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Structural MRI measures associated with psychosis onset in individuals at Clinical High Risk for Developing Psychosis: An ENIGMA Working Group mega-analysis

Short Title: Cortical Thickness in CHR

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Key Points

Question: How do brain morphometric features relate to later psychosis conversion in individuals at clinical high-risk for developing psychosis (CHR)?

Findings: In the largest coordinated international analysis to date, lower cortical thickness, but not cortical surface area or subcortical volume, was more pronounced in CHR, in a manner highly consistent with thinner cortex in established psychosis. Regions that displayed lower cortical thickness in future psychosis converters additionally displayed abnormal associations with age.

Meaning: CHR status and later transition to psychosis is robustly associated with lower cortical thickness. Abnormal age associations and specificity to cortical thickness may point to aberrant postnatal brain development in CHR, including pruning and myelination.

Abstract

Importance: The ENIGMA clinical high-risk for psychosis (CHR) initiative, the largest pooled CHR-neuroimaging sample to date, aims to discover robust neurobiological markers of psychosis risk.

Objective: We investigated baseline (i.e., when participants were initially ascertained) structural neuroimaging differences between CHR subjects and healthy controls (HC), and between CHR participants who later developed a psychotic disorder (CHR-PS+) and those who did *not* (CHR-PS-). We assessed associations with age by group and conversion status, and similarities between the patterns of effect size maps for psychosis conversion and those found in other large-scale psychosis studies.

Design, Setting, and Participants. Baseline T1-weighted MRI data were pooled from 31 international sites participating in the ENIGMA CHR Working Group. MRI scans were processed using harmonized protocols and analyzed within a mega- and meta-analysis framework from January-October 2020.

Main Outcome(s) and Measure(s): Measures of regional cortical thickness (CT), surface area (SA), and subcortical volumes were extracted from T1-weighted MRI scans. Independent variables were group (CHR, HC) and conversion status (CHR-PS+, CHR-PS-, HC).

Results: The final dataset consisted of 3,169 participants (CHR=1,792, HC=1,377, age range: 9.5 to 39.8 years, 45% female). Using longitudinal clinical information, we identified CHR-PS+ (N=253) and CHR-PS- (N=1,234). CHR compared to HC exhibited widespread lower CT measures (average *d*=-0.13, range: -0.09 to -0.17), but not SA or subcortical volume. Lower cortical thickness measures in the fusiform, superior temporal, and paracentral regions were associated with psychosis conversion (average *d*=-0.22, average confidence interval: -0.35-0.0). Age showed a stronger negative association with left fusiform CT measures (F=9.8, *p*=4.9e-05, *q*=5.9e-04) and left paracentral CT measures (F=5.9, *p*=4.9e-03, *q*=0.02) in HC, compared to CHR-PS+. CT measures of psychosis conversion effect sizes resembled patterns of CT differences observed in ENIGMA studies of schizophrenia (ρ=0.35, confidence interval=.12-.55, $p_{permute}$=0.004) and individuals with 22q11.2 Microdeletion and a psychotic disorder diagnosis (ρ=0.43, confidence interval=.20-.61 $p_{permute}$=0.001).

Conclusions and Relevance: We provide evidence for widespread subtle, lower CT measures in CHR. The pattern of CT measure differences in CHR-PS+ was similar to those reported in other large-scale investigations of psychosis. Additionally, a subset of these regions displayed abnormal age associations. Widespread disruptions in CT coupled with abnormal age associations in CHR may point to disruptions in postnatal brain developmental processes.

1. INTRODUCTION

The clinical high-risk paradigm is a widely used framework to investigate mechanisms underlying psychosis vulnerability. Help-seeking individuals who do not meet diagnostic criteria for a psychotic disorder, but typically present with subthreshold psychotic symptoms and accumulating risk factors, are considered at clinical high-risk (CHR) for developing psychosis[1]. An estimated 18-20% of CHR individuals develop a psychotic disorder within 2 years of identification[2], although conversion rates vary, likely due to heterogeneous recruitment and sampling strategies, and interventions applied[3]. However, despite decades of research, the nature of morphometrical differences associated with psychosis conversion remains largely unknown. Here, we aim to address this question by combining all available structural neuroimaging data in CHR to date, in an attempt to better understand group differences associated with psychosis risk and conversion in this population.

A large body of work has used structural magnetic resonance imaging (sMRI) to investigate morphometric brain differences in CHR individuals[4–20]. However, the extent to which characteristic baseline (i.e., when participants are initially ascertained and assessed at a first study visit) structural neuroimaging differences exist between those at CHR who later develop a psychotic disorder (CHR-PS+) compared to those who do *not* (CHR-PS-) is debated. Many studies failed to find baseline differences between CHR-PS+ and CHR-PS-[4,14,21,22], though a meta-analysis and multi-center study found lower prefrontal and temporal volumes or cortical thickness measured by MRI (which we will refer to as CT) in CHR-PS+[16,23]. High attrition rates in CHR samples[24], coupled with low psychosis conversion rates[2,25], often yield insufficient power to detect between-group structural brain differences. Moreover, small sample sizes can be associated with inflated effect sizes[26], so effect sizes of prior studies that found structural brain differences in CHR may be overestimated. Although multi-site consortia aim to address these challenges, the largest published sMRI studies to date included fewer than 50 CHR-PS+[21,23]. Furthermore, it is currently unknown whether group differences are robust enough to predict outcomes.

Importantly, many CHR participants are adolescents or young adults, a time frame associated with psychosis onset[27,28]. Prefrontal-temporal brain regions, which are typically implicated in psychosis, show protracted developmental courses continuing through adolescence[29,30], suggesting that morphometric differences associated with psychosis risk vary with age. Indeed, there are developmental influences on psychotic symptom presentation[31], perhaps driven by differences in regional brain changes. It is not fully understood how age-related patterns in brain morphometry in CHR differ from normal development. Thus, using a developmental framework to examine whether morphometric differences in CHR are influenced by age may provide important insights into mechanisms associated with psychosis risk, and the stability of neuroimaging measures associated with psychosis risk across development.

Finally, it is unknown whether baseline brain differences associated with future conversion to psychosis resemble those observed in other large-scale psychosis studies. Understanding whether morphometric differences in CHR overlap with those observed in individuals who have schizophrenia[32,33] and individuals with a genetic subtype of psychosis[34,35] will provide insights into convergent or distinct differences across the psychosis spectrum.

To address these questions, we founded the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Clinical High Risk for Psychosis Working Group in 2018. Using baseline sMRI data and longitudinal clinical information from 31 sites, this study addressed the following questions:

1. Do CHR and healthy control (HC) participants differ in CT, surface area (SA), and/or subcortical volumes?
2. Is there a neuroanatomic signature associated with future transition to a psychotic disorder (CHR-PS+ versus CHR-PS- versus HC)?
3. Do structural neuroimaging measures identified in Aims 1 and 2 display group differences in age associations, suggestive of abnormal developmental trajectories?
4. Is the pattern of morphometric alteration associated with psychosis conversion similar to that observed in ENIGMA studies of psychosis?

2. METHODS

Participants

We included 1,792 CHR and 1,377 HC from 31 sites participating in the ENIGMA CHR Working Group (Table 1). CHR data consisted of CHR-PS+ (N=253), CHR-PS- (N=1,234), and CHR individuals without follow-up data (CHR-UNK, N=305). CHR participants met CAARMS (N=821) or SIPS (N=971) CHR criteria (see details in Supplement). Site-specific inclusion/exclusion criteria are detailed in **eTable 1**. All sites obtained Institutional Review Board approval prior to data collection. Informed written consent was obtained from every participant or the participant's guardian (for participants <18 years). All studies were conducted in accordance with the Declaration of Helsinki[36].

Image Acquisition and Processing

Thirty-one sites contributed T1-weighted MRI brain scans from 50 MRI scanners: forty-two 3T scanners, and 8 1.5 Tesla scanners (**eTable 2**). Scanners were manufactured by Siemens (N=23), Phillips (N=8), GE (N=18), and Toshiba (N=1). A breakdown of the number of HCs, CHR-PS+, and CHR-PS- for each scanner is reported in **eTable 3**. After processing the data using Freesurfer analysis software[37–39], we extracted 68 CT, 68 SA, and 16 subcortical volume measures. We also examined 3 global neuroimaging measures: total intracranial volume, mean CT, and total SA, resulting in 155 neuroimaging measures. We implemented the ENIGMA consortium quality assessment pipeline[32–35,40,41]. *A priori* power calculations are included in the **Supplement**.

Statistical Analyses

Group and conversion-related differences in structural neuroimaging metrics

We assessed group differences using general linear models (GLMs) within a mega-analysis framework, with each sMRI measure (i.e., CT, SA or subcortical volume) as the dependent variable and group (HC/CHR) or conversion status (CHR-PS+/CHR-PS-/HC) as the independent variable. We included age, age^2, sex, and estimated total intracranial volume (ICV) as covariates in all models, and corrected for multiple comparisons (N=155) using the False Discovery Rate (FDR[42]) method. q-values<0.05 were considered statistically significant.

For all structural neuroimaging measures, we calculated Cohen's *d* effect sizes from the GLMs between two (CHR vs. HC) or three groups of interest (CHR-PS+ vs. HC; CHR-PS+ vs. CHR-PS-; CHR-PS- vs. HC). Based on recent work demonstrating that neuroCombat harmonization increases statistical power within a mega-analytic framework[43], primary analyses were conducted within a mega-analysis framework using data that were corrected for site/scanner effects using neuroCombat harmonization. Additional analyses were conducted to assess the robustness of results obtained using this approach (details and results reported in **Supplement**).

For all neuroimaging measures, we investigated sMRI differences associated with the specific psychosis-risk syndromes (e.g., Attenuated Positive Symptom Syndrome; details in **Supplement**).

To evaluate the stability of group and conversion status differences, we performed analyses statistically controlling for baseline psychotropic medication exposure. To assess site effects, we conducted jackknife resampling analyses, i.e., iteratively removing one site's data and re-running respective analyses[44]. sMRI measures that failed to show a group or conversion status effect at q<0.05 in >10% of jackknife iterations (i.e., 4/31 sites) were considered "unstable".

To assess the meaningfulness of obtained effect sizes we used two analytic approaches: equivalence testing (to assess whether observed differences fell within the upper and lower bounds of a predefined smallest effect size of interest, providing support for the *absence* of a meaningful effect) and minimal-effects testing (to assess whether observed effects *were greater* than the same pre-defined effect size[45]). Upper/lower bounds (representing the positive/negative predefined smallest effect size of interest) were set to d = +/- 0.15 (further details and effect size rationale in **Supplement**).

Group and conversion-related differences in sMRI age-associations

We used general additive models (GAM)[46,47] to model group and conversion status differences in the relationship between age and sMRI measures (further details in **Supplement**). First, we examined the effect of group (HC vs. CHR) as a function of age in the 56 neuroimaging measures that differed at q<.05 between HC and CHR. Next, we conducted GAM analyses on the four sMRI measures on which CHR-PS+, CHR-PS-, and HC differed from each other (i.e., left paracentral CT, right paracentral CT, left fusiform CT, right superior temporal CT) in analyses of psychosis conversion. We examined the effect of baseline age, group/conversion status, and the interaction between the two variables. Sex and estimated ICV were included as covariates. Similar to previous work examining age effects during adolescent development[48,49], we restricted our sample's age range to 12-25 years (**eTable 4**). Details on post-hoc analyses for significant interaction effects are provided in the **Supplement**.

Comparison of psychosis conversion-related effects to other ENIGMA findings

We computed Spearman's rank correlations to assess the extent to which the pattern of observed effect sizes (Cohen's *d's* for CHR-PS+ vs. HC and CHR-PS-) correlated with the pattern found in prior psychosis studies, specifically the ENIGMA Schizophrenia (SZ vs. HC[32,33]) and ENIGMA 22q11.2 Deletion Syndrome (22q11DS with psychosis vs. 22q11DS without psychosis[34,35]) Working Groups. As a control, we compared CHR-PS+/CHR-PS- vs. HC effect sizes to MDD vs. HC[40,41] effect sizes published by the Major Depressive Disorder Working Group (details in **Supplement**) .

3. RESULTS

Sample Characteristics

Site demographics are reported in **Table 1**. Intelligence quotient (IQ) comparisons between HC and CHR are reported in **eTable 5**. Within each site, baseline IQ measures were largely similar in CHR-PS+, CHR-PS-, and CHR participants without follow-up information (**eTable 6**). For symptom measures, CHR participants without follow-up data had less severe baseline positive, negative, and disorganized symptoms on the SIPs, in comparison to CHR-PS+ and CHR-PS- (**eTable 7**). In comparison to CHR-PS+ and CHR-PS-, CHR participants without follow-up data had less severe cognitive changes on the CAARMS (**eTable 7**). Few CHR participants reported typical (<1%) and/or atypical antipsychotic (12.4%) medication use (**eTable 8**).

Widespread lower CT in CHR versus HC

In neuroCombat-harmonized GLM mega-analyses, CHR participants compared to HC had smaller global neuroimaging measures: estimated ICV (*d*=-0.13, CI=-0.2 to -0.06), mean CT (*d*=-0.18, CI=-0.25 to -0.11) and total SA (*d*=-0.15, CI=-0.22 to -0.08). We also observed significant group effects in fifty-three additional GLMs (q<0.05, **eTable 9**). The largest group effects were observed for widespread lower CT in CHR vs. HC (42/68 comparisons, *d* range=-0.09 to -0.17; **Figure 1A** for overview; **eTable 9** and **eFigure 1** for details). Few subcortical (3/16) and SA (8/68) group differences were observed. No group-by-sex interactions were detected (all q>0.05).

We present results of possible confound analyses, including ICV, medication and site effects, equivalence testing, and effects of neuroCombat harmonization in the **Supplement**, **eTables 10-13**, and **eFigures 1-2.** No sMRI measures were uniquely sensitive to psychosis-risk syndrome (see **Supplement** and **eTables 14-17** for results).

Thinner paracentral, fusiform, and superior temporal CT are associated with psychosis conversion

Forty-eight structural neuroimaging measures exhibited a significant overall effect of psychosis conversion status in GLM mega-analyses using neuroCombat harmonized data (q<0.05, **Figure 1B**; **eFigure 3** and **eTable 18**). Most significant differences were observed for CT measures (N=37). Within these 48 regions, we conducted pairwise GLMs between HC vs. CHR-PS+, HC vs. CHR-PS- and CHR-PS+ vs. CHR-PS-. Out of these 48 regions, CHR-PS+ differed from CHR-PS- and HC on four neuroimaging measures.

In comparison to HC and CHR-PS-, CHR-PS+ exhibited lower CT in bilateral paracentral, right superior temporal, and left fusiform regions (**Figure 2**, average *d* of four sMRI measures=-0.22). CHR-PS+ and CHR-PS- (vs. HC) exhibited thinner cortex in the left superior temporal and right fusiform regions; similar trends were observed for CHR-PS+ vs. CHR-PS- differences (p<0.08; Figure 1C). Using minimal-effects testing, we observed that effect sizes for bilateral paracentral (L Z=-2.43, p=0.02; R Z=-1.86 p=0.06), right superior temporal (Z=-2.29, p=0.02) and left fusiform (Z=-2.00, p=0.05) in CHR-PS+ vs. HC were all significantly *greater* than 0.15, at least at trend level, underscoring the presence of notable group differences.

In all remaining comparisons of regions that exhibited a statistically significant effect of psychosis conversion status, CHR-PS+ and CHR-PS- differed from HC at p<.05. However, CHR-PS+ did not differ from CHR-PS- in any remaining comparisons (**eTable 18**). We observed no conversion status-by-sex interactions (all q>0.05) and results remained stable when length of follow-up period was included as a covariate.

We present results of confound analyses (medication, site effects, equivalence testing) in the **Supplement**, **eFigure 2**, and **eTables 19-21**. There were no statistically significant psychosis-risk syndrome-by-conversion status interactions (**eTable 22**).

Altered age-associations in CHR-PS+ and CHR-PS- compared to HC

In GAM analyses, we observed no statistically group-by-age interactions for the 56 neuroimaging measures that differed between CHR and HC (q>0.05, **eTable 23).** We then conducted GAM analyses on the four sMRI measures on which CHR-PS+ displayed lower CT compared to HC and CHR-PS- in psychosis conversion group analyses. These sMRI measures were left paracentral CT, right paracentral CT, left fusiform CT, and right superior temporal CT. Two measures displayed a significant psychosis conversion status-by-age interaction. For each group-by-age interaction analysis, we assessed group differences in age-effects in these comparisons (i.e., HC vs. CHR-PS+, HC vs CHR-PS-, and CHR-PS+ vs. CHR-PS-).

In left fusiform, age-CT associations differed between CHR-PS+ vs. HC (F=9.8, p=4.9e-05, q=5.9e-04) and CHR-PS- vs. HC (F=8.7, p=1.5e-04, q=9.1e-04, Figure 2A, left), but not between CHR-PS+ and CHR-PS- (F=1.3, p=0.3, q=0.5). Between ages 12-16, HC showed a stronger negative association between age and CT, compared to CHR-PS+ and CHR-PS-. Although the interaction was not statistically significant, a similar pattern emerged for the right fusiform CT (**Figure 3A**, right, and **eTable 24**).

Age-effects in the left paracentral CT differed between CHR-PS+ vs. HC (F=5.9, p=4.9e-03, q=0.02, Figure 2B, left), but not between CHR-PS- and HC (F=0.2, p=0.7,q=0.7) or CHR-PS+ and CHR-PS- (F=1.9, p=0.2, q=0.5). Between 12-15.8 years of age, HC showed a stronger negative association between age and CT in comparison to CHR-PS+. Age-CT associations did not differ between CHR-PS- vs. HC (F=0.2, p=0.69). This pattern of results was not observed for the right paracentral CT (**Figure 3B**, right, and **eTable 24**).

We found no significant age-by-conversion status interactions for the superior temporal CT (**Figure 3C**, and **eTable 24**); all groups showed negative CT-age associations.

CT aberrations in CHR-PS+ resemble the pattern observed in SZ and 22q11DS with a psychotic disorder diagnosis, but not MDD

eFigure 4A provides a visual overview of CT differences in CHR-PS+ relative to SZ and individuals with 22q11DS and a psychotic disorder. The pattern of baseline CT differences in CHR-PS+ (CHR-PS+ vs. HC effect sizes) correlated significantly with that observed in SZ (ρ=0.35, $p_{permute}$=0.004, **eFigure 4B** top) and individuals with 22q11DS and psychosis (ρ=0.43, $p_{permute}$=0.001, **eFigure 4B** bottom). CT differences in CHR-PS+ did *not* correlate with those observed in MDD (CHR-PS+ ρ=-0.03) and slopes for CHR-PS+/SZ and CHR-PS+/MDD correlations significantly differed (Steiger's Z=2.06, $p_{permute}$=0.008). No significant correlations were observed for SA (SZ ρ=-0.03; 22q11DS ρ=-0.06, **eFigures 5-6**). Subcortical volume differences in CHR-PS+ correlated with those observed in SZ (ρ=0.54, *p*=0.03) and a similar non-significant trend was observed for 22q11DS and psychosis (ρ=0.46, *p*=0.07, **eFigures 5-6**). Associations for CHR-PS- (vs. HC) effect sizes were similar to those reported here (see **Supplement**).

4. DISCUSSION

We conducted the largest multisite neuroimaging investigation to date in CHR participants, examining baseline structural neuroimaging measures associated with later transition to psychosis. We found widespread lower CTin CHR, consistent with previously-reported CT differences in individuals with an established psychotic disorder. Compared to CHR-PS- and HC, at baseline, CHR-PS+ exhibited thinner cortex in bilateral paracentral, right fusiform and left superior temporal regions, with effect sizes significantly greater than what we considered to be meaningful *a priori*. Our results were robust to effects of medication exposure, sex, site, and length of follow-up period. Findings from this international effort suggest that conversion to psychosis amongst those at high risk is associated with lower CT at baseline.

We identified widespread regional lower CT in CHR compared to HC. Lower CT has been observed in SZ, as well as other psychiatric disorders[32,40,50]. Importantly, the overall pattern of lower CT in CHR-PS+ and CHR-PS- resembled that observed in SZ and individuals with 22q11DS and a psychotic disorder, but not in MDD. For CHR-PS+, correlations with SZ CT differences were significantly greater than the relationship observed with MDD CT differences. Taken together, our results suggest that the overall constellation of reported CT differences in CHR resembles the general pattern of CT differences observed in SZ and genetic disorders associated with psychosis, and thus argues that widespread thinner cortex in CHR may be associated with their increased risk of psychosis.

We also found that lower CT in paracentral, superior temporal and fusiform regions was associated with psychosis conversion; CHR-PS+ exhibited significantly lower CT than CHR-PS- and HC in these regions. Lower baseline CT and/or volume in these regions has previously been reported in CHR-PS+[17,18] (data not used here). Furthermore, longitudinal CT decreases in these regions have been associated with transition to psychosis in CHR[6,19,20]. The magnitude of altered CT in CHR-PS+ in paracentral, superior temporal and fusiform regions was highly consistent with findings in SZ[33,51,52] and lower fusiform and paracentral CT has been observed in voice hearers without a diagnosis of SZ[53]. Given that both help-seeking and non help-seeking individuals on the psychosis spectrum exhibit alterations in these regions, CT in paracentral, superior temporal and fusiform areas may display a dose-response association with psychosis risk. While this interpretation also aligns with our observation that CT in these regions differed between CHR-PS+, CHR-PS- and HC (with the lowest CT for CHR-PS+), this explanation remains speculative in light of the cross-sectional nature of the data.

Consistent with previous CHR studies examining baseline neuroimaging associations with later conversion to psychosis[17], we did not observe widespread subcortical volume or SA differences associated with later psychosis transition. Taken together, these results suggest that CT reductions may be among the most widespread, robust, and specific morphometric changes associated with psychosis risk and conversion, compared to SA or subcortical volume.

An intriguing pattern of findings emerged from the psychosis conversion-by-age analyses. In comparison to HC, CHR-PS+ and CHR-PS- exhibited significantly lower paracentral and fusiform regions CT from ~12-18 years of age. Our analyses investigating age-associated rates of change (estimated using cross-sectional data) seemed to indicate a steeper decline in slope for HC during this timeframe, which reached a plateau in adulthood. CHR-PS-, however, displayed a slower decline, and results in CHR-PS+ were indicative of a reduced or delayed rate of change. Relative to the normative timetable (in HC), these findings may suggest

an accelerated developmental decrease in paracentral and/or fusiform CT in CHR-PS- and CHR-PS-, with the greatest declines occurring in CHR-PS+. If indeed normative CT decreases during adolescence represent a period of specialization (where higher-level systems that contribute to adult outcomes are formed[54,55]), lower CT, most apparent in CHR-PS+, could reflect impairments in optimal specialization. However, these observations are speculative and the veracity of these patterns will be most accurately captured with longitudinal analyses that encompass a wide age range (e.g., early childhood through adulthood).

The neuroanatomic pattern of group differences and age-associated disruptions observed in CHR may provide important insights into mechanisms underlying increased risk for psychosis. Pre-clinical models[56,57] and recent genome-wide association studies[58] suggest that genetic variants associated with SA are linked to the regulation of neural progenitor cells during fetal development, while genetic markers associated with CT were associated with regulatory processes in adulthood. Thus, CT differences may be the end result of maladaptive maturation-related mechanisms that occur during post-fetal development, including proliferation, synaptic pruning and/or myelination[59–62]. Thinner CT, particularly in early adolescence (**Figure 3**), could reflect abnormal synaptic plasticity or pruning, which have both been implicated in *in vitro* SZ models[63]. Although excessive synaptic pruning is one plausible explanation for thinner cortex associated with psychosis transition, recent evidence suggests that intracortical myelination and/or expression of myelin-related genes may be mechanisms of cortical thinning[64,65]. To better understand neurobiological mechanisms underlying psychosis transition in CHR, investigations of concomitant measures of cortical thickness, macroscale white matter tracts, and intracortical myelination are necessary. Finally, it is also possible that lower CT is not a mechanism of psychosis, and can instead be attributed to environmental factors or social determinants associated with psychosis[66,67], or that lower CT occurs in response to other possible biological mechanisms underlying psychosis (e.g., HPA stress response[68]).

Even if CT reductions in CHR were robust, effect sizes for between-group differences were nevertheless small-to-moderate and accounted for ~1% of the variance in CHR-PS+ vs. CHR-PS- comparisons. The subtle nature of these morphometric differences underscores the importance of adequate statistical power, achievable only through large-scale multi-site collaborations. Consistent with recent work showing that SZ polygenic risk scores only improved differentiation of CHR-PS+ and HC (not CHR-PS+ from CHR-PS-)[69], we anticipate that baseline, univariate sMRI metrics will have a similar impact on psychosis risk prediction algorithms. Given the logistic and financial challenges that MRI brings, the use of MRI metrics in isolation may not be feasible or useful for psychosis risk prediction. A viable solution may be to adopt sequential assessment frameworks, as recently implemented[70]. Alternatively, sMRI differences may be a better predictor of general psychopathology, and would be better suited for transdiagnostic risk prediction models[71].

Limitations

One limitation common to multi-site studies is that data were collected from multiple scanners, although leave-one-out analyses suggest that site effects were not prominent. Secondly, this initial study focused on baseline cross-sectional data, and did not investigate progressive sMRI changes associated with psychosis conversion, as identified in prior work[6,18–21,72]. Finally, CHR status is associated with heterogeneous outcomes[73–75] and neuroimaging phenotypes may differentiate amongst variability in psychosocial functioning and/or amongst

other psychiatric diagnoses (e.g., mood and anxiety disorders). These are two future goals of the ENIGMA CHR Working Group, now that feasibility of this collaboration has been established.

Conclusions and Future Directions

In the largest study of brain abnormalities in CHR to date, we found robust evidence for a subtle, widespread pattern of CT differences, consistent with observations in psychosis. The specificity of these differences to CT - as well as age-associated deviations in regions sensitive to psychosis conversion - may point to abnormal development processes. These findings also point to age ranges (i.e., early adolescence) when morphometric abnormalities in CHR might be greatest.

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Table and Figure Legends

Table 1. Demographic descriptives for every site in HC and CHR, and CHR-PS+ and CHR-PS-. The Ns for CHR-PS+ and CHR-PS- do not always sum to the sample CHR N because most sites lose individuals to follow-up (CHR-UNK).

Figure 1. Effect sizes for mega-analysis of group and conversion status. **A.** Overview of effect sizes for HC vs. CHR. The top row reflects the results of the overall generalized linear model. A deeper purple color indicates a greater effect of group (HC vs. CHR) in this region. We observed the greatest effects of group in cortical thickness measures. The second row indicates the pairwise effect sizes for HC vs. CHR, in regions that were statistically significant (q<0.05) in the overall comparison (top row of **A.**). Regions that were not statistically significant in the overall comparison are in gray. In comparison to HC, CHR exhibited lower cortical thickness across the cortex. Red color indicates that HC has a larger value in comparison to CHR for this region. **B.** Overview of effect sizes for HC vs. CHR-PS+ vs. CHR-PS-. The top row reflects the results of the overall generalized linear model. A deeper purple color indicates a greater effect of conversion status (HC vs. CHR-PS+ vs. CHR-PS-) in this region. The second and third rows indicate the pairwise effect sizes for HC vs. CHR-PS+ and CHR-PS- vs. CHR-PS+, respectively. Pairwise comparisons are presented in regions that were statistically significant (q<0.05) in the overall comparison (top row of **B.**). Regions that were not statistically significant in the overall comparison are in gray. Regions that CHR-PS+ had lower cortical thickness in comparison to HC and CHR-PS-, CHR-PS+ are highlighted in yellow.

Figure 2. Bar graphs for regions in which CHR-PS+ (pink) had lower CT in comparison to CHR-PS- (purple) and HC (green).

Figure 3. Age effects of regions that exhibited an effect of conversion status. HC are in green, CHR-PS+ are pink, and CHR-PS- are purple. Each graph has a line of best fit for the effect of age on the respective neuroimaging measures. Shading around the line indicates the standard error. The bars underneath the age plots reflect the derivative of the slope, i.e., the rate of change taking place at a particular age, scaled as a pseudo t-statistic, based on the posterior simulation. Age effects are plotted for A. fusiform cortical thickness, B. paracentral cortical thickness, and C. superior temporal cortical thickness.