Published in final edited form as:

J Child Psychol Psychiatry. 2017 March ; 58(3): 305–314. doi:10.1111/jcpp.12657.

Longitudinal Study of Cerebral Surface Morphology in Youth with 22q11.2 Deletion Syndrome, and Association with Positive Symptoms of Psychosis

Petya D. Radoeva¹, Ravi Bansal², Kevin M. Antshel³, Wanda Fremont⁴, Bradley S. Peterson², and Wendy R. Kates⁴

¹Department of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, New York, USA

²Children's Hospital Los Angeles and the Keck School of Medicine at the University of Southern California, Los Angeles, California, USA

³Department of Psychology, Syracuse University, Syracuse, New York, USA

⁴Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, New York, USA

Abstract

Background—22q11.2 deletion syndrome (22q11DS) is a genetic disorder that greatly increases risk of developing schizophrenia. We previously characterized cerebral surface morphology trajectories from late childhood to mid adolescence in a cohort of youth with 22q11DS. Herein, we extend the study period into early adulthood, and describe further the trajectories associated with severe psychiatric symptoms in this cohort.

Methods—Participants included 76 youth with 22q11DS and 30 unaffected siblings, assessed at three timepoints, during which high resolution, anatomic magnetic resonance images were acquired. High-dimensional, non-linear warping algorithms were applied to images in order to derive characteristics of cerebral surface morphology for each participant at each timepoint. Repeated measures, linear regressions using a mixed model were conducted, while covarying for age and sex.

Results—Alterations in cerebral surface morphology during late adolescence/early adulthood in individuals with 22q11DS were observed in the lateral frontal, orbitofrontal, temporal, parietal, occipital, and cerebellar regions. An Age $\times$ Diagnosis interaction revealed that relative to unaffected siblings, individuals with 22q11DS showed age-related surface protrusions in the prefrontal cortex (which remained stable or increased during early adulthood), and surface indentations in posterior regions (which seemed to level off during late adolescence). Symptoms of

Correspondence: Wendy R. Kates, Department of Psychiatry and Behavioral Sciences, State University of New York at Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210, USA; katesw@upstate.edu.

Supporting information

Additional Supporting Information may be found in the online version of this article.

Conflict of interest statement: No conflicts declared.

psychosis were associated with a trajectory of surface indentations in the orbitofrontal and parietal regions.

Conclusions—These results advance our understanding of cerebral maturation in individuals with 22q11DS, and provide clinically relevant information about the psychiatric phenotype associated with the longitudinal trajectory of cortical surface morphology in youth with this genetic syndrome.

Introduction

The 22q11.2 deletion syndrome (22q11DS), also called velo-cardio-facial syndrome (VCFS), is a genetic disorder caused by the deletion of more than 40 genes at the q11.2 locus on one copy of chromosome 22. Its population prevalence is most recently estimated to be 1 in 1,000 (Grati et al., 2015). Individuals with 22q11DS have a distinctive set of cognitive deficits (Antshel, Fremont, & Kates, 2008; Baker & Vorstman, 2012), neuroanatomical abnormalities (Tan, Arnone, McIntosh & Ebmeier, 2009), and an increased risk of psychiatric disorders, including ADHD (Antshel et al., 2006; Feinstein, Eliez, Blasey & Reiss, 2002), mood and anxiety disorders (Green et al., 2009), and psychosis (Bassett & Chow, 1999; Murphy, 2002; Schneider et al., 2014). Approximately 42% of adults with 22q11DS have a psychotic disorder by age 35 years (Schneider et al., 2014), with schizophrenia affecting approximately 25% (Murphy, Jones, & Owen, 1999). In contrast, the lifetime prevalence of schizophrenia in the general population is between 0.30 and 0.66% (Saha, Chant, Welham & McGrath, 2005). This deletion therefore constitutes a major genetic risk factor for schizophrenia (Murphy, 2002). The 22q11DS-associated schizophrenia is genetically more etiologically homogeneous than schizophrenia in the general population. Longitudinal studies of individuals with 22q11DS offer the opportunity to describe neurodevelopmental trajectories prior to the onset of psychosis (Bassett & Chow, 2008; Bassett et al., 2003).

Multiple neuroanatomical abnormalities have been associated with 22q11DS, including reduced brain volumes, white matter microstructural abnormalities, altered gyrification patterns, surface area and thickness of the cortex (Barnea-Goraly et al., 2003; Bearden et al., 2007; Gothelf et al., 2007; Kunwar et al., 2012; Radoeva et al., 2012; Tan et al., 2009; Jalbrzikowski et al., 2013; Schaer et al., 2009). A rostro-caudal gradient has been observed in volumetric reductions, with a relative preservation of frontal volumes, and most pronounced volumetric reductions in the occipital and cerebellar regions (Bish et al., 2004; Gothelf, Schaer, & Eliez, 2008; Tan et al., 2009). This gradient appears to be most prominent in children and may be attenuated in adulthood, when more diffuse gray and white matter loss is observed (Gothelf, Schaer & Eliez, 2008; Tan et al., 2009). Previous studies from our group and others have found that (prodromal) psychosis in 22q11DS is associated with volumetric alterations in frontal (Gothelf et al., 2005, 2011) and temporal lobe gray matter volumes (Chow et al., 2011; Kates et al., 2011a), as well as cortical thickness (Jalbrzikowski et al., 2013; Schaer et al., 2009).

The longitudinal study of cerebral surface morphology is of particular interest because changes in cerebral surface morphology may indicate disruptions in programmed synaptic

elimination during adolescence in individuals with 22q11DS. During the first phase of the longitudinal study we describe here, we reported that relative to controls, individuals with 22q11DS exhibited widespread alterations in cerebral surface morphology in late childhood (Time 1) and early – to – mid – adolescence (Time 2) (Kates et al., 2011b). Specifically, we observed surface indentations, defined as inward deformations on the surface of the brain relative to the template brain, which we interpret as smaller local volumes (Colibazzi et al., 2013; Marsh et al., 2013; Spann et al., 2015), throughout the perisylvian and cerebellar regions of the cortical surface; and surface protrusions, defined as outward deformations on the surface of the brain relative to the template, which we interpret as larger local volumes, in bilateral superior/middle frontal gyri and inferior temporal gyri. Moreover, surface indentations at Time 2 in the frontal, temporal, and cerebellar regions, as well as surface protrusions in the supramarginal gyrus, were associated with prodromal symptoms at Time 2 (Kates et al., 2011b).

This study complements and extends our previous report by characterizing neurodevelopmental trajectories into late adolescence and early adulthood, ie., Time 3, approximately 3 years beyond the previous report. At Time 3, individuals with 22q11DS were entering the window of increased risk for developing psychosis. Accordingly, re-assessing the cohort at this timepoint allowed us to examine alterations in cortical morphology during late adolescence in individuals with 22q11DS relative to controls, and, to determine more definitively the effects of longitudinal trajectories of cortical morphology on the development of symptoms of psychosis. We predicted that 1) individuals with 22q11DS would have altered trajectories of surface indentations and protrusions relative to unaffected siblings, and 2) in individuals with 22q11DS, symptoms of psychosis would be associated with faster or more pronounced surface indentations in frontal and temporal brain regions.

Methods

Participants

Participants included in this study were drawn from a larger longitudinal study of 22q11DS (Antshel et al., 2006; Antshel et al., 2010; Antshel et al., 2013; Kates et al., 2011b). The individuals with 22q11DS and their families were recruited primarily from the VCFS International Center at SUNY Upstate Medical University. The 22q11.2 deletion was confirmed by fluorescence *in situ* hybridization (FISH). The healthy controls were unaffected siblings of individuals with 22q11DS. Demographic information, exclusion criteria and sample size at each timepoint are described in Table S1 and Appendix S1. Medication and psychiatric diagnoses of participants are described in Table S2.

This study was approved by the Institutional Review Board of SUNY Upstate Medical University, and all participants and their parents (when appropriate) provided signed, informed consent.

Assessment of cognitive and psychiatric functioning

All participants underwent a battery of neuropsychiatric assessments. At Time 1, the Wechsler Intelligence Scale for Children—Third Edition (WISC-III) (Wechsler, 1991) was administered to all participants. At Times 2 and 3, either WISC-III or the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997) was administered based on the age of the participant, such that participants 17 years of age or older completed the WAIS-III.

The Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2002, 2003) was administered by doctoral-level clinicians. Embedded within the SIPS is a rating scale (the Scale of Prodromal Symptoms [SOPS]), which consists of items reflecting positive, negative, disorganized or general symptoms. The SOPS Positive Symptom Subscale (SOPS-PS), consisting of five items, each scored on a scale of 0 to 6, was used for further analysis. Inter-rater reliability for the SOPS-PS, calculated with the kappa coefficient, was consistently above 0.90 across all timepoints. Although our cortical morphology data is based on the first three timepoints of the study, the majority of participants returned for a fourth timepoint, during which the SIPS was readministered. Since we were interested in the extent to which cortical trajectories predicted symptoms of psychosis, and since at the fourth timepoint our participants were between the ages of 18 and 25 years, which is the greatest window of risk for developing psychosis, our analyses are based on their most recent SOPS-PS score, including Time 4 SOPS-PS scores when available. Accordingly, for individuals with 22q11DS, analyses included Time 4 SOPS-PS scores for 55 individuals with 22q11DS, and Time 3 SOPS-PS scores for 17 individuals, and Time 2 SOPS-PS scores for 4 individuals.

Neuroimaging data acquisition and processing

Image acquisition and pre-processing procedures are described in Appendix S2. The image analysis method utilized previously validated and automated algorithms (Bansal, Staib, Whiteman, Wang & Peterson, 2005; Peterson et al., 2007; Plessen et al., 2006), and had been employed in our earlier 22q11DS cerebral surface morphology paper (Kates et al., 2011b). Briefly, a Time 2 brain was selected as the template using a rigorous two-step procedure (Plessen et al., 2006), and the brains of all participants at Time 2 were coregistered and nonlinearly warped to the template brain, using a similarity transformation and then a high-dimensional, non-rigid warping algorithm based on the principles of fluid dynamics (Christensen, Rabbitt & Miller, 1994), such that all brains were warped to be identical in size and shape to the template brain. This normalization procedure allowed for the identification of the corresponding points on the surface of each participant's brain and the template. Next, we normalized a participant's Time 1 and Time 3 brains to the Time 2 brain. The normalization of the Time 2 brain to the template brain identified corresponding points across the surfaces of the Time 1, Time 2, and Time 3 brains and the template brain. Euclidean distances were then calculated between each point (on the subject brains at Time 1, Time 2 and Time 3) and the corresponding point on the template brain. The signed Euclidean distances were used for further analyses, where positive distances indicated protrusions, and negative distances indicated indentations, relative to the corresponding point on the template brain.

To assess the changes in morphology of the cerebral surface over time, we conducted repeated-measures linear regressions at each voxel on the cerebral surface, in which the signed Euclidean distances at Times 1, 2, and/or 3 were the dependent variable. We analyzed the repeated measures at the three time points for each participant using a mixed model

$$y = X\beta + Zu + \varepsilon,$$

where the vector y are the brain measures with mean $E(y) = X\beta$, the vector β are the fixed effects, the vector u are the random effects with zero mean and covariance matrix $var(u) = G$, and the vector ε are the errors of zero mean and specified covariance matrix $var(\varepsilon) = R$. Assuming that both errors and the random effects are Gaussian distributed, the best linear unbiased estimate (BLUE) $\hat{\beta}$ and the best linear unbiased predictor $\hat{u}$ for the vectors β and u are estimated by solving the mixed model equations (Henderson 1973):

$$\begin{pmatrix} X'R^{-1}X & X'R^{-1}Z \\ Z'R^{-1}X & Z'R^{-1}Z + G^{-1} \end{pmatrix} \begin{pmatrix} \hat{\beta} \\ \hat{u} \end{pmatrix} = \begin{pmatrix} X'R^{-1}y \\ Z'R^{-1}y \end{pmatrix}$$

This analytic method utilizes all available data for the participants in each group, and estimated the parameters and their variances using a method for restricted maximum likelihood (REML (Bartlett, 1937)), a method that is used within the procedure *mixed* of the statistical package SAS and computes unbiased estimates of the variance and covariance parameters. In the first repeated-measures analysis, we included as independent variables the main effects of Age (in years at Time 1, 2 and/or 3) and Diagnosis (22q11DS vs. siblings), and the effects of Age $\times$ Diagnosis interaction on brain measures. The interaction term Age $\times$ Diagnosis was used to assess whether the age effects differed in individuals with 22q11DS from those for their unaffected siblings. To study morphological correlates of psychiatric functioning, we conducted repeated-measures linear regressions with the independent variables Age, most recent SOPS-PS score, and Age $\times$ SOPS-PS.) For visualization purposes and creating comparison graphs, the SOPS-PS scores of the 22q11DS group were dichotomized into high and low SOPS-PS categories. The High SOPS-PS category includes individuals with 22q11DS who received a score of 3 or higher on any of the five items on their most recent SOPS-PS (Miller et al., 2003).

For all surface analyses, we corrected for multiple hypothesis testing by applying a method for false discovery rate (FDR), with FDR rate = 0.05 (Benjamini & Hochberg, 1995), to vertices across the entire surface of the brain. FDR was applied to the independent variable of interest in each longitudinal model.

Results

Figure 1 shows the differences in morphology of the cerebral surface between individuals with 22q11DS and unaffected siblings at Time 3. Time 1 and Time 2 data have been presented previously (Kates et al., 2011b), and are not included in the current report. As seen in Figure 1, there were surface indentations bilaterally in the lateral inferior frontal and anterolateral orbitofrontal region, inferior postcentral gyrus, occipital and parietal cortex,

and the cerebellum. Furthermore, there were surface protrusions in the dorsal frontal cortex and medial orbitofrontal cortex bilaterally, and the lateral surface of the left temporal lobe (Figure 1). Since, in our previous report, we used Gaussian Random Field (GRF) corrections, we also present differences in cerebral surface morphology at Time 3 based on GRF corrections, in order to provide the reader with the opportunity to directly compare these results to Times 1 and 2. GRF-corrected results for Time 3 are presented in Figure S1.

Alterations in trajectories of morphology of the cerebral surface in 22q11ds

An Age $\times$ Diagnosis interaction revealed significant differences in the cerebral surface morphology trajectories for several brain regions (Figure 2 and Table S3). In frontal regions (e.g., left superior frontal gyrus and left middle orbitofrontal gyrus, Points A and E respectively in Figure 2), individuals with 22q11DS had more prominent surface protrusions as compared to unaffected siblings at all time points, and this difference in surface protrusions became more pronounced with increasing age, especially in late adolescence and young adulthood. The left occipital-parietal region (Points B and C in Figure 2) showed surface indentations in 22q11DS individuals from childhood to early adulthood vs. surface expansions in unaffected siblings. The right parietal region (inferior parietal lobule, Point D in Figure 2) showed the opposite pattern: surface expansions in 22q11DS vs. surface indentations – in siblings, with divergence of surface morphology in young adulthood. Results did not change when we controlled for comorbid psychiatric diagnoses or medication usage (Appendix S3, Figure S2).

Association with severe psychiatric symptoms

Several regions showed a significant Age $\times$ SOPS-PS interaction in 22q11DS (Figure 3). Youth with 22q11DS and high SOPS-PS scores showed greater age-related decline in surface distances in bilateral middle frontal and left orbitofrontal (point B, Figure 3) cortices, right parietal and middle occipital (point A, Figure 3) cortices, and right cerebellum. In left inferior parietal, temporal and occipital cortices, and the cerebellum, the opposite pattern emerged: increasing surface protrusions over time were observed in individuals with high SOPS-PS scores relative to those with low SOPS-PS scores (Figure 3, points C – E).

Discussion

We found cerebral surface morphology alterations in individuals with 22q11DS compared to their unaffected siblings across the entire cerebral surface during late adolescence/early adulthood (at Time 3). The cerebral surface morphology trajectories in 22q11DS deviated from those of sibling controls by showing greater age-related decline in surface distances in the left occipito-parietal and cerebellar regions, as well as increase in surface distances in bilateral frontal (orbitofrontal and superior frontal gyrus) especially during late adolescence and young adulthood. Among the individuals with 22q11DS, greater surface indentations in the right orbitofrontal cortex and occipito-parietal regions (including the inferior parietal lobule, and middle occipital gyrus), and surface protrusions in left parietal-temporal-occipital regions during late adolescence/early adulthood were associated with more positive prodromal symptoms.

The widespread, Time 3 pattern of cerebral surface morphology changes in 22q11DS (relative to siblings) was similar to the pattern that we had observed during Times 1 and 2 (Kates et al., 2011b). As noted above, changes in cortical surface morphology has been interpreted as representing greater or smaller changes in local regional volumes of brain tissue or enlargements/reductions in specific regions (Colibazzi et al., 2013; Marsh et al., 2013; Spann et al., 2015). The bilateral surface indentations in 22q11DS across the occipito-parietal regions (i.e., inferior postcentral gyrus, occipital and parietal cortex), and the cerebellum are consistent with previous findings of volumetric alterations in 22q11DS, suggesting a rostro-caudal gradient (Gothelf, Schaer & Eliez, 2008). Surface indentations in posterior regions could underlie the visuospatial deficits in 22q11DS, whereas indentations in inferior frontal lobe could be related to greater impairments in social cognition, and behavioral dysregulation seen in individuals with 22q11DS.

Alterations in cerebral surface morphology trajectories in 22q11DS

While employing a somewhat different method of studying cerebral surface morphology, previous research has described in detail the neurodevelopmental trajectories in typically developing youth (Gogtay et al., 2004; Shaw et al., 2008; Tamnes et al., 2010; Zielinski et al., 2014). Cortical thickness appears to follow a U-shaped curve: with some regional exceptions (Shaw et al., 2008), overall thickness increases during early childhood, peaks by late childhood/early adolescence for most brain regions, then undergoes thinning during adolescence, and stabilizes in adulthood (Gogtay et al., 2004; Nie, Li & Shen 2013; Shaw et al., 2008; Tamnes et al., 2010; Zielinski et al., 2014) across almost the entire cortical surface. Changes of cortical thickness during typical development are thought to be related to programmed synaptic elimination (Huttenlocher & Dabholkar, 1997), and/or proliferation of myelin underlying the cortex during late childhood and adolescence (Shaw et al., 2008; Yakovlev & Lecours, 1967). Our findings of surface indentations during adolescence in unaffected siblings are thus in line with previous studies of typically developing adolescents cited above.

Our finding of cerebral surface protrusions in frontal brain regions in probands relative to siblings is consistent with several studies of 22q11DS. Disproportionately large frontal lobe volumes and cortical thickness relative to more posterior regions in individuals with 22q11DS have been reported previously (Kates et al., 2001; Jalbrzikowski et al., 2013) in cross-sectional studies. In addition, a separate longitudinal study of cortical thickness in 22q11DS, which used measures generated by the image processing program, FreeSurfer, described increased cortical thickness in the frontal cortex in children, and accelerated thinning during adolescence (Schaer et al., 2009). This result is in contrast with our current result of sustained/increasing frontal cerebral surface protrusions over time, most likely due to differences in image processing methods.

Consistent with our study, individuals at high genetic risk for schizophrenia (with at least one parent with schizophrenia) have also demonstrated increased or preserved cortical thickness in frontal cortex, relative to controls during adolescence (Prasad et al., 2010). This preserved cortical thickness, however, was accompanied by a decrease in cortical surface area (Prasad et al., 2010). Interestingly, a similar pattern (increased of cortical thickness

along with decreased surface area) was recently described in the middle and superior frontal cortices of youth with 22q11DS (Jalbrzikowski et al., 2013).

Occipital and parietal regions in individuals with 22q11DS have been consistently reported to have reduced volumes as compared to typically developing controls. Similarly, we found left occipito-parietal surface indentations over time in probands relative to siblings (Figure 2). Furthermore, this region seems to be part of the dorsal visual stream. Individuals with 22q11DS have marked impairments in visuospatial cognitive abilities and mathematical skills (De Smedt, Swillen, Verschaffel & Ghesquiere, 2009), which have been linked to structural alterations in the parietal lobes (Simon et al., 2008). Interestingly, similar cognitive impairments, and associated neuroanatomic alterations, have been noted in Williams syndrome, another contiguous gene deletion syndrome associated with intellectual disability (Fung et al., 2012; Zarchi et al., 2013). The altered neurodevelopmental trajectory in the dorsal stream could underlie worsening visuospatial deficits in 22q11DS over time, which could be explored in future studies.

Association with symptoms of psychosis

Our finding of association between increased symptoms of psychosis and more pronounced surface indentations in the middle orbitofrontal gyrus during young adulthood is consistent with our previous work as well as previous studies of individuals at high risk for schizophrenia and first-onset schizophrenia. Diffuse cortical thinning has been described in schizophrenia, with most prominent thinning in frontal and temporal regions (Hartberg et al., 2010; Rimol et al., 2010; Rimol et al., 2012; Schultz et al., 2010), which also correlates with cognitive functioning (including verbal IQ, verbal learning, and executive function) (Hartberg et al., 2010). Cortical thinning in frontal and temporal regions has been described in first-episode schizophrenia (Schultz et al., 2010). Gray matter alterations have been reported in adolescents at high risk for developing psychosis (Pantelis et al., 2003; Takahashi et al., 2009), suggesting that alterations in cortical thickness accompany and even precede the onset of schizophrenia. Notably, individuals with first-episode schizophrenia have strongest reductions of cortical thickness in orbitofrontal regions (7.1% as compared to controls) (Schultz et al., 2010). Interestingly, in a cross-sectional study using FreeSurfer, right medial orbitofrontal cortical thickness was associated positively with positive symptoms (of psychosis) in individuals with 22q11DS (Jalbrzikowski et al., 2013).

Accelerated surface indentations in right occipito-parietal regions (including the inferior parietal lobule, and middle occipital gyrus) from early to late adolescence were also found in individuals with severe psychiatric symptoms. These results complement our previous findings related to cortical gyrification in our 22q11DS sample (Kunwar et al., 2012). Longitudinal decreases in the gyrification index of the occipital lobes (from Time 1 to Time 2) correlated with more pronounced prodromal symptoms at Time 2 (Kunwar et al., 2012).

Increased surface protrusions in left inferior parietal-temporal-occipital regions, and cerebellum, of individuals with 22q11DS and symptoms of psychosis (Figure 3, points C – E) are somewhat puzzling. In both this and our prior report, we consistently observed a trajectory of increasing surface protrusion in the left superior parietal lobule in individuals with higher SOPS-PS scores. However, in contrast to the present results, we had observed

decreases in left cortical posterior and cerebellar morphology in our prior report (Kates et al., 2011). This is consistent with previous studies of schizophrenia that have reported cerebellar gray matter deficits in first-episode schizophrenia (Henze et al., 2011; Rasser et al., 2010). Accordingly we would have expected to see surface indentations in 22q11DS individuals and greater severity of symptoms. Potentially, our results might be confounded by subtle motion artifacts that are not visible to the human operator (although we did not observe overt imaging artifacts that necessitated the exclusion of any participants from the study). Interestingly, however, Guo and colleagues (2016) have reported recently that individuals with non-syndromic schizophrenia displayed similar increases in posterior cortical thickness, which they attributed to a potential compensatory process. It is possible that the use of antipsychotic medications may have contributed to these findings.

Animal studies have reported longitudinal volumetric reductions in both rodents (Vernon et al., 2014), and primates chronically treated with antipsychotic medications (Dorph-Petersen et al., 2005). Previous human studies of the potential effects of antipsychotic medications on gray matter have reported an association between the use of antipsychotic medications and longitudinal volumetric reductions (Ho, Andreasen, Ziebell, Pierson & Magnotta, 2011), though the effects on brain volumes may vary across brain regions, different antipsychotic medications (Ebdrup, Norbak, Borgwardt & Glenthøj, 2013), and clinical response (Molina, Martin, Ballesteros, de Herrera & Hernandez-Tamames, 2011). Accordingly, it is possible that some of the longitudinal, posterior surface protrusions that we observed in the group of individuals with 22q11DS who reported either prodromal or overt psychosis may be related to the usage of antipsychotic medication. Longitudinal studies of medication effects on brain development in 22q11DS, with larger samples, in those with and without symptoms of psychosis, are warranted.

Overall, our observations of the association of morphological alterations and symptoms of psychosis are limited to some extent by the relatively small number of individuals who displayed either ultra high risk (UHR) symptoms or overt psychosis relative to the rest of the sample (see Table S2). Since several participants were below 25 years of age at their most recent assessment, and therefore still within the window of highest risk for conversion to psychosis, it is possible that additional members of the cohort will convert to psychosis. It is also tempting to speculate that participation in this longitudinal study itself may have influenced rate of conversion: within the context of their participation in the study, participants have been receiving structured psychiatric evaluations since late childhood or early adolescence, and families have been receiving written reports with recommendations for whether treatment may be indicated. Accordingly, many of the participants at risk have been receiving psychiatric treatment throughout their adolescence, which may have mitigated conversion to psychosis.

It is interesting to consider the potential mechanisms underlying alterations in the cerebral surface morphology in individuals with 22q11DS. A recent review of the neurodevelopmental trajectories in animal models of 22q11DS suggests three phases in the neurodevelopmental disruptions, all of which likely related to diminished gene dosage of 22q11.2 genes (Meechan, Maynard, Tucker & LaMantia, 2011). Two of these phases occur during embryogenesis and involve altered tissue induction and morphogenesis as well as

alterations of neurogenesis and migration in the cerebral cortex. The third phase comprises abnormal mitochondrial function and synaptogenesis (Meechan et al., 2011). Our finding of relatively stable, cross-sectional cerebral surface morphology differences between youth with 22q11DS and age-matched controls from late childhood to early adulthood suggest that an overall pattern of alterations in 22q11DS may have already formed prior to our Time 1 study period (i.e., before late childhood). It is conceivable that at least some of the neuroanatomical alterations may have been present even at birth, and may be related to alterations in morphogenesis, neurogenesis and cell migration secondary to diminished dosage of 22q11.2 genes.

The mechanism underlying the relative enlargement of frontal regions in 22q11DS could be related to haploinsufficiency of (some of) the genes at the 22q11.2 locus. The catechol-O-methyltransferase (COMT) gene codes for an enzyme that degrades catecholamines and therefore plays a critical role in regulating dopaminergic levels in the PFC (Tunbridge, Harrison & Weinberger, 2006). Haploinsufficiency of COMT may result in a “hyperdopaminergic state” (Boot et al., 2008). It is possible that during adolescence, persistently high levels of dopamine in individuals with 22q11DS could continue to sustain dopaminergic cortical synapses, resulting in disruptions in programmed synaptic pruning, and subsequently stable and/or even increasing gray matter volumes specifically in the prefrontal cortex.

Conclusions

In summary, we described altered cerebral surface morphology trajectories in individuals with 22q11DS compared to their unaffected siblings, characterized by sustained, abnormal surface protrusions in frontal regions, and altered surface indentations in posterior regions. More prominent surface alterations over time in the orbitofrontal and occipito-parietal regions were associated with more pronounced symptoms of psychosis in individuals with 22q11DS. Thus, our current study contributes to the better understanding of cerebral maturation in youth with 22q11DS and the clinical phenotype associated with cortical surface morphology in 22q11DS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institutes of Health, R01 MH064824, to W.R.K.

References

- Antshel KM, Fremont W, Kates WR. The neurocognitive phenotype in velo-cardio-facial syndrome: A developmental perspective. *Developmental Disabilities Research Reviews*. 2008; 14:43–51. [PubMed: 18636636]
- Antshel KM, Shprintzen R, Fremont W, Higgins AM, Faraone SV, Kates WR. Cognitive and psychiatric predictors to psychosis in velocardiofacial syndrome: A 3-year follow-up study. *Journal*

of the American Academy of Child and Adolescent Psychiatry. 2010; 49:333–344. [PubMed: 20410726]

Antshel KM, Hendricks K, Shprintzen R, Fremont W, Higgins AM, Faraone SV, Kates WR. The longitudinal course of attention deficit/hyperactivity disorder in velo-cardio-facial syndrome. *Journal of Pediatrics*. 2013; 163:187–193. [PubMed: 23337092]

Antshel KM, Fremont W, Roizen NJ, Shprintzen R, Higgins AM, Dhamoon A, Kates WR. ADHD, major depressive disorder, and simple phobias are prevalent psychiatric conditions in youth with velocardiofacial syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2006; 45:596–603. [PubMed: 16670654]

Baker K, Vorstman JA. Is there a core neuropsychiatric phenotype in 22q11.2 deletion syndrome? *Current Opinion in Neurology*. 2012; 25:131–137. [PubMed: 22395003]

Bansal R, Staib LH, Whiteman R, Wang YM, Peterson BS. ROC-based assessments of 3D cortical surface-matching algorithms. *Neuroimage*. 2005; 24:150–162. [PubMed: 15588606]

Barnea-Goraly N, Menon V, Krasnow B, Ko A, Reiss A, Eliez S. Investigation of white matter structure in velocardiofacial syndrome: A diffusion tensor imaging study. *American Journal of Psychiatry*. 2003; 160:1863–1869. [PubMed: 14514502]

Bartlett MS. Properties of sufficiency and statistical tests. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences*. 1937; 160:268.

Bassett AS, Chow EW. 22q11 deletion syndrome: A genetic subtype of schizophrenia. *Biological Psychiatry*. 1999; 46:882–891. [PubMed: 10509171]

Bassett AS, Chow EW. Schizophrenia and 22q11. 2 deletion syndrome. *Current Psychiatry Reports*. 2008; 10:148–157. [PubMed: 18474208]

Bassett AS, Chow EW, AbdelMalik P, Gheorghiu M, Husted J, Weksberg R. The schizophrenia phenotype in 22q11 deletion syndrome. *American Journal of Psychiatry*. 2003; 160:1580–1586. [PubMed: 12944331]

Bearden CE, Van Erp TG, Dutton RA, Tran H, Zimmermann L, Sun D, Emanuel BS. Mapping cortical thickness in children with 22q11. 2 deletions. *Cerebral Cortex*. 2007; 17:1889–1898. [PubMed: 17056649]

Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological)*. 1995:289–300.

Bish JP, Nguyen V, Ding L, Ferrante S, Simon TJ. Thalamic reductions in children with chromosome 22q11. 2 deletion syndrome. *Neuroreport*. 2004; 15:1413–1415. [PubMed: 15194864]

Boot E, Booij J, Zinkstok J, Abeling N, De Haan L, Baas F, van Amelsvoort T. Disrupted dopaminergic neurotransmission in 22q11 deletion syndrome. *Neuropsychopharmacology*. 2008; 33:1252–1258. [PubMed: 17653112]

Chow EW, Ho A, Wei C, Voormolen EH, Crawley AP, Bassett AS. Association of schizophrenia in 22q11. 2 deletion syndrome and gray matter volumetric deficits in the superior temporal gyrus. *American Journal of Psychiatry*. 2011; 168:522–529. [PubMed: 21362743]

Christensen GE, Rabbitt RD, Miller MI. 3D brain mapping using a deformable neuroanatomy. *Physics in Medicine and Biology*. 1994; 39:609–618. [PubMed: 15551602]

Colibazzi T, Wexler BE, Bansal R, Hao X, Liu J, Sanchez-Peña J, Peterson BS. Anatomical abnormalities in gray and white matter of the cortical surface in persons with schizophrenia. *PloS One*. 2013; 8:e55783. [PubMed: 23418459]

De Smedt B, Swillen A, Verschaffel L, Ghesquiere P. Mathematical learning disabilities in children with 22q11. 2 deletion syndrome: a review. *Developmental Disabilities Research Reviews*. 2009; 15:4–10. [PubMed: 19213009]

Dorph-Petersen KA, Pierri JN, Perel JM, Sun Z, Sampson AR, Lewis DA. The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology*. 2005; 30:1649–1661. [PubMed: 15756305]

Ebdrup B, Norbak H, Borgwardt S, Glenthøj B. Volumetric changes in the basal ganglia after antipsychotic monotherapy: a systematic review. *Current Medicinal Chemistry*. 2013; 20:438–447. [PubMed: 23157636]

- Feinstein C, Eliez S, Blasey C, Reiss AL. Psychiatric disorders and behavioral problems in children with velocardiofacial syndrome: usefulness as phenotypic indicators of schizophrenia risk. *Biological Psychiatry*. 2002; 51:312–318. [PubMed: 11958782]
- Fung LK, Quintin EM, Haas BW, Reiss AL. Conceptualizing neurodevelopmental disorders through a mechanistic understanding of fragile X syndrome and Williams syndrome. *Curr Opin Neurol*. 2012; 25:112–124. [PubMed: 22395002]
- Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Rapoport JL. Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America*. 2004; 101:8174–8179. [PubMed: 15148381]
- Gothelf D, Schaer M, Eliez S. Genes, brain development and psychiatric phenotypes in velo-cardio-facial syndrome. *Developmental Disabilities Research Reviews*. 2008; 14:59–68. [PubMed: 18636637]
- Gothelf D, Penniman L, Gu E, Eliez S, Reiss AL. Developmental trajectories of brain structure in adolescents with 22q11. 2 deletion syndrome: a longitudinal study. *Schizophrenia Research*. 2007; 96:72–81. [PubMed: 17804201]
- Gothelf D, Hoeft F, Ueno T, Sugiura L, Lee AD, Thompson P, Reiss AL. Developmental changes in multivariate neuroanatomical patterns that predict risk for psychosis in 22q11. 2 deletion syndrome. *Journal of Psychiatric Research*. 2011; 45:322–331. [PubMed: 20817203]
- Gothelf D, Eliez S, Thompson T, Hinard C, Penniman L, Feinstein C, Morris MA. COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11. 2 deletion syndrome. *Nature Neuroscience*. 2005; 8:1500–1502. [PubMed: 16234808]
- Grati FR, Molina Gomes D, Ferreira JCPB, Dupont C, Alesi V, Gouas L, Piotrowski K. Prevalence of recurrent pathogenic microdeletions and microduplications in over 9500 pregnancies. *Prenatal Diagnosis*. 2015; 35:801–809. [PubMed: 25962607]
- Green T, Gothelf D, Glaser B, Debbane M, Frisch A, Kotler M, Eliez S. Psychiatric disorders and intellectual functioning throughout development in velocardiofacial (22q11. 2 deletion) syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2009; 48:1060–1068. [PubMed: 19797984]
- Guo S, Palaniyappan L, Liddle PF, Feng J. Dynamic cerebral reorganization in the pathophysiology of schizophrenia: a MRI-derived cortical thickness study. *Psychological Medicine*. 2016; 46:2201–2214. [PubMed: 27228263]
- Hartberg CB, Lawyer G, Nyman H, Jönsson EG, Haukvik UK, Saetre P, Agartz I. Investigating relationships between cortical thickness and cognitive performance in patients with schizophrenia and healthy adults. *Psychiatry Research: Neuroimaging*. 2010; 182:123–133. [PubMed: 20456929]
- Henderson CR. Sire evaluation and genetic trends. *Journal of Animal Science*, 1973(Symposium). 1973:10–41.
- Henze R, Brunner R, Thiemann U, Parzer P, Richterich A, Essig M, Stieltjes B. Gray Matter Alterations in First-Admission Adolescents with Schizophrenia. *Journal of Neuroimaging*. 2011; 21:241–246. [PubMed: 20572905]
- Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Archives of General Psychiatry*. 2011; 68:128–137. [PubMed: 21300943]
- Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. *Journal of Comparative Neurology*. 1997; 387:167–178. [PubMed: 9336221]
- Jalbrzikowski M, Jonas R, Senturk D, Patel A, Chow C, Green MF, Bearden CE. Structural abnormalities in cortical volume, thickness, and surface area in 22q11. 2 microdeletion syndrome: relationship with psychotic symptoms. *NeuroImage: Clinical*. 2013; 3:405–415. [PubMed: 24273724]
- Kates WR, Antshel KM, Faraone SV, Fremont WP, Higgins AM, Shprintzen RJ, McCarthy C. Neuroanatomic predictors to prodromal psychosis in velocardiofacial syndrome (22q11. 2 deletion syndrome): a longitudinal study. *Biological Psychiatry*. 2011a; 69:945–952. [PubMed: 21195387]

- Kates WR, Bansal R, Fremont W, Antshel KM, Hao X, Higgins AM, Peterson BS. Mapping cortical morphology in youth with velocardiofacial (22q11. 2 deletion) syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2011b; 50:272–282. [PubMed: 21334567]
- Kates WR, Burnette CP, Jabs EW, Rutberg J, Murphy AM, Grados M, Pearlson GD. Regional cortical white matter reductions in velocardiofacial syndrome: a volumetric MRI analysis. *Biological Psychiatry*. 2001; 49(8):677–684. [PubMed: 11313035]
- Kunwar A, Ramanathan S, Nelson J, Antshel KM, Fremont W, Higgins AM, Kates WR. Cortical gyrification in velo-cardio-facial (22q11. 2 deletion) syndrome: a longitudinal study. *Schizophrenia Research*. 2012; 137:20–25. [PubMed: 22365148]
- Marsh R, Stefan M, Bansal R, Hao X, Walsh BT, Peterson BS. Anatomical characteristics of the cerebral surface in bulimia nervosa. *Biological Psychiatry*. 2013; 77:616–623. [PubMed: 23978404]
- Meechan DW, Maynard TM, Tucker ES, LaMantia AS. Three phases of DiGeorge/22q11 deletion syndrome pathogenesis during brain development: patterning, proliferation, and mitochondrial functions of 22q11 genes. *International Journal of Developmental Neuroscience*. 2011; 29:283–294. [PubMed: 20833244]
- Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Venture J, McFarlane W, Perkins DO, Pearlson GD, Woods SW. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull*. 2003; 29(4):703–715. [PubMed: 14989408]
- Miller TJ, McGlashan TH, Rosen JL, Somjee L, Markovich PJ, Stein K. Prospective diagnosis of the initial prodrome for schizophrenia based on the structured interview for prodromal syndromes: Preliminary evidence of interrater reliability and predictive validity. *Am J Psychiatry*. 2002; 159(5):863–865. [PubMed: 11986145]
- Molina V, Martín C, Ballesteros A, de Herrera AGS, Hernández-Tamames JA. Optimized voxel brain morphometry: association between brain volumes and the response to atypical antipsychotics. *European Archives of Psychiatry and Clinical Neuroscience*. 2011; 261:407–416. [PubMed: 21191610]
- Murphy KC. Schizophrenia and velo-cardio-facial syndrome. *The Lancet*. 2002; 359:426–430.
- Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Archives of General Psychiatry*. 1999; 56:940–945. [PubMed: 10530637]
- Nie J, Li G, Shen D. Development of cortical anatomical properties from early childhood to early adulthood. *Neuroimage*. 2013; 76:216–224. [PubMed: 23523806]
- Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, Desmond P. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *The Lancet*. 2003; 361:281–288.
- Peterson BS, Choi HA, Hao X, Amat JA, Zhu H, Whiteman R, Bansal R. Morphologic features of the amygdala and hippocampus in children and adults with Tourette syndrome. *Archives of General Psychiatry*. 2007; 64:1281–1291. [PubMed: 17984397]
- Plessen KJ, Bansal R, Zhu H, Whiteman R, Amat J, Quackenbush GA, Hugdahl K. Hippocampus and amygdala morphology in attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*. 2006; 63:795–807. [PubMed: 16818869]
- Prasad KM, Goradia D, Eack S, Rajagopalan M, Nutche J, Magge T, Keshavan MS. Cortical surface characteristics among offspring of schizophrenia subjects. *Schizophrenia Research*. 2010; 116:143–151. [PubMed: 19962858]
- Radoeva PD, Coman IL, Antshel KM, Fremont W, McCarthy CS, Kotkar A, Kates WR. Atlas-based white matter analysis in individuals with velo-cardio-facial syndrome (22q11. 2 deletion syndrome) and unaffected siblings. *Behavioral and Brain Functions*. 2012; 8:38–48. [PubMed: 22853778]
- Rasser PE, Schall U, Peck G, Cohen M, Johnston P, Khoo K, Thompson PM. Cerebellar grey matter deficits in first-episode schizophrenia mapped using cortical pattern matching. *Neuroimage*. 2010; 53:1175–1180. [PubMed: 20633666]

- Rimol LM, Nesvåg R, Hagler DJ, Bergmann Ø, Fennema-Notestine C, Hartberg CB, Melle I. Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder. *Biological Psychiatry*. 2012; 71:552–560. [PubMed: 22281121]
- Rimol LM, Hartberg CB, Nesvåg R, Fennema-Notestine C, Hagler DJ, Pung CJ, Melle I. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. *Biological Psychiatry*. 2010; 68:41–50. [PubMed: 20609836]
- Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med*. 2005; 2:e141. [PubMed: 15916472]
- Schaer M, Debbané M, Cuadra MB, Ottet MC, Glaser B, Thiran JP, Eliez S. Deviant trajectories of cortical maturation in 22q11.2 deletion syndrome (22q11DS): a cross-sectional and longitudinal study. *Schizophrenia Research*. 2009; 115:182–190. [PubMed: 19836927]
- Schneider M, Debbané M, Bassett AS, Chow EW, Fung WLA, van den Bree MB, Antshel KM. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *American Journal of Psychiatry*. 2014
- Schultz CC, Koch K, Wagner G, Roebel M, Schachtzabel C, Gaser C, Schlösser RG. Reduced cortical thickness in first episode schizophrenia. *Schizophrenia Research*. 2010; 116:204–209. [PubMed: 19926451]
- Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N, Giedd JN. Neurodevelopmental trajectories of the human cerebral cortex. *The Journal of Neuroscience*. 2008; 28:3586–3594. [PubMed: 18385317]
- Simon TJ, Wu Z, Avants B, Zhang H, Gee JC, Stebbins GT. Atypical cortical connectivity and visuospatial cognitive impairments are related in children with chromosome 22q11.2 deletion syndrome. *Behavioral and Brain Functions*. 2008; 4:25. [PubMed: 18559106]
- Spann MN, Serino D, Bansal R, Hao X, Nati G, Toth Z, Kangarlu A. Morphological features of the neonatal brain following exposure to regional anesthesia during labor and delivery. *Magnetic Resonance Imaging*. 2015; 33:213–221. [PubMed: 25179140]
- Takahashi T, Wood SJ, Yung AR, Soulsby B, McGorry PD, Suzuki M, Pantelis C. Progressive gray matter reduction of the superior temporal gyrus during transition to psychosis. *Archives of General Psychiatry*. 2009; 66:366–376. [PubMed: 19349306]
- Tamnes CK, Østby Y, Fjell AM, Westlye LT, Due-Tønnessen P, Walhovd KB. Brain maturation in adolescence and young adulthood: regional age-related changes in cortical thickness and white matter volume and microstructure. *Cerebral Cortex*. 2010; 20:534–548. [PubMed: 19520764]
- Tan GM, Arnone D, McIntosh AM, Ebmeier KP. Meta-analysis of magnetic resonance imaging studies in chromosome 22q11.2 deletion syndrome (velocardiofacial syndrome). *Schizophrenia Research*. 2009; 115:173–181. [PubMed: 19819113]
- Tunbridge EM, Harrison PJ, Weinberger DR. Catechol-o-methyltransferase, cognition, and psychosis: Val 158 Met and beyond. *Biological Psychiatry*. 2006; 60:141–151. [PubMed: 16476412]
- Vernon AC, Crum WR, Lerch JP, Chege W, Natesan S, Modo M, Kapur S. Reduced cortical volume and elevated astrocyte density in rats chronically treated with antipsychotic drugs—linking magnetic resonance imaging findings to cellular pathology. *Biological Psychiatry*. 2014; 75:982–990. [PubMed: 24143881]
- Wechsler, D. Wechsler memory scale—Third edition. The Psychological Corporation; San Antonio, TX: 1997.
- Wechsler, D. WISC-III: Wechsler intelligence scale for children: Manual. Psychological Corporation; 1991.
- Yakovlev, PI., Lecours, AR. The myelogenetic cycles of regional maturation of the brain. In: Minokowski, A., editor. *Regional Development of the Brain in Early Life*. Oxford: Blackwell Scientific; 1967. p. 3-70.
- Zarchi O, Diamond A, Weinberger R, Abbott D, Carmel M, Frisch A, Michaelovsky E, Gruber R, Green T, Weizman A, Gothelf D. A comparative study of the neuropsychiatric and neurocognitive phenotype in two microdeletion syndromes: velocardiofacial (22q11.2 deletion) and Williams (7q11.23) syndrome. *Eur Psychiatry*. 2013; 29:203–210. [PubMed: 24054518]

Zielinski BA, Prigge MB, Nielsen JA, Froehlich AL, Abildskov TJ, Anderson JS, Alexander AL.
Longitudinal changes in cortical thickness in autism and typical development. *Brain*. 2014;
137:1799–1812. [PubMed: 24755274]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Key points

- 22q11.2 deletion syndrome (22q11DS) is a genetic disorder that greatly increases risk of developing schizophrenia. Examining longitudinal trajectories of neuroanatomic development could inform the early identification of patients at highest risk for severe psychiatric distress.
- Cerebral surface morphology was examined at three timepoints in youth with 22q11DS and unaffected siblings.
- Longitudinal alterations were observed in prefrontal cortex and parieto-occipital regions. Positive symptoms of psychosis were associated with a trajectory of surface decreases in the orbitofrontal and inferior parietal lobule.
- These results advance our understanding of cerebral maturation and association with psychiatric phenotype in individuals with 22q11DS.

Figure 1. Group differences in Cerebral Surface Distances between 22q11DS and Unaffected Siblings at Time 3

The colors represent the significance level (p -value) for the differences between the groups; warm colors indicate cerebral surface protrusions in the 22q11DS group as compared to unaffected siblings, whereas cold colors represent surface indentations. For a list of brain regions corresponding to the numbers displayed in the figure, see Appendix S4.

Figure 2. Differences in the longitudinal trajectories across individuals with 22q11DS and Unaffected Siblings: Brain regions showing significant Age-by-Diagnosis interaction

The colors overlaid on the brain surfaces represent the significance level (p -value) for the differences in cerebral surface morphology between the groups over time. Warm colors indicate an increasing divergence in age-related trajectories over time, whereas cool colors indicate an increasing convergence in those trajectories over time. Line graphs show the Age-by-Diagnosis interaction within the (A) Left Superior Frontal Gyrus (region 1); (B) Left Inferior Parietal Lobule (region 8); (C) Left Inferior Occipital Gyrus (region 16); (D) Right Inferior Parietal Lobule (region 8); (E) Left Middle Orbitofrontal Gyrus (region 12). For a list of brain regions corresponding to the numbers displayed in the figure, see Appendix S4. The points in the scatterplots represent individual datapoints for the participants. Linear regressions were fitted for each of the two groups.

Figure 3. Neurodevelopmental Trajectories Associated with Psychosis Symptoms in 22q11DS
Regions displaying Age $\times$ SOPS-PS interaction, and line graphs for points (A) Right Middle Occipital Gyrus; (B) Left Lateral Orbitofrontal Gyrus; (C) Left Inferior Temporal Gyrus; (D) Left Lateral Occipital Gyrus; and (E) Left Cerebellum. The points in the scatterplots represent individual datapoints for the participants. Linear regressions were fitted for each of the two groups. For a list of the brain regions corresponding to the numbers displayed in the figure, see Appendix S4. The High SOPS category (in red) includes individuals with 22q11DS and a score above 3 on at least one item of the SOPS Positive Symptom Subscale (SOPS-PS).