.
Tract-based spatial statistics (TBSS) skeleton.

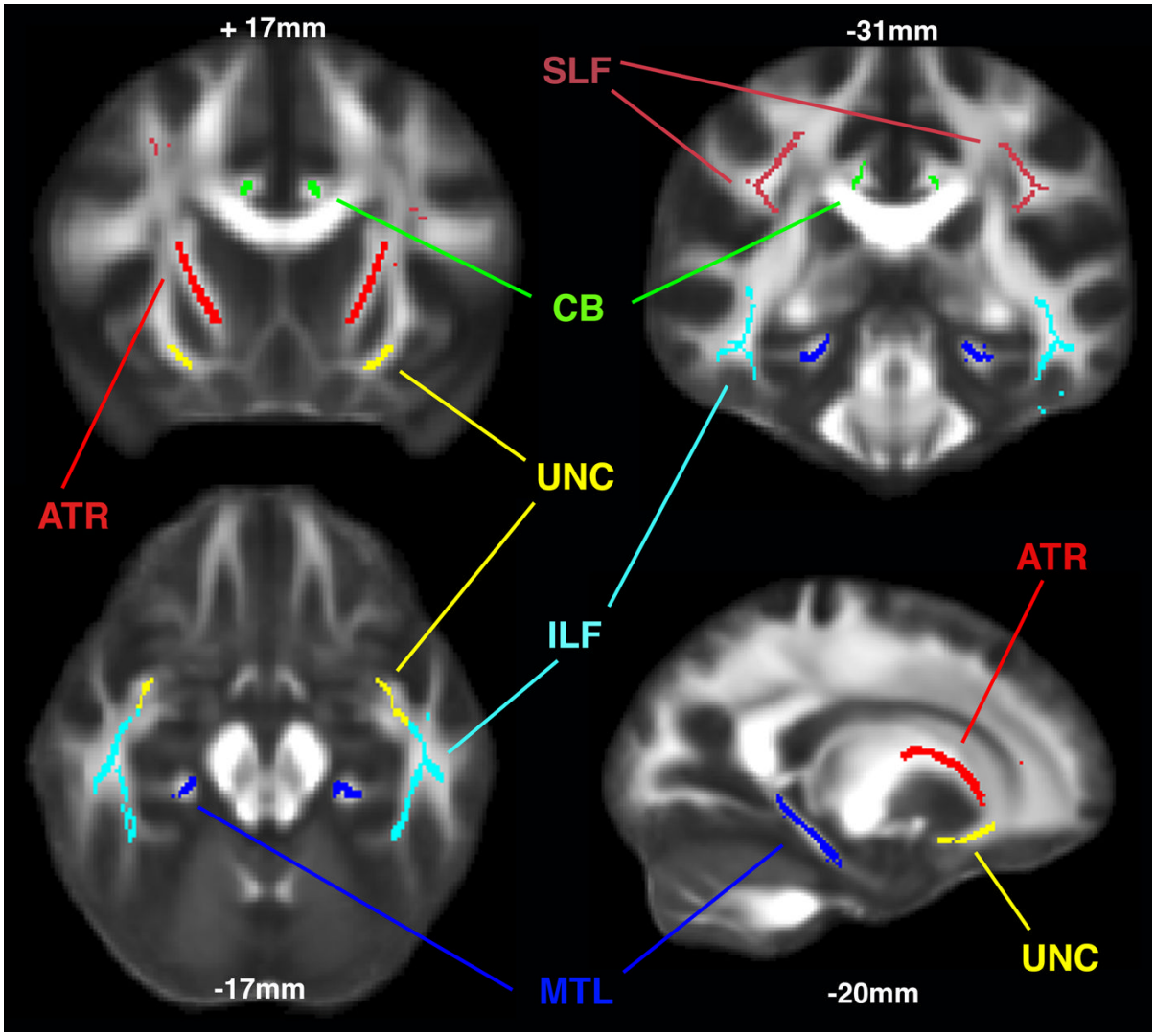

Figure 2.
Regions of Interest; SLF = superior longitudinal fasciculus; ILF = inferior longitudinal fasciculus; ATR = anterior thalamic radiation; MTL = medial temporal lobe; CB = cingulate bundle; UNC = uncinate fasciculus

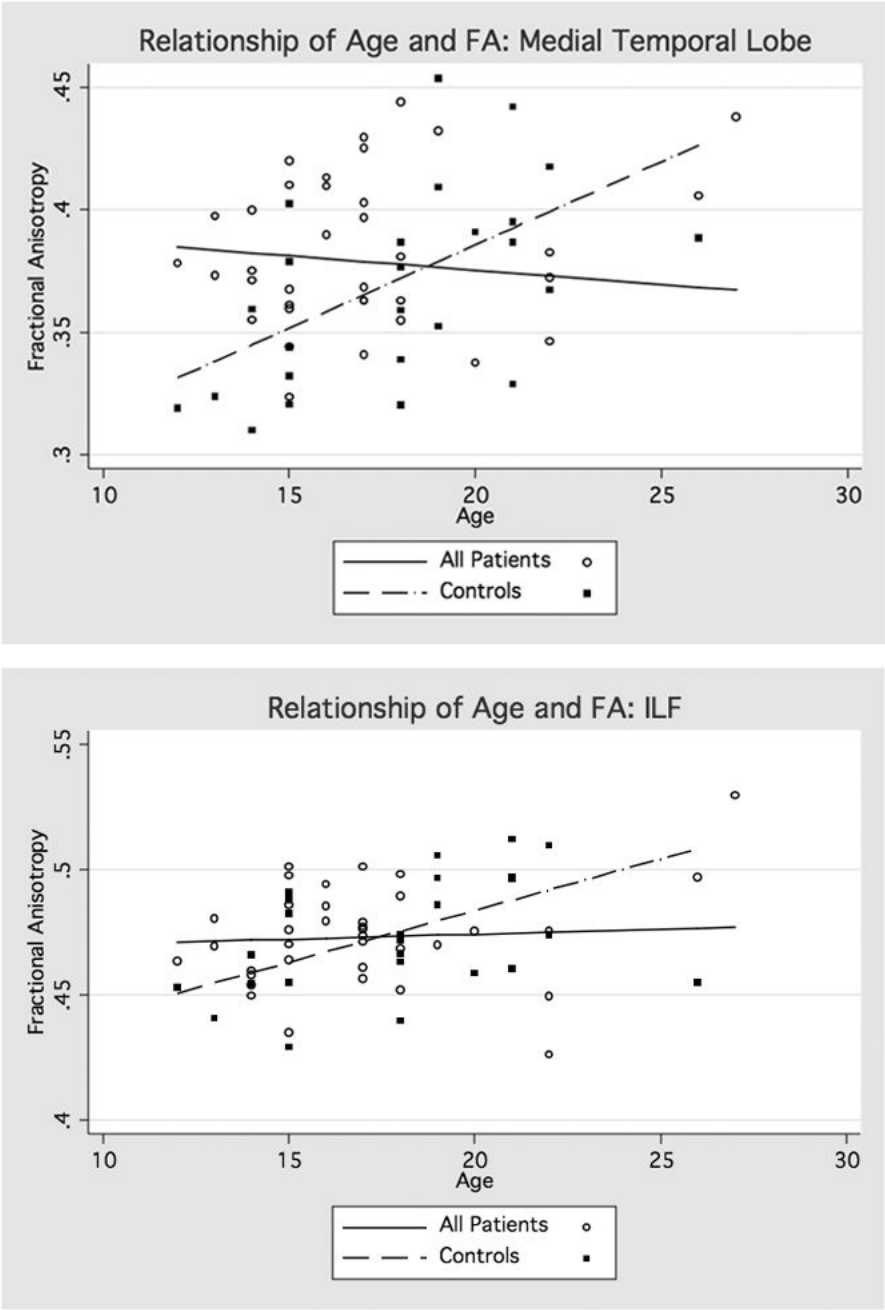

Figure 3.
Robust regression of age and FA in hippocampus (F(4,53)=6.47, p=.006) (top) and ILF (F (4,52)=3.49, p=.022) (bottom)

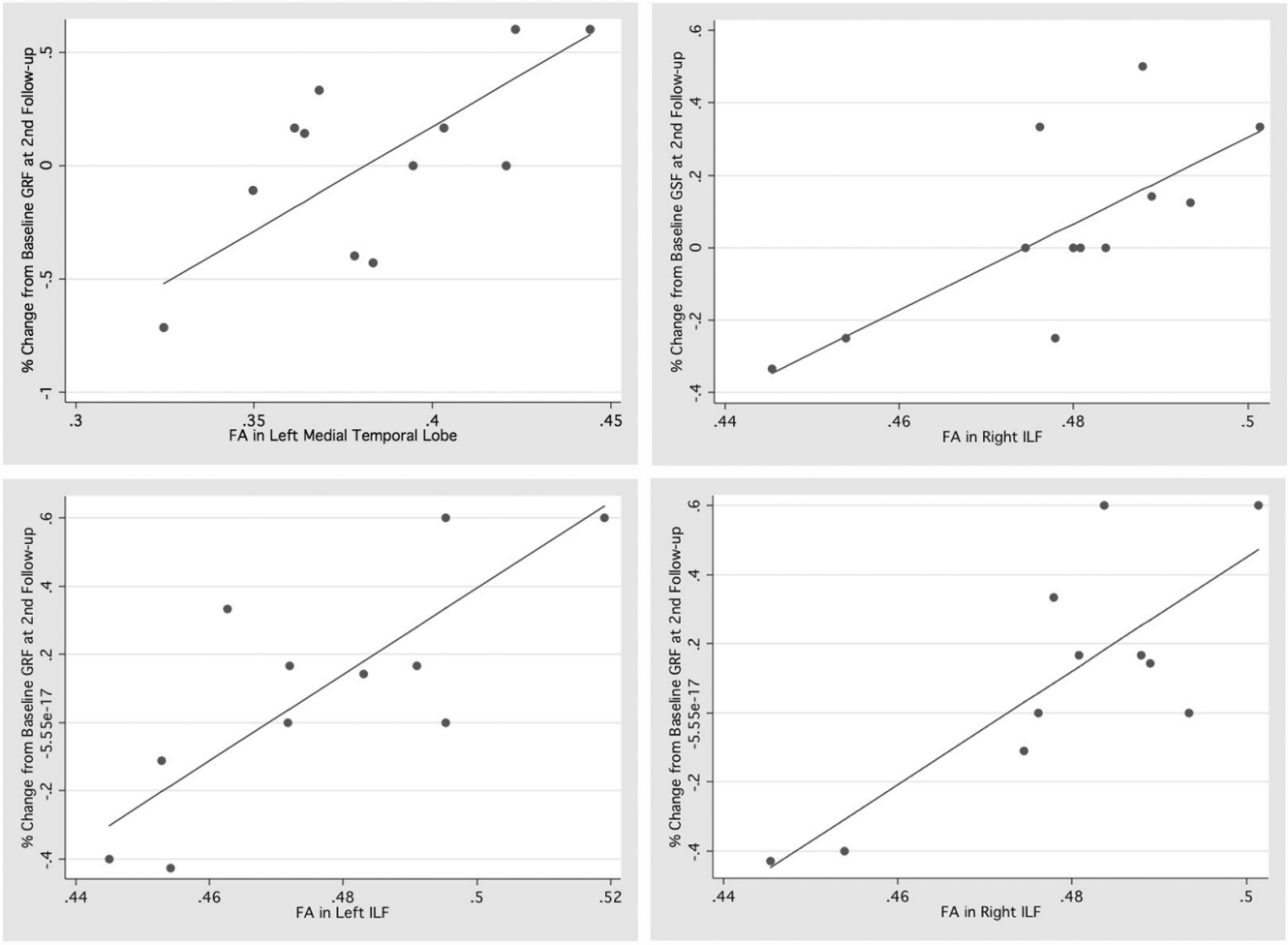

Figure 4.

Robust regression of functional outcome and FA: a. GFR and left hippocampus (F(3.8)=7.78, p=.003); b. GFS and right ILF (F(3.8)=12.39, p<.0001); c. GFR and left ILF F(3.7)=13.01, p=.004); d. GFR and right ILF (F(3.7)=14.26, p=.002)

Table 1

Subject Demographics

Characteristic	UHR Patients (n = 36)	Healthy Controls (n = 25)
Age at baseline examination, mean (±SD)	17.02 (3.37)	17.96 (3.40)
Years of Education, mean (± SD)	10.66 (2.54)	11.84 (2.77)
Parental Education (years), mean (± SD)		
Estimated WASI IQ, mean (± SD)[a]	110.58 (13.52)	111.82 (11.29)
Gender, n (%)		
Males	27 (75%)	12 (48%)
Females	9 (25%)	13 (52%)
Race, n (%)		
African American/Black	5 (14%)	3 (12%)
Asian American/Pacific Islander	3 (8%)	3 (12%)
Caucasian	22 (61%)	13 (52%)
Native American	0 (0%)	1 (4%)
Latino/Hispanic	4 (11%)	4 (16%)
Other	2 (6 %)	1 (4%)
Handedness, [b] n (%)		
Left or Mixed/Right	3 (9%)	2 (10%)
Primary SIPS-defined Prodromal Status, n (%)		
Brief Intermittent Psychotic Syndrome	7 (19%)	
Attenuated Positive Symptom Syndrome	28 (78%)	

Characteristic	UHR Patients (n = 36)	Healthy Controls (n = 25)
Genetic Risk & Deterioration Syndrome	1 (3%)	
Diagnosis of Schizotypal Personality Disorder, n	1	
Family History of Psychotic Disorder (First-degree relative), n	8	
Clinical Characteristics of Sample		
GAF score, mean (± SD) Baseline	45.25 (15.02)	
Follow-up 1	56.15 (13.59)	
Follow-up 2	60.38 (15.47)	
SOPS Positive Symptom Total, mean (± SD) Baseline	10.69 (4.34)	
Follow-up 1	7.96 (4.85)	
Follow-up 2	7.92 (2.3)	
SOPS Negative Symptom Total, mean (±SD) Baseline	10.75 (6.68)	
Follow-up 1	10.25 (7.15)	
Follow-up 2	8.76 (9.54)	
Global Functioning: Role score, mean (±SD) Baseline	6.38 (1.72)	
Follow-up 1	6.37 (1.86)	
Follow-up 2	6.07 (2.28)	
Global Functioning: Social score, mean (±SD) Baseline	6.22 (1.56)	
Follow-up 1	6.37 (1.96)	
Follow-up 2	6.76 (2.12)	
Conversion to DSM Diagnosis of Psychotic Disorder n (%)	6 (17%)	
Medication usage at baseline DTI scan, n (%)	21 (58%)	
Atypical Antipsychotics, n (%)	9 (25%)	
SSRIs, n (%)	12 (33%)	

[a] IQ and handedness data were missing for 3 control subjects

[b] Gender differed significantly between groups (χ^2=5.44, p=.02)