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Remission Status and Cortical Thickness in Childhood Onset Schizophrenia

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Abstract

OBJECTIVE—Few studies have examined prediction of schizophrenia outcome in relation to brain MRI measures. In this study, remission status at the time of discharge was examined in relation to admission cortical thickness for childhood-onset schizophrenia probands. We hypothesized that total, frontal, temporal, and parietal gray matter thickness would be greater in patients who subsequently remit.

METHOD—The relationship between admission cortical brain MRI thickness and remission status at the time of discharge an average of 3 months later was examined for 56 individuals (32 males) ages 6 through 19 diagnosed with childhood-onset schizophrenia. Cortical thickness was measured across the cerebral hemispheres at admission. Discharge remission criteria were adapted from the 2005 Remission in Schizophrenia Working Group criteria.

RESULTS—Patients remitted at discharge ($n=16$ (29%)) had thicker regional cortex in left orbital-frontal, left superior and middle temporal and bi-lateral post-central and angular gyri (all p values < 0.008).

CONCLUSION—Our results provide neuroanatomic correlates of clinical remission in schizophrenia and evidence that response to treatment may be mediated by these cortical brain regions.

Keywords

Childhood-onset Schizophrenia; MRI; Remission; Cortical thickness

Introduction

Childhood-onset schizophrenia (COS), defined as onset of psychosis before age 13, is a rare, severe form of the disorder¹. True episodes are very rare in patients with COS and most experience an insidious illness onset and a chronic course. With respect to anatomic brain MRI findings, comparable abnormalities have been demonstrated in the adult onset version of the disorder (AOS) and COS^{2, 3}. Specifically, AOS and COS cortical abnormalities include diminished total, frontal and temporal gray matter and increased lateral ventricles^{3–5}. Based on the few studies examining baseline neuroanatomic predictors of schizophrenia outcome, the temporal lobe⁶, left prefrontal cortex⁷, and ventricle volumes⁸ have been found to be predictive of future symptomatic, functional, and diagnostic outcome,

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respectively. However, the literature is inconsistent with other studies reporting no relationships between baseline MRI and clinical outcome^{9–11}.

A helpful addition to studying resilience in schizophrenia was provided by the Remission in Schizophrenia Working Group which established a set of symptom severity-based remission criteria¹². These criteria consist of low to mild core symptom severity and encompass the three validated dimensions of schizophrenia (negative symptoms, disorganization, and psychoticism)¹². Mild symptom severity criteria lasting at least six months were used because of previous failed efforts defining chronic illness remission as absence of symptoms, and remission in other psychiatric disorders such as anxiety disorders has been defined by mild, minimally impairing symptoms¹². Reliable and valid symptom ratings scales (e.g., SAPS/SANS) were selected for the purposes of practicality and objectivity, and scale items which map onto both the above 3 dimensions and the DSM-IV schizophrenia diagnostic criteria were selected. Subsequent publications have supported the clinical validity of the work group's taxonomy¹³ and have reported that remission status is predicted by negative symptoms, duration of untreated symptoms, early response to medication, marital status, education^{14, 15}, baseline social functioning¹⁶, and baseline severity¹⁷.

While empirical investigations have addressed social and symptom predictors, there have been no investigations of cortical predictors of remission. Cortical grey matter is thinner in COS samples relative to healthy controls³, and grey matter thickness has been shown to be associated with intelligence¹⁸ and overall functioning in healthy siblings of patients with COS (e.g., cortical thickness was positively related to GAS scores in bilateral frontal and temporal cortices)¹⁹. In this study, we examined admission total and regional cortical thickness in relation to discharge remission status for a group of 56 inpatients with COS.

We hypothesized that COS participants who remit would have greater baseline/admission overall, frontal, temporal, and parietal cortical thickness. Frontal and temporal regions were chosen based on their documented abnormality in schizophrenia, and parietal gray matter was hypothesized to be thicker in subjects with COS who remit as this region has been shown to normalize in COS during adolescence (i.e., parietal cortical thickness abnormalities diminish during adolescence)³. Our hypotheses involve groups classified according to the Working Group remission criteria without the six month duration criterion, as our participants are not typically hospitalized for six or more months.

Method

Participants

Since 1991, we have prescreened material from over 2000 referred cases and conducted over 300 in-person screenings. Ninety-four of these individuals met DSM-IV criteria for schizophrenia with onset of psychosis before their 13th birthday. Further details of patient recruitment and selection are described elsewhere^{20,21}. Fifty-six participants (32 males) had an admission MRI scan suitable for cortical thickness estimation (i.e., no excessive motion artifacts) and had clinical ratings reasonably close to their discharge date (mean difference between discharge date and date of rating was seven days (SD=11 days)). Exclusion criteria were a history of significant medical problems, substance abuse, or an IQ below 70 prior to the onset of psychosis. Most of the participants included in the current study were also used in previous imaging studies^{2,3,4}.

Although our sample is followed longitudinally at two year intervals, the variability in follow-up treatment and environmental support received by participants makes it difficult to determine follow-up remission status in a homogeneous manner. We thus limited the current investigation to NIH discharge remission status, which precludes our ability to determine

stability of remission over time but permits us some control over environment/therapeutic milieu, compliance, and quality of care when determining remission status.

Treatment—The duration of hospitalization lasted a mean of 17.9 weeks (SD= 5.7 weeks); for 44 (78.6%) of the 56 participants included in this paper, this entailed a trial of clozapine. Treatment consisted of medication adjustment, milieu treatment, regular family meetings, occupational and recreational therapy, and a two week drug free period in the first month of hospitalization. Weekly physician ratings, nurses notes, occupational and recreation therapy notes, and teacher notes were obtained during hospitalization. Most participants were admitted to one of three double blind medication studies: clozapine vs. haloperidol²⁰, clozapine vs. olanzapine²² and aripiprazole v risperidone (Rapoport et al., unpublished data), and after the blind was broken, medications were adjusted, augmented, or changed on an individualized basis. Children were discharged when they were considered optimally stabilized. In addition to antipsychotic medications (see Table 1), children were also discharged on anticonvulsants (valproic acid(n=1), gabapentin(n=3), divalproex(n=3), levetiracetam(n=1)), benzodiazepines (clonazepam(n=2), lorazepam(n=1)), SSRIs (sertraline(n=9), escitalopram(n=1), citalopram(n=1), and stimulants (methylphenidate(n=3) dextroamphetamine (n=2)). Discharged medication differed from admission medication by dose and/or medication for all participants.

Materials/Assessments

We used age-appropriate versions of the Wechsler intelligence scales, including the WISC-R²³, WISC-III²⁴, WAIS-R²⁵, WAIS-III²⁶ and the WASI²⁷ to measure intelligence, the Hollingshead scale²⁸ to measure socio-economic status (SES) (higher scores reflect lower SES), the Autism Screening Questionnaire (ASQ)²⁹ to measure developmental delay, and the Children's Global Assessment of Functioning score (GAS)³⁰ to measure overall functioning.

Remission Criteria—The Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS), which assess positive and negative symptoms respectively, were the ratings scales used in determining remission. They consist of 34 (SAPS) and 25 (SANS) items, and ratings are made on a likert scale ranging from 0 (absence of symptom) to 5 (severe)^{31,32}. Ratings were made by staff psychiatrists, and inter-rater reliability was required of all raters (ICC > 0.70). SAPS and SANS ratings closest to a participant's discharge date from the NIH inpatient child psychiatric unit were used. In accordance with criteria set forth by the Remission in Schizophrenia Working Group (2005), we classified a child as remitted given mild severity (ratings = 2) on SAPS item numbers 7 (global rating of hallucinations), 24 (repetitive or stereotyped behavior), 25 (global rating of bizarre behavior), and 34 (global rating of formal thought disorder), and SANS items 7 (lack of vocal inflections), 13(global rating of alogia), 17 (global rating of avolition-apathy), and 22 (global rating of anhedonia-asociality). Because the six-month duration criterion set forth by the Remission in Schizophrenia Working Group cannot be established for most of our participants, we can only assert non-sustained remission. For the purposes of simplicity, we will refer to this non-sustained remission as "remission" with the understanding that we can not determine sustained remission as our participants are not typically hospitalized for six or more months.

The research protocol was approved by the NIH institutional review board. Written informed consent was obtained from parents and patients over 18; written informed assent was obtained from minors.

MRI Acquisition and Image Analysis

Participants were typically scanned within two weeks following inpatient admission. T1-weighted images with contiguous 1.5-mm slices in the axial plane and 2.0-mm slices in the coronal plane were obtained with 3D spoiled gradient recalled echo in the steady state on a 1.5-T General Electric Signa scanner (Milwaukee, WI). Imaging parameters were echo time of 5 ms, repetition time of 24 ms, flip angle of 45°, number of excitations equals 1, and 24 cm field of view. The images were collected in a 192×256 acquisition matrix and were 0-filled in *k* space to yield an image of 256×256 pixels, resulting in an our effective voxel resolution of $0.9375 \times 0.9375 \times 1.5$ cc. Head placement was standardized as previously described³³. MRI scans were registered into standardized space using a linear transformation and corrected for non-uniformity artifacts³⁴. Registered and corrected volumes were segmented with an advanced neural net classifier³⁵ and gray and white matter surfaces were fitted with a surface deformation algorithm^{36,37}. This algorithm first determines the white matter surface, then expands outward to find the gray matter-CSF intersection. As a result, gray and white matter surfaces with over 80,000 polygons each are fit and non-linearly aligned³⁸ so each vertex of the white matter surface corresponds to a gray matter surface counterpart, thereby generating linked polygons on the gray and white matter surfaces. Cortical thickness can be defined as the distance between linked vertices of the gray and white matter boundaries. We used a 30mm surface based blurring kernel, as it has been found to maximize statistical power while minimizing false positives³⁹, and cortical thickness was calculated in native space at 40,962 cortical points.

This cortical thickness extraction method has been validated using a phantom brain⁴⁰, population simulation³⁹, and through manual measurement using this 1.5T image acquisition and resolution in both child and adult populations^{41,42}. It has also been able to capture the established pattern of cortical degeneration within the medial temporal lobes in Alzheimer's disease⁴³. However, cortical thickness measurement for four regions (left and right insula, right cuneus, and right parahippocampus) did not meet validity criteria⁴¹ and thus are not addressed in this study.

Statistical Analysis

Demographics—We tested demographic differences between groups using *t* tests or Mann Whitney U tests (if the normality assumption was violated) for continuous variables, chi-square tests of independence for categorical variables, and exact tests for categorical variables if there was an expected cell count less than five.

Cross-cortex group comparisons—We performed a linear model at each of the 40,962 cortical points with gray matter thickness as the dependent measure and group membership (remitted v not-remitted) as the independent variable. We then projected *t* statistics onto corresponding cortical points on a template brain to visualize group differences. To account for increased risk of type I errors, we set a *t* threshold of 2.65 (corresponding to a *p* value of 0.01 given our degrees of freedom) as the lower limit for significance at each cortical point. We calculated mean cortical thickness by averaging values across all cortical points for each scan/participant.

Regional analyses—For each gyri (defined using a probabilistic atlas)^{38,44} with significant group differences (based on results from the cross-cortex group comparison), we selected *only* the statistically significant cortical points (*p* < .01). We then averaged these points within a gyri per scan/participant to represent summary values. We conducted *t* tests on these averaged values, and calculated Cohen's *d*s (mean1 - mean2 divided by the pooled standard deviation) to summarize significant group effects within each gyrus. Additionally, we conducted analyses of covariance which controlled for mean cortical thickness to

determined if group differences on averaged thickness values would survive. Effect sizes for adjusted means were also calculated (adjusted mean1 –adjusted mean2 divided by the square root of the model mean square error). Finally, we conducted receiver operating characteristics (ROC) analyses and single predictor logistic regression analyses with remission status as the dependent variable and summary thickness values as the independent variables to examine the accuracy with which remission status can be determined based on admission cortical thickness. Data were screened for outliers and statistical assumptions were checked for demographic and regional thickness analyses. We set alpha at 0.01 for the cross-cortex group comparisons, and for all other tests, we used an alpha of 0.05. All statistical tests were 2-tailed. Statistical analyses were conducted using R, SPSS version 12.0 and SAS version 9.0.

Results

Sample Demographics

Twenty nine percent (n=16) of our sample met modified criteria for remission upon discharge. The two groups (participants who remitted vs. those who did not) were statistically comparable relative to age at scan, age at psychosis onset, years ill at scan, ASQ score, socio-economic status, sex, Full Scale IQ, admission GAS score, number of days between scan and discharge ratings, total cerebral volume, total grey matter, and average cortical thickness. As such, we did not include these variables as covariates in our primary analysis. There were no significant relationships between remission status at discharge and either admission or discharge antipsychotic medication. As expected, the discharge GAS scores were significantly higher in the group who remitted (see Table 1).

Group Cortical Thickness Differences

There was a trend for greater mean cortical thickness in the group of COS who remitted ($p=.08$) (see Table 1). Figure 1 shows that at the t cutoff of 2.65, the group of COS who remitted had several fairly circumscribed areas of significantly thicker cortex in frontal, temporal and parietal lobes. Specifically, significant differences were evident in the superior and middle left temporal gyri, the left orbital frontal gyrus, and bilateral angular and postcentral gyri. There were no points where the group of COS who remitted had significantly thinner cortex. Differences in the insula and inferior regions have not yet been validated and are not addressed here.

Regional Differences

The number of cortical points that went into each average thickness measure ranged from 34 (right post central) to 158 (superior temporal). Table 2 contains the means, standard deviations, t and p values, and effect sizes for the significant points averaged within each gyri (i.e., for all scans, all significant points within a given gyrus were isolated and averaged to quantify significant group differences within a gyrus). Effect sizes fell in the large range (> 0.80). After covarying for mean cortical thickness, all group differences remained significant and effect sizes fell in the medium-large and large ranges.

Logistic Regression and ROC analyses

The seven single variable predictor logistic regression results indicated positive relationships between summary thickness values and remission status (all p values $< .01$), with larger thickness values significantly associated with greater likelihood of remission. Sensitivity levels were poor (18.8% to 37.5%) but specificity levels were all 90% and above, as most cases were classified into the largest group (not remitted). ROC analysis results indicated

poor to fair categorization accuracy (area under the curve falling between .70 and .75 with .50 equivalent to chance) (see Table 3).

Discussion

This is the first study to examine the relationship between cortical thickness at baseline (or any MRI measure) and subsequent remission status based on modified criteria proposed by Andreasen and colleagues (2005). Our results are consistent with prior reports of frontal and temporal volumes as predictors of AOS outcome (i.e., Milev et al., 2003) and provide greater regional resolution. Additionally, the current results coincide with prior GM abnormalities reported in COS relative to controls^{45, 2, 4} and spatially overlap with locations where the COS group as a whole had thinner cortex relative to controls³. Our findings indicate that participants with COS who remitted approximately three months (on average) after admission scan had defined areas of significantly thicker gray matter in left orbital-frontal, superior and middle temporal gyri, and bilateral angular and post-central parietal gyri. These results are associated with large effect sizes but are limited in terms of clinical predictive value (sensitivity under 40%, with prediction accuracy not much better than chance) as demonstrated by ROC and logistic regression results. Demographic variables such as age, IQ, sex, socio-economic status, and age of onset, and clinical variables such as admission functioning and scores on a measure of developmental delays (the ASQ) did not significantly differ between the groups.

Our results implicating frontal, temporal, and parietal involvement in remission are consistent with the schizophrenia imaging literature. Specifically, the left superior temporal gyrus is consistently found to be abnormal in schizophrenia⁴⁶ and has been identified as having a role in auditory hallucinations⁴⁷. Also, orbitofrontal abnormalities have been implicated in negative symptoms^{48–50}. Bilateral frontal and temporal cortical thickness have also been found to positively relate to overall functioning in a sample of non-psychotic siblings of COS probands¹⁹. Thus, there appears to be accumulating evidence to suggest that pre-frontal and temporal cortices have an important role in illness, outcome and possibly functioning in general.

Relative to evidence supporting frontal and temporal involvement in schizophrenia, there is a dearth of information regarding parietal involvement⁴⁶. However, results from a recently published COS study indicate that during adolescence superior parietal abnormalities normalize³. It is therefore possible that this normalization and/or treatment response may be linked by a common underlying mechanism. While the group of COS who remitted and the group of COS who did not remit did not significantly differ on mean cortical thickness, there was a statistical trend for increased overall gray matter thickness in the group who remitted. Total gray matter volume differences did not approach trend level significance, however. Because total gray matter volume is a function of thickness and surface area, this suggests that cortical surface area may be of interest to future studies of remission in relation to clinical follow-up status.

A major limitation to the current study is the individual variability in medication status, rendering medication effects on remission and cortical thickness too complicated to piece apart. However, because all of the participants were discharged on a tailored medication regimen, we speculate that this optimized medication combined with lengthy inpatient treatment contributed to our 29% remission rate. We also believe that that this remission rate overestimates good outcome frequency, and when participants are functioning with less support and increased demands, remission rates decline. Other limitations to this study include increased type I and type II error risks, and the less than six-month/non-sustained remission. Regarding the former, we were only powered to detect large effects, and thus

have an increased type II error risk when assessing statistical significance for small and medium effect sizes associated with both cortical thickness and demographic variables. While our alpha level of 0.01 was liberal, a more conservative approach would have further reduced already relatively low power (for medium and small effect) and possibly eliminated our ability to detect large effects. Given the exploratory nature of the study, we thus decided to favor type I error risk over type II error risk when thresholding significance for cortical thickness analyses. Regarding remission duration criterion proposed by Andreasen and colleagues, the six-month time frame could not be established for our participants, as we do not typically hospitalize our participants for six or more months. As such, we technically do not meet criteria for the remission definition. However, this is not unprecedented, as a recent schizophrenia outcome study was also not able to meet the six month Working Group criterion but still found the amended remission definition useful in understanding outcome predictors⁵¹.

Circumscribed areas of gray matter in frontal, temporal, and parietal regions were significantly thicker for participants with COS who went on to remit approximately three months later (on average). Our results provide neuroanatomic correlates of the remission criteria set forth by Andreasen and colleagues and evidence for the localization of brain regions involved in resilience and/or treatment efficacy in schizophrenia. More attention is warranted to understand the relevance of gray matter correlates of clinical remission in COS.

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Figure 1. Areas where participants who remitted at discharge ($n=16$) had significantly thicker cortex than non-remitters ($n=40$) at admission scan

Table 1

Descriptive statistics for remitted and non-remitted participants with childhood-onset schizophrenia

	Remitted (n=16)	Not Remitted (n=40)		
	Mean(SD)	Mean(SD)	t(df) or Mann-Whitney U z score	p
Age at Psychosis Onset	9.78(1.60)	10.32(2.09)	z=1.53	0.12
Years Ill at Scan	3.83(2.28)	3.80(2.01)	t=.05(52)	0.96
Age at Scan	13.61(2.06)	14.17(2.50)	t=0.79(54)	0.43
ASQ ⁺ Score	6.13(9.09)	8.85(8.02)	z=1.38	0.17
Socio Economic Status	2.44(1.26)	2.80(0.99)	z=1.02	0.31
Full Scale IQ	74.93(17.66)	66.67(14.34)	z=1.28	0.20
GAS ⁺⁺ at Admission	32.44(8.48)	30.60(10.66)	t=0.61(54)	0.54
GAS at Discharge	51(9.82)	42(7.57)	3.72(53)	0.0005
Days from Scan to Discharge Rating	99.19 (23.88)	98.53 (42.66)	t=.074(48) [*]	0.94
Total Cerebral Volume (GM + WM + Lat. ventricles)	1158.70(156.06)	1116.02(118.69)	t=1.11(54)	0.27
Gray Matter	700.04(86.53)	667.88(75.82)	t=1.38(54)	0.17
Mean Cortical Thickness	3.92(0.42)	3.73(0.34)	t=1.79(54)	0.08
	Count	Count	Chi-Square(df)	p
Sex F:M	7:9	17:23	.007(df=1)	0.93
Admission Antipsychotic Meds ^{**}				
One atypical	6	14	na	exact p= 0.15
Two atypicals	0	9		
Typical	6	11		
Both typical and atypical	4	4		
No medications	0	2		
Discharge Antipsychotic Medication				
clozapine	11	31	na	exact p =0.24
clozapine + haloperidol	0	2		
olanzapine	4	4		
olanzapine + chlorpromazine	1	0		
Other Atypical(quetiapine or risperidone)	0	2		

^{*} t for equal variances not assumed⁺ Autism Screening Questionnaire⁺⁺ Children's Global Assessment of Functioning Scale

^{**} Atypicals included clozapine(8), olanzapine(11), aripiprazole(4), ziprasidone (1), quetiapine (11), risperidone (11); typicals included haloperidol (8), thiothixine (3), thioridazine(1), chlorpromazine(4), perphenazine(1), flufenazine(2), pimozide(1), molindone (1), loxapine (1), trifluoperazine(2)

Table 2

Group differences: Adjusted and unadjusted statistics for significant points averaged within each gyri

	Unadjusted Model					Adjusted Model- Covariate= Mean Cortical Thickness						
	Remitted (n=16)		Not Remitted (n=40)		p	Effect Size	Remitted (n=16)		Not Remitted (n=40)		p	Effect Size
	Mean(SD)		Mean(SD)				t(df=54)	Adjusted Mean(SE)	Adjusted Mean(SE)	F(df=1,53)		
Left Frontal Orbital Gyrus	4.07(0.51)		3.70(0.41)		2.89	0.005	0.85	3.94 (0.06)	3.75(0.04)	5.94	0.02	0.74
Left Superior Temporal Gyrus	4.16(0.46)		3.79(0.39)		3.08	0.003	0.91	4.03(0.05)	3.84(0.03)	8.42	0.005	0.88
Left Middle Temporal Gyrus	4.41(0.50)		4.00(0.42)		3.07	0.003	0.91	4.26(0.05)	4.06(0.03)	9.35	0.003	0.93
Left Angular Gyrus	3.87(0.41)		3.51(0.38)		3.13	0.003	0.93	3.75(0.05)	3.56(0.03)	8.75	0.005	0.90
Left Post Central Gyrus	3.46(0.40)		3.13(0.35)		3.10	0.003	0.92	3.37(0.07)	3.17(0.04)	6.19	0.02	0.76
Right Angular Gyrus	4.12(0.51)		3.71(0.47)		2.90	0.005	0.86	3.96(0.06)	3.77(0.04)	7.72	0.01	0.85
Right Post Central Gyrus	3.56(0.38)		3.23 (0.35)		3.13	0.003	0.93	3.45(0.054)	3.27(0.03)	7.65	0.008	0.85

Table 3

Results from single variable logistic regression analyses and single variable receiver operating characteristics (ROC) analyses classifying participants with childhood-onset schizophrenia who remitted after an inpatient hospitalization

Significant points averaged within each gyri	Coefficient (SE)	Wald Chi-Square (df=1)	p	Odds Ratio*	Sensitivity (remitted correctly classified)	Specificity (not-remitted correctly classified)	Percent Correctly Classified Total (n=56)	ROC Analyses-Area Under the Curve Total (n=56)
Left Orbital Frontal Gyrus	1.90(0.79)	5.70	0.017	6.66	18.8%	95.0%	73.2%	0.70
Left Superior Temporal Gyrus	2.23(0.86)	6.72	0.01	9.34	25.0%	92.5%	73.2%	0.72
Left Middle Temporal Gyrus	2.07(0.77)	7.15	0.007	7.92	37.5%	95.0%	78.6%	0.71
Left Angular Gyrus	2.20(0.82)	7.18	0.007	9.05	31.3%	92.5%	75.0%	0.75
Left Post Central Gyrus	2.29(0.86)	7.04	0.008	9.87	31.5%	90.0%	75.0%	0.74
Right Angular Gyrus	1.76(0.70)	6.35	0.012	5.83	18.8%	95.0%	73.2%	0.73
Right Post Central Gyrus	2.51(0.94)	7.06	0.008	12.28	25.0%	92.5%	73.2%	0.74

* Predicted change in odds of remitting for a unit increase in the predictor