DEVELOPMENTAL NEUROGENETICS OF CORTICAL THICKNESS AND CORTICAL SURFACE AREA IN SCHIZOPHRENIA: A MULTIPLEX EXTENDED PEDIGREE STUDY

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Peak age of onset for schizophrenia occurs during late adolescence and early adulthood, a critical period for brain development (Häfner, 2003). Schizophrenia genetic effects on neurodevelopment may remain stable from childhood (as proposed by early neurodevelopmental models), increase during adulthood closer to the peak age-of-onset (late neurodevelopmental models) (Pogue-Geile, 1991), or increase long after the peak age-of-onset (neurodegenerative models) (Lieberman, 1999). To our knowledge, no study to date has directly tested these developmental neurogenetic effects. To address this question, 230 participants (age range: 12-85 years) from 32 multigenerational families with at least two first-degree schizophrenia relatives and 276 unrelated controls underwent diagnostic interview and magnetic resonance imaging (MRI). Participants were stratified into age-risk periods based on their ages relative to population incidences of schizophrenia onset at the peak (22 years) and plateau (42 years): rising effects (younger than 23 years), peak effects (23-42 years), and plateau effects (older than 42 years). Quantitative imaging genetic analyses were conducted using SOLAR-Eclipse maximum-likelihood genetic variance decomposition algorithms on FreeSurfer MRI parcellations of bilateral cortical thickness and surface area. The effects of schizophrenia genetic risk were found to influence different aspects of brain structure before and after schizophrenia peak age-of-onset: early schizophrenia genetic effects influenced frontal and

cingulate surface area, whereas late schizophrenia genetic effects are more widespread and influence both regional thickness (across frontal, parietal, temporal, and cingulate regions) and regional surface area (across parietal, temporal, and cingulate regions). Furthermore, neurodegenerative schizophrenia genetic effects particularly influenced frontal and temporal thickness. This pattern was diagnostically specific to schizophrenia and not found in depression. Our findings bear important implications for multiple levels of systems genetic investigations: targets of genome-wide searches for schizophrenia genetic risk variants may be refined by examining specific cortical regions depending on the participants' ages relative to schizophrenia peak age-of-onset and changes in the expression of schizophrenia genetic risk variants across neurodevelopment of specific cortical regions may provide mechanistic insights into the development of schizophrenia. Overall, our findings emphasize the utility of using developmental approaches to inform genetic investigations of schizophrenia.

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PREFACE

There is a saying in my culture of origin which speaks to the ties that bind us across generations: 前人種樹，後人乘涼 – "In the shade of trees planted by our forebears, we rest."

I am thankful to the family from whom I gained an intellectual tradition: To my advisor, Michael Pogue-Geile, for helping me mine and polish myriad facets of my thinking into this crystallized work. To my mentors, Shaun Eack and Keith Nuechterlein, for providing me with many mirrors upon which to reflect parallel and intersecting ideas. To my milestone committee members for lending their prismatic perspectives to further illuminate the possibilities of this work.

I am thankful to the families who made space for my roles as a scientist and as a clinician: To the families who participated in this research for allowing me to glimpse how we can naturally be our distinct selves yet share profound likenesses. To the families under my care, past and present, for showing me how we can nurture healing in virtually any environment.

I am thankful to the family with whom I grew up, on both sides of the ocean most wide and deep: To those who live in the liminal space between the realities we share and the realities we cannot all perceive, for inspiring us by finding meaning in things that would otherwise seem impersonal and engaging with life beyond that which is merely in front of us. To my late great-grandmother for leading with wisdom that no written words could amply convey. To my late grandfather for instilling the pursuit of learning as a mindful daily practice. To my brother, Zachary, for supporting us with unvarnished honesty. To my brother, Roy, for supporting us with steadfast calm. To my mother, Phoebe, most of all, for embodying perceptiveness and perseverance in ways that are as quiet as they are resonant.

In the shade of your trees, I rest.

1.0 INTRODUCTION

Affecting approximately 1% of individuals worldwide, schizophrenia is a debilitating disorder characterized by positive and negative symptoms that are most likely to arise in late adolescence and young adulthood (Tandon, Keshavan, & Nasrallah, 2008), with men showing an earlier peak age of onset compared to women (Rajji, Ismail, & Mulsant, 2009). This peak in the age of onset of schizophrenia in young adulthood presumably arises from genetic and/or environmental factors at least some of which exert their maximal effects around the time of young adulthood (Pogue-Geile, 1991). This pivotal period is crucial not only for the development of schizophrenia but also for brain maturation in general (Feinberg, 1983; Murray & Lewis, 1987; Weinberger, 1987). In particular, this period marks an acceleration of synaptic pruning that increases the efficiency of neuronal transmissions (Huttenlocher, 1979). Therefore, it is possible that age-dependent causes of schizophrenia affect the course of brain development among those at risk.

Most studies investigating structural brain features in schizophrenia have examined volume, finding that individuals with schizophrenia generally have smaller brain volumes on average compared to controls in many regions (Haijma et al., 2013; Kuo & Pogue-Geile, 2019). Volumetric measurements, however, cannot differentiate between cortical thickness and cortical surface area, which appear to be driven by different cellular mechanisms; cortical thickness represents cell density in the cortex whereas cortical surface area represents the number of cortical columns that in turn affects the degree of cortical folding (Rakic, 1988). The distinction between cortical thickness and cortical surface area is important as they show different patterns of change across development (Lemaitre et al., 2012). Furthermore, although cortical thickness and cortical surface area are each highly heritable, genetic effects on each appear to be independent (Panizzon

et al., 2009). This suggests that genetic effects on cortical thickness and cortical surface area may differ during the age-period of greatest risk for schizophrenia.

The primary aim of this study was to examine age-related differences in cortical thickness and cortical surface area and schizophrenia liability, using a multiplex (multiple affected relatives per family), extended pedigree design. We hypothesized that genetic effects shared between schizophrenia liability and cortical thickness and cortical surface area changes across the lifespan, with the peak age of onset for schizophrenia in young adulthood representing a particularly important inflection point. To inform this work, the following sections first review developmental theories of schizophrenia and brain development.

1.1 DEVELOPMENT OF SCHIZOPHRENIA

1.1.1 Age of Onset in Schizophrenia

Schizophrenia is most likely to arise during young adulthood, from ages 20 to 35 (with males about five years earlier than females), followed by a subsequent period of increased risk in females around the period of menopause (Häfner, 2003). When averaged across males and females, the age of schizophrenia onset peaks by approximately 22 years of age for both sexes whereas the age at which schizophrenia onset starts to level off or plateau starts at approximately 42 years of age (Häfner, 2003). These observations are widely replicated despite variation across studies in definitions of age of onset for schizophrenia (including age at first positive psychotic symptoms, age at first contact with mental health professionals, and age at first admission), most of which are correlated and usually occur within 6 to 18 months of each other (DeLisi, 1992). This peak age of

onset suggests that young adulthood is the period during which developmental factors contributing to schizophrenia may maximally exert their effects. Such age-related effects may arise from changes in gene expression, environmental exposures, and/or interactions between genetic and environmental effects, ultimately contributing to alterations in brain development (T. D. Cannon et al., 2003). Acknowledging the temporal overlap between the peak age of schizophrenia onset and a period of major brain development, three general neurodevelopmental models of schizophrenia have been proposed, distinguished by the timing of brain changes reflecting the etiology of schizophrenia (Pogue-Geile, 1991): the early neurodevelopmental model (Murray & Lewis, 1987; Weinberger, 1987), the late neurodevelopmental model (Feinberg, 1983), and the neurodegenerative model (Lieberman, 1999).

1.1.2 Early Neurodevelopmental Theories of Schizophrenia

Models of neurodevelopment in schizophrenia may be heuristically classified as "early" or "late" developmental models (Pogue-Geile, 1991), recognizing that "mixed" models incorporating both features are possible as well as heterogeneity hypotheses in which different models apply to different schizophrenia patients. Early neurodevelopmental models propose that schizophrenia may arise from schizophrenia specific early insults to brain development that result in overt behavioral abnormalities much later in young adulthood (Murray & Lewis, 1987; Weinberger, 1987). Although neural structures are compromised during prenatal or neonatal development, the behavioral abnormalities of schizophrenia only emerge during young adulthood when the brain undergoes non-specific normative developmental changes, such as synaptic pruning or myelination (Murray & Lewis, 1987; Weinberger, 1987). Thus, the early neurodevelopmental insult is posited to remain largely symptomatically silent throughout the first decades of life and

only becomes clinically manifest through normal nonspecific developmental processes occurring during young adulthood (Pogue-Geile, 1991).

The early neurodevelopmental model of schizophrenia is supported by observations of a wide range of cognitive, social and emotional changes in many children who go on to develop schizophrenia (Murray et al., 2004; Tarbox & Pogue-Geile, 2008). A subgroup of adults with schizophrenia also show minor physical anomalies that are apparent markers of early developmental insults (John, Arunachalam, Ratnam, & Isaac, 2008). Furthermore, prenatal and obstetric complications and infections have been found to be associated with increased risk for developing schizophrenia (M. Cannon, Jones, & Murray, 2002).

Some specific neuropathological abnormalities detected post–onset have also been seen as supportive of early developmental hypotheses on the presumption that such features are unchanging from birth. For example, assuming that cortical folding is a neurodevelopmental process that is largely complete before birth and remains stable soon after birth, any reduced gyrification observed in schizophrenia post-onset may suggest a prenatal neurodevelopmental insult (Pantelis et al., 2005). Such structural brain changes in schizophrenia have been observed in the absence of glial proliferation or neuronal loss that would be expected in post-maturational neurodegeneration (Casanova, Stevens, & Kleinman, 1990; Harrison, 1999).

Although considerable evidence has accrued for early neurodevelopmental models of schizophrenia, it is largely limited to behavioral rather than neural antecedent abnormalities. Without invoking heterogeneity, such models also have difficulty accounting for the many individuals who do not have apparent perinatal risk factors or childhood behavioral abnormalities prior to onset. Most important is the question of diagnostic specificity. Perinatal insults and childhood behavioral abnormalities are risk factors for many adult outcomes and the extent to

which they increase risk for schizophrenia or psychosis specifically is less certain. Furthermore, early models do not account for the sometimes observed progressive reductions in certain brain structure volumes in schizophrenia occurring after illness onset (McGrath, Feron, Burne, Mackay-Sim, & Eyles, 2003). It is also unclear from follow-up studies of eventual schizophrenic individuals whether early abnormalities observed reflect genetic or environmental effects. Thus, many questions remain concerning how and even whether such early abnormalities lead specifically to later schizophrenia in adulthood.

1.1.3 Late Neurodevelopmental Models of Schizophrenia

In contrast to early neurodevelopmental models of schizophrenia, late neurodevelopmental models of schizophrenia propose that abnormalities in brain maturation lead specifically to frank symptoms of psychosis, with relatively little delay between neurological changes and behavioral consequences (Feinberg, 1983). Here, the normal development of neural structures during adolescence/young adulthood itself goes awry (Thompson, Pogue-Geile, & Grace, 2004), better accounting for the relative lack of early risk factors, lesions or childhood functional deficits in many individuals with schizophrenia (Feinberg, 1983) and being more parsimonious in not requiring a long latent period between insult and clinical expression. Such late developmental models do not ignore the possible role of early insults but rather view them as non-specific factors that may increase risk for schizophrenia as well as many other adult outcomes.

Excessive synaptic pruning has been posited to be a primary late neurodevelopmental process that goes awry to produce schizophrenia (Feinberg, 1983). Synaptic connections reach maximal density around 3 years of age, at approximately double the density observed in adulthood. Synaptic density declines thereafter through adolescence, and remains stable through adulthood

until senescence (Huttenlocher, 1979), with synaptic pruning predominantly targeting connections to excitatory glutamatergic neurons (Storm-Mathisen & Ottersen, 1990).

Reports of structural differences in the brain are consistent with reduced synaptic connections in schizophrenia relative to controls, including ventricular enlargement, decreased cortical thickness, increased neuronal density in certain brain regions, and reduced dendritic spine densities and synaptic markers in the cortex (reviewed in Faludi & Mirnics, 2011). Furthermore, substantially lower gray and white matter volumes in schizophrenia are present beginning at the first episode (Andreasen et al., 2011). Given that the numbers of neurons and glia do not appear to be reduced in schizophrenia compared to controls, the substantially lower cortical volumes observed from the onset of schizophrenia are likely attributable to reductions in dendrites and synapses (McGlashan & Hoffman, 2000). Major questions remain however concerning to what extent such reductions in brain volume in schizophrenia begin in adolescence and young adulthood or earlier during childhood.

1.1.4 Neurodegenerative Models of Schizophrenia

In contrast to early and late neurodevelopmental models, neurodegenerative hypotheses of schizophrenia posit neural abnormalities that not only persist, but progress, throughout illness course (DeLisi et al., 1997; Lieberman, 1999). Most neurodegenerative models do not specify the timing of initial brain abnormalities, but instead focus only on degeneration during the post-onset period and thus are compatible with either early or late neurodevelopmental models.

Much of the evidence supporting neurodegenerative models has centered on the consistent finding that a subset of individuals with schizophrenia show a deteriorating course rather than stability or recovery (Rabinowitz, Levine, Haim, & Hafner, 2007). Furthermore, duration of

untreated illness is predictive of symptom remission and functional outcome, suggesting a progressive process (Perkins, Gu, Boteva, & Lieberman, 2005). Neuroimaging findings also partially support a progressive disease process in schizophrenia. Although lower total brain volume and ventricle enlargement are largely stable across illness course in schizophrenia (Heilbronner, Samara, Leucht, Falkai, & Schulze, 2016), regional age-related changes may be suggestive of neurodegeneration. In particular, regional declines across age in frontal lobe volume, gray matter volume, white matter volume, cortical thickness and cortical surface area have been observed in schizophrenia; notably, these morphological changes have been associated with various measures of illness severity (Heilbronner et al., 2016).

Although these models differ in their relative emphasis on the timing and course of neural insults associated with schizophrenia, they all hypothesize that processes occurring around peak age of schizophrenia onset are important to understanding the etiology and development of the disorder, be they non-specific or schizophrenia, stable or progressive.

1.1.5 Neurodevelopmental Models and the Role of Genetics in Schizophrenia and Brain Development

Given that schizophrenia shows substantial heritability, with approximately 65% to 80% of liability attributable to genetic variation (Lichtenstein et al., 2009), it is generally hypothesized that most of the brain pathophysiology observed in schizophrenia is a result of genetic risk variants. Just as normative neurodevelopmental processes are driven in large part by genes that become active at different times across development, neurodevelopmental processes leading to schizophrenia may also be attributable to genetic effects that vary across development.

Importantly, the different neurodevelopmental models vary in their implications concerning which age periods may be most important for schizophrenia genetic effects on brain development.

Specifically, the different neurodevelopmental theories suggest that the genetic relationship between brain and schizophrenia is likely to be highest at the point in development when schizophrenia-related neural insults are hypothesized to become prominent. These possibilities can be considered for each theory in turn. First, the early neurodevelopmental theory suggests that schizophrenia deviations from normative brain development will become evident in early childhood, long before the age of peak schizophrenia onset, and then persist thereafter. Here, genetic effects on schizophrenia should show substantial overlap with genetic effects on cortical development early in childhood long before age of peak schizophrenia onset and then continue, if persistent, showing little change across adolescence and adulthood. In contrast, the late neurodevelopmental theory suggests that schizophrenia deviations from normative brain development may only become evident during the age of peak schizophrenia onset. Here, genetic effects on cortical development should show little overlap with schizophrenia liability during childhood but then increase at the age of peak schizophrenia onset and then, if persistent, continue unchanged across later adulthood. Finally, although the neurodegenerative theory does not specify timing of the onset of brain abnormalities, to the extent that neurodegeneration becomes more evident with increasing duration of illness, genetic effects on cortical development may show overlap with schizophrenia liability after the age of peak schizophrenia onset that then continue to increase across later adulthood.

Although many neurodevelopmental theories emphasize the contribution of genetic influences on brain development in schizophrenia, others emphasize the contribution of environmental influences to brain development in schizophrenia (Laurens et al., 2015). During

the period for early schizophrenia-related brain insult, environmental influences that have been linked to the subsequent diagnosis of schizophrenia include prenatal exposure to maternal infections (Sorensen, Mortensen, Reinisch, & Mednick, 2009), obstetric complications (M. Cannon et al., 2002), childhood illness (Dalman et al., 2008), residence in an urban area (Laursen, Munk-Olsen, Nordentoft, & Bo Mortensen, 2007), childhood trauma (Morgan & Fisher, 2007), and migration and ethnicity (Corcoran et al., 2009). In contrast, fewer potential late-occurring environmental exposures have been investigated, but supportive evidence has been found especially for substance misuse during adolescence and negative life-events (Arseneault et al., 2002). To the extent that environmental influences contributing to schizophrenia overlap with environmental influences adversely impacting brain development, environmental correlations across the age of peak schizophrenia onset should show changes similar to those hypothesized for genetic correlations.

The proposed study aims to investigate these implications of the different neurodevelopmental models by examining how, using an extended pedigree design, the genetic correlations between schizophrenia and cortical measures change across the following age periods: prior to peak age of schizophrenia onset in the 20s, after peak age of onset but before the plateau in the 40s, and after the plateau of onset. As a context for the proposed study, normative development and genetic effects on cortical brain structures will be reviewed first. Subsequently, shared genetic influences between schizophrenia and cortical brain measures and their modulation by age will be described. Finally, age- and duration-related changes in these brain measures will be summarized in post-onset schizophrenia. Although subcortical regions have been found to show important differences in schizophrenia, the focus of the current study is on cortical brain

structures, as cortical thickness and surface area have been examined primarily in cortical regions compared to subcortical regions.

1.2 NEUROIMAGING MEASURES OF NORMATIVE BRAIN DEVELOPMENT

Hypotheses concerning the pathophysiology of schizophrenia have centered upon changes occurring in the brain ever since the disorder was initially conceptualized (Kraepelin, 1911-1971). In examining in vivo structural brain changes in schizophrenia, most investigations have focused on comparing volumes of brain structures in schizophrenia versus controls. Over the past century, measures of brain volume in schizophrenia have progressed from global volumetric measures of the ventricles and brain tissue using pneumoencephalography and computed tomography to regional volumetric measures of specific brain structures using magnetic resonance imaging (MRI).

MRI studies consistently demonstrate that volumes of many brain tissue structures are smaller than average in schizophrenia, suggesting that changes in brain structure may be a core feature of the pathophysiology of schizophrenia (Haijma et al., 2013). Across the reviewed studies, volumetric reductions in schizophrenia were generally larger for gray matter than for white matter structures. As noted above, understanding contributors to changes in cortical gray matter volume in schizophrenia necessitates distinguishing the components of gray matter volume, cortical thickness and cortical surface area. These two measures have only been quantifiable with millimeter-level resolution during the last two decades with the introduction of surface-based morphometry (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000). Here, developmental changes

in brain volume will first be reviewed before describing changes in cortical thickness and cortical surface area.

1.2.1 Normative Changes in Brain Volume Across the Lifespan

Total brain volume shows striking patterns of normative growth and decline across the lifespan. Brain volume doubles during the first year of life and increases by approximately 15% during the second year of life (Knickmeyer et al., 2008). Brain volume continues to increase during childhood and early adolescence until sometime between the ages of 10 and 15 (Hedman, van Haren, Schnack, Kahn, & Hulshoff Pol, 2012; Mills et al., 2016). Brain volume then decreases throughout adolescence and young adulthood until the early twenties (Mills et al., 2016; Schnack et al., 2015) when it stabilizes until approximately age 40 (Hedman et al., 2012). After age 40, brain volume starts to decrease at an annual rate of approximately 0.2%, speeds up to reach an annual rate of 0.5% by age 60, and declines thereafter at a more precipitous rate (Hedman et al., 2012). These patterns of brain volume change are similar across the sexes (Hedman et al., 2012).

Most longitudinal studies indicate that cortical gray matter volume peaks in childhood and decreases through adolescence (Aubert-Broche et al., 2013; Giedd et al., 1999; Lebel & Beaulieu, 2011; Mills et al., 2016; Wierenga, Langen, Oranje, & Durston, 2014). The rate of reduction for gray matter volume slows down around age 30 and stabilizes thereafter (Hedman et al., 2012; Mills et al., 2016). In contrast, cortical white matter volume continues to increase at least until late adolescence and perhaps through early adulthood (Aubert-Broche et al., 2013; Lebel & Beaulieu, 2011; Mills et al., 2016). White matter volume then stabilizes through age 40, followed by accelerating reduction through senescence (Hedman et al., 2012; Mills et al., 2016). Thus, both gray matter and white matter volume show unique developmental trajectories with significant

changes occurring during early adulthood (slowing of decrease in gray matter volume and slowing of increase for white matter volume), suggesting that these structural brain features may be somehow related to schizophrenia risk.

1.2.2 Normative Genetic Contributions to Brain Volume Across the Lifespan

Meta-analysis of neuroimaging twin studies suggests that volumes of all brain regions examined are under significant genetic control, with heritability estimates for brain structures ranging from 20% to 85% (Blokland, de Zubicaray, McMahon, & Wright, 2012). Larger brain regions generally show greater and more robust genetic influence whereas smaller brain regions show smaller and less consistent heritability estimates, perhaps due to differences in measurement precision. Overall, the relative contribution of genetic influences on total brain volume increases throughout childhood, peaks during adolescence and early adulthood (ages 15-25), then decreases linearly into senescence (Batouli, Trollor, Wen, & Sachdev, 2014). A recent review of twin and family studies indicated that genetic influences on global, lobal, and subcortical brain volumes show similar patterns of change across the lifespan (Batouli, Trollor, Wen, & Sachdev, 2014). There are some indications that genetic effects on gray matter show developmental patterns that parallel those for whole brain volume.

Taken together, genetic effects on brain volume increase throughout the first decade of life along with substantial mean growth. In contrast, during adolescence, brain volume starts to decrease as genetic effects continue to increase. Interestingly, in early adulthood, around the age of peak schizophrenia onset, brain volume ceases its reduction and stabilizes just as genetic effects peak. After young adulthood, brain volume stabilizes for approximately two decades until the 40s whereas genetic effects decrease (and environmental influences increase). After the 40s (when

schizophrenia onset stabilizes), environmental influences on brain volume continue to increase, as brain volume decreases with acceleration. Genetic effects on gray matter volume appear to follow trajectories similar to those of whole brain volume. In contrast, white matter volume peaks later in young adulthood, stabilizes until the 40s and then declines, and shows low heritability throughout adulthood. Compared to developmental trajectories of genetic effects on white matter volume, developmental trajectories of genetic effects on gray matter volume show greater similarities with developmental trajectories of schizophrenia risk.

1.2.3 Independence of Genetic Effects on Cortical Thickness and Cortical Surface Area

In considering developmental changes in cortical volume of gray matter, it is important to consider separately whether its components, cortical thickness and cortical surface area, may follow different trajectories. The spatial organization of neurons in the brain reflects the temporal sequence of their generation and maturation. According to the radial unit hypothesis of cortical development, the cortex is formed from inside out. New neural stem cells migrate within their respective radial columns to their final locations at the outer layer of the cortex, where they ultimately mature (Rakic, 1988). Cortical neurons are ultimately organized into ontogenetic columns that are aligned perpendicularly to the surface of the brain (Mountcastle, 1997). This theory suggests that cortical surface area reflects the number of columns at each region whereas cortical thickness reflects the number of cells within each column (Rakic, 1995). Cortical thickness and cortical surface area are driven by different cellular and molecular mechanisms, which can be manipulated to induce changes in one but not the other (O'Leary & Sahara, 2008; Pontious, Kowalczyk, Englund, & Hevner, 2007). Indeed, cortical thickness and cortical surface

area are phenotypically uncorrelated in both global and lobal brain structures (Panizzon et al., 2009; Winkler et al., 2010).

Given the distinct biological processes involved in their generation and maintenance, cortical surface area and thickness may be driven by separable genetic influences. Here, genetic correlations (r_g) may be used to estimate the proportion of variance shared between two traits due to overlapping genetic effects. Indeed, although both cortical phenotypes are strongly influenced by genetic effects, with heritabilities of global measures ranging from 70% to 80% in adults, cortical thickness and cortical surface area are genetically uncorrelated (r_g= -0.15, p=0.08) (Panizzon et al., 2009; Winkler et al., 2010). Furthermore, genetic effects on cortical gray matter volume appear to be most correlated with genetic effects on cortical surface area rather than cortical thickness (Winkler et al., 2010). Thus, as potential markers of genetic effects contributing to schizophrenia, cortical thickness and cortical surface area should be considered separately.

1.2.4 Methodological Considerations Concerning the Measurement of Age-Related Changes in Cortical Thickness and Cortical Surface Area

Before delving into studies of cortical thickness and cortical surface area, sources of methodological heterogeneity in these cortical measurements should be noted as they may impact the interpretation of findings.

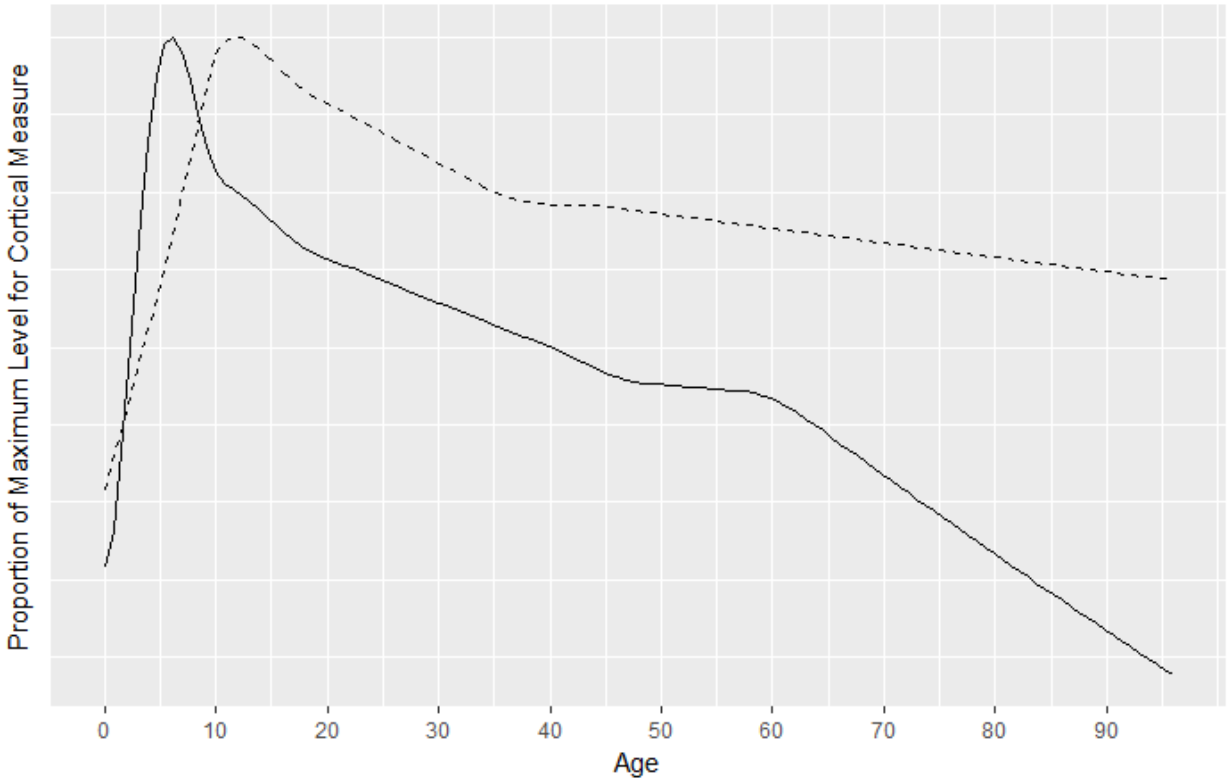
Demographic compositions of the samples differ substantially among studies. A number of studies include samples with wide age ranges without examining differences in measures by age, rendering it difficult to describe the effects of age on cortical measures. Furthermore, heterogeneity across studies in sample demographics may impact findings of age-related changes in cortical measures (LeWinn, Sheridan, Keyes, Hamilton, & McLaughlin, 2017).

Neuroimaging processing methods also differ substantially among studies. With regards to neuroimaging analytical software, most studies have utilized FreeSurfer and a few studies have used other software packages, such as BRAINS2 and CLASP. Furthermore, segmentation of brain regions can vary; for example, for some studies, the cingulate was segmented separately from the frontal, temporal, parietal, and occipital lobes, whereas other studies subsumed cingulate regions in adjacent cortical lobes. Some studies examined regions bilaterally whereas other studies examined regions by hemisphere. Furthermore, heterogeneity across studies in neuroimaging quality control may impact findings of age-related changes in cortical measures (Ducharme et al., 2016).

Analytical methods also differ substantially across studies. Broadly, neuroimaging analyses of cortical thickness and cortical surface area can be divided into two main approaches: vertex-based analyses compare cortical measures of all vertices across the cortex, whereas region of interest (ROI) analyses compare cortical measures in specified regions of the cortex a priori, often defined based on regions that have been found to show significant group differences in prior vertex-based analyses. Furthermore, different adjustments are made for potential confounds across studies. Generally, adjustments included age, sex, and handedness; however, some studies of regional cortical measures additionally adjusted for total brain volume, or global cortical thickness or global cortical surface area.

This heterogeneity across studies in sample demographics, neuroimaging processing methods, and neuroimaging analysis methods complicate the following tentative attempts to describe age-related changes in cortical measures.

1.2.5 Normative Development of Cortical Thickness and Cortical Surface Area



Note. Solid line indicates age-related changes in global cortical thickness. Dotted line indicates age-related changes in global cortical surface area.

Figure 1. Schematic of age-related changes in global cortical thickness and global cortical surface area across development.

Figure 1 depicts age-related changes in cortical morphology based on findings from studies to date that have examined cortical thickness and cortical surface area within the same sample. Global cortical thickness increases rapidly throughout early childhood and peaks before or by the age of 8 (Brown et al., 2012; LeWinn et al., 2017; Raznahan et al., 2011; Schnack et al., 2015; Wierenga et al., 2014). Global cortical thickness shows the most rapid declines before age 10, immediately after reaching peak thickness, and continues to decline until age 30 (Potvin, Dieumegarde, &

Duchesne, 2017; Schnack et al., 2015). From age 30 to 60, global cortical thickness declines less with age compared to the prior decades, showing a plateau around age 48 (Potvin et al., 2017; Schnack et al., 2015). After age 60, global cortical thickness declines precipitously with age (Potvin et al., 2017). Global cortical thickness declines by more than three standard deviations from age 18 to 96 (Potvin et al., 2017). Differences in cortical thickness appear between hemispheres during the initial period of greatest decline (between ages 10 to 20), with the right hemisphere showing changes approximately three years before the left hemisphere (Schnack et al., 2015). Age-related changes in lobal and regional cortical thickness across age 18 to 96 show some variability in ages of peak, decline and plateau, with linear, quadratic, and cubic age-related changes represented within different regions across lobes (Forde et al., 2017; Hogstrom, Westlye, Walhovd, & Fjell, 2013; Koolschijn & Crone, 2013; Ostby et al., 2009; Potvin et al., 2017; Wierenga et al., 2014).

In contrast, in the same studies examining both cortical thickness and cortical surface area within the same sample, global cortical surface area expands from early childhood to puberty, up until the age of 12 (Brown et al., 2012; LeWinn et al., 2017; Raznahan et al., 2011; Schnack et al., 2015; Wierenga et al., 2014). Global cortical surface area initially declines rapidly until age 18, then declines at a relatively constant gradual rate throughout adulthood until age 40 (Potvin et al., 2017; Schnack et al., 2015). Global cortical surface area subsequently declines more rapidly thereafter through age 96 (Potvin et al., 2017; Schnack et al., 2015). In contrast to the substantial changes in cortical thickness over adulthood, global cortical surface area declines by only one standard deviation from age 18 to 96 (Potvin et al., 2017). Differences in cortical surface area appear between hemispheres during between the ages of 10 and 20, with the right hemisphere showing changes approximately one year before the left hemisphere (Schnack et al., 2015). As

with age-related changes in cortical thickness, age-related changes in lobal and regional cortical surface area show variability in ages of peak, decline and plateau (Forde et al., 2017; Hogstrom et al., 2013; Koolschijn & Crone, 2013; Ostby et al., 2009; Potvin et al., 2017; Wierenga et al., 2014).

Overall, acknowledging important sources of heterogeneity in age-related changes in cortical measures across studies, normative cortical thickness leads cortical surface area, such that cortical thickness peaks during early childhood whereas cortical surface area peaks during adolescence. Similarly, rapid declines in each cortical measure occur during the age-period immediately after peak attainment, immediately preceding the age of peak schizophrenia risk. Thereafter, both cortical thickness and cortical surface area decline at a slower pace during the age of peak schizophrenia risk, reaching a plateau after the age of peak schizophrenia risk. In old age, both cortical thickness and surface area decline more rapidly than in the prior three decades. The extent to which these age-related changes are mediated by genetic influences in these brain regions will be discussed in the following section.

1.2.6 Genetic Effects on Normative Development of Cortical Thickness and Cortical Surface Area

For posterior regions that reach peak cortical thickness earlier in development, including primary sensorimotor regions (precentral and postcentral gyrus), medial frontal, anterior cingulate, temporal, inferior parietal regions (Lenroot et al., 2009; Schmitt et al., 2014), heritability peaks early (by age 10) then decreases until about 18 years old. In contrast, heritability peaks later (by age 14) in anterior regions that reach peak cortical thickness later in development, including the prefrontal cortex, orbitofrontal cortex, inferior postcentral gyrus, superior temporal lobe and inferior temporal lobe (Lenroot et al., 2009; Schmitt et al., 2014). Heritability of all regional

cortical thickness then remains stable from ages 18 to 77 (Chouinard-Decorte et al., 2014). Taken together, genetic effects on regional cortical thickness peak by early to late adolescence moving from posterior to anterior regions and plateaus at about age 18.

Compared to heritabilities of cortical thickness across age, heritabilities of cortical surface area have not been examined across age to our knowledge. Among cross-sectional studies, genetic effects on regional cortical surface area are moderate and remain relatively constant across all lobes from late childhood (age 8) through middle age (age 55) (Eyler et al., 2011; Ma et al., 2016; Patel et al., 2018; van Soelen et al., 2012; Yoon, Perusse, & Evans, 2012). Thus, after adolescence, the plateau in heritability of regional cortical surface area across age mirrors the plateau in heritability of regional cortical thickness across age.

Overall, heritability of regional cortical thickness appears to reach a peak by adolescence, and both regional cortical thickness and surface area plateau from early adulthood through senescence. The next section reviews the literature to date on the genetic relationship between schizophrenia and cortical measures across the age of peak schizophrenia onset.

1.3 GENETIC INFLUENCES ON SCHIZOPHRENIA AND BRAIN DEVELOPMENT

1.3.1 Methodological Considerations Concerning Genetic Studies of Schizophrenia Liability

In examining the genetic relationship between schizophrenia and cortical thickness and surface area, two study designs are informative. The more common study design quantifies differences in cortical thickness between controls and first-degree relatives of individuals with schizophrenia.

The other class of more powerful designs are genetic studies conducted in twin or extended pedigree samples that include multiple classes of kinship. In such studies, variance decomposition analyses can be conducted to produce estimates of the genetic overlap between cortical measurements and schizophrenia risk.

Before delving into these studies, sources of methodological heterogeneity for genetic studies of schizophrenia liability will be noted as they may impact the interpretation of findings. Beyond the neuroimaging processing and analytical heterogeneity described in previous sections, additional sources of heterogeneity include sample recruitment, treatment of age, reporting of age, and reporting of results. For each source of methodological consideration, relevant study features are noted in the descriptive summary tables of the studies (Tables 1 to 5).

First, the demographic and psychiatric characteristics of relatives may impact the results substantially. Although most studies exclude relatives who themselves have psychosis, not all screen for a history of psychosis in these relatives, thereby potentially inflating the genetic effects of schizophrenia on cortical measures. Importantly, studies including first-degree relatives may sometimes combine offspring, siblings, and/or parents of individuals with schizophrenia. Consider that if an index individual (proband) with schizophrenia recently experienced their first psychotic episode around the age of peak schizophrenia onset, their offspring may not yet have reached age of peak schizophrenia onset, their siblings are in the age of peak schizophrenia onset, and their parents have passed the age of peak schizophrenia onset and are likely to be within range of the age of plateau schizophrenia onset. Combining different classes of relatives across generations thus makes it difficult to parse age-related genetic effects. In addition, these classes of relatives also differ in the nature of their shared genetic effects with probands as well as their environmental experiences. Parents and offspring do not share genetic dominance effects, whereas siblings do.

Furthermore, shared environmental effects differ between these classes of relatives; siblings are typically reared with a sibling who does not have schizophrenia but eventually develops schizophrenia around the time of leaving home to live independently, whereas children who live with a parent with schizophrenia are reared in an environment where the parent has already developed schizophrenia. In contrast to siblings and children of individuals with schizophrenia, parents of individuals with schizophrenia also demonstrate reproductive fitness effects, such that schizophrenia individuals are substantially less likely to have offspring than the general population. In summary, combining relatives across these classes confounds age, genetic, and environmental effects on expressed liability for schizophrenia.

Genetic effects on brain measures change substantially over age, as described in the previous sections. Genetic liability among relatives who do not themselves have schizophrenia may be classified as genetic liability that is to-be-expressed as a schizophrenia diagnosis, genetic liability that will remain unexpressed as a schizophrenia diagnosis, or a lack of genetic liability for schizophrenia. Notably, the former two can be differentiated with advancing age, as an increasing number of relatives develop schizophrenia and are no longer "unaffected" relatives, having manifestly expressed their genetic liability for schizophrenia. Thus, the to-be-expressed genetic liability for schizophrenia decreases with advancing age among relatives whereas the expressed genetic liability for developing schizophrenia accumulates with advancing age, such that approximately 15% of relatives eventually develop schizophrenia (Kendler et al., 1993). The other 85% of relatives, who do not ultimately develop schizophrenia, on average show cognitive and pathophysiological features that differ on average from normative controls (Boos, Aleman, Cahn, Hulshoff Pol, & Kahn, 2007; Snitz, Macdonald, & Carter, 2006), indicating that the unexpressed genetic liability for schizophrenia shows phenotypic effects even among relatives who will not

later develop schizophrenia. To-be-expressed liability evidently changes with age, as suggested by epidemiological patterns of age of onset for schizophrenia, and has been the focus of many studies attempting to predict schizophrenia onset. However, the key question of interest in the proposed study is whether liability changes with age even among those relatives who are unlikely to later develop schizophrenia. Thus, studies are most informative when samples have a narrow age range or when age effects are examined across a wide age range without collapsing across ages.

Finally, the reporting of relative/control comparisons for brain structures is variable across studies. Given the large number of regions examined, some studies reported results only for regions where significant differences were observed between relatives and controls. Furthermore, some studies presented heat maps of effect sizes or p-values across the cortex, whereas others reported effect sizes for specified regions.

In the following sections, for the purposes of identifying cortical regions that may show maximal correlation with schizophrenia genetic liability across age, findings are indicated where relatives show significant differences from controls in at least one cortical region within the lobe. Given the diverse methods for segmenting brain regions and the various regions that were examined, findings were summarized by lobe and hemisphere, such that for a study, a significant result for the lobe is indicated if any cortical region within the lobe showed a significant group difference (e.g. decreased cortical thickness in relatives compared to controls for the left superior temporal gyrus or any other temporal region is indicated as a significant difference in the left temporal lobe in the tables).

1.3.2 Developmental Genetic Relationship between Schizophrenia and Cortical Thickness

Table 1 summarizes cross-sectional studies of cortical thickness in relatives and controls arranged by the mean age of their samples. Here, the results are summarized by region indicating the directionality and significance of results.

Six studies examined cortical thickness in relatives compared to controls on average during adolescence and early adulthood, with one study (Sprooten et al., 2013) drawing upon a sample that is more than twice as large as any sample in the five other studies (Byun et al., 2012; Harms et al., 2010; Karnik-Henry et al., 2012; Li et al., 2012; Prasad et al., 2010). This large study indicated that relatives show similar cortical thickness compared to controls for most regions except for left temporal regions, which show decreased cortical thickness (Sprooten et al., 2013). In contrast, findings are mixed for regional cortical thickness investigated in the other, smaller studies (Byun et al., 2012; Harms et al., 2010; Karnik-Henry et al., 2012; Li et al., 2012; Prasad et al., 2010). Thus, schizophrenia genetic liability appears to be associated with few differences in regional cortical thickness except for perhaps decreased cortical thickness of left temporal regions during adolescence and young adulthood.

Four studies examined cortical thickness in relatives compared to controls on average during adulthood before age 40, with one study (Goldman et al., 2009) drawing upon a sample that is at least four times larger than any sample in the three other studies (Bohlken, Brouwer, Mandl, Kahn, & Hulshoff Pol, 2016; Goghari, Rehm, Carter, & MacDonald, 2007; Hulshoff Pol et al., 2012), though it should be noted that the age range for this sample was from late adolescence to middle age. This study indicated that relatives show widespread reductions in regional cortical thickness across all cortical lobes compared to controls (Goldman et al., 2009), in contrast to mixed findings for regional cortical thickness across the lobes in other, much smaller studies (Goghari et

al., 2007; Hulshoff Pol et al., 2012). Thus, after early adulthood before age 40, schizophrenia genetic liability appears to be associated with widespread decreases in regional cortical thickness across all lobes.

Two studies examined cortical thickness in relatives compared to controls on average in middle age after age 40, with one study (Yang et al., 2010) drawing upon a sample that is twice as large as the other study (Goghari, Truong, & Spilka, 2015). The larger study indicates that relatives show similar cortical thickness to controls for regions across all lobes except for decreased cortical thickness for left occipital regions (Yang et al., 2010), in contrast to mixed findings in the opposite direction for most regions in the smaller study (Goghari et al., 2015). Thus, schizophrenia genetic liability may be associated with few differences in regional cortical thickness in mature adulthood, except perhaps for decreased cortical thickness for left occipital regions.

Overall, during adolescence and early adulthood, schizophrenia genetic liability appears to be associated with few differences in regional cortical thickness except perhaps for decreased cortical thickness for left temporal regions. After this period and before age 40, schizophrenia genetic liability may be associated with widespread decreases in regional cortical thickness across the brain. However, these decreases appear to be transient, as schizophrenia genetic liability after age 40 may be associated only with decreased cortical thickness for left occipital regions. These conclusions are tentative given not only the lack of convergence in the literature, but because the studies are grouped by average age and show overlapping age ranges. The extent to which schizophrenia genetic liability may be associated with deviations from normative development for cortical surface area is examined in the following section.

Table 1. Summary of cross-sectional studies of cortical thickness in relatives of schizophrenia patients.

	Sample					Age at First Scan			Analysis						Regions				
Study	Index Relatives (N)	Patient (N)	Controls (N)	Control Relatives (N)	Relative's Relation to Proband	Mean (SD)	Age range	Processing	Effect Sizes Reported in Study	Vertex-wise	A priori ROI	Bilateral or Hemispheric	Number of ROIs	Whole Brain	Frontal	Parietal	Temporal	Occipital	Cingulate
ADOLESCENCE AND EARLY ADULTHOOD																			
Prasad 2010	31		33		offspring	16.26 (2.76)		BRAINS2	Cohen's d & r (raw means & SDs)		X	Bilateral Lobal	4	L, R	L, R	L-, R-	L, R	L, R	
Sprooten 2013	144	34	36		sibling	21.19 (3.01)		FreeSurfer	F-statistics (raw means & SDs)	X		Hemispheric	34x2		L, R	L, R	L-, R	L, R	L, R
Li 2012	21	20	48		first-degree relative	21.1 (5.5)	16-30	FreeSurfer	raw means & SDs		X	Hemispheric	14x2		L+, R+	L, R+	L, R+	L, R	
Karnik-Henry 2012	33	39	47	50	sibling	22.1	14-28	FreeSurfer	F-statistics (least square means & SEs)		X	Hemispheric	1x2				L-, R-		
Harms 2010	26	26	40	40	sibling	22.3 (3.4)		FreeSurfer	least square means & SEs		X	Bilateral	3		L, R				
Byun 2012	31	31	29		first-degree relative	22.61 (5.47)		CLASP	regional maps p-values	X					L-, R-	R-	L-		R-
ADULTHOOD																			
Goghari 2007	19		22		sibling	34.2 (11)		FreeSurfer	partial eta-squared		X	Hemispheric	13x2	L, R	L, R	L, R	L, R	L, R	L-, R-
Hulshoff Pol 2012	26	25	83	81	co-twin	37.4 (11.4)		CLASP	(heritability), Rg	X					L, R	L, R+	L+, R-	R	
Bohlken 2016	33	37	65	65	co-twin	37.136		FreeSurfer	(heritability), Rg	X		Bilateral		L-, R-					
Goldman 2009	192	115	196		sibling	37.49 (9.77)	17.49-58.25	FreeSurfer	Risch lambdas	X		Bilateral	33		L-, R-	L-, R-	L-, R-	L-, R-	L-, R-
MIDDLE AGE																			
Goghari 2015	26	25	23		first-degree relative	40.85 (15.67)		FreeSurfer	Cohen's d (raw means & SDs)	X		Hemispheric	33x2		L+, R+	L+, R+	L, R	L+, R+	L+, R+
Yang 2010	66	48	27	77	parent or sibling	46.9		3D Deformation	ANOVA Permutation Testing p-values	X		Hemispheric	31x2	L, R	L, R	L, R	L, R	L-, R	

Note. Findings were summarized by lobe and hemisphere, such that any cortical region within each lobe showing significant group differences was shown for each study (e.g. decreased cortical thickness in relatives compared to controls for the left superior temporal gyrus or any other temporal region is indicated as a significant difference in the left temporal lobe). L denotes region in left hemisphere examined, R denotes region in right

hemisphere examined. Significantly decreased cortical thickness for relatives compared to controls is indicated by '-', whereas significantly increased cortical thickness for relatives compared to controls is indicated by '+'. If there is no + or – sign, no significant difference in cortical thickness was detected between groups. The twin study by Hulshoff Pol et al. (2012) included 13 discordant DZ pairs, 44 MZ control (1 incomplete) and 39 DZ (1 incomplete) control twin pairs. The twin study by Bohlken et al. (2016) included 14 discordant MZ pairs (2 incomplete), 2 concordant MZ pairs, 36 control MZ pairs, 21 discordant DZ pairs (2 incomplete) and 31 control DZ pairs (4 incomplete).

1.3.3 Developmental Genetic Relationship between Schizophrenia and Cortical Surface Area

Table 2 summarizes cross-sectional studies of cortical surface area in relatives and controls stratified by average of the samples.

Three small, similarly-sized studies examined cortical surface area on average during adolescence and early adulthood (Harms et al., 2010; Li et al., 2012; Prasad et al., 2010). These studies indicate that relatives generally show similar levels of regional cortical surface area compared to controls, except for perhaps decreased cortical surface area in bilateral frontal and parietal regions (Harms et al., 2010; Li et al., 2012; Prasad et al., 2010). These positive findings were reported in one study (Prasad et al., 2010), whereas the other two studies reported no significant differences in regional cortical surface area in relatives compared to controls (Harms et al., 2010; Li et al., 2012). Overall, the limited evidence suggests that schizophrenia genetic liability is associated with few differences in cortical surface area during adolescence and early adulthood, except for perhaps decreased cortical surface area for bilateral frontal and parietal regions.

Two small studies examined cortical surface area in relatives and controls on average after early adulthood and before age 40 (Bohlken et al., 2016; Goghari et al., 2007). The larger study only examined global cortical surface area, finding no differences between relatives and controls in global cortical surface area (Bohlken et al., 2016). The smaller study generally found no differences in cortical surface area of most regions except for cortical surface area of bilateral temporal regions, where findings across left temporal regions were mixed (Goghari et al., 2007). Overall, the evidence suggests that schizophrenia genetic liability is associated with few differences in cortical surface area in adulthood, except for perhaps bilateral temporal regions.

Only one study examined cortical surface area in relatives and controls in adulthood after age 40 (Glahn et al., 2015). This study is large and encompasses participants who range in age from 34 to 67. This study indicated that relatives show decreased cortical surface area for bilateral frontal, parietal, and temporal regions (Glahn et al., 2015).

Overall, schizophrenia genetic liability does not appear to be robustly associated with decreased regional cortical surface area in adolescence and early adulthood and in adulthood up until age 40, although there were some positive findings for frontal, parietal, and temporal cortical structures. In contrast, after age 40, schizophrenia seems to be associated with decreases in cortical surface area of the frontal, parietal, and temporal lobes. These findings suggest that schizophrenia genetic liability may be most associated with decreased cortical surface area after the age of peak schizophrenia risk. As with conclusions regarding the association between schizophrenia genetic liability and cortical thickness across age periods, these conclusions are tentative due to the limited convergence across studies and the overlapping age ranges of some of the samples. The extent to which schizophrenia genetic liability may be associated with deviations from normative age-related changes for cortical thickness and cortical surface area is examined in the following section.

Table 2. Summary of cross-sectional studies of cortical thickness in relatives of schizophrenia patients.

		Sample				Age at First Scan			Analysis						Regions				
tudy	ndex Relativ es (N)	atient (N)	ontrols (N)	ontrol Relative s (N)	elative's Relation to Proband	ean (SD)	ge range	rocessing	ffect Sizes Reported in Study	ertex-wise	priori ROI	ilateral or Hemisphe ric	umber of ROIs	hole Brain	rontal	arietal	emporal	ccipital	ingulate
	ADOLESCENCE AND EARLY ADULTHOOD																		
rasad 2010	1		3		ffspring	6.26 (2.76)		RAINS2	ohen's d & r (raw means & SDs)			ilateral Lobal		, R	-, R-	-, R-	, R	, R	
i 2012	1	0	8		irst-degree relative	1.1 (5.5)	6-30	reeSurfer	aw means & SDs			emispheri c	4x2		, R	, R	, R	, R	
arms 2010	6	6	0	0	ibling	2.3 (3.4)		reeSurfer	east square means & SEs			ilateral			, R				
	ADULTHOOD																		
oghari 2007	9		2		ibling	4.2 (11)		reeSurfer	artial eta-squared			emispheri c	3x2	+, R	, R	, R	+/-, R-	, R	, R-
ohlken 2016	3	7	5	5	o-twin	7.136		reeSurfer	heritability), Rg			ilateral		, R					
	MIDDLE AGE																		
lahn 2015	33		373		edigree	6.87 (13.45)	4-67	reeSurfer	chizophren ia Relatednes s betas and p-values			ilateral	3		-, R-	-, R-	-, R-	, R	, R

Note. Findings were summarized by lobe and hemisphere, such that any cortical region within each lobe showing significant group differences was shown for each study (e.g. decreased cortical surface area in relatives compared to controls for the left superior temporal gyrus or any other temporal region is indicated as a significant difference in the left temporal lobe). L denotes region in left hemisphere examined, R denotes region in right hemisphere examined. Significantly decreased cortical surface area for relatives compared to controls is indicated by '-', whereas significantly increased cortical surface area for relatives compared to controls is indicated by '+'; if different regions within a lobe showed significantly decreased cortical surface area in one regions and significantly increased cortical surface area in another region, this was indicated by '+/-'. If there is no + or – sign, no significant difference in cortical surface area was detected between groups. The twin study by Bohlken et al. (2016) included 14 discordant MZ pairs (2 incomplete), 2 concordant MZ pairs, 36 control MZ pairs, 21 discordant DZ pairs (2 incomplete) and 31 control DZ pairs (4 incomplete).

1.3.4 Genetic Overlap between Schizophrenia and Age-Related Changes in Cortical Thickness and Cortical Surface Area

To date, only two studies of cortical thickness and cortical surface area have provided longitudinal data on relatives of individuals with schizophrenia (Bois et al., 2015; Prasad et al., 2010), both of which sampled young relatives and are summarized in Table 3. Notably, one study (Bois et al., 2015) has a substantially larger sample than the other (Prasad et al., 2010) by a factor of 10. Inferences regarding age-related changes in cortical measures are constrained by the short follow-up period in both studies, which was only one year.

During adolescence and early adulthood, both studies indicated that relatives show smaller age-related decreases in frontal lobe thickness compared to controls (Bois et al., 2015; Prasad et al., 2010). In addition, the larger of the two studies indicated that relatives showed larger age-related decreases in cortical thickness for bilateral occipital regions and smaller age-related decreases for cingulate regions (Bois et al., 2015; Prasad et al., 2010). Thus, before the age of peak schizophrenia onset, schizophrenia genetic liability may be associated with smaller age-related decreases in cortical thickness for bilateral frontal regions and perhaps bilateral cingulate regions, as well as larger age-related decreases in cortical thickness for bilateral occipital regions.

In characterizing cortical surface area changes related to genetic risk for schizophrenia, the larger of two studies indicated that relatives show similar decreases to controls for regional cortical surface area for all lobes (Bois et al., 2015), whereas the smaller study suggested smaller age-related decreases in cortical surface area for frontal regions (Prasad et al., 2010). Overall, schizophrenia genetic liability may be associated with few differences in age-related decreases for cortical surface area across the brain, except for perhaps smaller age-related decreases in cortical surface area for frontal regions.

In summary, cross-sectional and longitudinal studies of cortical morphology suggest that schizophrenia genetic liability may be associated with different patterns of cortical development across the age of peak schizophrenia onset, particularly for frontal, parietal, and temporal regions. Schizophrenia genetic liability appears to be associated with few differences in regional cortical thickness during adolescence and early adulthood. Widespread decreases in regional cortical thickness associated with schizophrenia genetic liability become more apparent after young adulthood but may not persist into mature adulthood. The timing of the changes for cortical thickness is more consistent with late neurodevelopmental models of schizophrenia in that few effects were detected in younger relatives, whereas adult relatives showed effects. Similarly, schizophrenia genetic liability may also be most associated with decreased cortical surface area after the age of peak schizophrenia risk, although some positive findings emerge earlier. The extent to which post-onset differences may be observed in cortical thickness and cortical surface area will be examined in the next section.

Table 3. Summary of longitudinal studies of cortical thickness and cortical surface area in relatives of schizophrenia patients.

	Sample	Age at First Scan			Analysis						Regions					
Study	Index Relatives (N)	Mean (SD)	Age range	Interscan Interval (Years)	Processing	Effect Sizes Reported in Study	Vertex-wise	A priori ROI	Bilateral or Hemispheric	Number of ROIs	Whole Brain	Frontal	Parietal	Temporal	Occipital	Cingulate
CORTICAL THICKNESS																
Prasad 2010	16	16.26 (2.76)		1	BRAINS2	Cohen's d & r (raw means & SDs)		X	Bilateral Lobal	4	L, R	L+, R+	L, R	L, R	L, R	
Bois 2015	142	21.19 (3.01)		1.68		adjusted means & SDs (age, sex, IQ)		X	Bilateral Lobal	6	L, R	L+, R+	L, R	L, R	L-, R-	L+, R+
CORTICAL SURFACE AREA																
Prasad 2010	16	16.26 (2.76)		1	BRAINS2	Cohen's d & r (raw means & SDs)		X	Bilateral Lobal	4	L+, R+	L+, R+	L, R	L, R	L, R	
Bois 2015	142	21.19 (3.01)		1.68		adjusted means & SDs (age, sex, IQ)		X	Bilateral Lobal	6	L, R	L, R	L, R	L, R	L, R	L, R

Note. Findings were summarized by lobe and hemisphere, such that any cortical region within each lobe showing significant group differences was shown for each study (e.g. larger decreases across time in cortical thickness in relatives compared to controls for the left superior temporal gyrus or any other temporal region is indicated as a significant difference in the left temporal lobe). L denotes left hemisphere examined, R denotes right hemisphere examined. Larger decreases in cortical thickness across time for relatives compared to controls are indicated by '-', whereas smaller decreases in cortical thickness across time for relatives compared to controls are indicated by '+'. If there is no + or – sign, no significant difference in slopes of cortical thickness declines with age were detected.

1.3.5 Post-Onset Development of Cortical Thickness and Cortical Surface Area in Schizophrenia

Neurodegenerative hypotheses of schizophrenia suggest that changes in the brain occur following the onset of schizophrenia, such that the effects increase with longer duration of illness. Here, deviations from normative decreases in cortical thickness and cortical surface area should be increasingly observable at later stages of the illness. Thus, age-related differences in cortical thickness and cortical surface area in schizophrenia are compared to normative development after the onset of schizophrenia. To date, nine studies have examined age-related changes in cortical thickness in schizophrenia compared to controls, whereas one study has examined age-related changes in cortical surface area in schizophrenia compared to controls. It should be noted that studies of older patients may be constrained by selection effects, such that individuals who recover from schizophrenia are unlikely to be recruited into these studies, whereas those with recurring symptoms are recruited into these studies. Thus, these studies may be biased towards individuals with greater illness severity and greater expressed genetic liability for schizophrenia. In contrast to examining main effects for cortical measures within each age-risk group across studies of relatives, the findings reviewed here are based on diagnosis-by-age interactions in cross-sectional studies and diagnosis-by-time interactions in longitudinal studies of schizophrenia patients. This allows for the examination of potential changes in cortical measures with advancing illness duration in schizophrenia.

Table 4 summarizes cross-sectional studies of age-related differences in cortical thickness in schizophrenia compared to controls, stratified by patients' mean age at MRI scan. Four cross-sectional studies to date have reported diagnosis-by-age interactions for cortical thickness. One study investigated age-related changes in regional cortical thickness in adulthood before age 40,

finding normative age-related decreases in cortical thickness in schizophrenia compared to controls, though it should be noted that the age range of this sample encompassed adolescence to middle age (Kubota et al., 2011). Three other studies investigated age-related differences in regional cortical thickness in adulthood after age 40, finding that overall, schizophrenia showed normative age-related differences in cortical thickness for most regions except for perhaps larger age-related decreases in cortical thickness for left frontal regions, as found in the largest study of the three (Kuperberg et al., 2003; Nesvag et al., 2008; Zhang et al., 2015). Overall, after adolescence and early adulthood, schizophrenia may be associated with normative levels of age-related decreases in cortical thickness across most regions except for perhaps greater age-related decreases in cortical thickness of left frontal regions in adulthood after 40.

Table 4. Summary of cross-sectional studies of group by age interactions in cortical thickness for schizophrenia patients post-onset.

	Sample		Age at First Scan			Scans			Analysis				Regions				
Study	Patient (N)	Controls (N)	Mean (SD)	Age range	Duration of Illness	Number of Scans	Inter-scan Interval	Processing	Vertex-wise	A priori ROI	A posteriori ROI	Whole Brain	Frontal	Parietal	Temporal	Occipital	Cingulate
ADULTHOOD																	
Kubota et al. (2011)	83	90	35.7 (10.1)	18-55	11.0 (9.2)	1		FreeSurfer	X		X		L, R	R	R		
MIDDLE AGE																	
Kuperberg et al. (2003)	32	32	40 (10)		16 (10)	1		FreeSurfer		X			L, R	L, R	L, R	L, R	L, R
Nesvåg et al. (2008)	96	107	42.1 (7.3)	25-57	17.3 (8.6)	1		FreeSurfer	X	X			L-, R	L, R	L, R	L, R	
Zhang et al. (2015)	25	33	46.68 (13.54)		21.04 (12.00)	1		FreeSurfer	X		X		R-	L+	L-		

Note. Findings were summarized by lobe and hemisphere, such that any cortical region within each lobe showing significant group differences was shown for each study (e.g. larger age-related changes in cortical thickness in schizophrenia compared to controls for the left superior temporal gyrus or any other temporal region is indicated as a significant difference in the left temporal lobe). L denotes region in left hemisphere examined, R denotes region in right hemisphere examined. Significantly larger age-related decreases in cortical thickness for patients compared to controls is indicated by '-', whereas significantly smaller age-related decreases in cortical thickness for patients compared to controls is indicated by '+'. If there is no + or – sign, no significant difference in slopes of cortical thickness declines with age were detected.

Table 5 summarizes longitudinal studies of age-related changes in cortical thickness in schizophrenia compared to controls, stratified by patients' mean age at the baseline MRI scan. Five longitudinal studies to date have investigated differences in the rate of cortical thinning in schizophrenia compared to controls. Two of these studies examined age-related changes in cortical thickness in schizophrenia patients during adolescence and early adulthood (Epstein & Kumra, 2015; Palaniyappan et al., 2013) over approximately a two year period in small samples, finding that schizophrenia patients show normative age-related decreases in cortical thickness for most regions, except perhaps greater age-related decreases in cortical thickness for left frontal regions. Two longitudinal studies have examined age-related changes in cortical thickness for schizophrenia during adulthood and before age 40 (Cobia, Smith, Wang, & Csernansky, 2012; Roiz-Santianez et al., 2015). These studies, which followed individuals for two to three years, indicated that schizophrenia showed greater age-related decreases in cortical thickness of bilateral frontal regions and perhaps bilateral temporal regions compared to controls in adulthood before age 40. Finally, one longitudinal study, with a follow-up period of five years, examined the period of adulthood after age 40, finding that schizophrenia demonstrates normative age-related decreases in frontal cortical thickness (Nesvag et al., 2012). Overall, schizophrenia may show greater age-related decreases in cortical thickness of bilateral frontal regions in adulthood, which does not continue into later adulthood after age 40.

Only one longitudinal study to date has compared age-related changes in cortical surface area in schizophrenia compared to controls, finding that, around age 30, schizophrenia patients show normative age-related decreases in cortical surface area across two years for frontal and temporal regions (Cobia et al., 2012).

Table 5. Summary of longitudinal studies of differences in changes over time in cortical thickness in schizophrenia patients post-onset.

	Sample		Age at First Scan			Scans			Analysis				Regions				
Study	Patient (N)	Controls (N)	Mean (SD)	Age range	Duration of Illness	Number of Scans	Inter-scan Interval	Processing	Vertex-wise	A priori ROI	A posteriori ROI	Whole Brain	Frontal	Parietal	Temporal	Occipital	Cingulate
ADOLESCENCE AND EARLY ADULTHOOD																	
Palaniyappan et al. (2013)	18	19	16.1 (1.15)	13.5-17.8		2	2	FreeSurfer		X			L		R		L
Epstein and Kumra (2015)	17	34	16.3 (1.3)			2	1.5	FreeSurfer		X			L-, R	L, R	L		
ADULTHOOD																	
Roiz-Santianez et al. (2015)	109	76	29.44 (8.21)		2.0 (2.3)	2+ (2-4)	3 (1 per year)	BRAINS2		X		L-, R-	L-, R-	L, R	L, R	L, R	
Cobia, Smith, Wang, and Csernansky (2012)	20	20	31.9 (11.1)	17-65 (incl. crit.)	12.4 (12.9)	2+	2	FreeSurfer		X			L-, R-		L-, R-		
MIDDLE AGE																	
Nesvag et al. (2012)	52	63	41.4 (6.9)		17.3 (8.0)	2	5	FreeSurfer	X			L, R	L, R				

Note. Findings were summarized by lobe and hemisphere, such that any cortical region within each lobe showing significant group differences was shown for each study (e.g. larger decreases in cortical thickness across time in schizophrenia compared to controls for the left superior temporal gyrus or any other temporal region is indicated as a significant difference in the left temporal lobe). L denotes left hemisphere examined, R denotes right hemisphere examined. Larger decreases in cortical thickness across time for schizophrenia patients compared to controls are indicated by '-', whereas smaller decreases in cortical thickness across time for schizophrenia patients compared to controls are indicated by '+'. If there is no + or – sign, no significant difference in slopes of cortical thickness declines with age were detected.

In summary, after onset, schizophrenia appears to be associated with increased rates of decline in regional cortical thickness during adolescence, young adulthood, and adulthood after age 40 for bilateral frontal regions. Schizophrenia also appears to be associated with normative age-related decreases in cortical surface area during adulthood before age 40. These findings suggest that post-onset effects of schizophrenia are most evident in cortical thickness for frontal regions during the age period of peak schizophrenia risk. Overall, this pattern of results is only partially consistent with neurodegenerative models of schizophrenia, which suggest increasing deficits in cortical measures following the onset of schizophrenia.

1.4 AIMS AND HYPOTHESES

In summary, early neurodevelopmental theories posit that changes in brain development contributing to schizophrenia should be evident before the peak age of risk for schizophrenia whereas late neurodevelopmental theories suggest that such pathological changes in brain development are more evident during the age of peak risk for schizophrenia. Neurodegenerative theories posit that changes in cortical measures should increase with advancing illness duration after schizophrenia onset. Normative cortical development is characterized by peak cortical thickness in early childhood and peak cortical surface area during early adolescence, followed by rapid declines for both features and slower decline during the peak age of risk for schizophrenia. Genetic influences on normative cortical development mirror these phenotypic developmental changes, at least for cortical thickness, such that heritability peaks in childhood through adolescence, then plateaus from adulthood through senescence, whereas the heritability of cortical surface area appears to remain relatively stable over development.

The extant literature suggests that schizophrenia genetic liability may influence regional cortical thickness during peak age of schizophrenia onset, decreasing cortical thickness and perhaps cortical surface area throughout the cortex in the period after young adulthood, which is more consistent with late neurodevelopmental models of schizophrenia. Furthermore, post-onset changes in cortical thickness for frontal regions may emerge after age of peak schizophrenia onset but may not continue through later adulthood, which is only partially consistent with neurodegenerative models of schizophrenia, whereas post-onset changes in cortical surface area in schizophrenia appear to be normative.

Overall, despite considerable theoretical work on the relationship between age and liability to schizophrenia, little empirical study has been conducted to date. Although previous studies may bear to some degree on these questions, they have many methodological constraints and their findings are mixed. To examine these neurodevelopmental theories of schizophrenia more directly, the primary aim of this study is to determine whether schizophrenia genetic effects on regional cortical thickness and regional cortical surface area change across peak age of onset for schizophrenia. This study uses a multiplex (multiple schizophrenia relatives per family), extended pedigree design (first through fourth degree relatives of schizophrenia probands) (Gur et al., 2007), which bears several advantages. In particular, the multiple kinship nature of the pedigrees allows us to estimate additive genetic effects on cortical measures by comparing cortical measures in the relatives to what would be expected by their degree of relation to the schizophrenia proband. The multiplex nature of the pedigrees may increase the detectable genetic effects on schizophrenia. In addition, the extensive age range of the relatives allows us to compare genetic effects on cognition before, during and after the age of risk for schizophrenia. Finally, the sample does not exclude relatives of schizophrenic probands who meet diagnostic criteria for disorders other than

schizophrenia, rendering it especially suitable for addressing the specificity of this association to schizophrenia relative to other diagnoses. Given that this sample included participants who were at least 15 years old, this study is most well-suited for examining late neurodevelopmental models and neurodegenerative models of schizophrenia but is not a strong test of early neurodevelopmental models of schizophrenia. Specifically, we seek to address the following questions:

1. Are individual differences in regional cortical measures in general heritable in families with increased genetic liability for schizophrenia? Based on the literature, we hypothesize that regional cortical measures will be significantly heritable before the peak age of onset, immediately after the peak age of onset, and during the subsequent plateau in schizophrenia onset.
2. Do overall genetic effects on cortical measures change across age of risk for schizophrenia? Given that heritability of cortical measures appears to stabilize to adult levels by adolescence, at least in normative development, we hypothesize that the heritability of cortical measures in this sample will be stable across the age periods before the peak age of onset, immediately after the peak age of onset, and during the subsequent plateau in schizophrenia onset. Given that these genetic effects also encompass those that are not specific to schizophrenia, stability in genetic effects on cortical measures across age-risk groups does not closely bear on the models of schizophrenia brain development.
3. Are overall genetic effects on regional cortical measures shared across periods of age of risk for schizophrenia? Given that genetic effects on cortical measures appear to be shared across age in late adolescence through senescence, we hypothesize that genetic effects on regional cortical measures will overlap across the periods before the peak age

of onset, immediately after the peak age of onset, and during the subsequent plateau in schizophrenia onset. High genetic correlations across these age periods suggest an overlapping set of genetic effects on regional cortical measures across development (pleiotropy). As before, given that these genetic effects also encompass those that are not specific to schizophrenia, stability in the genetic effects on cortical measures across age-risk groups does not bear directly on the models tested.

4. Most importantly, do genetic effects shared between schizophrenia and regional cortical measures differ across age periods of schizophrenia risk? Presuming persistent effects, early neurodevelopmental models of schizophrenia suggest that genetic correlations between schizophrenia and regional cortical measures will begin high and not change from prior to peak age of onset, during peak age of onset, and afterward during older adulthood. In contrast, late developmental models would predict that genetic correlations between schizophrenia and cortical measures begin low prior to peak age of onset, increase during peak age of onset, and then stabilize in later adulthood. Finally, neurodegenerative models suggest that genetic correlations between schizophrenia and regional cortical measures will significantly increase in later adulthood compared to prior periods.
5. Are developmental genetic effects on regional cortical measures diagnostically specific to schizophrenia? Diagnostic specificity to schizophrenia would suggest nonsignificant genetic correlations between major depression and regional cortical measures. In contrast, transdiagnostic models would suggest significant genetic relationships between depression and cortical measures and similar patterns across age periods to those found with schizophrenia.

2.0 METHODS

The current project is part of the Multiplex Genetics Investigation of Schizophrenia (MGI) Study (Gur et al., 2007), which is a multi-site study based at the University of Pittsburgh and the University of Pennsylvania. Participants were initially recruited for a study of schizophrenia, genetics, and cognition and were subsequently recalled to complete MRI scanning a few years after initial assessments. A subset of these initial participants completed MRI scanning, and additional participants, including probands, relatives, and controls, were also recruited to complete MRI scanning.

2.1 PARTICIPANTS

2.1.1 Recruitment and Inclusion Criteria

Probands were recruited at the University of Pittsburgh and the University of Pennsylvania through mental health and consumer organizations throughout Pennsylvania, New Jersey, Delaware, Ohio, West Virginia, Kentucky, Michigan and Indiana. Probands had a DSM-IV diagnosis of schizophrenia, were of European-American descent, proficient in English, at least 18 years old, and provided consent to contact at least one first-degree relative with a diagnosis of schizophrenia or schizoaffective disorder – depressed type and ten or more first- through fourth-degree relatives. Inclusion criteria for relatives included being at least 15 years old, European-American, proficient in English, and free of any brain injury or disorder that would interfere with interpretation of

cognitive measures. All participants provided consent (or assent when applicable) according to protocols approved by their respective Institutional Review Boards.

European-American individuals aged 18-84 were recruited for the comparison group. At Pittsburgh, potential comparison individuals residing in the regions (based on zipcode) from which most probands and their relatives had been recruited were contacted through random-digit dialing and were group-matched to the relatives based on average age and sex. Comparison participants at the University of Pennsylvania were recruited through advertisements. All were excluded if they or a first-degree relative had been diagnosed with a schizophrenia spectrum or psychotic disorder, were taking antipsychotic medications, experienced a recent exacerbation of non-psychotic psychiatric symptoms, underwent electroconvulsive therapy or treatment for substance use in the past six months, or reported a medical condition, head injury or sensory or physical impairments that could interfere with completion of study measures. Other psychiatric diagnoses were not excluded from the comparison group.

2.2 PROCEDURES

2.2.1 Diagnostic Assessment

Participants underwent clinical evaluation using the Diagnostic Interview for Genetic Studies, version 2.0 (DIGS) (Nurnberger et al., 1994), the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992), and a review of medical records if available. Initial assessment was conducted in person, usually in the person's home, by trained interviewers who were not blind to the participant's status (i.e., proband/relative/control). At least two investigators (licensed

psychologists and psychiatrists) reviewed each case and resolved differences by consensus to provide DSM-IV lifetime diagnoses. Those who were recalled underwent diagnostic re-evaluation. Relatives were classified into four hierarchical, mutually exclusive diagnostic groups: schizophrenia (including schizoaffective disorder bipolar type and depressed type), depression, other diagnosis, and no diagnosis.

2.2.2 MRI Acquisition

A 5-minute magnetization-prepared, rapid acquisition gradient echo T1-weighted (MPRAGE) image (repetition time 1680 msec, echo time 4.67 msec, field of view 180 × 240 mm, matrix 192 × 256, flip angle =15 degrees, effective voxel resolution of 0.94 × 0.94 × 1 mm) was acquired with Siemens Tim Trio 3T (Erlangen, Germany) systems at both sites. Radio frequency transmission used a quadrature body coil and reception used an 8-channel head coil. Every effort was made to minimize potential differences between sites by using identical scanners, head coils, and acquisition protocols. A pilot study testing on phantom standards indicated good comparability between the two imaging sites in image quality.

2.2.3 MRI Image Processing

The FreeSurfer image analysis suite, version 5.3 (Fischl, 2012) was used to derive cortical thickness and cortical surface area, using the following standard pre-processing steps: motion correction, transformation of images to standard Talairach space, intensity normalization, removal of non-brain tissue, segmentation of white matter and subcortical structures, and final segmentation of cortical surfaces. Values for cortical regions of interest were based on the Desikan

FreeSurfer atlas (Desikan et al., 2006). Cortical measures for each region were derived using an automated computer algorithm to parcellate a total of 34 regions for each hemisphere. Estimates of cortical thickness were calculated from the distance between the gray-white matter border and the pial surface at each vertex. Estimates of cortical surface area were calculated by summing the area of the vertices in each parcellation.

MRI quality assessment was completed using a three-class system of manual ratings (Reuter et al., 2015; Savalia et al., 2017). Here, a "0" denotes images that suffer from gross artifacts and are considered unusable, "1" denotes images with some artifact but which are still considered usable, and "2" denotes images that do not show visible artifacts. First, anchors and exemplars for each of the three quality classes were agreed upon through consensus of five experts, including a board-certified neuroradiologist, an MR physicist, a cognitive neuroscientist, an experienced image analyst, and a neuropsychiatrist. Two experts created a training sample by rating 100 images independently, resolving discrepancies by consensus. This dataset of 100 images was used to train three image analysts to >85% agreement. The three image analysts then rated the complete dataset. An average manual rating of 1 or greater was considered acceptable scan quality for inclusion.

2.2.4 MRI Measures

The following cortical measures were examined:

1. Global cortical measures: intracranial volume, lateral ventricle volume, mean cortical thickness, and total cortical surface area.
2. Regional cortical measures: cortical thickness and cortical surface area for 34 parcellated regions in each hemisphere.

2.3 STATISTICAL ANALYSES

2.3.1 Defining Age-Risk Groups Based on Schizophrenia Onset

Non-schizophrenia relatives and controls were classified into three age-risk groups based on their age at MRI assessment compared to aspects of the ages at onset for schizophrenia as determined by epidemiological study (Häfner, 2003): 1) Rise: before age of peak risk for schizophrenia onset (younger than 23 years old), 2) Peak: after age of peak risk for onset but before slowing of decline in risk (between 23 and 42 years old) and 3) Plateau: after age of slowing decline of risk for schizophrenia onset (older than 42 years). The cutoffs of 23 years and 42 years are based upon the approximate average of the age of onset for males and females at the peak and plateau, respectively. Schizophrenia patients were not divided by age on the assumption that the schizophrenia genetic liability of their relatives should not vary by the age of assessment of probands.

2.3.2 Primary Analyses

Quantitative genetic analyses were performed in Sequential Oligogenic Linkage Analysis Routines-Eclipse, version 4.0.7 (SOLAR-Eclipse; Almasy & Blangero, 1998) using maximum-likelihood variance decomposition to estimate model parameters and likelihood-ratio tests to evaluate their statistical significance. Maximum-likelihood estimates utilize all the data that are relevant to a given parameter, and parameters were conservatively estimated using the t-distribution, which is robust to non-normal trait distributions (Blangero, Williams, & Almasy, 2001). All SOLAR-Eclipse analyses included site, age, age^2, and sex as adjustments. To maximize

the information available to estimate genetic liability to schizophrenia in relatives, all schizophrenia participants, including those without any neuroimaging data, were included. Furthermore, to provide a better estimate of general population means and variances, the control group was also included in all analyses.

Phenotypic variance for a trait can be decomposed into heritability (proportion of phenotypic variance attributable to additive genetic effects) and environmentality (proportion of phenotypic variance not attributable to additive genetic effects). Heritability is estimated by the degree to which the observed phenotypic covariance between relatives is linearly predicted by their kinship (i.e., first-degree relatives share 50% of their additive genetic effects, second-degree relative share 25%, etc.). Environmental effects are estimated as that phenotypic variation not predicted linearly by their degree of kinship, which are often termed non-shared environmental effects (also includes measurement error and instability). The presence of environmental effects that vary linearly with degree of kinship (i.e., shared environmental effects) will inflate heritability estimates.

Similarly, phenotypic covariance between two traits can be decomposed into that due to correlated genetic effects and that due to correlated environmental effects. The total genetic contribution to the phenotypic correlation between traits reflects the heritabilities of each trait along with the degree to which these genetic effects are correlated with each other, termed their genetic correlation (R_g). A significant genetic correlation suggests that both traits are influenced by a common set of genetic effects (often termed pleiotropy). Appropriately, the significance of a genetic correlation is affected by the strength of the individual trait heritabilities (Verhulst, 2017). For example, even a high genetic correlation may not be significant if one (or both) of the traits has a low heritability and thus overall genetic effects account for little of the observed phenotypic

correlation between traits. Similarly, the total contribution of environmental effects to the correlation between traits reflects the environmentality of each trait and the correlation of these environmental effects.

To examine overall genotype-by-age interactions, different ages can be conceptualized as unique environments in which genetic effects influence a trait in the context of genotype-by-environment interactions (Blangero, 1993; Glahn et al., 2013). Thus, a genotype-by-age interaction implies that additive genetic variance for a trait changes across age and that the genetic correlation between the trait's expression in the two age-risk groups is less than 1.0. In contrast, the genotype-by-age interaction is not significant if the additive variances do not differ across age-risk groups and the genetic correlation between the trait's expression in the two age-risk groups does not differ from 1.0. If the genetic correlation between the two age-risk groups is 1.0, this suggests complete pleiotropy, where a common set of genes accounts for the heritability of the traits across age.

To examine the key and more specific question of whether schizophrenia genetic effects on cortical measures differ across age- risk groups, genetic correlations between schizophrenia and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).

For each series of analyses across global cortical measures, cortical thickness measures, and cortical surface area measures, the p-values were adjusted to control for the false discovery rate (the expected proportion of false discoveries in all of the rejected hypotheses). Using the Benjamini-Hochberg procedure, the individual p-values for each region were ranked in ascending order, and a given p-value's Benjamini-Hochberg critical value was computed from the formula

$(i/m)\times Q$, where i is the individual p-value's rank, m is the total number of conducted tests, and Q is the false discovery rate (chosen to be 5%) (Benjamini & Hochberg, 1995).

3.0 RESULTS

3.1 SAMPLE COMPOSITION

The sample for the initial MGI study was comprised of 865 participants, including 111 schizophrenia participants and 534 non-schizophrenia relatives from 43 families and 220 controls with diagnostic information. Every effort was made to contact and recruit as many of these participants as possible for the MRI study. Overall, a total of 193 participants (40 schizophrenia participants and 125 non-schizophrenia relatives from 28 families, and 28 controls) returned to undergo eligibility assessment for the MRI study. In addition, 442 new participants were added (12 schizophrenia participants and 133 non-schizophrenia relatives from 19 existing families and 9 new families, and 297 controls), leading to a total sample of 635 participants assessed for MRI eligibility (52 schizophrenia participants and 258 relatives from 37 families, and 325 controls). From this group, 539 completed MRI scanning, 33 of whom were ruled out based on MRI scan quality assurance, resulting in a final sample of 506 with adequate MRI scans. To maximize our power to examine diagnostic specificity, diagnostic information was included in the genetic analyses from all 1307 participants recruited in the initial study and the MRI study (totaling 123 schizophrenia participants, 667 non-schizophrenia relatives and 517 controls), from 52 families.

Overall, the MRI sample (*N*=506) included 230 relatives (of whom 30 were diagnosed with schizophrenia) from 32 multiplex, multigenerational families and 276 unrelated healthy controls. As shown in Table 6, the number of participants with MRI data in each pedigree ranged from 1 to 26 (median=4), and all but three pedigrees included at least two participants with MRI data. Of the relatives, 28 were diagnosed with schizophrenia and two were diagnosed with schizoaffective

disorder (one with bipolar type and one with depressed type), 38 with depression, 61 with other psychopathology (diagnoses listed in Table 7), and 101 without psychopathology. Of the controls, 32 were diagnosed were depression, 48 had other psychopathology (diagnoses listed in Table 7), and 196 had no diagnosis.

The age range of the sample was 12 to 85 years. The age distributions of the relatives and controls are shown in Figure 2: the Rise group consisted of 61 participants (35 non-schizophrenia relatives and 26 controls), the Peak group consisted of 193 participants (61 non-schizophrenia relatives and 132 controls), and the Plateau group consisted of 222 participants (104 non-schizophrenia relatives and 118 controls) with quality-standard MRI data.

Table 6. Numbers of participants in the MRI sample from each pedigree.

Number of Relatives	Schizophrenia Relatives	Non-Schizophrenia Relatives	Total
1	15	6	3
2	6	4	4
3	1	4	3
4	0	3	7
5	0	3	4
6	0	1	1
7	0	0	1
8	0	2	2
9	0	1	0
10	0	0	1
12	0	1	0
14	0	1	1
17	0	0	1
20	0	1	1
21	0	1	0
22	0	0	1
24	0	1	1
25	0	1	0
26	0	0	1

Table 7. Primary diagnoses for relatives or controls in the MRI sample in the Other Diagnosis group.

Other Diagnosis	Relatives	Controls
Substance Dependence	16	19
Substance Abuse	12	13
Depressive Disorder (Not Otherwise Specified)	10	6
Attention Deficit/Hyperactivity Disorder	4	0
Bipolar I Disorder	3	0
Mood Disorder (Not Otherwise Specified)	2	1
Delusional Disorder	2	0
Adjustment Disorder	2	1
Bereavement	2	0
Anxiety Disorder (Not Otherwise Specified)	1	3
Brief Psychotic Disorder	1	0
Unspecified Psychosis	1	0
Asperger Syndrome	1	0
Schizotypal Personality Disorder	1	0
Intermittent Explosive Disorder	1	0
General Anxiety Disorder	0	1
Unspecified Non-Psychotic Mental Disorder	0	1
Anorexia Nervosa	0	1
Reading Disorder	0	1
Other Mental Condition	2	1

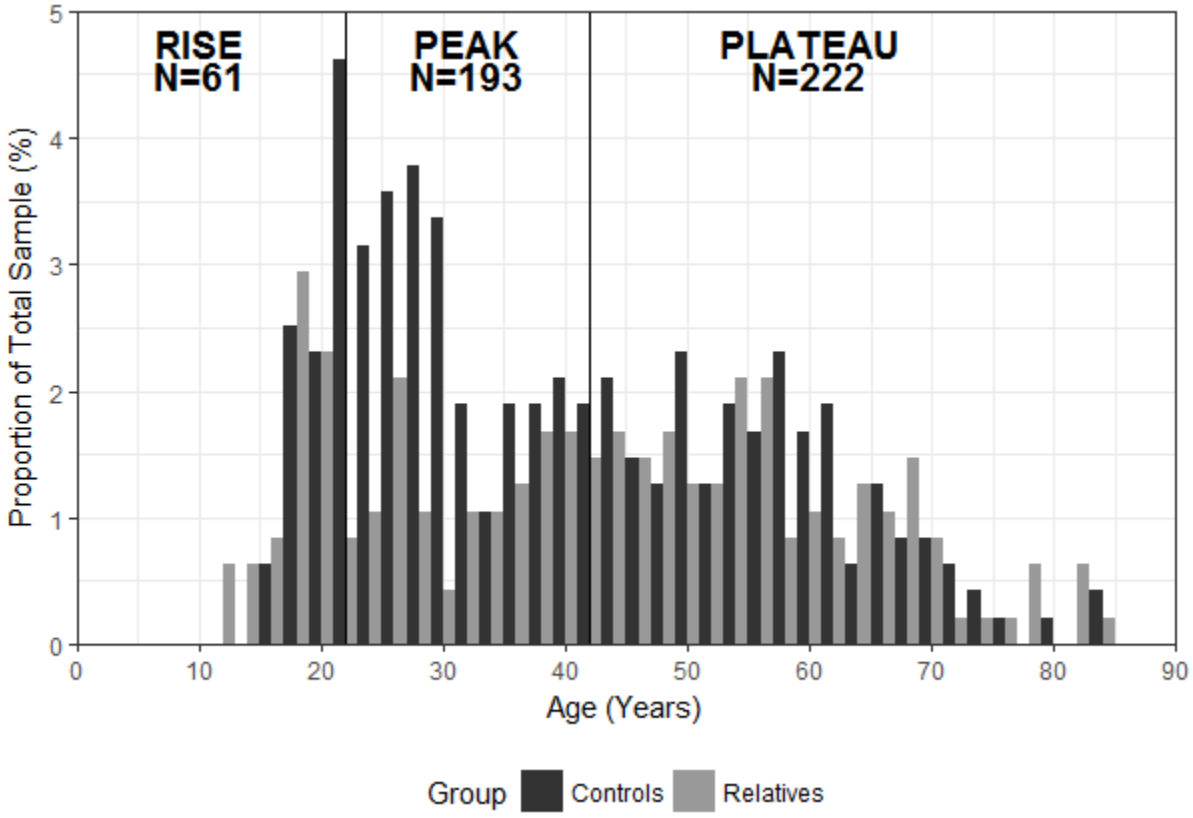


Figure 2. Age distribution in the sample of non-schizophrenia relatives and controls.

3.2 DEMOGRAPHIC COMPARISONS

3.2.1 Age-Risk Group Characteristics

Demographic characteristics between non-schizophrenia relatives and controls and each age-risk group were compared using 2×3 ANOVAs for continuous variables (age, parental education, and education) and chi-square tests for categorical variables (site, non-schizophrenia diagnoses, sex, handedness, and scan quality). Demographic characteristics were also compared between schizophrenia participants and controls. As summarized in Table 8, site, rates of depression, other

diagnoses, and no diagnoses did not differ significantly across relatives' or controls' age-risk groups. As expected, age differed significantly across age-risk groups. Sex ratios did not differ by relative status or age-risk group, though there was a preponderance of males in the schizophrenia group compared to controls. Handedness did not differ by relative status or age-risk groups, nor between schizophrenia and controls.

Education differed by both relative status and age-risk groups. On average, relatives had attained fewer years of education than controls. As might be expected, given their age, participants in the Rise age-risk group had attained fewer years of education than participants in the Peak and Plateau age-risk groups, who did not differ significantly from each other in education. Furthermore, a significant group-by-age interaction was observed, in which relatives and controls in the Rise group had larger differences in education compared to relatives and controls in the Peak and Plateau age-risk groups. Schizophrenia participants also attained fewer years of education than controls.

Similarly, parental education differed by both relative status and age-risk groups. Relatives had lower levels of parental education than controls. Across age-risk groups, perhaps due to cohort effects, participants in the Plateau age-risk group had significantly lower levels of parental education than participants in the Rise and Peak age-risk groups, who did not differ significantly from each other for parental education. Furthermore, a significant group-by-age interaction was observed, in which relatives and controls in Rise and Peak age-risk groups showed greater differences in parental education than relatives and controls in the Plateau age-risk group. Schizophrenia participants also had lower levels of parental education than controls.

Scan quality ratings differed significantly across age-risk groups, with participants in the Rise and Peak age-risk groups being rated as having higher quality cortical data than participants

in the Plateau age-risk group. Furthermore, there was a significant group-by-age interaction, where differences in scan quality were most evident between controls in the Peak compared to the Plateau group. Schizophrenia participants also had lower quality scans than controls.

Table 8. Demographic and cortical characteristics of the MRI sample.

Characteristic	Group	MRI Sample		Rise		Peak		Plateau		Effects		
		Mean/N	(SD)/%	Mean/N	(SD)/%	Mean/N	(SD)/%	Mean/N	(SD)/%	Group	Age	Group x Age
Sample Size	SZ	30	6%									
	FM	200	40%	35	18%	61	30%	104	52%			
	NC	276	54%	26	9%	132	48%	118	43%			
	FM+NC	476	94%	61	13%	193	40%	222	47%			
	Total	506	100%									
Site	SZ	11 †	37%									
(% recruited	FM	99	50%	12	34%	30	49%	57	55%	$\chi^2(1)=0.238$	$\chi^2(2)=3.069$	$\chi^2(5)=5.588$
at PITT)	NC	138 †	50%	13	50%	60	45%	65	55%	$p=0.626$	$p=0.216$	$p=0.348$
Depression	FM	38	19%	5	14%	12	20%	21	20%		$\chi^2(4)=2.695$	
Other Diagnoses		61	31%	12	34%	22	36%	27	26%		$p=0.610$	
No Diagnoses		101	50%	18	51%	27	44%	56	54%			
Depression	NC	32	12%	4	15%	16	12%	12	10%		$\chi^2(4)=2.281$	
Other Diagnoses		48	17%	2	8%	24	18%	22	19%		$p=0.684$	
No Diagnoses		196	71%	20	77%	92	70%	84	71%			
Age	SZ	52.20 †	(11.14)									
(Years)	FM	43.29	(18.24)	17.94 [a]	(2.48)	32.59 [b]	(6.34)	58.1 [c]	(10.49)	F(1)=0.327	F(2)=416.978	F(2,470)=1.344
	NC	40.38 ‡	(16.36)	19.12 [a]	(1.40)	29.89 [b]	(5.84)	56.8 [c]	(9.69)	$p=0.568$	$p<0.001$	$p=0.262$
Sex	SZ	23 †	77%									
(% Male)	FM	101	51%	21	60%	31	59%	49	47%	$\chi^2(1)=0.833$	$\chi^2(2)=2.437$	$\chi^2(5)=4.184$
	NC	124 ‡	45%	14	54%	57	43%	53	45%	$p=0.361$	$p=0.296$	$p=0.523$
Handedness	SZ	24 †	80%									
(% Right)	FM	177	89%	32	91%	53	87%	92	88%	$\chi^2(1)=0.012$	$\chi^2(2)=0.833$	$\chi^2(5)=0.882$
	NC	244 †	88%	24	92%	116	88%	104	88%	$p=0.914$	$p=0.696$	$p=0.972$
Parental	SZ	12.05 †	(2.65)									
Education	FM	12.41	(2.89)	13.43 [bc]	(2.67)	13.04 [b]	(2.64)	11.70 [a]	(2.94)	F(1)=13.422	F(2)=8.401	F(2,465)=3.215
(Years)	NC	13.79 ‡	(2.72)	15.88 [d]	(2.34)	14.61 [cd]	(2.26)	12.39 [ab]	(2.61)	$p<0.001$	$p<0.001$	$p=0.041$
Education	SZ	12.60 †	(1.90)									
(Years)	FM	13.68	(2.67)	11.24 [a]	(2.09)	13.56 [bc]	(2.36)	14.56 [cd]	(2.51)	F(1)=8.379	F(2)=26.993	F(2,465)=5.109
	NC	15.29 ‡	(2.34)	12.96 [b]	(1.48)	15.76 [e]	(2.14)	15.28 [de]	(2.41)	$p=0.004$	$p<0.001$	$p=0.006$
Scan Quality	SZ	18 †	60%									
(% without	FM	152	76%	28 [ab]	80%	47 [ab]	77%	77 [ab]	74%	$\chi^2(1)=0.137$	$\chi^2(2)=9.598$	$\chi^2(5)=13.639$
visible artifact)	NC	219 ‡	79%	21 [ab]	81%	116 [b]	88%	82 [a]	69%	$p=0.712$	$p=0.008$	$p=0.018$

Note. SZ: schizophrenia individuals; FM: non-schizophrenia family members; NC: normal controls.
Parental education was calculated from the mean of maternal and paternal education; if either was unavailable, the education level of one parent was used. Parental education data were unavailable for five participants (one relative and four controls).
Education data were unavailable for five participants (three relatives and two controls).
Scan quality was categorized as 2 if the average quality rating was 2 (no visible artifacts) and 1 if the average quality rating was at least 1 and less than 2 (visible artifacts but usable). Cortical data with an average quality rating under 1 were excluded from analyses.
p-values for comparisons are presented for main effect of group (FM, NC), main effect of age-risk period (Rise, Peak, Plateau), and interaction effect of group by age.
Differences in sex, handedness, and cortical ratings across groups were compared using continuity-corrected Cochran-Mantel-Haenszel chi-square tests. Counts sharing superscripts did not differ significantly ($p \geq 0.05$) from each other according to Fisher's exact tests and are only provided where main or interaction effects are significant.
Differences in age, parental education, and education across groups were examined using 2×3 ANOVAs based on Type III unweighted sum of squares. Statistics sharing superscripts did not differ significantly ($p \geq 0.05$) from each other according to Tukey's HSD test (i.e., were included in a homogeneous subset) and are only provided where main or interaction effects are significant.
Group comparisons between schizophrenia individuals and controls (statistics sharing superscripts did not differ significantly ($p \geq 0.05$) from each other):
Site: $\chi^2(1)=1.429$, $p=0.232$
Age: $F(1, 304)=14.890$, $p<0.001$
Sex: $\chi^2(1)=9.686$, $p=0.002$
Handedness: $\chi^2(1)=1.070$, $p=0.301$
Parental Education: $F(1, 300)=11.158$, $p=0.001$
Education: $F(1, 302)=37.081$, $p<0.001$
Scan Quality: $\chi^2(1)=4.745$, $p=0.029$

3.3 CORTICAL MEASURES

3.3.1 Cortical Measures by Hemisphere

To examine the extent to which cortical measures are similar across hemispheres and determine whether the cortical measures could be aggregated across hemispheres, we examined both mean differences between hemispheres as well as covariation between hemispheres for each cortical measure. First, paired t-tests of the hemispheric difference for each cortical measures indicated that cortical measures did not differ significantly between hemispheres except for the following measures: pars orbitalis thickness, paracentral thickness, pars orbitalis area, and caudal anterior cingulate area (all of which were smaller in the left hemisphere compared to the right hemisphere). Mixed 2×2 ANOVAs comparing schizophrenia participants and controls between hemispheres further indicated no significant group-by-hemisphere interactions in any cortical measure.

Pearson correlations between hemispheres for each cortical measure were all significant (p<0.001) and ranged from 0.33 to 0.90 for cortical thickness measures and 0.17 to 0.80 for cortical surface area measures, as shown in Table 9. Given the wide range of interhemispheric correlations and the cross-sectional nature of this study, we looked to the empirical literature for estimates of the reliability for repeated cortical measures to examine the extent to which measurement error may contribute to each cortical measure and their interhemispheric correlation. The most relevant study to date included 30 participants aged 20 to 30, who were each scanned 10 times at regular intervals over the course of a month (Madan & Kensinger, 2017). This study used similar cortical parcellation procedures to those used in the current study, including the same version of the FreeSurfer image processing software and the same brain atlas, to estimate regional cortical

thickness. The intraclass coefficients (ICC) for cortical thickness measures within each hemisphere ranged from 0.42 to 0.87, as shown in Table 9.

Table 9. Comparison of interhemispheric correlations for the current study and reliability for repeated cortical measures.

		Within-Subject Correlations in Current Study		Reliability for Repeated Measures of Cortical Thickness*		
Lobe	Region	Interhemispheric Correlation for Cortical Thickness	Interhemispheric Correlation for Cortical Surface Area	Intraclass Correlation Coefficient for Left Hemisphere	Intraclass Correlation Coefficient for Right Hemisphere	Estimated Maximum Interhemispheric Correlation‡
Frontal	Frontal Pole	0.43	0.36	N/A	N/A	N/A
	Superior Frontal	0.90	0.80	0.76	0.82	0.62
	Rostral Middle Frontal	0.81	0.79	0.82	0.76	0.62
	Caudal Middle Frontal	0.71	0.61	0.83	0.80	0.66
	Pars Opercularis	0.65	0.45	0.77	0.78	0.60
	Pars Triangularis	0.62	0.54	0.77	0.84	0.65
	Pars Orbitalis	0.57	0.54	0.76	0.69	0.52
	Lateral Orbitofrontal	0.61	0.77	0.48	0.59	0.28
	Medial Orbitofrontal	0.57	0.57	0.51	0.59	0.30
	Precentral	0.82	0.66	0.76	0.78	0.59
	Paracentral	0.76	0.57	0.75	0.73	0.55
Parietal	Superior Parietal	0.83	0.67	0.76	0.85	0.65
	Inferior Parietal	0.75	0.69	0.64	0.84	0.54
	Supramarginal	0.71	0.62	0.70	0.80	0.56
	Postcentral	0.77	0.69	0.85	0.87	0.74
	Precuneus	0.80	0.75	0.73	0.78	0.57
Temporal	Superior Temporal	0.71	0.75	0.66	0.72	0.48
	Superior Temporal Sulcus	0.42	0.43	N/A	N/A	N/A
	Middle Temporal	0.68	0.69	0.59	0.75	0.44
	Inferior Temporal	0.67	0.66	0.53	0.42	0.22
	Fusiform	0.72	0.67	0.66	0.64	0.42
	Transverse Temporal	0.50	0.53	0.80	0.85	0.68
	Entorhinal	0.60	0.45	0.54	0.50	0.27
	Temporal Pole	0.59	0.25	N/A	N/A	N/A
	Parahippocampal	0.64	0.45	0.83	0.86	0.71
Occipital	Lateral Occipital	0.75	0.65	0.82	0.78	0.64
	Lingual	0.70	0.64	0.73	0.78	0.57
	Cuneus	0.66	0.55	0.82	0.80	0.66
	Pericalcarine	0.59	0.65	0.76	0.74	0.56
Cingulate	Rostral Anterior Cingulate	0.46	0.46	0.57	0.49	0.28
	Caudal Anterior Cingulate	0.33	0.17	0.74	0.47	0.35
	Posterior Cingulate	0.62	0.45	0.64	0.63	0.40
	Isthmus Cingulate	0.52	0.60	0.85	0.75	0.64
	Insula	0.64	0.68	0.52	0.65	0.34

Note. *Intraclass correlations for repeated measures are reported by Madan and Kensinger (2017).

‡ Estimated Maximum Interhemispheric Correlation for each unadjusted cortical measure based upon product of intraclass correlations for left and right hemispheres.

N/A denotes that this measure was not examined by Madan and Kensinger (2017).

To estimate the maximum interhemispheric correlation for each cortical measure, we computed the product of the ICCs for the left and right hemispheres for each cortical thickness measure in the multiple-scan study. Across almost all measures, the observed interhemispheric correlations in the current study were higher than the estimated maximum correlation based on hemispheric reliabilities, suggesting that the similarities across hemispheres in the current study are greater than or equal to what would be expected based on constraints of measurement error. To the extent that cortical measures in the multiple-scan study are comparable to cortical measures in the current study, the findings of the multiple-scan study support the aggregation of cortical measures across hemispheres in the current study. Given that no studies to our knowledge have examined reliability for repeated measures of cortical surface area, we applied the same procedures for measures of cortical thickness and surface area. To aggregate cortical measures across hemispheres, we averaged the scores for the left hemisphere and the right hemisphere. These scores were then standardized to the control mean and standard deviation.

3.3.2 Relationship between Cortical Thickness and Cortical Surface Area

We also examined correlations between adjusted cortical thickness scores and adjusted cortical surface area scores within regions, as presented in Table 10. Thickness and surface area showed small negative correlations (although many were significant) for all regions throughout the cortex ($r \leq -0.412$), such that regions with smaller cortical surface area had larger cortical thickness. Based on the small to negligible correlations between cortical thickness and cortical surface area, we proceeded with examining cortical thickness measures and cortical surface area measures separately.

Table 10. Correlations between cortical thickness and cortical surface area within regions.

Lobe	Region	Correlation
Frontal	Frontal Pole	-0.206*
	Superior Frontal	-0.334*
	Rostral Middle Frontal	-0.300*
	Caudal Middle Frontal	-0.072
	Pars Opercularis	-0.134*
	Pars Triangularis	-0.195*
	Pars Orbitalis	-0.254*
	Lateral Orbitofrontal	-0.402*
	Medial Orbitofrontal	-0.320*
	Precentral	-0.272*
	Paracentral	-0.120*
Parietal	Superior Parietal	-0.358*
	Inferior Parietal	-0.235*
	Supramarginal	-0.275*
	Postcentral	-0.059
	Precuneus	-0.329*
Temporal	Superior Temporal	-0.165*
	Superior Temporal Sulcus	-0.005
	Middle Temporal	-0.229*
	Inferior Temporal	-0.240*
	Fusiform	-0.311*
	Transverse Temporal	-0.281*
	Entorhinal	-0.368*
	Temporal Pole	-0.173*
	Parahippocampal	-0.412*
Occipital	Lateral Occipital	-0.333*
	Lingual	-0.053
	Cuneus	-0.112*
	Pericalcarine	-0.041
Cingulate	Rostral Anterior Cingulate	-0.324*
	Caudal Anterior Cingulate	-0.049
	Posterior Cingulate	-0.160*
	Isthmus Cingulate	-0.334*
	Insula	-0.364*

Note. * denotes $p<0.05$. Correlations are conducted on measures with basic adjustments.

3.3.3 Relationship between Cortical Measures and Key Sample Characteristics

To examine the extent to which cortical measures covaried with demographic, scanning, and diagnostic characteristics, we computed Pearson correlations in the total MRI sample.

3.3.3.1 Relationship between Global Cortical Measures and Key Sample Characteristics

Table 11 presents correlations between global cortical measures and demographic, scanning, and diagnostic characteristics. Site showed a low correlation with total surface area, with participants at PITT having slightly smaller total surface area than participants at PENN. Age and sex showed low to moderate correlations across all global cortical measures, with smaller cortical measures observed in older participants and female participants. However, handedness was not significantly correlated with any global cortical measure. Furthermore, parental education, but not personal education, showed low positive correlations with all global cortical measures, such that better quality scans had greater thickness. Scan quality also showed low positive correlations with global cortical measures. As can be expected, intracranial volume was correlated with larger ventricle volume and larger total surface area. Neither of the non-schizophrenia diagnostic categories, depression and other diagnoses, were significantly correlated with any global cortical measure. Overall, most global cortical measures showed low to moderate correlations with age, sex, parental education, scan quality, and intracranial volume.

Table 11. Correlations between global cortical measures and demographic and diagnostic characteristics.

Lobe	Region	Site	Age	Sex	Handedness	Parental Education	Education	Scan Quality	Intracranial Volume	Depression	Other Diagnoses
Global	Intracranial Volume	-0.037	-0.100*	-0.560*	0.054	0.099*	-0.002	0.007	1.000*	-0.009	0.011
	Lateral Ventricle Volume	-0.037	0.489*	-0.254*	0.072	-0.140*	0.080	-0.217*	0.344*	0.044	-0.058
	Mean Thickness	0.044	-0.592*	0.033	-0.027	0.308*	-0.055	0.356*	0.069	-0.082	0.013
	Total Surface Area	-0.113*	-0.251*	-0.469*	0.028	0.106*	-0.035	-0.013	0.733*	0.034	0.059

Note. Cortical measures are unadjusted. Site (scored PITT = 1, PENN = 0), Sex (scored female = 1, male = 0), Handedness (scored right-handed = 1, left-handed or ambidextrous = 0), Scan Quality (scored no visible artifacts = 1, visible artifacts = 0), Depression (scored Depression group = 1, not in Depression group = 0), Other Diagnoses (scored Other Diagnoses group = 1, not in Other Diagnoses group = 0).
* denotes $p<0.05$.

3.3.3.2 Relationship between Cortical Thickness and Key Sample Characteristics

Table 12 presents correlations between regional cortical thickness measures and demographic, scanning, and diagnostic characteristics. Site showed very low correlations with three temporal thickness measures and two occipital thickness measures, such that participants at PITT had larger cortical thickness for these measures than participants at PENN. Age showed low to moderate negative correlations with almost all cortical thickness measures. Sex also showed low correlations with a few cortical thickness measures, with female participants showing smaller regional cortical thickness than males. Furthermore, handedness showed a very low correlation with a cingulate thickness measure. Parental education showed low positive correlations with almost all cortical thickness measures. In contrast, personal education showed low negative correlations with only two frontal thickness measures and two cingulate thickness measures. Scan quality showed low positive correlations with almost all cortical thickness measures. Furthermore, intracranial volume showed low correlations with several cortical thickness measures across most lobes. Depression diagnosis showed low negative correlations with several cortical thickness measures across most lobes. The diagnostic category of Other Diagnoses was not significantly correlated with any cortical thickness measure. Overall, most cortical thickness measures showed low to moderate correlations with age, parental education, scan quality, intracranial volume, and some with depression.

Table 12. Correlations between cortical thickness and demographic and diagnostic characteristics.

Lobe	Region	Site	Age	Sex	Handedness	Parental Education	Education	Scan Quality	Intracranial Volume	Depression	Other Diagnoses
Frontal	Frontal Pole	0.008	-0.279*	0.126*	-0.018	0.151*	-0.089*	0.251*	-0.169*	-0.093*	0.014
	Superior Frontal	0.012	-0.668*	0.060	-0.034	0.311*	-0.078	0.277*	0.014	-0.060	0.021
	Rostral Middle Frontal	0.000	-0.593*	0.019	-0.041	0.309*	-0.083	0.330*	0.019	-0.067	0.029
	Caudal Middle Frontal	0.046	-0.629*	0.018	-0.047	0.298*	-0.048	0.294*	0.102*	-0.055	0.002
	Pars Opercularis	-0.009	-0.657*	-0.068	-0.017	0.323*	-0.040	0.244*	0.166*	-0.087	0.049
	Pars Triangularis	-0.016	-0.625*	-0.013	-0.033	0.331*	-0.055	0.264*	0.051	-0.080	0.045
	Pars Orbitalis	-0.036	-0.467*	0.012	0.016	0.242*	-0.036	0.358*	0.020	-0.067	0.003
	Lateral Orbitofrontal	-0.060	-0.490*	-0.053	0.013	0.262*	-0.093*	0.273*	0.025	-0.120*	0.048
	Medial Orbitofrontal	0.017	-0.464*	-0.015	-0.048	0.219*	-0.085	0.218*	0.003	-0.145*	0.023
	Precentral	0.028	-0.502*	0.042	-0.001	0.245*	-0.011	0.375*	0.096*	-0.037	0.015
	Paracentral	-0.016	-0.452*	0.103*	0.016	0.206*	-0.055	0.345*	-0.003	-0.068	-0.019
Parietal	Superior Parietal	0.034	-0.481*	0.067	0.010	0.218*	-0.067	0.360*	0.038	0.004	0.002
	Inferior Parietal	0.086	-0.532*	0.070	-0.035	0.262*	-0.031	0.352*	0.023	-0.071	0.003
	Supramarginal	0.062	-0.597*	0.077	-0.047	0.293*	-0.058	0.353*	0.035	-0.075	-0.018
	Postcentral	0.058	-0.423*	0.091*	0.001	0.225*	-0.009	0.304*	0.059	-0.001	-0.016
	Precuneus	0.036	-0.538*	-0.016	-0.046	0.281*	-0.073	0.297*	0.106*	-0.068	0.007
Temporal	Superior Temporal	0.008	-0.521*	0.009	-0.025	0.273*	-0.031	0.326*	0.096*	-0.052	0.037
	Superior Temporal Sulcus	0.092*	-0.531*	-0.021	-0.047	0.323*	-0.008	0.211*	0.101*	-0.059	-0.019
	Middle Temporal	0.108*	-0.499*	-0.036	0.000	0.273*	0.001	0.370*	0.115*	-0.063	-0.014
	Inferior Temporal	0.091*	-0.335*	-0.025	0.039	0.184*	-0.049	0.365*	0.130*	-0.074	0.023
	Fusiform	0.062	-0.353*	-0.043	-0.041	0.286*	0.019	0.334*	0.078	-0.116*	-0.025
	Transverse Temporal	-0.018	-0.381*	0.048	0.039	0.237*	-0.029	0.263*	0.108*	-0.054	-0.001
	Entorhinal	0.002	0.090*	-0.057	0.012	-0.013	0.033	0.216*	0.004	-0.013	-0.015
	Temporal Pole	-0.055	-0.027	0.000	-0.023	0.045	0.028	0.221*	-0.040	-0.107*	0.038
	Parahippocampal	-0.030	-0.231*	0.121*	0.010	0.191*	0.018	0.093*	-0.099*	-0.079	0.007
Occipital	Lateral Occipital	0.134*	-0.237*	0.149*	-0.070	0.102*	-0.040	0.215*	-0.053	-0.060	0.028
	Lingual	0.101*	-0.420*	-0.038	-0.013	0.276*	-0.035	0.213*	0.139*	-0.118*	0.019
	Cuneus	0.031	-0.303*	-0.017	0.000	0.147*	-0.067	0.213*	0.134*	-0.021	-0.014
	Pericalcarine	-0.027	-0.370*	-0.011	0.003	0.205*	-0.068	0.209*	0.112*	-0.049	0.026
Cingulate	Rostral Anterior Cingulate	0.023	-0.355*	0.011	-0.042	0.169*	-0.093*	0.123*	-0.004	-0.133*	0.025
	Caudal Anterior Cingulate	0.064	-0.174*	0.136*	-0.061	0.050	-0.112*	0.025	-0.157*	0.016	0.029
	Posterior Cingulate	0.049	-0.472*	-0.044	-0.031	0.211*	-0.079	0.160*	0.062	-0.080	0.036
	Isthmus Cingulate	0.069	-0.375*	0.001	-0.095*	0.154*	-0.063	0.053	-0.058	-0.085	-0.007
	Insula	0.021	-0.381*	-0.019	-0.017	0.201*	-0.027	0.146*	0.037	-0.140*	0.048

Note. Cortical measures are unadjusted. Site (scored PITT = 1, PENN = 0), Sex (scored female = 1, male = 0), Handedness (scored right-handed = 1, left-handed or ambidextrous = 0), Scan Quality (scored no visible artifacts = 1, visible artifacts = 0), Depression (scored Depression group = 1, not in Depression group = 0), Other Diagnoses (scored Other Diagnoses group = 1, not in Other Diagnoses group = 0).
* denotes $p<0.05$.

3.3.3.3 Relationship between Cortical Surface Area and Key Sample Characteristics

Table 13 presents correlations between regional cortical surface area measures and demographic, scanning, and diagnostic characteristics. Site showed very low correlations with several cortical surface area measures across most lobes, such that participants at PITT showed smaller cortical surface area than participants at PENN. Age and sex showed low to moderate correlations with almost all cortical surface area measures, such that smaller surface area was observed in older participants and female participants. In contrast, handedness was not significantly correlated with any cortical surface area measure. Parental education, but not personal education, showed very low positive correlations with most cortical surface area measures across all lobes. Scan quality showed low positive correlations with only two frontal surface area measures. Furthermore, intracranial volume showed low to moderate positive correlations with all cortical surface area measures. Depression diagnosis showed a low positive correlation with a cingulate surface area measure. Other Diagnoses showed very low positive correlations with a parietal surface area measure and an occipital area measure. Overall, most cortical surface area measures showed low to moderate correlations with age, sex, parental education, and intracranial volume.

Table 13. Correlations between cortical surface area and demographic and diagnostic characteristics.

Lobe	Region	Site	Age	Sex	Handedness	Parental Education	Education	Scan Quality	Intracranial Volume	Depression	Other Diagnoses
Frontal	Frontal Pole	-0.049	-0.294*	-0.293*	0.023	0.102*	-0.007	-0.030	0.429*	0.021	0.070
	Superior Frontal	-0.128*	-0.317*	-0.389*	0.067	0.144*	-0.019	-0.005	0.649*	0.020	0.024
	Rostral Middle Frontal	-0.086	-0.251*	-0.393*	0.041	0.056	-0.070	-0.035	0.616*	0.003	0.060
	Caudal Middle Frontal	-0.093*	-0.240*	-0.294*	0.001	0.116*	-0.054	0.019	0.526*	-0.001	-0.004
	Pars Opercularis	-0.152*	-0.303*	-0.256*	-0.041	0.125*	-0.028	0.018	0.442*	0.020	0.033
	Pars Triangularis	-0.111*	-0.319*	-0.319*	-0.061	0.164*	-0.001	0.058	0.432*	-0.001	0.014
	Pars Orbitalis	-0.061	-0.291*	-0.352*	-0.042	0.083	-0.083	0.007	0.508*	0.020	0.086
	Lateral Orbitofrontal	-0.102*	-0.224*	-0.319*	-0.001	0.122*	0.020	0.046	0.610*	0.017	0.001
	Medial Orbitofrontal	-0.180*	-0.133*	-0.390*	0.029	0.080	0.035	0.101*	0.643*	0.075	0.005
	Precentral	-0.067	-0.115*	-0.396*	0.006	0.048	-0.040	-0.101*	0.589*	0.015	0.078
	Paracentral	-0.094*	-0.137*	-0.296*	0.032	0.075	-0.010	-0.071	0.533*	0.008	0.024
Parietal	Superior Parietal	-0.046	-0.217*	-0.341*	-0.006	0.076	-0.006	-0.034	0.555*	0.046	0.037
	Inferior Parietal	-0.073	-0.167*	-0.370*	-0.020	0.100*	-0.058	-0.071	0.601*	-0.031	0.064
	Supramarginal	-0.114*	-0.182*	-0.439*	0.067	0.063	0.007	0.010	0.643*	0.054	0.100*
	Postcentral	-0.077	-0.124*	-0.403*	0.026	0.048	-0.020	-0.027	0.604*	0.039	0.032
	Precuneus	-0.062	-0.224*	-0.399*	0.032	0.053	-0.029	0.034	0.628*	0.033	0.061
Temporal	Superior Temporal	-0.126*	-0.144*	-0.375*	0.062	0.073	0.006	-0.052	0.650*	0.020	0.020
	Superior Temporal Sulcus	-0.049	-0.100*	-0.281*	0.035	0.104*	-0.026	-0.062	0.515*	0.054	0.069
	Middle Temporal	-0.133*	-0.256*	-0.373*	-0.003	0.146*	-0.037	0.025	0.614*	0.025	0.052
	Inferior Temporal	-0.148*	-0.236*	-0.383*	-0.006	0.124*	-0.048	-0.016	0.601*	0.045	0.052
	Fusiform	-0.092*	-0.262*	-0.401*	0.037	0.102*	-0.013	0.027	0.601*	0.027	0.057
	Transverse Temporal	-0.095*	-0.075	-0.266*	0.054	0.010	0.039	-0.053	0.431*	0.014	0.048
	Entorhinal	-0.083	-0.072	-0.317*	0.037	0.056	-0.020	-0.014	0.424*	0.005	0.041
	Temporal Pole	0.051	-0.217*	-0.314*	0.036	0.077	-0.037	0.068	0.361*	-0.006	0.016
	Parahippocampal	-0.020	-0.209*	-0.300*	-0.042	0.040	-0.041	-0.037	0.470*	0.022	0.028
Occipital	Lateral Occipital	-0.084	-0.158*	-0.452*	0.030	0.038	-0.064	-0.045	0.592*	0.065	0.074
	Lingual	-0.047	-0.185*	-0.322*	0.039	0.102*	-0.017	0.010	0.483*	0.030	0.096*
	Cuneus	-0.050	-0.164*	-0.359*	0.071	0.034	-0.041	0.017	0.439*	0.030	0.056
	Pericalcarine	-0.020	-0.163*	-0.299*	0.012	0.077	-0.026	0.044	0.404*	0.044	0.038
Cingulate	Rostral Anterior Cingulate	-0.140*	-0.042	-0.299*	0.054	0.056	0.019	0.039	0.567*	0.117*	-0.004
	Caudal Anterior Cingulate	-0.087	-0.112*	-0.287*	0.018	0.070	-0.063	0.032	0.517*	0.051	0.052
	Posterior Cingulate	-0.080	-0.203*	-0.357*	0.032	0.095*	-0.052	0.012	0.550*	0.031	0.065
	Isthmus Cingulate	-0.027	-0.125*	-0.379*	-0.019	0.045	-0.044	0.028	0.613*	0.055	0.007
	Insula	-0.058	-0.033	-0.437*	0.046	0.025	0.008	0.020	0.620*	0.028	0.016

Note. Cortical measures are unadjusted. Site (scored PITT = 1, PENN = 0), Sex (scored female = 1, male = 0), Handedness (scored right-handed = 1, left-handed or ambidextrous = 0), Scan Quality (scored no visible artifacts = 1, visible artifacts = 0), Depression (scored Depression group = 1, not in Depression group = 0), Other Diagnoses (scored Other Diagnoses group = 1, not in Other Diagnoses group = 0).
* denotes $p<0.05$.

3.3.4 Residualization and Standardization of Cortical Measures

Cortical data were complete for all participants in the MRI sample.

For analyses including basic adjustments, based on the control sample, each cortical measure was residualized for site, age, age^2, sex, and handedness in the pedigree sample. Specifically, for each participant, a predicted score based on regression in the control sample for a given cortical measure was estimated from their recruitment site, age, age^2, sex, and handedness, and was subtracted from the actual score for the cortical measure to produce the residualized score for the cortical measure. The residualized score for each cortical measure was then standardized to the mean and standard deviation of the control group.

For analyses including conservative adjustments, based on the control sample, each cortical measure was residualized for site, age, age^2, sex, and handedness, as well as parental education, scan quality, and intracranial volume in the pedigree sample. As with the analyses including basic adjustments, the residualized score for each cortical measure was then standardized to the mean and standard deviation of the control group. These conservative adjustments included variables that differed between schizophrenia and control and thus may be etiologically related to schizophrenia.

These residualized and standardized cortical measures were used in all subsequent analyses unless noted otherwise.

3.3.5 Outlier Treatment for Cortical Measures

For each cortical measure, any single score that was at least 3.0 standard deviations from the nearest neighboring score was winsorized to the nearest neighboring score. Thus, two scores were

winsorized for analyses using basic adjustments and analyses using conservative adjustments: the highest score for entorhinal surface area and the lowest score for caudal anterior cingulate thickness.

3.3.6 Cortical Measures by Group

To examine whether cortical measures differed between schizophrenia and controls, we conducted for each cortical measure an ANOVA as well as an ANCOVA covarying key sample characteristics which were found to show significant group differences between schizophrenia and controls (age, sex, scan quality, parental education, and intracranial volume). Given that both education measures (parental education and personal education) differed significantly between schizophrenia and controls, we examined only parental education because it was most correlated with cortical measures.

3.3.6.1 Global Cortical Measures by Group

Table 14 presents mean group comparisons between schizophrenia and controls for global cortical measures. Intracranial volume, mean thickness, and total surface area were significantly smaller in schizophrenia participants than controls, whereas lateral ventricle volume was significantly larger in schizophrenia participants than controls. Group differences remained significant after covarying site, age, sex, scan quality, parental education, and intracranial volume.

Table 14. Mean group comparisons between schizophrenia and controls for global cortical measures.

		Schizophrenia		Controls		ANOVA		ANCOVA		Adjustments ǂ					
Lobe	Region	Mean	(SD)	Mean	(SD)	F	p-value	F	p-value	Site	Age	Sex	Scan Quality	Parental Education	Intracranial Volume
Global	Intracranial Volume	-0.454	(1.070)	0.000	(1.000)	5.513	0.020*	4.286	0.039*	0.049	1.384	0.150	2.846	0.995	-
	Lateral Ventricle Volume	1.096	(2.062)	0.000	(1.000)	24.799	0.000*	32.097	0.000*	0.228	0.337	10.909*	9.016*	0.337	46.144*
	Mean Thickness	-0.697	(1.116)	0.000	(1.000)	12.829	0.000*	8.802	0.003*	0.245	2.931	0.000	28.987*	0.472	0.005
	Total Surface Area	-0.818	(0.965)	0.000	(1.000)	18.219	0.000*	10.473	0.001*	0.281	2.224	66.373*	1.031	0.358	229.267*

Note. All cortical measures had basic adjustments (site, age, age^2, sex, and handedness) and were standardized based on the control group means and standard deviations. Results of ANOVAs (*df*=1, 304) based on Type III unweighted sum of squares. Results of ANCOVAs (*df*=7, 294) based on Type III unweighted sum of squares include demographic adjustments shown to have significant group differences between schizophrenia and controls. Parental education data were unavailable for five participants (one relative and four controls). * denotes False Discovery Rate correction at $p<0.05$. ǂ F-statistic presented for ANCOVA of group differences in the cortical measure adjusting for the given adjustment.

3.3.6.2 Cortical Thickness Measures by Group

Table 15 presents mean group comparisons between schizophrenia and controls for regional cortical thickness measures. Most cortical thickness measures across all lobes showed significant group differences, before and after covarying for key demographic and scanning characteristics, with schizophrenia showing smaller cortical thickness measures than controls. Only ten thickness measures did not show significant overall group differences in cortical thickness, with or without adjustments: two frontal thickness measures (frontal pole, paracentral thickness), three parietal thickness measures (superior parietal, postcentral, and precuneus thickness), two temporal thickness measures (transverse temporal, temporal pole thickness), three occipital thickness measures (lateral occipital, cuneus, and pericalcarine thickness), and one cingulate thickness measure (caudal anterior cingulate thickness).

Table 15. Mean group comparisons between schizophrenia and controls for cortical thickness.

		Schizophrenia		Controls		ANOVA		ANCOVA		Adjustments ǂ					
Lobe	Region	Mean	(SD)	Mean	(SD)	F	p-value	F	p-value	Site	Age	Sex	Scan Quality	Parental Education	Intracranial Volume
Frontal	Frontal Pole	0.058	(0.893)	0.000	(1.000)	0.092	0.762	0.010	0.919	0.096	0.016	3.417	12.110*	0.003	12.547*
	Superior Frontal	-0.750	(1.226)	0.000	(1.000)	14.508	0.000*	12.302	0.001*	0.230	1.275	0.630	11.804*	0.284	1.695
	Rostral Middle Frontal	-0.668	(1.101)	0.000	(1.000)	11.833	0.001*	9.373	0.002*	0.002	2.608	0.177	21.394*	0.732	1.027
	Caudal Middle Frontal	-0.702	(1.162)	0.000	(1.000)	12.888	0.000*	8.308	0.004*	0.491	2.267	0.453	10.952*	0.535	1.574
	Pars Opercularis	-0.952	(1.041)	0.000	(1.000)	24.321	0.000*	18.400	0.000*	0.031	2.322	0.576	7.415*	0.576	2.482
	Pars Triangularis	-0.779	(1.036)	0.000	(1.000)	16.322	0.000*	12.808	0.000*	0.085	0.978	0.243	6.641*	0.765	0.570
	Pars Orbitalis	-0.496	(1.035)	0.000	(1.000)	6.603	0.011*	5.309	0.022*	0.029	1.018	0.694	27.021*	0.001	1.495
	Lateral Orbitofrontal	-0.474	(0.990)	0.000	(1.000)	6.088	0.014*	6.500	0.011*	0.003	0.103	4.182	12.454*	0.002	10.217*
	Medial Orbitofrontal	-0.436	(1.099)	0.000	(1.000)	5.037	0.026*	5.617	0.018*	0.011	0.054	2.007	3.571	0.028	6.939
	Precentral	-0.592	(1.117)	0.000	(1.000)	9.279	0.003*	5.194	0.023*	0.231	1.255	0.427	26.676*	0.008	1.394
	Paracentral	-0.143	(1.373)	0.000	(1.000)	0.514	0.474	0.129	0.720	0.200	0.605	0.004	17.055*	0.306	0.018
Parietal	Superior Parietal	-0.222	(1.167)	0.000	(1.000)	1.295	0.256	0.200	0.655	0.149	2.246	0.216	25.882*	0.394	0.805
	Inferior Parietal	-0.438	(1.098)	0.000	(1.000)	5.095	0.025*	2.732	0.099	0.266	1.777	0.024	22.334*	0.230	0.036
	Supramarginal	-0.587	(1.159)	0.000	(1.000)	9.041	0.003*	5.793	0.017*	0.250	3.666	0.025	28.864*	0.578	0.257
	Postcentral	-0.295	(1.040)	0.000	(1.000)	2.340	0.127	0.660	0.417	0.043	1.589	0.977	12.206*	0.328	2.283
	Precuneus	-0.373	(1.257)	0.000	(1.000)	3.570	0.060	1.509	0.220	0.304	2.788	0.822	16.434*	0.344	2.650
Temporal	Superior Temporal	-0.542	(1.130)	0.000	(1.000)	7.730	0.006*	4.911	0.027*	0.055	2.511	0.003	20.886*	0.426	0.017
	Superior Temporal Sulcus	-0.768	(1.389)	0.000	(1.000)	14.666	0.000*	10.279	0.001*	0.195	2.113	0.094	2.187	3.144	0.004
	Middle Temporal	-0.749	(1.146)	0.000	(1.000)	14.738	0.000*	10.742	0.001*	0.564	3.063	0.033	33.762*	0.431	0.571
	Inferior Temporal	-0.691	(0.964)	0.000	(1.000)	12.999	0.000*	8.759	0.003*	0.220	2.376	0.312	23.116*	0.004	0.566
	Fusiform	-0.864	(0.882)	0.000	(1.000)	20.642	0.000*	15.209	0.000*	0.052	4.230	0.087	26.967*	3.799	1.722
	Transverse Temporal	-0.218	(0.917)	0.000	(1.000)	1.306	0.254	0.158	0.691	0.128	2.759	1.130	11.708*	1.183	2.524
	Entorhinal	-0.510	(0.998)	0.000	(1.000)	7.050	0.008*	5.665	0.018*	0.324	1.057	1.042	16.746*	0.100	2.295
	Temporal Pole	-0.334	(0.901)	0.000	(1.000)	3.082	0.080	2.975	0.086	0.183	0.114	1.255	7.121*	0.105	4.019
	Parahippocampal	-0.593	(1.294)	0.000	(1.000)	8.946	0.003*	9.400	0.002*	0.035	0.145	2.335	1.796	0.482	2.720
Occipital	Lateral Occipital	0.001	(0.783)	0.000	(1.000)	0.000	0.998	0.024	0.877	0.000	0.222	0.009	5.093*	0.213	0.063
	Lingual	-0.486	(0.818)	0.000	(1.000)	6.594	0.011*	3.768	0.053	0.349	1.872	0.380	5.070*	1.748	1.977
	Cuneus	-0.029	(1.032)	0.000	(1.000)	0.022	0.882	0.069	0.793	0.089	1.022	0.365	8.220*	0.003	3.824
	Pericalcarine	0.236	(0.882)	0.000	(1.000)	1.546	0.215	2.088	0.150	0.001	0.857	0.106	6.947*	0.007	1.650
Cingulate	Rostral Anterior Cingulate	-0.457	(1.177)	0.000	(1.000)	5.448	0.020*	7.375	0.007*	0.091	0.365	1.948	0.011	0.894	8.530*
	Caudal Anterior Cingulate	-0.205	(1.003)	0.000	(1.000)	1.131	0.288	2.654	0.104	0.218	1.267	3.665	0.262	2.845	11.974*
	Posterior Cingulate	-0.534	(1.352)	0.000	(1.000)	7.158	0.008*	7.292	0.007*	0.008	0.141	0.147	1.805	2.928	1.303
	Isthmus Cingulate	-0.344	(0.970)	0.000	(1.000)	3.217	0.074	5.793	0.017*	0.074	0.879	1.901	0.492	2.841	9.202*
	Insula	-0.529	(1.074)	0.000	(1.000)	7.452	0.007*	7.404	0.007*	0.043	0.000	0.966	1.473	0.146	2.276

Note. All cortical measures had basic adjustments (site, age, age^2, sex, and handedness) and were standardized based on the control group means and standard deviations. Results of ANOVAs (df=1, 304) based on Type III unweighted sum of squares. Results of ANCOVAs (df=7, 294) based on Type III unweighted sum of squares include demographic adjustments shown to have significant group differences between schizophrenia and controls. Parental education data were unavailable for five participants (one relative and four controls). * denotes False Discovery Rate correction at p<0.05. ǂ F-statistic presented for ANCOVA of group differences in the cortical measure adjusting for the given adjustment.

3.3.6.3 Cortical Surface Area Measures by Group

Table 16 presents mean group differences between schizophrenia and controls for cortical surface area measures. As with cortical thickness, most surface area measures across all lobes showed significant group differences with schizophrenia being smaller than controls, before and after covarying for key sample characteristics. Only ten surface area measures did not show significant overall group differences in surface area, with or without adjustments: three frontal surface area measures (pars triangularis, precentral, and paracentral area), two temporal surface area measures (superior temporal sulcus and temporal pole area), one occipital surface area measure (cuneus area), and four cingulate surface area measures (rostral anterior cingulate, caudal anterior cingulate, posterior cingulate, and isthmus cingulate area).

Table 16. Mean group comparisons between schizophrenia and controls for cortical surface area.

		Schizophrenia		Controls		ANOVA		ANCOVA		Adjustments ‡					
Lobe	Region	Mean	(SD)	Mean	(SD)	F	p-value	F	p-value	Site	Age	Sex	Scan Quality	Parental Education	Intracranial Volume
Frontal	Frontal Pole	-0.528	(1.120)	0.000	(1.000)	7.351	0.007*	4.040	0.045	0.344	0.061	5.787*	0.751	0.067	21.057*
	Superior Frontal	-0.736	(1.077)	0.000	(1.000)	14.419	0.000*	7.654	0.006*	0.483	1.178	39.622*	1.110	0.488	153.116*
	Rostral Middle Frontal	-0.665	(0.835)	0.000	(1.000)	12.330	0.001*	7.162	0.008*	0.016	0.047	35.621*	4.043	3.909	119.806*
	Caudal Middle Frontal	-0.619	(0.662)	0.000	(1.000)	10.947	0.001*	5.478	0.020	0.174	0.237	16.109*	0.776	0.095	62.030*
	Pars Opercularis	-0.684	(1.079)	0.000	(1.000)	12.476	0.000*	7.593	0.006*	0.332	0.282	6.976*	0.396	0.005	30.091*
	Pars Triangularis	-0.385	(1.111)	0.000	(1.000)	3.918	0.049	1.263	0.262	0.000	1.978	8.381*	1.892	0.067	35.120*
	Pars Orbitalis	-0.544	(0.896)	0.000	(1.000)	8.171	0.005*	3.778	0.053	0.094	0.299	13.238*	0.323	0.083	51.251*
	Lateral Orbitofrontal	-0.674	(0.975)	0.000	(1.000)	12.358	0.001*	5.467	0.020	0.354	1.888	36.542*	0.081	0.068	124.757*
	Medial Orbitofrontal	-0.650	(1.025)	0.000	(1.000)	11.378	0.001*	4.255	0.040	0.043	4.898	39.395*	5.538	0.092	135.160*
	Precentral	-0.376	(1.068)	0.000	(1.000)	3.773	0.053	0.940	0.333	0.004	1.728	20.785*	1.555	0.057	76.280*
	Paracentral	-0.265	(1.149)	0.000	(1.000)	1.846	0.175	0.107	0.744	0.384	1.552	19.443*	2.781	0.411	71.738*
Parietal	Superior Parietal	-0.844	(1.065)	0.000	(1.000)	19.032	0.000*	10.911	0.001*	0.920	0.316	22.030*	0.972	0.191	74.972*
	Inferior Parietal	-0.613	(0.758)	0.000	(1.000)	10.588	0.001*	3.921	0.049	0.047	1.231	38.959*	3.118	0.212	114.230*
	Supramarginal	-0.642	(1.058)	0.000	(1.000)	11.012	0.001*	4.829	0.029	0.039	0.542	34.582*	0.094	1.641	108.582*
	Postcentral	-0.617	(0.906)	0.000	(1.000)	10.486	0.001*	4.731	0.030	0.055	1.343	33.414*	1.340	0.112	116.394*
	Precuneus	-0.760	(0.913)	0.000	(1.000)	15.879	0.000*	8.242	0.004*	0.062	0.382	34.145*	0.040	1.829	107.118*
Temporal	Superior Temporal	-0.445	(0.871)	0.000	(1.000)	5.474	0.020*	0.964	0.327	0.178	1.416	47.737*	1.228	0.061	158.722*
	Superior Temporal Sulcus	-0.273	(1.094)	0.000	(1.000)	1.976	0.161	0.006	0.940	0.011	4.088	26.922*	1.561	4.509	79.932*
	Middle Temporal	-0.764	(0.887)	0.000	(1.000)	16.110	0.000*	7.088	0.008*	0.526	2.200	33.075*	0.647	1.022	99.261*
	Inferior Temporal	-0.683	(0.809)	0.000	(1.000)	13.057	0.000*	5.759	0.017	0.526	0.599	23.426*	0.565	0.182	78.388*
	Fusiform	-0.525	(0.858)	0.000	(1.000)	7.651	0.006*	2.156	0.143	0.246	1.686	33.080*	0.113	0.113	107.834*
	Transverse Temporal	-0.618	(1.262)	0.000	(1.000)	9.790	0.002*	5.571	0.019	0.098	0.001	11.207*	0.409	1.745	45.688*
	Entorhinal	-0.543	(0.838)	0.000	(1.000)	8.222	0.004*	3.544	0.061	0.041	1.570	9.015*	0.308	1.116	30.797*
	Temporal Pole	-0.248	(0.920)	0.000	(1.000)	1.686	0.195	0.530	0.467	0.180	0.021	1.779	2.325	0.453	8.871*
	Parahippocampal	-0.743	(0.990)	0.000	(1.000)	14.979	0.000*	8.562	0.004*	0.109	0.069	15.127*	1.353	0.590	40.504*
Occipital	Lateral Occipital	-0.699	(0.989)	0.000	(1.000)	13.230	0.000*	7.641	0.006*	0.023	0.340	23.308*	0.845	0.721	87.337*
	Lingual	-0.447	(1.063)	0.000	(1.000)	5.349	0.021*	2.414	0.121	0.059	0.741	11.232*	0.054	0.044	42.949*
	Cuneus	-0.358	(0.985)	0.000	(1.000)	3.477	0.063	1.710	0.192	0.020	0.109	8.842*	0.631	0.970	38.182*
	Pericalcarine	-0.458	(1.046)	0.000	(1.000)	5.632	0.018*	3.462	0.064	0.080	0.371	5.171*	0.194	0.481	26.067*
Cingulate	Rostral Anterior Cingulate	-0.156	(1.061)	0.000	(1.000)	0.654	0.419	0.489	0.485	0.029	2.253	29.647*	2.216	0.030	101.212*
	Caudal Anterior Cingulate	-0.197	(1.089)	0.000	(1.000)	1.031	0.311	0.045	0.833	0.001	1.661	19.781*	0.030	0.118	63.740*
	Posterior Cingulate	-0.365	(1.009)	0.000	(1.000)	3.606	0.059	0.466	0.495	0.003	2.327	23.375*	0.184	0.776	83.949*
	Isthmus Cingulate	-0.273	(1.057)	0.000	(1.000)	1.996	0.159	0.036	0.850	0.011	0.686	26.585*	0.646	1.188	103.239*
	Insula	-0.527	(1.089)	0.000	(1.000)	7.373	0.007*	1.913	0.168	0.073	1.948	37.846*	1.142	0.623	126.581*

Note. All cortical measures had basic adjustments (site, age, age^2, sex, and handedness) and were standardized based on the control group means and standard deviations. Results of ANOVAs (df=1, 304) based on Type III unweighted sum of squares. Results of ANCOVAs (df=7, 294) based on Type III unweighted sum of squares include demographic adjustments shown to have significant group differences between schizophrenia and controls. Parental education data were unavailable for five participants (one relative and four controls). * denotes False Discovery Rate correction at p<0.05. ‡ F-statistic presented for ANCOVA of group differences in the cortical measure adjusting for the given adjustment.

3.3.6.4 Selection of Cortical Measures for Primary Analyses

To reduce the number of comparisons in the primary genetic analyses, we focused on examining only measures that showed significant overall group differences between schizophrenia and controls, with or without covarying for key demographic and scanning characteristics. Thus, genetic analyses examined a total of 51 measures, including the following:

1. Four global cortical measures:
    a. Intracranial volume
    b. Lateral ventricle volume
    c. Mean thickness
    d. Total surface area
2. 23 cortical thickness measures:
    a. Nine frontal thickness measures: superior frontal, rostral middle frontal, caudal middle frontal, pars opercularis, pars triangularis, pars orbitalis, lateral orbitofrontal, medial orbitofrontal, and precentral thickness;
    b. Two parietal thickness measures: inferior parietal and supramarginal thickness;
    c. Seven temporal thickness measures: superior temporal, superior temporal sulcus, middle temporal, inferior temporal, fusiform, entorhinal, and parahippocampal thickness;
    d. One occipital thickness measure: lingual area;
    e. Four cingulate thickness measures: rostral anterior cingulate, posterior cingulate, isthmus cingulate, and insula thickness
3. 24 cortical surface area measures:

a. Eight frontal surface area measures: frontal pole, superior frontal, rostral middle frontal, caudal middle frontal, pars opercularis, pars orbitalis, lateral orbitofrontal, and medial orbitofrontal area;
b. Five parietal surface area measures: superior parietal, inferior parietal, supramarginal, postcentral, and precuneus area;
c. Seven temporal surface area measures: superior temporal sulcus, middle temporal, inferior temporal, fusiform, transverse temporal, entorhinal, and parahippocampal area;
d. Three occipital surface area measures: lateral occipital, lingual, and pericalcarine area; and
e. One cingulate surface area measure: insula area.

FDR corrections were thus based separately on: four global measures, 23 cortical thickness measures, and 24 surface area measures (all bilateral).

3.4 PRIMARY ANALYSES

As noted above, genetic analyses were conducted using SOLAR-Eclipse (Almasy & Blangero, 1998) using the False Discovery Rate (FDR) correction to control for multiple comparisons.

First, results from global cortical measures, then regional cortical thickness measures, followed by regional cortical surface area measures will be presented.

3.4.1 Global Cortical Measures

3.4.1.1 Global Cortical Measures: Overall Genetic Effects

To examine overall genetic effects on global cortical measures during the Rise, Peak, and Plateau periods, the univariate heritability of each cortical measure was estimated in each age-risk group. As can be seen in Table 17, global cortical measures with basic adjustments showed nonsignificant heritabilities despite the heritabilities being generally moderate to high in magnitude during the Rise period, likely due to the smaller sample size. In contrast, global cortical measures were all significantly heritable during the Peak and Plateau periods. Analyses including conservative adjustments found similar age-related patterns of heritability for global cortical measures except for total surface area, for which the heritability was low and not significant for both the Rise and Plateau periods, perhaps due to the high correlation between intracranial volume and total surface area.

As shown in Appendix Table 1, differences in overall genetic effects across age-risk groups were not significant for any global cortical measure. Appendix Table 1 also presents correlations of overall genetic effects across age-risk periods on global cortical measures, finding high correlations across age-risk groups, which did not differ significantly from 1 or -1, consistent with pleiotropic genetic effects.

Table 17. Overall genetic effects on global cortical measures.

		Heritabilities with Basic Adjustments						Heritabilities with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value
Global	Intracranial Volume	0.970	(0.056)	1.000	(0.000*)	0.983	(0.000*)	0.970	(0.100)	0.969	(0.001*)	0.919	(0.000*)
	Lateral Ventricle Volume	0.531	(0.153)	0.539	(0.051)	0.558	(0.001*)	0.332	(0.321)	0.554	(0.053)	0.552	(0.001*)
	Mean Thickness	0.234	(0.296)	0.761	(0.041*)	0.655	(0.000*)	0.273	(0.343)	0.867	(0.021*)	0.877	(0.000*)
	Total Surface Area	0.689	(0.215)	0.830	(0.001*)	0.758	(0.000*)	0.062	(0.445)	0.090	(0.391)	0.649	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Univariate heritabilities were estimated including all schizophrenia participants (N=30 with cortical data). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume (except for intracranial volume, for which conservative adjustments additionally included only parental education and scan quality).

As shown in Appendix Table 1, differences in overall genetic effects across age-risk periods were not significant for any global cortical measure. Moreover, correlations of overall genetic effects across age-risk periods on global cortical measures showed consistently high correlations across age-risk periods which did not differ significantly from 1 or -1, which was indicative of pleiotropic genetic effects.

3.4.1.2 Global Cortical Measures: Genetic Correlations with Schizophrenia

To address the first of this study's key questions, Table 18 presents genetic correlations between schizophrenia and global cortical measures. Genetic correlations between schizophrenia and cortical measures were first estimated and tested for significance separately for each age-risk group.

The genetic correlation between schizophrenia and a given cortical measure during the Rise period allows us to infer schizophrenia genetic effects on the cortical measure that were present before schizophrenia peak age-of-onset, pointing to early neurodevelopmental effects. Evidence supporting early neurodevelopmental effects is considered present if the genetic correlation is significant during the Rise period; a nonsignificant genetic correlation during the Rise period does not construe evidence against early neurodevelopmental effects due to the relatively small sample size for the Rise period.

In contrast, the genetic correlation between schizophrenia and the cortical measure during the Peak period allows us to infer schizophrenia genetic effects on the cortical measure that were present immediately after schizophrenia peak age-of-onset. In order to determine if schizophrenia genetic effects on cortical phenotypes increase from the Rise to the Peak periods, as predicted by late neurodevelopmental models, these genetic correlations between cortical phenotypes and schizophrenia were compared across the age-risk periods. Given that schizophrenia is hypothesized to be genetically correlated with decreased cortical measures, evidence supporting late neurodevelopmental effects is considered "suggestive" if there is a significantly more negative genetic correlation from the Rise to the Peak period and "strong" if the genetic correlation is additionally significant during the Peak period.

The correlation between schizophrenia and the cortical measure during the Plateau period allows us to infer schizophrenia genetic effects on the cortical measure that were present during schizophrenia plateau age-of-onset. The genetic correlation during the Peak period and that during the Plateau period were compared to detect neurodegenerative effects. Evidence supporting neurodegenerative effects is considered suggestive if there is a significantly more negative genetic correlation from the Peak to the Plateau period and strong if the genetic correlation is additionally significant during the Plateau period.

For each cortical measure, the evidence for each developmental effect was evaluated separately for analyses with basic adjustments and analyses with conservative adjustments. Significant findings with basic adjustments suggest that schizophrenia developmental neurogenetic effects for a given cortical measure are unlikely to be attributable to demographic factors (age, age^2, sex, and site), whereas significant results with conservative adjustments suggest that schizophrenia developmental neurogenetic effects for the cortical measure are unlikely to be attributable to demographic factors or additional factors that may reflect schizophrenia effects (parental education, scan quality, and intracranial volume).

As shown in Table 18, different global cortical measures showed varied patterns of genetic overlap with schizophrenia across age-risk periods. For intracranial volume, the genetic correlation was negative and moderate throughout the Rise and Peak periods, then declined significantly during the Plateau period. In contrast, lateral ventricle volume showed low, nonsignificant genetic correlation with schizophrenia without significant changes across age-risk periods.

For mean thickness, the genetic correlation with schizophrenia was initially low and non-significant during the Rise period becoming significantly more negative during the Peak period

then significantly weaker during the Plateau period. In contrast, for total surface area, the genetic correlation with schizophrenia was strong and negative during the Rise period, declined during the Peak period then further declined during the Plateau period. Thus, genetic overlap with schizophrenia for smaller total surface area was maximally high before schizophrenia peak age-of-onset and continued to decline after schizophrenia peak age-of-onset through schizophrenia plateau age-of-onset.

Analyses including conservative adjustments produced nonsignificant genetic correlations for all global cortical measures except for total surface area, as shown in Table 18. Although age-related patterns were similar for intracranial volume and lateral ventricle volume, these additional adjustments rendered the genetic correlations low and stable across all age-risk periods for mean thickness. Furthermore, genetic overlap with schizophrenia for smaller surface area was high even after schizophrenia peak age-of-onset and only declined during schizophrenia plateau age-of-onset.

Table 18. Genetic correlations between schizophrenia and global cortical measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Measure	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Global	Intracranial Volume	-0.592	(NC)	-0.400	(NC)	-0.225	(NC)	-0.623	(NC)	-0.334	(0.221)	-0.237	(0.204)
	Lateral Ventricle Volume	0.041	(1.000)	0.029	(1.000)	0.095	(0.513)	0.211	(0.737)	0.173	(0.399)	0.209	(0.204)
	Mean Thickness	0.108	(1.000)	-0.360	(0.012*)	-0.092	(0.513)	-0.289	(0.366)	-0.038	(1.000)	-0.081	(0.744)
	Total Surface Area	-0.839	(NC)	-0.636	(0.004*)	-0.354	(0.008*)	-1.000	(NC)	-1.000	(0.003*)	-0.321	(0.204)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Measure	*z*	*p*-value	Change	*Z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Global	Intracranial Volume	-2.032	(0.056)	Stable	-2.112	(0.046*)	Decrease	-3.026	(0.010*)	Decrease	-1.137	(0.511)	Stable
	Lateral Ventricle Volume	-0.090	(0.928)	Stable	0.713	(0.476)	Stable	-0.315	(1.000)	Stable	0.403	(0.687)	Stable
	Mean Thickness	3.844	(0.000*)	Increase	-3.076	(0.004*)	Decrease	-2.060	(0.079)	Stable	0.474	(0.687)	Stable
	Total Surface Area	-3.703	(0.000*)	Decrease	-4.124	(0.000*)	Decrease	0.000	(1.000)	Stable	-86.812	(0.000*)	Decrease

		Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
		Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
		25.0%	50.0%	25.0%	0.0%	25.0%	75.0%	0.0%	75.0%	25.0%	0.0%	75.0%	25.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all schizophrenia participants (N=30 with cortical data). Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume (except for intracranial volume, for which conservative adjustments additionally included only parental education and scan quality). NC indicates that the significance of the parameter was not computable.

For comparisons across age-risk periods, genetic correlations between schizophrenia and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).

As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period. This comparison applies to all cortical measures except lateral ventricle volume, for which genetic correlations are expected to be positive rather than negative; here, "increase" indicates a significantly more positive genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less positive genetic correlation from the earlier to the later age-risk period.

Phenotypic correlations between schizophrenia and global cortical measures are presented in Appendix Table 2-3 and environmental correlations between schizophrenia and global cortical measures are presented in Appendix Table 6-7.

3.4.1.3 Global Cortical Measures: Summary of Schizophrenia Developmental Neurogenetic Effects

Overall, as summarized in the lower half of Table 18, schizophrenia genetic effects on these global cortical measures were mainly stable or decreasing between Rise and Peak periods with only mean thickness showing an increase at the Peak period and also a significant genetic correlation with schizophrenia during the Peak period, providing strong evidence for late neurodevelopmental effects, although the increase was not significant with the conservative adjustments. Heritability of mean thickness was also significant during the Peak period. As none of these global measures showed increased genetic correlations with schizophrenia during the Plateau period, neurodegenerative effects were not supported for these measures.

3.4.2 Cortical Thickness – Frontal

3.4.2.1 Cortical Thickness – Frontal: Overall Genetic Effects

As noted above, only regional measures that showed significant group differences between schizophrenia and controls will be discussed.

As shown in Table 19, heritabilities were generally low and not significant for any frontal thickness measure during the Rise period and despite some heritabilities being moderate to high in magnitude, only precentral thickness was significantly heritable during the Peak period. In contrast, all frontal thickness measures except for medial orbitofrontal thickness showed significant, low to moderate heritabilities during the Plateau period. Analyses including conservative adjustments also found similar age-related patterns of heritability for frontal thickness measures.

Table 19. Overall genetic effects on frontal thickness measures.

		Heritabilities with Basic Adjustments						Heritabilities with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value
Frontal	Frontal Pole	0.000	(NA)	0.263	(NA)	0.691	(NA)	0.000	(NA)	0.567	(NA)	0.692	(NA)
	Superior Frontal	0.253	(0.458)	0.361	(0.284)	0.763	(0.003*)	0.160	(0.500)	0.257	(0.307)	0.749	(0.002*)
	Rostral Middle Frontal	0.435	(0.458)	0.587	(0.130)	0.564	(0.003*)	0.126	(0.500)	0.572	(0.108)	0.628	(0.002*)
	Caudal Middle Frontal	0.182	(0.458)	0.296	(0.284)	0.668	(0.004*)	0.105	(0.500)	0.093	(0.422)	0.744	(0.002*)
	Pars Opercularis	0.260	(0.458)	0.345	(0.164)	0.552	(0.011*)	0.222	(0.500)	0.253	(0.238)	0.600	(0.007*)
	Pars Triangularis	0.000	(0.500)	0.067	(0.468)	0.592	(0.000*)	0.000	(0.500)	0.104	(0.407)	0.583	(0.000*)
	Pars Orbitalis	0.203	(0.458)	0.887	(0.054)	0.630	(0.009*)	0.158	(0.500)	0.839	(0.058)	0.699	(0.006*)
	Lateral Orbitofrontal	0.000	(0.500)	0.561	(0.124)	0.455	(0.013*)	0.000	(0.500)	0.554	(0.102)	0.505	(0.010*)
	Medial Orbitofrontal	0.000	(0.500)	0.170	(0.350)	0.300	(0.073)	0.000	(0.500)	0.379	(0.147)	0.396	(0.040*)
	Precentral	0.615	(0.458)	0.820	(0.041*)	0.493	(0.008*)	0.605	(0.500)	0.708	(0.069)	0.586	(0.002*)
	Paracentral	0.026	(NA)	0.305	(NA)	0.766	(NA)	0.000	(NA)	0.335	(NA)	0.910	(NA)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Univariate heritabilities were estimated including all schizophrenia participants (N=30 with cortical data). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.

As shown in Appendix Table 10, differences in overall genetic effects across age-risk periods were not significant for any frontal thickness measure. Moreover, correlations of overall genetic effects across age-risk periods on frontal thickness measures showed consistently high correlations across age-risk periods which did not differ significantly from 1 or -1, which was indicative of pleiotropic genetic effects.

3.4.2.2 Cortical Thickness – Frontal: Genetic Correlations with Schizophrenia

Table 20 presents genetic correlations between schizophrenia and frontal thickness measures. None of the genetic correlations between schizophrenia and frontal thickness measures were significant during any age-risk period. Although not significant, unexpectedly, during the Rise period, most genetic correlations between schizophrenia and frontal thickness measures were positive, indicating increased cortical thickness among schizophrenia relatives, and although four of the nine correlations were low, the five others were quite high. All genetic correlations became negative, and low to moderate during the Peak period and through the Plateau period.

From the Rise to the Peak period, many frontal thickness measures (44.4%) showed a more negative genetic correlation, whereas some (33.3%) showed a stable genetic correlation and a few (22.2%) showed a less negative genetic correlation. In contrast, from the Peak to the Plateau period, the genetic correlation generally remained stable (55.6%) or was less negative (44.4%).

With a more conservative set of adjustments, genetic correlations between schizophrenia and frontal thickness measures tended to be smaller compared to genetic correlations with basic adjustments. Comparisons across age-risk periods also shifted. From the Rise to the Peak period, the genetic correlations between schizophrenia and frontal thickness measures were generally stable (55.6%), with some becoming less negative (33.3%) and one becoming more negative (11.1%), in contrast to the genetic correlations becoming more negative when estimated with basic adjustments. Furthermore, from the Peak to the Plateau period, the genetic correlations between schizophrenia and frontal thickness measures were equally likely to become more negative, stable, or less negative, rather than only stable or less negative when estimated with basic adjustments.

Table 20. Genetic correlations between schizophrenia and frontal thickness measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Frontal	Frontal Pole	0.900	(NA)	0.352	(NA)	0.178	(NA)	0.900	(NA)	0.229	(NA)	0.025	(NA)
	Superior Frontal	-0.321	(0.446)	-0.252	(0.323)	-0.067	(NC)	-0.516	(1.000)	-0.092	(0.926)	0.017	(1.000)
	Rostral Middle Frontal	0.090	(0.915)	-0.391	(NC)	0.053	(0.804)	-0.078	(1.000)	-0.243	(NC)	-0.036	(1.000)
	Caudal Middle Frontal	-0.290	(1.000)	-0.375	(0.118)	-0.054	(0.804)	-0.289	(1.000)	-0.055	(0.926)	0.058	(0.943)
	Pars Opercularis	-1.000	(0.204)	-0.704	(0.118)	-0.251	(0.443)	-0.900	(0.254)	-0.561	(0.067)	-0.202	(0.394)
	Pars Triangularis	-0.900	(0.709)	-0.670	(0.118)	-0.242	(0.355)	-0.900	(0.768)	-0.593	(0.178)	-0.247	(0.236)
	Pars Orbitalis	0.900	(0.709)	-0.177	(NC)	-0.170	(0.489)	0.423	(1.000)	-0.064	(0.926)	-0.251	(0.151)
	Lateral Orbitofrontal	0.022	(1.000)	-0.044	(1.000)	-0.229	(0.563)	0.025	(1.000)	-0.016	(1.000)	-0.355	(0.151)
	Medial Orbitofrontal	0.900	(0.642)	-0.199	(0.669)	-0.272	(0.471)	-0.145	(1.000)	-0.073	(0.926)	-0.333	(0.151)
	Precentral	0.198	(0.994)	-0.065	(NC)	-0.093	(0.804)	0.195	(1.000)	0.188	(0.617)	-0.090	(0.743)
	Paracentral	0.085	(NA)	-0.013	(NA)	0.169	(NA)	-0.900	(NA)	0.187	(NA)	0.197	(NA)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Frontal	Frontal Pole	8.758	(NA)	-	2.033	(NA)	-	9.817	(NA)	-	2.234	(NA)	-
	Superior Frontal	-0.592	(0.579)	Stable	-2.056	(0.055)	Stable	-3.789	(0.000*)	Decrease	-1.174	(0.276)	Stable
	Rostral Middle Frontal	3.990	(0.000*)	Increase	-5.029	(0.000*)	Decrease	1.347	(0.228)	Stable	-2.281	(0.047*)	Decrease
	Caudal Middle Frontal	0.766	(0.486)	Stable	-3.677	(0.000*)	Decrease	-1.919	(0.074)	Stable	-1.208	(0.275)	Stable
	Pars Opercularis	-59.700	(0.000*)	Decrease	-6.689	(0.000*)	Decrease	-6.641	(0.000*)	Decrease	-4.617	(0.000*)	Decrease
	Pars Triangularis	-5.246	(0.000*)	Decrease	-6.093	(0.000*)	Decrease	-6.256	(0.000*)	Decrease	-4.626	(0.000*)	Decrease
	Pars Orbitalis	13.089	(0.000*)	Increase	-0.073	(0.942)	Stable	4.085	(0.000*)	Increase	2.069	(0.068)	Stable
	Lateral Orbitofrontal	0.523	(0.601)	Stable	2.052	(0.055)	Stable	0.328	(0.813)	Stable	3.811	(0.001*)	Increase
	Medial Orbitofrontal	13.293	(0.000*)	Increase	0.827	(0.470)	Stable	-0.577	(0.648)	Stable	2.929	(0.010*)	Increase
	Precentral	2.101	(0.048*)	Increase	0.309	(0.792)	Stable	0.056	(0.955)	Stable	3.020	(0.008*)	Increase
	Paracentral	0.776	(NA)	-	-1.991	(NA)	-	-13.165	(NA)	-	-0.105	(NA)	-

	Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
	Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
	44.4%	33.3%	22.2%	0.0%	55.6%	44.4%	11.1%	55.6%	33.3%	33.3%	33.3%	33.3%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all schizophrenia participants (N=30 with cortical data). Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments. NC indicates that the significance of the parameter was not computable.

For comparisons across age-risk periods, genetic correlations between schizophrenia and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).
As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.
Phenotypic correlations between schizophrenia and frontal thickness measures are presented in Appendix Table 11-12 and environmental correlations between schizophrenia and frontal thickness measures are presented in Appendix Table 15-16.

3.4.2.3 Cortical Thickness – Frontal: Summary of Schizophrenia Developmental Neurogenetic Effects

Overall, with basic adjustments, most (44.4%) genetic correlations between schizophrenia and frontal thickness measures (rostral middle frontal, pars orbitalis, medial orbitofrontal, and precentral thickness) became more negative from the Rise to the Peak period, whereas analyses with conservative adjustments of parental education, scan quality, and intracranial volume found only one thickness measure (pars orbitalis thickness) with a significant increase. None of these genetic correlations with schizophrenia were significant during the Peak period, providing only suggestive evidence for late neurodevelopmental effects. Across findings with basic or conservative adjustments, genetic correlations between schizophrenia and frontal thickness measures generally became less negative or did not change significantly from the Peak to the Plateau period, arguing against general neurodegenerative effects. However, there was suggestive evidence of neurodegenerative effects for lateral orbitofrontal, medial orbitofrontal, and precentral thickness, which had increased negative genetic correlations from Peak to Plateau periods, although not significant genetic correlations during the Plateau period with conservative adjustments.

3.4.3 Cortical Thickness – Parietal

3.4.3.1 Cortical Thickness – Parietal: Overall Genetic Effects

As shown in Table 21, heritabilities were low and not significant for either of the parietal thickness measures examined during the Rise period or the Peak period. In contrast, both measures showed significant, low to moderate heritabilities during the Plateau period. Similar age-related patterns of heritabilities were observed with conservative adjustments.

Table 21. Overall genetic effects on parietal thickness measures.

		Heritabilities with Basic Adjustments						Heritabilities with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value
Parietal	Superior Parietal	0.000	(NA)	0.101	(NA)	0.295	(NA)	0.000	(NA)	0.434	(NA)	0.604	(NA)
	Inferior Parietal	0.183	(0.458)	0.374	(0.234)	0.356	(0.028*)	0.298	(0.500)	0.560	(0.095)	0.598	(0.002*)
	Supramarginal	0.204	(0.458)	0.715	(0.073)	0.418	(0.023*)	0.088	(0.500)	0.605	(0.073)	0.791	(0.002*)
	Postcentral	0.109	(NA)	0.320	(NA)	0.554	(NA)	0.176	(NA)	0.323	(NA)	0.645	(NA)
	Precuneus	0.010	(NA)	0.623	(NA)	0.305	(NA)	0.000	(NA)	0.757	(NA)	0.654	(NA)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Univariate heritabilities were estimated including all schizophrenia participants (N=30 with cortical data). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.

As shown in Appendix Table 10, differences in overall genetic effects across age-risk periods were not significant for any parietal thickness measure. Moreover, correlations of overall genetic effects across age-risk periods on parietal thickness measures showed consistently high correlations across age-risk periods which did not differ significantly from 1 or -1, which was indicative of pleiotropic genetic effects.

3.4.3.2 Cortical Thickness – Parietal: Genetic Correlations with Schizophrenia

As shown in Table 22, which presents genetic correlations between schizophrenia and parietal thickness measures, none of the genetic correlations for the two parietal thickness measures were significant during any age-risk period. During the Rise period, the genetic correlations between schizophrenia and parietal thickness measures were both positive, with one being very high and the other being low. Both genetic correlations became negative, and low to moderate during the Peak period, then became close to zero during the Plateau period. From the Rise to the Peak period, the genetic correlations for all parietal thickness measures (100.0%) became more negative. However, from the Peak to the Plateau period, the genetic correlation remained stable (50.0%) or became less negative (50.0%).

With a more conservative set of adjustments, genetic correlations between schizophrenia and parietal thickness measures, though not significant for any age-risk period, were all positive for inferior parietal thickness and negative for supramarginal thickness. Comparisons across age-risk periods were generally similar to comparisons with basic adjustments except for supramarginal thickness, which remained stable rather than becoming more negative from the Rise to the Peak period.

Table 22. Genetic correlations between schizophrenia and parietal thickness measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Parietal	Superior Parietal	0.007	(NA)	0.344	(NA)	0.109	(NA)	-0.070	(NA)	0.398	(NA)	0.042	(NA)
	Inferior Parietal	1.000	(0.446)	-0.058	(1.000)	0.061	(0.804)	0.727	(0.768)	0.121	(0.926)	0.008	(1.000)
	Supramarginal	0.252	(0.709)	-0.471	(0.182)	-0.073	(0.804)	-0.218	(1.000)	-0.312	(0.253)	-0.079	(0.743)
	Postcentral	0.900	(NA)	-0.279	(NA)	-0.012	(NA)	0.798	(NA)	0.008	(NA)	-0.005	(NA)
	Precuneus	-0.374	(NA)	0.011	(NA)	-0.063	(NA)	-0.078	(NA)	-0.083	(NA)	0.048	(NA)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Parietal	Superior Parietal	-2.790	(NA)	-	2.700	(NA)	-	-3.888	(NA)	-	4.069	(NA)	-
	Inferior Parietal	67.105	(0.000*)	Increase	-1.290	(0.239)	Stable	6.348	(0.000*)	Increase	1.222	(0.275)	Stable
	Supramarginal	6.098	(0.000*)	Increase	-4.737	(0.000*)	Decrease	0.805	(0.510)	Stable	-2.618	(0.023*)	Decrease
	Postcentral	13.941	(NA)	-	-2.962	(NA)	-	8.605	(NA)	-	0.138	(NA)	-
	Precuneus	-3.206	(NA)	-	0.803	(NA)	-	0.039	(NA)	-	-1.412	(NA)	-

		Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
		Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
		100.0%	0.0%	0.0%	0.0%	50.0%	50.0%	50.0%	50.0%	0.0%	0.0%	50.0%	50.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all schizophrenia participants (N=30 with cortical data). Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.

For comparisons across age-risk periods, genetic correlations between schizophrenia and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).

As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Phenotypic correlations between schizophrenia and parietal thickness measures are presented in Appendix Table 11-12 and environmental correlations between schizophrenia and parietal thickness measures are presented in Appendix Table 15-16.

3.4.3.3 Cortical Thickness – Parietal: Summary of Schizophrenia Developmental Neurogenetic Effects

Overall, with basic adjustments, genetic correlations between schizophrenia and both parietal thickness measures (inferior parietal and supramarginal thickness) evaluated became more negative from the Rise to the Peak period, whereas with conservative adjustments, only one measure (inferior parietal thickness) became more negative. Unexpectedly, these changes were from positive genetic correlations during the Rise period and in any case none of the genetic correlations at the Peak period were significantly different from zero, thus providing only suggestive support for late neurodevelopmental effects. With basic or conservative adjustments, genetic correlations between schizophrenia and both parietal thickness measures remained stable or became less negative during the Plateau period, arguing against neurodegenerative effects.

3.4.4 Cortical Thickness – Temporal

3.4.4.1 Cortical Thickness: Overall Genetic Effects

As shown in Table 23, heritabilities were not significant for any of the temporal thickness measures during the Rise period, despite ranging from low to moderate. However, heritabilities for a few measures were high and significant during the Peak period, and heritabilities for all except one temporal thickness measure were moderate and significant during the Plateau period. Analyses with conservative adjustments showed the same age-related patterns for heritabilities.

Table 23. Overall genetic effects on temporal thickness measures.

		Heritabilities with Basic Adjustments						Heritabilities with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value
Temporal	Superior Temporal	0.000	(0.500)	0.144	(0.351)	0.552	(0.003*)	0.000	(0.500)	0.225	(0.264)	0.608	(0.001*)
	Superior Temporal Sulcus	0.443	(0.458)	0.000	(0.500)	0.382	(0.009*)	0.401	(0.500)	0.000	(0.500)	0.370	(0.007*)
	Middle Temporal	0.616	(0.458)	0.997	(0.030*)	0.578	(0.003*)	0.749	(0.348)	0.960	(0.028*)	0.783	(0.000*)
	Inferior Temporal	0.757	(0.458)	0.970	(0.037*)	0.355	(0.039*)	0.970	(0.218)	0.983	(0.034*)	0.529	(0.007*)
	Fusiform	0.317	(0.458)	0.000	(0.500)	0.418	(0.009*)	0.191	(0.500)	0.161	(0.387)	0.433	(0.007*)
	Transverse Temporal	0.418	(NA)	0.572	(NA)	0.763	(NA)	0.053	(NA)	0.547	(NA)	0.724	(NA)
	Entorhinal	0.221	(0.458)	0.701	(0.103)	0.103	(0.241)	0.371	(0.500)	0.651	(0.102)	0.055	(0.371)
	Temporal Pole	0.000	(NA)	0.830	(NA)	0.177	(NA)	0.000	(NA)	0.710	(NA)	0.184	(NA)
	Parahippocampal	0.484	(0.458)	0.785	(0.040*)	0.606	(0.007*)	0.585	(0.500)	0.758	(0.034*)	0.578	(0.007*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Univariate heritabilities were estimated including all schizophrenia participants (N=30 with cortical data). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.

As shown in Appendix Table 10, differences in overall genetic effects across age-risk periods were not significant for any temporal thickness measure. Moreover, correlations of overall genetic effects across age-risk periods on temporal thickness measures showed consistently high correlations across age-risk periods which did not differ significantly from 1 or -1, which was indicative of pleiotropic genetic effects.

3.4.4.2 Cortical Thickness – Temporal: Genetic Correlations with Schizophrenia

As shown in Table 24, which presents genetic correlations between schizophrenia and temporal thickness measures, none of the genetic correlations for the temporal thickness measures were significant during any age-risk period. During the Rise period, the genetic correlations between schizophrenia and temporal thickness measures were generally positive and ranged from low to high. After the Rise period these genetic correlations all became negative and remained negative, ranging from low to high in magnitude.

Comparisons across age-risk periods showed that most of the genetic correlations between schizophrenia and temporal thickness measures became more negative (85.7%) from the Rise to the Peak period with only one measure becoming less negative (14.3%) across these periods. In addition, most of the genetic correlations between schizophrenia and temporal thickness measures became less negative (71.4%) from the Peak to the Plateau period.

Analyses with conservative adjustments also found most temporal thickness measures showed a more negative genetic correlation with schizophrenia from the Rise to the Peak period. However, analyses with conservative adjustments showed that, instead of generally becoming less negative from the Peak to the Plateau period, genetic correlations generally did not change significantly across these periods.

Table 24. Genetic correlations between schizophrenia and temporal thickness measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Temporal	Superior Temporal	-0.065	(1.000)	-0.437	(0.484)	-0.037	(0.833)	-0.900	(1.000)	-0.210	(1.000)	-0.054	(0.873)
	Superior Temporal Sulcus	0.033	(1.000)	-1.000	(0.412)	-0.090	(0.804)	0.018	(1.000)	-0.973	(0.926)	-0.102	(0.743)
	Middle Temporal	0.465	(0.709)	-0.300	(NC)	-0.058	(0.804)	0.201	(0.777)	-0.192	(NC)	-0.125	(0.567)
	Inferior Temporal	0.497	(0.642)	-0.459	(NC)	-0.130	(0.804)	0.237	(1.000)	-0.306	(NC)	-0.185	(0.743)
	Fusiform	0.900	(0.446)	-1.000	(0.473)	-0.332	(0.355)	0.900	(0.768)	-0.249	(0.926)	-0.391	(0.151)
	Transverse Temporal	-0.460	(NA)	-0.377	(NA)	0.036	(NA)	-0.663	(NA)	-0.147	(NA)	0.035	(NA)
	Entorhinal	-0.570	(0.709)	-0.326	(0.393)	-0.900	(0.191)	-0.633	(1.000)	-0.290	(0.277)	-0.900	(0.151)
	Temporal Pole	1.000	(NA)	-0.037	(NA)	-0.263	(NA)	0.900	(NA)	-0.076	(NA)	-0.393	(NA)
	Parahippocampal	0.319	(0.709)	-0.221	(0.393)	-0.347	(0.191)	0.217	(0.768)	-0.245	(0.594)	-0.400	(0.034*)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Temporal	Superior Temporal	3.202	(0.002*)	Increase	-4.666	(0.000*)	Decrease	-9.973	(0.000*)	Decrease	-1.717	(0.127)	Stable
	Superior Temporal Sulcus	66.907	(0.000*)	Increase	-89.863	(0.000*)	Decrease	17.124	(0.000*)	Increase	-21.947	(0.000*)	Decrease
	Middle Temporal	6.454	(0.000*)	Increase	-2.720	(0.011*)	Decrease	3.155	(0.003*)	Increase	-0.735	(0.483)	Stable
	Inferior Temporal	8.257	(0.000*)	Increase	-3.954	(0.000*)	Decrease	4.415	(0.000*)	Increase	-1.386	(0.224)	Stable
	Fusiform	78.314	(0.000*)	Increase	-87.115	(0.000*)	Decrease	13.683	(0.000*)	Increase	1.704	(0.127)	Stable
	Transverse Temporal	-0.805	(NA)	-	-4.674	(NA)	-	-5.151	(NA)	-	-1.964	(NA)	-
	Entorhinal	-2.450	(0.021*)	Decrease	12.253	(0.000*)	Increase	-3.556	(0.001*)	Decrease	12.625	(0.000*)	Increase
	Temporal Pole	66.932	(NA)	-	2.511	(NA)	-	12.264	(NA)	-	3.656	(NA)	-
	Parahippocampal	4.398	(0.000*)	Increase	1.490	(0.174)	Stable	3.731	(0.000*)	Increase	1.865	(0.102)	Stable

								Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments					
								Rise/Peak			Peak/Plateau		
								Increase	Stable	Decrease	Increase	Stable	Decrease
								85.7%	0.0%	14.3%	14.3%	14.3%	71.4%

								Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
								Rise/Peak			Peak/Plateau		
								Increase	Stable	Decrease	Increase	Stable	Decrease
								71.4%	0.0%	28.6%	14.3%	71.4%	14.3%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all schizophrenia participants (N=30 with cortical data). Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments. NC indicates that the significance of the parameter was not computable.
For comparisons across age-risk periods, genetic correlations between schizophrenia and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).

As indicated by comparisons across age-risk periods, “increase” indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, “stable” indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and “decrease” indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.
Phenotypic correlations between schizophrenia and temporal thickness measures are presented in Appendix Table 11-12 and environmental correlations between schizophrenia and temporal thickness measures are presented in Appendix Table 15-16.

3.4.4.3 Cortical Thickness – Temporal: Summary of Schizophrenia Developmental Neurogenetic Effects

Overall, with basic or conservative adjustments, genetic correlations between schizophrenia and almost all temporal thickness measures became more negative from the Rise to the Peak period. However, none of these genetic correlations with schizophrenia during the Peak period were significantly different from zero, providing only suggestive support for late neurodevelopmental effects. From the Peak to the Plateau period, genetic correlations with basic adjustments generally became less negative and genetic correlations with conservative adjustments generally remained stable, arguing against general neurodegenerative effects. However, there was some suggestive evidence of degeneration effects for entorhinal thickness, which showed increased negative genetic correlations with schizophrenia from Peak to Plateau periods, although the genetic correlations at the Plateau period were not significant.

3.4.5 Cortical Thickness – Occipital

3.4.5.1 Cortical Thickness – Occipital: Overall Genetic Effects

As shown in Table 25, the heritability for the only occipital thickness measure evaluated, lingual thickness, was moderate and not significant during the Rise and Peak periods becoming significant during the Plateau period. The same pattern was observed when using conservative adjustments.

Table 25. Overall genetic effects on occipital thickness measures.

		Heritabilities with Basic Adjustments						Heritabilities with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value
Occipital	Lateral Occipital	0.189	(NA)	0.000	(NA)	0.588	(NA)	0.197	(NA)	0.000	(NA)	0.723	(NA)
	Lingual	0.404	(0.458)	0.656	(0.164)	0.716	(0.002*)	0.561	(0.500)	0.666	(0.147)	0.656	(0.002*)
	Cuneus	0.000	(NA)	0.027	(NA)	0.345	(NA)	0.000	(NA)	0.000	(NA)	0.504	(NA)
	Pericalcarine	0.000	(NA)	0.000	(NA)	0.370	(NA)	0.000	(NA)	0.000	(NA)	0.367	(NA)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Univariate heritabilities were estimated including all schizophrenia participants (N=30 with cortical data). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.

As shown in Appendix Table 10, differences in overall genetic effects across age-risk periods were not significant for any occipital thickness measure. Moreover, correlations of overall genetic effects across age-risk periods on occipital thickness measures showed consistently high correlations across age-risk periods which did not differ significantly from 1 or -1, which was indicative of pleiotropic genetic effects.

3.4.5.2 Cortical Thickness – Occipital: Genetic Correlations with Schizophrenia

As shown in Table 26, the genetic correlation between schizophrenia and the only occipital thickness measure was moderate and not significant for the Rise and the Peak period and low and not significant during the Plateau period. The genetic correlation was stable from the Rise to the Peak period and became less negative from the Peak to the Plateau period. This overall pattern was the similar after including conservative adjustments, except that the genetic correlation only became less negative from the Rise to the Peak period and did not change significantly from the Peak to the Plateau period.

Table 26. Genetic correlations between schizophrenia and occipital thickness measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Occipital	Lateral Occipital	0.900	(NA)	1.000	(NA)	0.097	(NA)	-0.473	(NA)	1.000	(NA)	0.080	(NA)
	Lingual	-0.587	(0.774)	-0.499	(0.428)	-0.255	(0.277)	-0.367	(1.000)	-0.093	(0.926)	-0.291	(0.151)
	Cuneus	-1.000	(NA)	-0.129	(NA)	-0.001	(NA)	0.004	(NA)	0.900	(NA)	0.156	(NA)
	Pericalcarine	-1.000	(NA)	0.205	(NA)	0.403	(NA)	-1.000	(NA)	-0.216	(NA)	0.421	(NA)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Occipital	Lateral Occipital	-54.970	(NA)	-	89.795	(NA)	-	-70.668	(NA)	-	89.532	(NA)	-
	Lingual	-0.989	(0.371)	Stable	-3.110	(0.003*)	Decrease	-2.311	(0.032*)	Decrease	2.222	(0.050)	Stable
	Cuneus	-65.612	(NA)	-	-1.392	(NA)	-	-11.635	(NA)	-	14.136	(NA)	-
	Pericalcarine	-68.289	(NA)	-	-2.374	(NA)	-	-64.856	(NA)	-	-7.194	(NA)	-

		Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
		Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
		0.0%	100.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	100.0%	0.0%	100.0%	0.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all schizophrenia participants (N=30 with cortical data). Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.

For comparisons across age-risk periods, genetic correlations between schizophrenia and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).

As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Phenotypic correlations between schizophrenia and occipital thickness measures are presented in Appendix Table 11-12 and environmental correlations between schizophrenia and occipital thickness measures are presented in Appendix Table 15-16.

3.4.5.3 Cortical Thickness – Occipital: Summary of Schizophrenia Developmental Neurogenetic Effects

Overall, across analyses with basic or conservative adjustments, the genetic correlations between schizophrenia and the one occipital thickness region evaluated were stable or became less negative from the Rise to the Peak period, arguing against late neurodevelopmental effects. The genetic correlations became less negative or did not change significantly from the Peak to the Plateau period, also not supporting neurodegenerative effects.

3.4.6 Cortical Thickness – Cingulate

3.4.6.1 Cortical Thickness – Cingulate: Overall Genetic Effects

As can be seen in Table 27, heritabilities of cingulate thickness measures were low to moderate and nonsignificant during the Rise period. Only one cingulate thickness measure showed significant heritability during the Peak period, and all measures showed significant, moderate heritabilities during the Plateau period. When including conservative adjustments, heritabilities were also nonsignificant during the Rise period but most showed significant moderate and significant heritabilities during the Peak and Plateau periods.

Table 27. Overall genetic effects on cingulate thickness measures.

		Heritabilities with Basic Adjustments						Heritabilities with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value
Cingulate	Rostral Anterior Cingulate	0.623	(0.458)	0.849	(0.037*)	0.542	(0.005*)	0.334	(0.500)	0.775	(0.034*)	0.473	(0.007*)
	Caudal Anterior Cingulate	0.000	(NA)	0.058	(NA)	0.112	(NA)	0.000	(NA)	0.151	(NA)	0.079	(NA)
	Posterior Cingulate	0.000	(0.500)	0.222	(0.350)	0.533	(0.003*)	0.000	(0.500)	0.323	(0.238)	0.708	(0.000*)
	Isthmus Cingulate	0.329	(0.458)	0.862	(0.054)	0.349	(0.010*)	0.791	(0.500)	0.781	(0.047*)	0.354	(0.013*)
	Insula	0.000	(0.500)	0.619	(0.060)	0.622	(0.004*)	0.000	(0.500)	0.748	(0.034*)	0.663	(0.002*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Univariate heritabilities were estimated including all schizophrenia participants (N=30 with cortical data). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.

As shown in Appendix Table 10, differences in overall genetic effects across age-risk periods were not significant for any cingulate thickness measure. Moreover, correlations of overall genetic effects across age-risk periods on cingulate thickness measures showed consistently high correlations across age-risk periods which did not differ significantly from 1 or -1, which was indicative of pleiotropic genetic effects.

3.4.6.2 Cortical Thickness – Cingulate: Genetic Correlations with Schizophrenia

Table 28 shows the genetic correlations between schizophrenia and cingulate thickness measures. None were significantly different from zero at any of the risk periods. Genetic correlations either became more negative (50.0%) or did not change significantly (50.0%) from the Rise to the Peak period. In contrast, genetic correlations either became less negative (50.0%) or did not change significantly (50.0%) from the Peak to the Plateau period. Analyses including conservative adjustments suggested a similar overall pattern of age-related changes in genetic correlations.

Table 28. Genetic correlations between schizophrenia and cingulate thickness measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Cingulate	Rostral Anterior Cingulate	0.755	(0.446)	-0.032	(NC)	-0.218	(0.443)	0.900	(0.768)	-0.161	(0.926)	-0.257	(0.236)
	Caudal Anterior Cingulate	0.900	(NA)	0.899	(NA)	-0.088	(NA)	0.092	(NA)	-0.121	(NA)	-0.134	(NA)
	Posterior Cingulate	-0.113	(1.000)	-0.312	(1.000)	-0.033	(1.000)	-0.309	(1.000)	-0.282	(0.926)	-0.071	(0.930)
	Isthmus Cingulate	0.452	(0.295)	-0.447	(0.118)	-0.119	(0.804)	0.285	(0.768)	-0.616	(NC)	-0.207	(0.494)
	Insula	-0.038	(1.000)	-0.266	(0.232)	-0.236	(0.483)	-0.031	(1.000)	-0.292	(0.222)	-0.261	(0.151)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Cingulate	Rostral Anterior Cingulate	8.064	(0.000*)	Increase	2.047	(0.055)	Stable	12.955	(0.000*)	Increase	1.079	(0.307)	Stable
	Caudal Anterior Cingulate	0.039	(NA)	-	16.814	(NA)	-	1.699	(NA)	-	0.136	(NA)	-
	Posterior Cingulate	1.657	(0.118)	Stable	-3.129	(0.003*)	Decrease	-0.228	(0.857)	Stable	-2.360	(0.042*)	Decrease
	Isthmus Cingulate	7.679	(0.000*)	Increase	-3.909	(0.000*)	Decrease	8.022	(0.000*)	Increase	-5.469	(0.000*)	Decrease
	Insula	1.859	(0.081)	Stable	-0.344	(0.792)	Stable	2.137	(0.047*)	Increase	-0.354	(0.723)	Stable

Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
50.0%	50.0%	0.0%	0.0%	50.0%	50.0%	75.0%	25.0%	0.0%	0.0%	50.0%	50.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all schizophrenia participants ($N=30$ with cortical data). Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments. NC indicates that the significance of the parameter was not computable.

For comparisons across age-risk periods, genetic correlations between schizophrenia and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).

As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Phenotypic correlations between schizophrenia and cingulate thickness measures are presented in Appendix Table 11-12 and environmental correlations between schizophrenia and cingulate thickness measures are presented in Appendix Table 15-16.

3.4.6.3 Cortical Thickness – Cingulate: Summary of Schizophrenia Developmental Neurogenetic Effects

Overall, across analyses with basic or conservative adjustments, several genetic correlations between schizophrenia and cingulate thickness became more negative from the Rise to the Peak period. However, in these cases, the genetic correlations were not significantly different from zero at the Peak period, lending only suggestive support to late neurodevelopmental effects on rostral anterior cingulate, isthmus cingulate, and insula thickness. All genetic correlations became less negative or did not change significantly from the Peak to the Plateau period, arguing against any neurodegenerative effects.

3.4.7 Regional Cortical Thickness: Summary of Schizophrenia Developmental Neurogenetic Effects

Overall, early neurodevelopmental effects were not supported for any regional cortical thickness measure in schizophrenia.

In contrast, a suggestive level of support (significantly more negative genetic correlation with schizophrenia from Rise to Peak periods but genetic correlation with schizophrenia not significant from zero during Peak period, both with conservative adjustments) for late schizophrenia neurodevelopmental effects was observed for multiple cortical thickness measures, including a frontal thickness measure (pars orbitalis thickness), a parietal thickness measure (inferior parietal thickness), all but two temporal thickness measures (including superior temporal sulcus, middle temporal, inferior temporal, fusiform, and parahippocampal thickness), and three cingulate thickness measures (rostral anterior cingulate, isthmus cingulate, and insula thickness). Furthermore, a lower level of suggestive evidence (pattern above but only significant with basic

adjustments) for late schizophrenia neurodevelopmental effects was found for three additional frontal thickness measures (rostral middle frontal, medial orbitofrontal, and precentral thickness), a parietal thickness measure (supramarginal thickness), and a temporal thickness measure (superior temporal thickness). No strong levels of support were found for any cortical thickness measure (i.e., significantly more negative genetic correlation with schizophrenia from Rise to Peak periods and genetic correlation with schizophrenia significantly different from zero during Peak period).

A suggestive level of evidence for schizophrenia neurodegenerative effects was observed only for three frontal thickness measures (lateral orbitofrontal, medial orbitofrontal, and precentral thickness) and one temporal thickness measure (entorhinal thickness). No strong level of support for neurodegenerative effects was found for any cortical thickness measure.

3.4.8 Surface Area - Frontal

3.4.8.1 Surface Area – Frontal: Overall Genetic Effects

As shown in Table 29, heritabilities ranged from very low to very high yet were not significant for any frontal area measures during the Rise period. However, heritabilities were moderate to high and most were significant during the Peak period. Furthermore, heritabilities were moderate to high and all significant during the Plateau period. Analyses using conservative adjustments showed that most heritabilities were very low and not significant during the Rise and Peak periods (probably due to the effect of the intracranial volume covariate), whereas heritabilities were generally moderate to high and significant during the Plateau period.

Table 29. Overall genetic effects on frontal area measures.

		Heritabilities with Basic Adjustments						Heritabilities with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value
Frontal	Frontal Pole	0.546	(0.424)	0.357	(0.155)	0.603	(0.004*)	0.715	(0.378)	0.000	(0.500)	0.534	(0.013*)
	Superior Frontal	1.000	(0.187)	1.000	(0.000*)	0.990	(0.000*)	0.762	(0.366)	0.566	(0.201)	0.864	(0.000*)
	Rostral Middle Frontal	0.553	(0.424)	0.467	(0.043*)	0.699	(0.000*)	0.079	(0.500)	0.000	(0.500)	0.612	(0.000*)
	Caudal Middle Frontal	0.000	(0.500)	0.531	(0.053)	0.395	(0.017*)	0.000	(0.500)	0.000	(0.500)	0.286	(0.083)
	Pars Opercularis	0.000	(0.500)	0.618	(0.018*)	0.660	(0.001*)	0.000	(0.500)	0.042	(0.500)	0.729	(0.001*)
	Pars Triangularis	0.000	(NA)	0.502	(NA)	0.537	(NA)	0.000	(NA)	0.000	(NA)	0.577	(NA)
	Pars Orbitalis	0.123	(0.500)	0.569	(0.022*)	0.492	(0.005*)	0.095	(0.500)	0.391	(0.402)	0.521	(0.009*)
	Lateral Orbitofrontal	0.783	(0.424)	1.000	(0.000*)	0.653	(0.001*)	0.000	(0.500)	0.387	(0.427)	0.719	(0.002*)
	Medial Orbitofrontal	0.417	(0.500)	0.803	(0.004*)	0.571	(0.001*)	0.000	(0.500)	0.342	(0.402)	0.328	(0.027*)
	Precentral	0.000	(NA)	0.679	(NA)	0.592	(NA)	0.000	(NA)	0.321	(NA)	0.421	(NA)
	Paracentral	0.668	(NA)	0.820	(NA)	0.527	(NA)	0.263	(NA)	0.305	(NA)	0.455	(NA)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Univariate heritabilities were estimated including all schizophrenia participants (N=30 with cortical data). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.

As shown in Appendix Table 19, differences in overall genetic effects across age-risk periods were not significant for any frontal area measure. Moreover, correlations of overall genetic effects across age-risk periods on frontal area measures showed consistently high correlations across age-risk periods which did not differ significantly from 1 or -1, which was indicative of pleiotropic genetic effects.

3.4.8.2 Surface Area – Frontal: Genetic Correlations with Schizophrenia

Table 30 presents genetic correlations between schizophrenia and frontal surface area measures. These analyses show that all genetic correlations between schizophrenia and frontal area were negative, as expected, suggesting that schizophrenia genetic risk is associated with decreased frontal area. Only one of the genetic correlations between schizophrenia and frontal area was significant during the Rise period, despite ranging from low to high. In contrast, genetic correlations ranged from moderate to high, and all but one were significant during the Peak period. Genetic correlations were low to moderate during the Plateau period, and only two were significant.

From the Rise to the Peak period, most frontal area measures (75.0%) became less negative, with high but not significant genetic correlations during the Rise period becoming moderate genetic correlations during the Peak period. From the Peak to the Plateau period, genetic correlations between schizophrenia and all frontal area measures became significantly less negative, from low or moderate, significant genetic correlations during the Peak period to low genetic correlations during the Plateau period.

With a more conservative set of adjustments, genetic correlations between schizophrenia and frontal area were generally comparable to those estimated with basic adjustments.

Table 30. Genetic correlations between schizophrenia and frontal area measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Frontal	Frontal Pole	-0.263	(0.196)	-0.900	(0.054)	-0.434	(0.032*)	0.046	(1.000)	-0.900	(0.079)	-0.430	(0.097)
	Superior Frontal	-0.735	(NC)	-0.492	(NC)	-0.308	(NC)	-0.965	(NC)	-0.876	(0.017*)	-0.214	(NC)
	Rostral Middle Frontal	-1.000	(NC)	-0.804	(0.017*)	-0.291	(0.121)	-1.000	(0.017*)	-1.000	(0.003*)	-0.224	(0.271)
	Caudal Middle Frontal	-0.900	(0.121)	-0.900	(0.007*)	-0.205	(0.246)	-0.900	(0.515)	-0.900	(0.077)	-0.015	(0.934)
	Pars Opercularis	-1.000	(0.035*)	-0.672	(0.008*)	-0.232	(0.121)	-1.000	(0.050)	-1.000	(0.030*)	-0.205	(0.307)
	Pars Triangularis	-1.000	(NA)	-0.818	(NA)	-0.098	(NA)	-1.000	(NA)	-0.900	(NA)	-0.035	(NA)
	Pars Orbitalis	-1.000	(NC)	-0.555	(0.006*)	-0.292	(0.121)	-0.900	(0.040*)	-0.543	(0.286)	-0.218	(0.307)
	Lateral Orbitofrontal	-0.812	(0.036*)	-0.489	(0.007*)	-0.221	(0.121)	-1.000	(0.126)	-0.900	(0.232)	-0.137	(0.413)
	Medial Orbitofrontal	-0.900	(NC)	-0.717	(0.003*)	-0.374	(0.037*)	-1.000	(0.050)	-0.900	(0.017*)	-0.502	(0.135)
	Precentral	-0.900	(NA)	-0.456	(NA)	-0.179	(NA)	-0.900	(NA)	-0.687	(NA)	-0.166	(NA)
	Paracentral	-0.675	(NA)	-0.376	(NA)	-0.030	(NA)	-0.900	(NA)	-0.575	(NA)	0.104	(NA)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Frontal	Frontal Pole	9.536	(0.000*)	Increase	-10.891	(0.000*)	Decrease	12.030	(0.000*)	Increase	-10.886	(0.000*)	Decrease
	Superior Frontal	-3.173	(0.002*)	Decrease	-2.385	(0.026*)	Decrease	-5.163	(0.000*)	Decrease	-12.250	(0.000*)	Decrease
	Rostral Middle Frontal	-57.845	(0.000*)	Decrease	-8.756	(0.000*)	Decrease	0.000	(1.000)	Stable	-87.941	(0.000*)	Decrease
	Caudal Middle Frontal	0.001	(0.999)	Stable	-13.665	(0.000*)	Decrease	0.001	(1.000)	Stable	-15.672	(0.000*)	Decrease
	Pars Opercularis	-60.192	(0.000*)	Decrease	-6.243	(0.000*)	Decrease	0.000	(1.000)	Stable	-88.148	(0.000*)	Decrease
	Pars Triangularis	-57.507	(NA)	-	-11.386	(NA)	-	-54.934	(NA)	-	-15.455	(NA)	-
	Pars Orbitalis	-61.682	(0.000*)	Decrease	-3.511	(0.001*)	Decrease	-6.847	(0.000*)	Decrease	-4.158	(0.000*)	Decrease
	Lateral Orbitofrontal	-4.732	(0.000*)	Decrease	-3.357	(0.001*)	Decrease	-54.934	(0.000*)	Decrease	-14.344	(0.000*)	Decrease
	Medial Orbitofrontal	-4.526	(0.000*)	Decrease	-5.496	(0.000*)	Decrease	-54.934	(0.000*)	Decrease	-9.901	(0.000*)	Decrease
	Precentral	-7.767	(NA)	-	-3.363	(NA)	-	-4.986	(NA)	-	-7.260	(NA)	-
	Paracentral	-3.371	(NA)	-	-3.942	(NA)	-	-6.483	(NA)	-	-8.158	(NA)	-

	Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
	Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
	12.5%	12.5%	75.0%	0.0%	0.0%	100.0%	12.5%	37.5%	50.0%	0.0%	0.0%	100.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all schizophrenia participants (N=30 with cortical data). Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments. NC indicates that the significance of the parameter was not computable.

For comparisons across age-risk periods, genetic correlations between schizophrenia and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).
As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.
Phenotypic correlations between schizophrenia and frontal area measures are presented in Appendix Table 21-22 and environmental correlations between schizophrenia and frontal area measures are presented in Appendix Table 24-25.

3.4.8.3 Surface Area – Frontal: Summary of Schizophrenia Developmental Neurogenetic Effects

Overall, with either basic or conservative adjustments, genetic correlations between schizophrenia and frontal areas largely became less negative from the Rise to the Peak period, arguing against general late neurodevelopmental effects. However, the frontal pole became more negative from the Rise to the Peak period and had borderline significant genetic correlations at the Peak period for both basic and conservative adjustments, although the overall heritability of the fusiform area was not significant during the Peak period. In addition, all genetic correlations between schizophrenia and frontal area became less negative from the Peak to the Plateau period, arguing against neurodegenerative effects.

3.4.9 Surface Area - Parietal

3.4.9.1 Surface Area – Parietal: Overall Genetic Effects

As shown in Table 31, although heritabilities were very low to very high, none were significant for any parietal area measures during the Rise period. However, heritabilities for all except one measure were generally moderate to high and most were significantly heritable during the Peak period. Furthermore, heritabilities were low to moderate and all significant during the Plateau period. Analyses using conservative adjustments showed that most heritabilities were low to moderate and not significant the Rise and Peak periods (perhaps due to the intracranial volume covariate), whereas heritabilities were generally moderate and significant during the Plateau period.

Table 31. Overall genetic effects on parietal area measures.

		Heritabilities with Basic Adjustments						Heritabilities with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value
Parietal	Superior Parietal	0.000	(0.500)	0.839	(0.007*)	0.551	(0.003*)	0.397	(0.500)	0.548	(0.414)	0.500	(0.007*)
	Inferior Parietal	0.780	(0.310)	0.084	(0.387)	0.650	(0.008*)	0.742	(0.366)	0.207	(0.414)	0.505	(0.049*)
	Supramarginal	1.000	(0.191)	0.947	(0.007*)	0.469	(0.013*)	0.947	(0.366)	0.487	(0.402)	0.168	(0.213)
	Postcentral	0.000	(0.500)	0.579	(0.007*)	0.147	(0.206)	0.000	(0.500)	0.073	(0.500)	0.168	(0.159)
	Precuneus	0.000	(0.500)	0.857	(0.007*)	0.814	(0.000*)	0.000	(0.500)	0.724	(0.315)	0.591	(0.001*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Univariate heritabilities were estimated including all schizophrenia participants ($N=30$ with cortical data). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume.

As shown in Appendix Table 19, differences in overall genetic effects across age-risk periods were not significant for any parietal area measure. Moreover, correlations of overall genetic effects across age-risk periods on parietal area measures showed consistently high correlations across age-risk periods which did not differ significantly from 1 or -1, which was indicative of pleiotropic genetic effects.

3.4.9.2 Surface Area – Parietal: Genetic Correlations with Schizophrenia

Table 32 presents genetic correlations between schizophrenia and parietal area measures. These analyses show all genetic correlations between schizophrenia and parietal area were negative, as expected, indicating that schizophrenia genetic risk is associated with decreased parietal area. None of the genetic correlations between schizophrenia and parietal area were significant during the Rise period, despite ranging from moderate to high. However, genetic correlations ranged from moderate to high and two of the five were significant during the Peak period. Furthermore, genetic correlations were low to moderate during the Plateau period, with only one being significant.

From the Rise to the Peak period, most parietal area measures (80.0%) became significantly less negative from high but nonsignificant genetic correlations during the Rise period to moderate or high genetic correlations, less than half of which were significant, during the Peak period. One of the parietal area measures (20.0%) became significantly more negative from a moderate, nonsignificant genetic correlation during the Rise period to a high but nonsignificant genetic correlation during the Peak period. From the Peak to the Plateau period, most parietal area measures remained stable (60.0%) or became less negative (40.0%).

With a more conservative set of adjustments, genetic correlations between schizophrenia and parietal area measures were generally similar to those estimated with basic adjustments. Comparisons across age-risk periods shifted slightly, with a smaller proportion of genetic correlations becoming less negative from the Rise to the Peak period and a larger proportion of genetic correlations becoming less negative from the Peak to the Plateau period. From the Rise to the Peak period, two parietal area measures (40.0%) became significantly more negative from a low to moderate, nonsignificant genetic correlation to a high genetic

correlation. From the Peak to the Plateau period, one parietal area measure (20.0%) became more negative from a very low positive genetic correlation to a low negative genetic correlation.

Table 32. Genetic correlations between schizophrenia and parietal area measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Parietal	Superior Parietal	-0.945	(0.148)	-0.597	(0.007*)	-0.537	(0.001*)	-0.744	(0.239)	-0.900	(0.017*)	-0.545	(0.002*)
	Inferior Parietal	-0.645	(0.148)	-0.900	(0.228)	-0.111	(NC)	-0.353	(NC)	0.037	(1.000)	-0.161	(0.413)
	Supramarginal	-0.624	(NC)	-0.418	(0.038*)	-0.234	(0.155)	-0.560	(0.198)	-0.473	(0.264)	-0.127	(0.934)
	Postcentral	-0.900	(0.148)	-0.476	(0.068)	-0.557	(0.086)	-0.086	(1.000)	-0.900	(0.286)	-0.308	(0.331)
	Precuneus	-0.900	(0.148)	-0.383	(0.124)	-0.349	(NC)	-0.900	(0.312)	-0.276	(0.425)	-0.273	(0.307)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Parietal	Superior Parietal	-8.672	(0.000*)	Decrease	-0.966	(0.382)	Stable	4.059	(0.000*)	Increase	-9.261	(0.000*)	Decrease
	Inferior Parietal	5.593	(0.000*)	Increase	-14.705	(0.000*)	Decrease	-3.218	(0.002*)	Decrease	2.145	(0.037*)	Increase
	Supramarginal	-2.278	(0.025*)	Decrease	-2.231	(0.036*)	Decrease	-0.939	(0.439)	Stable	-4.161	(0.000*)	Decrease
	Postcentral	-7.571	(0.000*)	Decrease	1.198	(0.306)	Stable	10.979	(0.000*)	Increase	-12.404	(0.000*)	Decrease
	Precuneus	-8.473	(0.000*)	Decrease	-0.420	(0.704)	Decrease	-9.419	(0.000*)	Decrease	-0.039	(0.969)	Stable

		Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
		Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
		20.0%	0.0%	80.0%	0.0%	60.0%	40.0%	40.0%	20.0%	40.0%	20.0%	20.0%	60.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all schizophrenia participants ($N=30$ with cortical data). Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments. NC indicates that the significance of the parameter was not computable.

For comparisons across age-risk periods, genetic correlations between schizophrenia and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).

As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Phenotypic correlations between schizophrenia and parietal area measures are presented in Appendix Table 21-22 and environmental correlations between schizophrenia and parietal area measures are presented in Appendix Table 24-25.

3.4.9.3 Surface Area – Parietal: Summary of Schizophrenia Developmental Neurogenetic Effects

Overall, genetic correlations between schizophrenia and parietal area generally became less negative from the Rise to the Peak period. However, genetic correlations for superior parietal, inferior parietal, and postcentral areas became more negative across these periods and the superior frontal area was significantly different from zero during the Peak period, providing support for late neurodevelopmental effects. The heritability of the superior parietal area was also significant with basic, although not conservative adjustments.

Furthermore, genetic correlations between schizophrenia and parietal area generally remained stable or became less negative from the Peak to the Plateau period whether estimated with basic or conservative adjustments, arguing against neurodegenerative effects. The exception to this was the inferior parietal area which had suggestive evidence of neurodegenerative effects.

3.4.10 Surface Area - Temporal

3.4.10.1 Surface Area – Temporal: Overall Genetic Effects

As shown in Table 33, heritabilities of temporal area measures were very low to very high but were not significant during the Rise period. However, heritabilities were generally moderate to high and significant during the Peak period and were generally low to moderate and significant during the Plateau period. These patterns were similar, although generally lower, for heritabilities estimated with conservative adjustments.

Table 33. Overall genetic effects on temporal area measures.

		Heritabilities with Basic Adjustments						Heritabilities with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value
Temporal	Superior Temporal	0.644	(NA)	0.596	(NA)	0.471	(NA)	0.000	(NA)	0.040	(NA)	0.236	(NA)
	Superior Temporal Sulcus	0.100	(0.500)	0.292	(0.093)	0.334	(0.041*)	0.458	(0.500)	0.044	(0.500)	0.284	(0.056)
	Middle Temporal	0.309	(0.424)	0.681	(0.012*)	0.633	(0.002*)	0.100	(0.500)	0.000	(0.500)	0.534	(0.005*)
	Inferior Temporal	0.000	(0.500)	0.829	(0.007*)	0.486	(0.002*)	0.000	(0.500)	0.000	(0.500)	0.584	(0.001*)
	Fusiform	0.000	(0.500)	0.368	(0.139)	0.344	(0.055)	0.000	(0.500)	0.000	(0.500)	0.403	(0.027*)
	Transverse Temporal	0.885	(0.191)	0.526	(0.020*)	0.668	(0.001*)	0.720	(0.366)	0.277	(0.414)	0.301	(0.059)
	Entorhinal	0.906	(0.424)	1.000	(0.007*)	0.268	(0.114)	0.479	(0.500)	0.995	(0.201)	0.300	(0.111)
	Temporal Pole	0.340	(NA)	0.000	(NA)	0.288	(NA)	0.543	(NA)	0.000	(NA)	0.296	(NA)
	Parahippocampal	0.436	(0.424)	0.840	(0.007*)	0.513	(0.008*)	0.560	(0.385)	0.589	(0.201)	0.612	(0.005*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Univariate heritabilities were estimated including all schizophrenia participants (N=30 with cortical data). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.

As shown in Appendix Table 19, differences in overall genetic effects across age-risk periods were not significant for any temporal area measure. Moreover, correlations of overall genetic effects across age-risk periods on temporal area measures showed consistently high correlations across age-risk periods which did not differ significantly from 1 or -1, which was indicative of pleiotropic genetic effects.

3.4.10.2 Surface Area – Temporal: Genetic Correlations with Schizophrenia

As shown in Table 34, genetic correlations between schizophrenia and temporal area measures were all negative except for one which was very low and positive, indicating that schizophrenia genetic effects are generally associated with decreased temporal area. During the Rise period, genetic correlations were moderate to high but not significant, though the significance of the genetic correlation was unable to be tested for two measures. During the Peak period, most genetic correlations were also low to high, but two became significant. Finally, genetic correlations were generally low to moderate and two were significant during the Plateau period. Genetic correlations between schizophrenia and temporal area measures generally became less negative from the Rise to the Peak period (71.4%), although the fusiform significantly increased and had a significant genetic correlation at the Peak period. Genetic correlations either remained stable (57.1%) or became less negative (42.9%) from the Peak to the Plateau period.

With conservative adjustments, genetic correlations between schizophrenia and temporal area measures generally showed similar range in magnitude, but none were significant during any age-risk period. Compared to genetic correlations estimated with basic adjustments, changes across age-risk periods for genetic correlations estimated with conservative adjustments were generally similar across the Rise and Peak periods, with only the fusiform showing a significant increase (and a borderline significant genetic correlation at the Peak period). Results were more often less negative from the Peak to the Plateau period.

Table 34. Genetic correlations between schizophrenia and temporal area measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Temporal	Superior Temporal	-0.876	(NA)	-0.339	(NA)	-0.219	(NA)	-0.900	(NA)	0.045	(NA)	-0.195	(NA)
	Superior Temporal Sulcus	-0.572	(0.148)	-0.279	(0.162)	0.018	(0.967)	-0.508	(0.312)	-0.129	(1.000)	0.160	(0.629)
	Middle Temporal	-0.966	(NC)	-0.724	(0.017*)	-0.404	(0.086)	-1.000	(0.198)	-0.900	(0.130)	-0.342	(0.121)
	Inferior Temporal	-0.772	(0.148)	-0.523	(0.085)	-0.440	(0.023*)	-0.017	(1.000)	-1.000	(0.264)	-0.285	(0.307)
	Fusiform	-0.870	(0.223)	-1.000	(0.003*)	-0.357	(0.155)	0.016	(1.000)	-1.000	(0.055)	-0.210	(0.331)
	Transverse Temporal	-0.451	(NC)	-0.305	(0.162)	-0.237	(0.121)	-0.421	(0.239)	-0.239	(0.642)	-0.212	(0.413)
	Entorhinal	-0.900	(0.302)	-0.341	(1.000)	-0.420	(0.046*)	-0.900	(0.856)	-0.359	(0.079)	-0.364	(0.230)
	Temporal Pole	-0.644	(NA)	-0.900	(NA)	-0.519	(NA)	-0.398	(NA)	0.170	(NA)	-0.655	(NA)
	Parahippocampal	-0.439	(0.426)	-0.113	(1.000)	-0.100	(1.000)	-0.180	(1.000)	-0.416	(0.173)	-0.082	(0.629)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Temporal	Superior Temporal	-7.955	(NA)	-	-1.404	(NA)	-	-12.021	(NA)	-	2.611	(NA)	-
	Superior Temporal Sulcus	-2.886	(0.005*)	Decrease	-3.286	(0.002*)	Decrease	-3.407	(0.001*)	Decrease	-3.138	(0.002*)	Decrease
	Middle Temporal	-8.784	(0.000*)	Decrease	-5.255	(0.000*)	Decrease	-54.934	(0.000*)	Decrease	-12.005	(0.000*)	Decrease
	Inferior Temporal	-3.527	(0.001*)	Decrease	-1.169	(0.306)	Stable	66.461	(0.000*)	Increase	-87.239	(0.000*)	Decrease
	Fusiform	56.081	(0.000*)	Increase	-86.810	(0.000*)	Decrease	66.727	(0.000*)	Increase	-88.092	(0.000*)	Decrease
	Transverse Temporal	-1.355	(0.183)	Stable	-0.792	(0.467)	Stable	-1.623	(0.139)	Stable	-0.308	(0.827)	Stable
	Entorhinal	-8.852	(0.000*)	Decrease	1.001	(0.380)	Stable	-8.686	(0.000*)	Decrease	0.056	(0.969)	Stable
	Temporal Pole	5.601	(NA)	-	-9.696	(NA)	-	-4.696	(NA)	-	10.268	(NA)	-
	Parahippocampal	-2.837	(0.006*)	Decrease	-0.143	(0.886)	Stable	2.074	(0.054)	Stable	-3.884	(0.000*)	Decrease

	Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
	Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
	14.3%	14.3%	71.4%	0.0%	57.1%	42.9%	28.6%	28.6%	42.9%	0.0%	28.6%	71.4%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all schizophrenia participants ($N=30$ with cortical data). Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments. NC indicates that the significance of the parameter was not computable.
As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

For comparisons across age-risk periods, genetic correlations between schizophrenia and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).
Phenotypic correlations between schizophrenia and temporal area measures are presented in Appendix Table 21-22 and environmental correlations between schizophrenia and temporal area measures are presented in Appendix Table 24-25.

3.4.10.3 Surface Area – Temporal: Summary of Schizophrenia Developmental Neurogenetic Effects

Overall, genetic correlations between schizophrenia and temporal area measures tended to become less negative from the Rise to the Peak period, whether estimated with basic or conservative adjustments, generally not supporting late neurodevelopmental effects. However, the fusiform region was an exception to this pattern, demonstrating increasingly negative genetic correlations with schizophrenia from Rise to Peak periods and significant genetic correlations with schizophrenia during the Peak period, although its heritability was not significant during the Peak period. Genetic correlations also all remained stable or became less negative from the Peak to the Plateau period, arguing against neurodegenerative effects.

3.4.11 Surface Area - Occipital

3.4.11.1 Surface Area – Occipital: Overall Genetic Effects

As shown in Table 35, heritabilities of occipital area measures were very low and nonsignificant during the Rise period. Heritabilities were moderate and generally nonsignificant during the Peak period, whereas heritabilities were moderate to high and all significant during the Plateau period. Heritabilities estimated with conservative adjustments were generally similar except that none were significant during the Peak period.

Table 35. Overall genetic effects on occipital area measures.

		Heritabilities with Basic Adjustments						Heritabilities with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value
Occipital	Lateral Occipital	0.000	(0.500)	0.441	(0.053)	0.549	(0.002*)	0.000	(0.500)	0.000	(0.500)	0.600	(0.001*)
	Lingual	0.000	(0.500)	0.447	(0.117)	0.731	(0.001*)	0.000	(0.500)	0.128	(0.500)	0.504	(0.006*)
	Cuneus	0.000	(NA)	0.000	(NA)	0.456	(NA)	0.000	(NA)	0.000	(NA)	0.356	(NA)
	Pericalcarine	0.200	(0.500)	0.594	(0.048*)	0.972	(0.000*)	0.000	(0.500)	0.121	(0.500)	0.910	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Univariate heritabilities were estimated including all schizophrenia participants (N=30 with cortical data). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.

As shown in Appendix Table 19, differences in overall genetic effects across age-risk periods were not significant for any occipital area measure. Moreover, correlations of overall genetic effects across age-risk periods on occipital area measures showed consistently high correlations across age-risk periods which did not differ significantly from 1 or -1, which was indicative of pleiotropic genetic effects.

3.4.11.2 Surface Area – Occipital: Genetic Correlations with Schizophrenia

As can be seen in Table 36, genetic correlations between schizophrenia and occipital area measures were negative across all age-risk periods, indicating that schizophrenia genetic effects are associated with decreased occipital area. Genetic correlations were all nonsignificant and ranged from low to high during the Rise period. Furthermore, genetic correlations were moderate to high and most were significant during the Peak period. Genetic correlations were all low and nonsignificant during the Plateau period. From the Rise to the Peak period, genetic correlations generally became more negative (66.7%). In contrast, from the Peak to the Plateau period, genetic correlations all became less negative.

Using a more conservative set of adjustments, age-related patterns of genetic correlations generally were similar to those estimated with basic adjustments, except that genetic correlations generally remained stable instead of becoming more negative from the Rise to the Peak period.

Table 36. Genetic correlations between schizophrenia and occipital area measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Occipital	Lateral Occipital	-1.000	(0.223)	-0.858	(0.007*)	-0.415	(0.075)	-0.900	(0.160)	-0.900	(0.017*)	-0.319	(0.135)
	Lingual	-0.900	(0.223)	-1.000	(0.003*)	-0.195	(0.293)	-0.900	(0.755)	-0.900	(0.017*)	-0.128	(0.478)
	Cuneus	-1.000	(NA)	-0.900	(NA)	-0.317	(NA)	-0.900	(NA)	-0.900	(NA)	-0.325	(NA)
	Pericalcarine	-0.304	(0.474)	-0.565	(0.068)	-0.201	(NC)	0.158	(1.000)	-0.900	(0.253)	-0.161	(NC)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Occipital	Lateral Occipital	-56.434	(0.000*)	Decrease	-9.144	(0.000*)	Decrease	0.000	(1.000)	Stable	-12.275	(0.000*)	Decrease
	Lingual	54.970	(0.000*)	Increase	-88.711	(0.000*)	Decrease	0.000	(1.000)	Stable	-14.452	(0.000*)	Decrease
	Cuneus	-54.970	(NA)	-	-12.364	(NA)	-	0.000	(NA)	-	-12.211	(NA)	-
	Pericalcarine	2.587	(0.011*)	Increase	-4.719	(0.000*)	Decrease	12.927	(0.000*)	Increase	-14.087	(0.000*)	Decrease

Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
66.7%	0.0%	33.3%	0.0%	0.0%	100.0%	33.3%	66.7%	0.0%	0.0%	0.0%	100.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all schizophrenia participants (N=30 with cortical data). Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments. NC indicates that the significance of the parameter was not computable.

For comparisons across age-risk periods, genetic correlations between schizophrenia and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).

As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Phenotypic correlations between schizophrenia and occipital area measures are presented in Appendix Table 21-22 and environmental correlations between schizophrenia and occipital area measures are presented in Appendix Table 24-25.

3.4.11.3 Surface Area – Occipital: Summary of Schizophrenia Developmental Neurogenetic Effects

Overall, genetic correlations between schizophrenia and occipital area measures generally became more negative and were more likely to become significant from the Rise to the Peak period when estimated with basic adjustments. Genetic correlations generally remained stable and were more likely to become significant across these age-risk periods when estimated with conservative adjustments. Taken together, these findings provide strong support for late neurodevelopmental effects of schizophrenia on lingual (although its heritability was not significant during the Peak period) and suggestive support for pericalcarine surface areas. Genetic correlations between schizophrenia and occipital area measures all became less negative and nonsignificant from the Peak to the Plateau periods, arguing against neurodegenerative effects.

3.4.12 Surface Area - Cingulate

3.4.12.1 Surface Area – Cingulate: Overall Genetic Effects

As can be seen in Table 37, the one cingulate area measure evaluated (insula) showed high but nonsignificant heritability during the Rise period and high and significant heritability during the Peak and Plateau period. When estimated with conservative adjustments, heritability of insula surface area was nonsignificant during the Rise and Peak periods and was high and significant during the Plateau period.

Table 37. Overall genetic effects on cingulate area measures.

		Heritabilities with Basic Adjustments						Heritabilities with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value	h^2	*p*-value
Cingulate	Rostral Anterior Cingulate	0.000	(NA)	0.352	(NA)	0.630	(NA)	0.000	(NA)	0.000	(NA)	0.261	(NA)
	Caudal Anterior Cingulate	0.725	(NA)	0.312	(NA)	0.389	(NA)	0.108	(NA)	0.000	(NA)	0.162	(NA)
	Posterior Cingulate	0.181	(NA)	0.995	(NA)	0.588	(NA)	0.000	(NA)	0.231	(NA)	0.354	(NA)
	Isthmus Cingulate	0.128	(NA)	0.747	(NA)	0.530	(NA)	0.037	(NA)	0.179	(NA)	0.314	(NA)
	Insula	0.968	(0.310)	0.718	(0.018*)	0.832	(0.000*)	0.360	(0.500)	0.693	(0.222)	0.823	(0.002*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Univariate heritabilities were estimated including all schizophrenia participants (N=30 with cortical data). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.

As shown in Appendix Table 19, differences in overall genetic effects across age-risk periods were not significant for any cingulate area measure. Moreover, correlations of overall genetic effects across age-risk periods on cingulate area measures showed consistently high correlations across age-risk periods which did not differ significantly from 1 or -1, which was indicative of pleiotropic genetic effects.

3.4.12.2 Surface Area – Cingulate: Genetic Correlations with Schizophrenia

As shown in Table 38, the significance of the genetic correlations between schizophrenia and the cingulate area measure (insula) was not able to be tested for any age-risk period with basic adjustments. However, the genetic correlations were negative and moderate for each age-risk period, suggesting that schizophrenia genetic effects were associated with decreased cingulate area. The genetic correlation became less negative from the Rise to the Peak period and also became less negative from the Peak to the Plateau period. Analyses with conservative adjustments showed that the genetic correlation was moderate and significant during the Rise period and low and nonsignificant during the Peak and Plateau periods. Similar to analyses with basic adjustments, the genetic correlation became less negative from the Rise to the Peak period and from the Peak to the Plateau period.

Table 38. Genetic correlations between schizophrenia and cingulate area measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Cingulate	Rostral Anterior Cingulate	-0.900	(NA)	-0.535	(NA)	-0.073	(NA)	-1.000	(NA)	-0.900	(NA)	0.021	(NA)
	Caudal Anterior Cingulate	-0.594	(NA)	-0.304	(NA)	-0.071	(NA)	-0.756	(NA)	-0.001	(NA)	0.140	(NA)
	Posterior Cingulate	-0.847	(NA)	-0.266	(NA)	-0.114	(NA)	-0.900	(NA)	-0.175	(NA)	0.045	(NA)
	Isthmus Cingulate	-0.900	(NA)	-0.153	(NA)	-0.106	(NA)	-0.900	(NA)	0.346	(NA)	0.009	(NA)
	Insula	-0.660	(NC)	-0.421	(NC)	-0.132	(NC)	-0.691	(0.040*)	-0.239	(0.335)	0.016	(0.934)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Cingulate	Rostral Anterior Cingulate	-6.941	(NA)	-	-5.660	(NA)	-	-54.934	(NA)	-	-16.054	(NA)	-
	Caudal Anterior Cingulate	-2.937	(NA)	-	-2.618	(NA)	-	-7.810	(NA)	-	-1.525	(NA)	-
	Posterior Cingulate	-7.705	(NA)	-	-1.712	(NA)	-	-10.263	(NA)	-	-2.382	(NA)	-
	Isthmus Cingulate	-10.456	(NA)	-	-0.525	(NA)	-	-14.524	(NA)	-	3.781	(NA)	-
	Insula	-2.720	(0.008*)	Decrease	-3.414	(0.001*)	Decrease	-4.801	(0.000*)	Decrease	-2.785	(0.006*)	Decrease

		Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
		Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
		0.0%	0.0%	100.0%	0.0%	0.0%	100.0%	0.0%	0.0%	100.0%	0.0%	0.0%	100.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all schizophrenia participants ($N=30$ with cortical data). Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments. NC indicates that the significance of the parameter was not computable.

For comparisons across age-risk periods, genetic correlations between schizophrenia and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).

As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Phenotypic correlations between schizophrenia and cingulate area measures are presented in Appendix Table 21-22 and environmental correlations between schizophrenia and cingulate area measures are presented in Appendix Table 24-25.

3.4.12.3 Surface Area – Cingulate: Summary of Schizophrenia Developmental Neurogenetic Effects

Across findings with basic or conservative adjustments, the genetic correlations between schizophrenia and the cingulate area measure generally became less negative from the Rise to the Peak period, arguing against late neurodevelopmental effects of schizophrenia on the insula. In addition, the genetic correlations became even less negative from the Peak to the Plateau period, arguing against neurodegenerative effects of schizophrenia on the insula.

3.4.13 Regional Cortical Surface Area: Summary of Schizophrenia Developmental Neurogenetic Effects

Overall, early neurodevelopmental effects were supported in schizophrenia for a few surface area measures, all of which were in frontal and cingulate regions. In particular, early neurodevelopmental effects were observed for two frontal area measures (rostral middle frontal and pars orbitalis area) and one cingulate area measure (insula area) with conservative adjustments, and for two other frontal area measures (pars opercularis and lateral orbitofrontal area) with basic adjustments. None of these areas were significantly heritable overall during the Rise period.

Evidence for late neurodevelopmental effects on regional surface area measures was found in more regions compared to evidence for early neurodevelopmental effects. In particular, relatively strong support was observed for a frontal area (frontal pole), a parietal area (superior parietal), a temporal area measure (fusiform area) and an occipital area measure (lingual area), whereas a suggestive level of support was found for two parietal areas (inferior parietal and postcentral area), a temporal area measure (inferior temporal area) and an occipital area measure (pericalcarine area).

Only one surface area measure (inferior parietal area) showed suggestive support for neurodegenerative effects.

3.4.14 Overview of Evidence for Schizophrenia Developmental Neurogenetic Effects on Cortical Measures

Table 39 summarizes the evidence for schizophrenia developmental neurogenetic effects based on the genetic correlations between schizophrenia and cortical measures within and across age-risk periods. As described previously, "suggestive" support is only a significantly more negative genetic correlation with schizophrenia at a later period compared to an earlier period. "Strong" support is when the genetic correlation with schizophrenia is also significantly different than zero during the later period. Overall, support is also considered "conservative" if the significant results are with the conservative adjustments compared to if they are only significant with the basic adjustments.

Table 39. Summary of evidence for schizophrenia developmental neurogenetic effects based on genetic correlations between schizophrenia and cortical measures within and across age-risk periods.

Lobe	Region	Significant Difference SZ vs. HC	Significant Rise R_G	Rise/Peak R_G Comparison	Significant Peak R_G	Peak/Plateau R_G Comparison	Significant Plateau R_G	Evidence for Early Neurodevelopmental Effects	Evidence for Late Neurodevelopmental Effects	Evidence for Neurodegenerative Effects
Global	Intracranial Volume	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Lateral Ventricle Volume	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Mean Thickness	X	*(n.s.)* / *(n.s.)*	+ / –	-0.36 / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ + / –	– / –
	Total Surface Area	X	*(n.s.)* / *(n.s.)*	– / –	-0.64 / -1.00	– / –	-0.35 / *(n.s.)*	– / –	– / –	– / –
TH Frontal	Frontal Pole									
	Superior Frontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Rostral Middle Frontal	X	*(n.s.)* / *(n.s.)*	+ / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / –	– / –
	Caudal Middle Frontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Pars Opercularis	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Pars Triangularis	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Pars Orbitalis	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Lateral Orbitofrontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	– / –	– / +
	Medial Orbitofrontal	X	*(n.s.)* / *(n.s.)*	+ / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	+ / –	– / +
	Precentral	X	*(n.s.)* / *(n.s.)*	+ / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	+ / –	– / +
	Paracentral									
TH Parietal	Superior Parietal									
	Inferior Parietal	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Supramarginal	X	*(n.s.)* / *(n.s.)*	+ / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / –	– / –
	Postcentral									
	Precuneus									
TH Temporal	Superior Temporal	X	*(n.s.)* / *(n.s.)*	+ / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / –	– / –
	Superior Temporal Sulcus	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Middle Temporal	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Inferior Temporal	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Fusiform	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Transverse Temporal									
	Entorhinal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	– / –	+ / +
	Temporal Pole									
	Parahippocampal	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / -0.40	– / –	+ / +	– / –
TH Occipital	Lateral Occipital									
	Lingual	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Cuneus									
	Pericalcarine									
TH Cingulate	Rostral Anterior Cingulate	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Caudal Anterior Cingulate									

	Posterior Cingulate	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Isthmus Cingulate	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Insula	X	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / +	– / –
SA Frontal	Frontal Pole	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	-0.43 / *(n.s.)*	– / –	+ / +	– / –
	Superior Frontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / -0.88	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Rostral Middle Frontal	X	*(n.s.)* / -1.00	– / –	-0.80 / -1.00	– / –	*(n.s.)* / *(n.s.)*	– / +	– / –	– / –
	Caudal Middle Frontal	X	*(n.s.)* / *(n.s.)*	– / –	-0.90 / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Pars Opercularis	X	-1.00 / *(n.s.)*	– / –	-0.67 / -1.00	– / –	*(n.s.)* / *(n.s.)*	+ / –	– / –	– / –
	Pars Triangularis									
	Pars Orbitalis	X	*(n.s.)* / -0.90	– / –	-0.56 / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	– / –	– / –
	Lateral Orbitofrontal	X	-0.81 / *(n.s.)*	– / –	-0.49 / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	+ / –	– / –	– / –
	Medial Orbitofrontal	X	*(n.s.)* / *(n.s.)*	– / –	-0.72 / -0.90	– / –	-0.37 / *(n.s.)*	– / –	– / –	– / –
	Precentral									
	Paracentral									
SA Parietal	Superior Parietal	X	*(n.s.)* / *(n.s.)*	– / +	-0.60 / -0.90	– / –	-0.54 / -0.55	– / –	– / + +	– / –
	Inferior Parietal	X	*(n.s.)* / *(n.s.)*	+ / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	+ / –	– / +
	Supramarginal	X	*(n.s.)* / *(n.s.)*	– / –	-0.42 / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Postcentral	X	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / +	– / –
	Precuneus	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
SA Temporal	Superior Temporal									
	Superior Temporal Sulcus	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Middle Temporal	X	*(n.s.)* / *(n.s.)*	– / –	-0.72 / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Inferior Temporal	X	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	-0.44 / *(n.s.)*	– / –	– / +	– / –
	Fusiform	X	*(n.s.)* / *(n.s.)*	+ / +	-1.00 / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ + / +	– / –
	Transverse Temporal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Entorhinal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	-0.42 / *(n.s.)*	– / –	– / –	– / –
	Temporal Pole									
	Parahippocampal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
SA Occipital	Lateral Occipital	X	*(n.s.)* / *(n.s.)*	– / –	-0.86 / -0.90	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Lingual	X	*(n.s.)* / *(n.s.)*	+ / –	-1.00 / -0.90	– / –	*(n.s.)* / *(n.s.)*	– / –	+ + / –	– / –
	Cuneus									
	Pericalcarine	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
SA Cingulate	Rostral Anterior Cingulate									
	Caudal Anterior Cingulate									
	Posterior Cingulate									
	Isthmus Cingulate									
	Insula	X	*(n.s.)* / -0.69	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	– / –	– / –

Note. SZ indicates schizophrenia and HC indicates healthy control. TH indicates thickness and SA indicates surface area. An 'X' for significant group difference indicates that the cortical measure was examined because it showed a significant group difference between schizophrenia and controls. Significant R_G indicates that the significant genetic correlation between schizophrenia and the cortical measure for the given age-risk

period was presented. Genetic correlations are presented only when significant and are indicated with '*(n.s.)*' when nonsignificant or when the significance could not be computed.

For each measure, results are first presented for analyses with basic adjustments (age, age^2, sex, and site) then presented for analyses with conservative adjustments (age, age^2, sex, site, parental education, scan quality, and intracranial volume), separated by '/'. i.e. analysis with basic adjustments / analysis with conservative adjustments.

For the R_G comparison across age-risk periods using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003), a '+' (increase) indicates that there is a significantly more negative genetic correlation from the earlier to the later age-risk period, whereas a '–' (decrease) indicates a significantly less negative or nonsignificant genetic correlation from the earlier to the later age-risk period.

Evidence for each effect is indicated as follows: '+ +' indicates strong evidence supporting the effect, '+' indicates suggestive evidence supporting the effect, and '–' indicates no evidence supporting the effect.

Evidence supporting early neurodevelopmental effects is present if the genetic correlation is significant during the Rise period; a nonsignificant genetic correlation during the Rise period does not construe evidence against early neurodevelopmental effects due to the relatively small sample size for the Rise period.

Evidence supporting late neurodevelopmental effects is suggestive if there is a significantly more negative genetic correlation from the Rise to the Peak period (i.e. '+' in the Rise/Peak R_G Comparison) and strong if the genetic correlation is additionally significant during the Peak period.

Similarly, evidence supporting neurodegenerative effects is suggestive if there is a significantly more negative genetic correlation from the Peak to the Plateau period (i.e. '+' in the Peak/Plateau R_G Comparison) and strong if the genetic correlation is additionally significant during the Plateau period.

Table 40 summarizes the evidence for the diagnostic specificity to schizophrenia of schizophrenia developmental neurogenetic effects based on the genetic correlations between depression and cortical measures within and across age-risk periods, for only cortical measures that showed any level of evidence for neurodevelopmental or neurodegenerative effects in schizophrenia, using the conventions described above. Individual tables by region as well as a summary of genetic correlations with depression for all cortical measures that were evaluated in schizophrenia can be found in Appendix Table 4a-j and Appendix Table 6.

Table 40. Summary of evidence for diagnostic specificity of schizophrenia developmental neurogenetic models based on genetic correlations between depression and cortical measures within and across age-risk periods.

Lobe	Region	Significant Difference SZ vs. HC	Significant Rise R_G	Rise/Peak R_G Comparison	Significant Peak R_G	Peak/Plateau R_G Comparison	Significant Plateau R_G	Evidence for Early Neurodevelopmental Effects	Evidence for Late Neurodevelopmental Effects	Evidence for Neurodegenerative Effects
Global	Intracranial Volume									
	Lateral Ventricle Volume									
	Mean Thickness	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		– / –	
	Total Surface Area									
TH Frontal	Frontal Pole									
	Superior Frontal	X								
	Rostral Middle Frontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		– / –	
	Caudal Middle Frontal	X								
	Pars Opercularis	X								
	Pars Triangularis	X								
	Pars Orbitalis	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		– / –	
	Lateral Orbitofrontal	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		+ / +	– / –
	Medial Orbitofrontal	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		+ / +	– / –
	Precentral	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		– / –	– / –
	Paracentral									
TH Parietal	Superior Parietal									
	Inferior Parietal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		– / –	
	Supramarginal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		– / –	
	Postcentral									
	Precuneus									
TH Temporal	Superior Temporal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		– / –	
	Superior Temporal Sulcus	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	+ / –	*(n.s.)* / *(n.s.)*		– / –	
	Middle Temporal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*		– / –	
	Inferior Temporal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*		– / –	
	Fusiform	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		– / –	
	Transverse Temporal									
	Entorhinal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*			– / –
	Temporal Pole									
	Parahippocampal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		– / –	
TH Occipital	Lateral Occipital									
	Lingual	X								
	Cuneus									
	Pericalcarine									
TH Cingulate	Rostral Anterior Cingulate	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*		– / –	
	Caudal Anterior Cingulate									
	Posterior Cingulate	X								

	Isthmus Cingulate	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*		– / –		
	Insula	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		– / –		
SA Frontal	Frontal Pole	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		+ / +		
	Superior Frontal	X									
	Rostral Middle Frontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –			
	Caudal Middle Frontal	X									
	Pars Opercularis	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –			
	Pars Triangularis										
	Pars Orbitalis	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –			
	Lateral Orbitofrontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –			
	Medial Orbitofrontal	X									
	Precentral										
	Paracentral										
SA Parietal	Superior Parietal	X	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*		– / +		
	Inferior Parietal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*		– / –		– / +
	Supramarginal	X									
	Postcentral	X	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*		– / +		
	Precuneus	X									
SA Temporal	Superior Temporal										
	Superior Temporal Sulcus	X									
	Middle Temporal	X									
	Inferior Temporal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		– / –		
	Fusiform	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		– / –		
	Transverse Temporal	X									
	Entorhinal	X									
	Temporal Pole										
	Parahippocampal	X									
SA Occipital	Lateral Occipital	X									
	Lingual	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*		– / –		
	Cuneus										
	Pericalcarine	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*		– / –		
SA Cingulate	Rostral Anterior Cingulate										
	Caudal Anterior Cingulate										
	Posterior Cingulate										
	Isthmus Cingulate										
	Insula	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –			

Note. SZ indicates schizophrenia and HC indicates healthy control. TH indicates thickness and SA indicates surface area. An 'X' for significant group difference indicates that the cortical measure was examined because it showed a significant group difference between schizophrenia and controls. Significant R_G indicates that the significant genetic correlation between depression and the cortical measure for the given age-risk period was presented. Genetic correlations are presented only when significant and are indicated with '*(n.s.)*' when nonsignificant or when the significance could not be computed.

For each measure, results are first presented for analyses with basic adjustments (age, age^2, sex, and site) then presented for analyses with conservative adjustments (age, age^2, sex, site, parental education, scan quality, and intracranial volume), separated by '/'. i.e. analysis with basic adjustments / analysis with conservative adjustments.

For the R_G comparison across age-risk periods using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003), a '+' (increase) indicates that there is a significantly more negative genetic correlation from the earlier to the later age-risk period, whereas a '–' (decrease) indicates a significantly less negative or nonsignificant genetic correlation from the earlier to the later age-risk period.

Evidence for each effect is indicated as follows: '+ +' indicates strong evidence supporting the effect, '+' indicates moderate evidence supporting the effect, and '–' indicates no evidence supporting the effect.

Evidence supporting early neurodevelopmental effects is present if the genetic correlation is significant during the Rise period; a nonsignificant genetic correlation during the Rise period does not construe evidence against early neurodevelopmental effects due to the relatively small sample size for the Rise period.

Evidence supporting late neurodevelopmental effects is suggestive if there is a significantly more negative genetic correlation from the Rise to the Peak period (i.e. '+' in the Rise/Peak R_G Comparison) and strong if the genetic correlation is additionally significant during the Peak period.

Similarly, evidence supporting neurodegenerative effects is suggestive if there is a significantly more negative genetic correlation from the Peak to the Plateau period (i.e. '+' in the Peak/Plateau R_G Comparison) and strong if the genetic correlation is additionally significant during the Plateau period.

3.4.14.1 Global Cortical Measures: Evidence for Schizophrenia Developmental Neurogenetic Effects

In general, neither neurodevelopmental nor neurodegenerative effects on global cortical measures were clearly supported in analyses with either basic or conservative adjustments, as can be seen in Table 39. However, for mean thickness, there was strong evidence for late neurodevelopmental effects with basic but not conservative adjustments and the heritability of mean thickness was also significant. As shown in Table 40, these developmental neurogenetic effects on mean thickness were not observed in depression, suggesting that these effects are diagnostically specific to schizophrenia.

3.4.14.2 Cortical Thickness Measures: Evidence for Schizophrenia Developmental Neurogenetic Effects

Across all regional cortical thickness measures that were examined, there was no support for early neurodevelopmental effects (see Table 39).

The strongest level of support for late neurodevelopmental effects on any regional cortical thickness measure was conservative suggestive evidence. Specifically, this level of evidence was observed for a frontal thickness measure (pars orbitalis thickness), a parietal thickness measure (inferior parietal thickness), all but two temporal thickness measures (including superior temporal sulcus, middle temporal, inferior temporal, fusiform, and parahippocampal thickness), and three cingulate thickness measures (rostral anterior cingulate, isthmus cingulate, and insula thickness). Furthermore, suggestive evidence for late neurodevelopmental effects was observed with only basic but not conservative adjustments for three additional frontal thickness measures (rostral middle frontal, medial orbitofrontal, and precentral thickness), a parietal thickness measure (supramarginal thickness), and a temporal thickness measure (superior temporal thickness).

In contrast, schizophrenia neurodegenerative effects were supported only by suggestive evidence for only four cortical thickness measures: three frontal (lateral orbital frontal, medial orbitofrontal, precentral) and one temporal (entorhinal). In contrast to the frontal thickness measures, notably, there was no support for late neurodevelopmental models for entorhinal thickness, suggesting that schizophrenia neurogenetic effects may not be apparent immediately after peak age-of-onset but may arise during plateau age-of-onset for this structure.

As can be seen in Table 40, for almost all cortical thickness measures that showed developmental neurogenetic effects shared with schizophrenia, there was no evidence that these effects were shared with depression, supporting the diagnostic specificity of developmental neurogenetic effects to schizophrenia. Indeed, only two frontal thickness measures (lateral orbitofrontal and medial orbitofrontal thickness) showed evidence for late developmental neurogenetic effects in both schizophrenia and depression.

3.4.14.3 Cortical Surface Area Measures: Evidence for Schizophrenia Developmental Neurogenetic Effects

Across all regional cortical surface area measures that were examined, support for early neurodevelopmental effects was observed only after conservatively adjusting for parental education, scan quality, and intracranial volume for two frontal area measures (rostral middle frontal and pars orbitalis area) and one cingulate area measure (insula area), suggesting a medium level of cumulative evidence. Furthermore, there was also evidence for early neurodevelopmental effects on two frontal area measures that were observed only with basic but not with conservative adjustments (pars opercularis and lateral orbitofrontal area).

There were strong levels of support for late neurodevelopmental effects on three regional surface area measures: one parietal (superior parietal area), one temporal (fusiform area), and one

occipital (lingual area). In addition, there was suggestive support for late neurodevelopmental effects for a frontal area measure (frontal pole area), two parietal area measures (inferior parietal and postcentral area), one temporal area measure (inferior temporal area), and an occipital area measure (pericalcarine area).

In contrast to findings for regional cortical thickness measures, there was only suggestive support for neurodegenerative effects on only one cortical surface area measure (inferior parietal area).

As can be seen in Table 40, for most cortical area measures that showed developmental neurogenetic effects shared with schizophrenia, there was no evidence that these effects were shared with depression, suggesting the diagnostic specificity of developmental neurogenetic effects to schizophrenia. Indeed, only one frontal area measure (frontal pole area) and two parietal area measures (superior parietal and postcentral area) showed any suggestive evidence for late developmental neurogenetic effects in both schizophrenia and depression. Furthermore, the only regional surface area measure to show suggestive neurodegenerative effects in schizophrenia (inferior parietal area) also showed suggestive effects in depression, suggesting that schizophrenia neurodegenerative effects are not supported for any cortical surface area measure.

4.0 DISCUSSION

4.1 SUMMARY OF FINDINGS

In summary, although there was generally low support for neurodevelopmental and neurodegenerative effects of schizophrenia across cortical thickness and cortical surface area measures, perhaps due to relatively limited sample size, schizophrenia developmental neurogenetic effects were most apparent in many, although not all, brain regions. There was some support that most regional cortical thickness measures were influenced by late schizophrenia neurodevelopmental effects (15 of 23 regions examined, plus total mean thickness) and to a much more limited extent, schizophrenia neurodegenerative effects (4 of 23 regions), whereas there was no support for early schizophrenia neurodevelopmental effects. In contrast, evidence supported fewer regional cortical surface area measures being influenced by late schizophrenia neurodevelopmental effects (8 of 24 regions examined), although for some the evidence was the strongest (superior parietal, fusiform, and lingual area). In contrast, there was suggestive evidence supporting schizophrenia neurodegenerative effects for only one region and only support for five cortical surface area measures with early developmental effects. These developmental neurogenetic effects were almost all diagnostically specific to schizophrenia and were not observed in depression.

Overall, as can be seen in Table 41, which further summarizes the findings of the current study, early neurodevelopmental effects were not supported for any regional cortical thickness measure and were only supported for four frontal surface area measures. Schizophrenia-specific late neurodevelopmental effects were supported most consistently for all temporal thickness

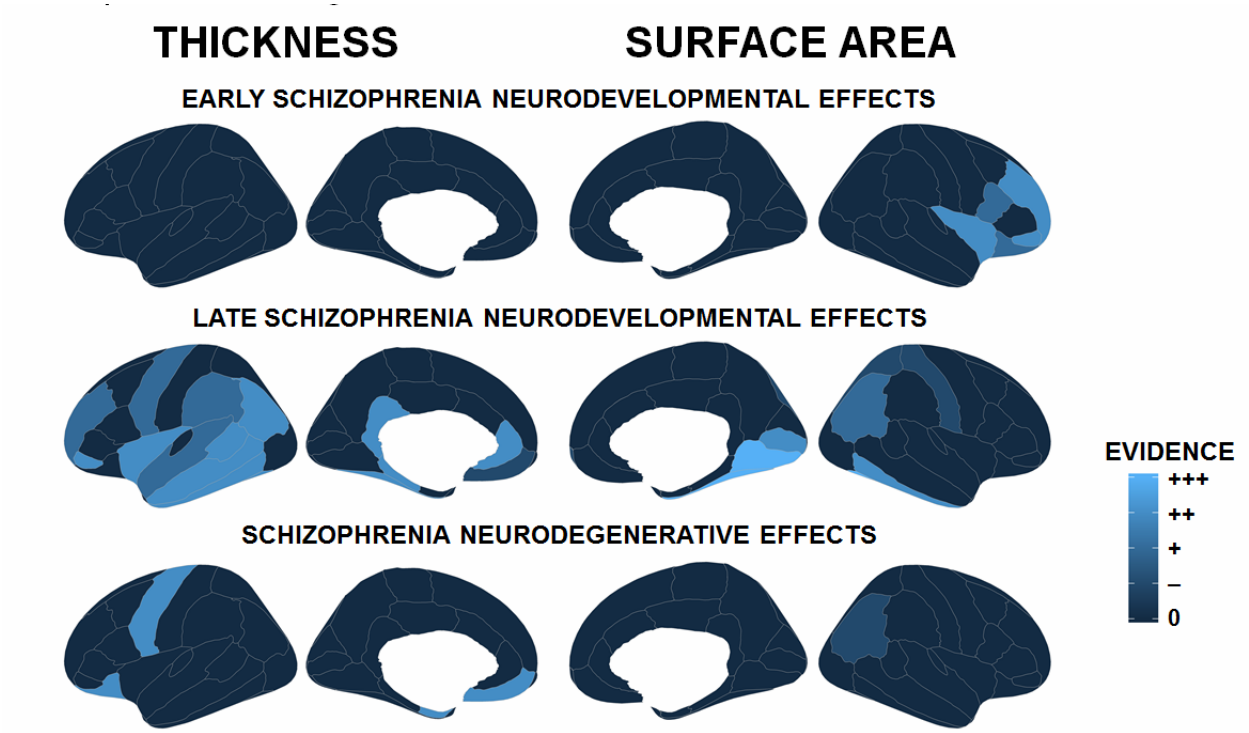
measures except for entorhinal thickness. More tentative support for schizophrenia-specific late neurodevelopmental effects were found for frontal, parietal, and cingulate thickness measures, whereas no support was found for occipital thickness measures. Schizophrenia-specific late neurodevelopmental effects were most strongly supported for frontal, temporal, and occipital area measures, and to a lesser extent, parietal area measures. In contrast, schizophrenia-specific neurodegenerative effects received moderate support for only entorhinal thickness and more tentative support for frontal thickness measures. Neurodegenerative effects did not receive any support for cortical surface area measures. Figure 3 depicts Desikan-Killany brain atlases of early neurodevelopmental, late neurodevelopmental, and neurodegenerative effects on regional cortical thickness and cortical surface area.

Table 41. Summary of cortical measures with evidence for schizophrenia developmental neurogenetic effects.

Lobe (*k*)	Cortical Measures with Evidence for Early Neurodevelopmental Effects	Cortical Measures with Evidence for Late Neurodevelopmental Effects	Cortical Measures with Evidence for Neurodegenerative Effects
Global (4)		**mean thickness +++**	
TH Frontal (9)		**pars orbitalis ++** **rostral middle frontal +** **precentral +** medial orbitofrontal +	**lateral orbitofrontal ++** **medial orbitofrontal ++** **precentral ++**
TH Parietal (2)		**inferior parietal ++** **supramarginal +**	
TH Temporal (7)		**superior temporal +** **superior temporal sulcus ++** **middle temporal ++** **inferior temporal ++** **fusiform ++** **parahippocampal ++**	**entorhinal ++**
TH Occipital (1)			
TH Cingulate (4)		**rostral anterior cingulate ++** **isthmus cingulate ++** **insula ++**	
SA Frontal (8)	**rostral middle frontal ++** **pars orbitalis ++** **pars opercularis +** **lateral orbitofrontal +**	frontal pole ++	
SA Parietal (5)		superior parietal ++++ **inferior parietal +** postcentral ++	inferior parietal ++
SA Temporal (7)		**inferior temporal ++** **fusiform +++**	
SA Occipital (3)		**lingual +++** **pericalcarine ++**	
SA Cingulate (1)	**insula ++**		

Note. *k* indicates number of cortical measures examined within a given lobe. TH indicates thickness and SA indicates surface area. Cortical measures showing any level of supporting evidence for developmental neurogenetic effects are listed.
'++++' indicates highest level of cumulative evidence for developmental neurogenetic effects on the cortical measure (i.e. significantly more negative genetic correlation with schizophrenia for later compared to earlier period and genetic correlation with schizophrenia significantly different from zero for later period; both with conservative adjustments)
'+++' indicates next highest level of cumulative evidence for developmental neurogenetic effects on the cortical measure (i.e. significantly more negative genetic correlation with schizophrenia for later compared to earlier period and genetic correlation with schizophrenia significantly different from zero for later period; only for basic adjustments)
'++' indicates a lower level of cumulative evidence for developmental neurogenetic effects on the cortical measure (i.e. significantly more negative genetic correlation with schizophrenia for later compared to earlier period but genetic correlation with schizophrenia not significantly different from zero for later period; with conservative adjustments).
'+' indicates lowest level of cumulative evidence for neurodevelopmental effects on cortical measure (i.e. significantly more negative genetic correlation with schizophrenia for later compared to earlier period but genetic correlation with schizophrenia not significantly different from zero for later period; only with basic adjustments)

Bolded cortical measures indicate diagnostic specificity to schizophrenia (i.e. no evidence supporting the effect in depression using either basic adjustments or conservative adjustments).



Levels of Evidence for Schizophrenia Developmental Neurogenetic Effects	
+++	significantly more negative Rg for later compared to earlier period Rg significantly different from zero for later period only with basic adjustments; specific to schizophrenia
++	significantly more negative Rg for later compared to earlier period Rg not significantly different from zero for later period only with conservative adjustments; specific to schizophrenia
+	significantly more negative Rg for later compared to earlier period Rg not significantly different from zero for later period only with basic adjustments; specific to schizophrenia
–	significantly more negative Rg for later compared to earlier period either with basic or conservative adjustments also observed in depression and not specific to schizophrenia
0	no change in Rg for later compared to earlier period either with basic or conservative adjustments

Note. 'Rg' denotes genetic correlation.

Figure 3. Summary of regional cortical measures with evidence for schizophrenia developmental neurogenetic effects.

4.1.1 Summary of Findings: Overall Genetic Effects on Cortical Measures

To examine genetic effects on cortical measures that were shared with schizophrenia genetic effects, we started by estimating overall genetic effects on cortical measures to determine whether genetic effects on cortical measures in the current sample are comparable to those found in prior studies of normative development. We then examined the extent to which these effects change and are shared across age of risk for schizophrenia, which allowed us to examine whether these genetic effects may not only change across normative development, but across the development of schizophrenia. The results of these general analyses are summarized below.

Our first question was whether individual differences in regional cortical measures were heritable in families with increased genetic liability for schizophrenia. As shown in Appendix Table 5, which summarizes significant overall genetic effects on cortical measures, there were more cortical surface area measures that were significantly heritable compared to cortical thickness measures. Regional cortical measures were usually heritable immediately after the peak age of onset (7/23 cortical thickness measures and 21/24 cortical surface area measures) and during the subsequent plateau in schizophrenia onset (17/23 cortical thickness measures and 22/24 cortical surface area measures). Although the heritabilities were often high before peak age of schizophrenia onset, regional cortical measures were generally not significantly heritable during this age-risk period, likely due to the limited sample size of this age-risk group. This pattern of genetic effects on cortical measures suggests that although this study may not well detect genetic effects on cortical measures before peak age of onset, this study better assesses overall genetic effects on cortical measures immediately after peak age of onset and during the plateau age of onset for schizophrenia. Thus, our findings for early neurodevelopmental effects on schizophrenia may be limited by small sample sizes at this period.

Our second question was whether overall genetic effects on cortical measures change across age of risk for schizophrenia. We found that the heritability of cortical measures was largely stable across age-risk periods, which is consistent with literature indicating that the heritability of cortical measures appears to stabilize to adult levels by adolescence in normative development (Chouinard-Decorte et al., 2014; Eyler et al., 2011; Ma et al., 2016). This stability of genetic effects on cortical measures suggests that developmental patterns of overall genetic effects on cortical measures in multiplex families are consistent with developmental patterns of overall genetic effects on cortical measures in families in the general population.

Our third question was whether overall genetic effects on regional cortical measures were shared across age-risk periods for schizophrenia. We found that genetic effects on regional cortical measures overlapped across the periods before the peak age of onset, immediately after the peak age of onset, and during the plateau in schizophrenia onset. The high genetic correlations across these age-risk periods suggest that overall genetic effects on regional cortical measures largely overlap across development (pleiotropy).

In summary, overall genetic effects on cortical thickness were similar in selected families with increased genetic liability for schizophrenia compared to unselected families in the general population. Few studies have examined these issues for measures of surface area. Our study was limited in detecting overall genetic effects on cortical measures immediately before peak age of onset for schizophrenia but better detected overall genetic effects on cortical measures immediately after peak age of onset and during the plateau age of onset for schizophrenia. Consistent with prior literature in genetic effects on cortical thickness and cortical surface area in adults, in the current study, which was comprised of mostly adults, genetic effects on cortical measures were generally stable across age-risk periods in our sample. Furthermore, genetic effects

on cortical measures were generally shared across age-risk periods. Thus, overall genetic effects on cortical measures were generally significant, stable, and pleiotropic across schizophrenia age of onset.

Our central question was whether these overall genetic effects on cortical measures may share overlap with schizophrenia genetic effects, and whether this overlap may differ across age-risk periods for schizophrenia.

4.1.2 Summary of Evidence for Early Schizophrenia Neurodevelopmental Effects

In the current study, we did not find evidence supporting early schizophrenia neurodevelopmental effects for any global cortical measure, consistent with prior literature which found no effects on global cortical thickness or surface area (Prasad et al., 2010). Notably, schizophrenia genetic liability did not overlap with genetic effects on non-tissue brain structures, specifically intracranial volume or ventricle volume, both of which show increased variability in schizophrenia compared to controls (Kuo & Pogue-Geile, 2019). These findings suggest that, to the extent that early schizophrenia genetic effects influence cortical thickness or cortical surface area, these effects are not global but may instead be localized to specific brain regions.

Early schizophrenia effects were not supported for regional cortical thickness measures in the current study. Consistent with prior studies which have generally found little evidence for an association between schizophrenia genetic liability and decreased cortical thickness before peak age of schizophrenia onset (Byun et al., 2012; Harms et al., 2010; Karnik-Henry et al., 2012; Li et al., 2012; Prasad et al., 2010; Sprooten et al., 2013), we did not find evidence for an association between schizophrenia genetic liability and decreased mean thickness or any regional thickness measure before peak age of schizophrenia onset. Although the largest relevant study (N = 144)

suggested an association between schizophrenia genetic liability and decreased temporal thickness, particularly left middle temporal thickness (Sprooten et al., 2013), we did not find evidence of such an association in the current study. Taken together, early schizophrenia genetic effects appear to share little overlap with genetic effects on cortical thickness before peak age of schizophrenia onset.

In contrast to the lack of evidence for early developmental neurogenetic effects on cortical thickness, we found limited evidence for early developmental genetic effects on cortical surface area which were furthermore diagnostically specific to schizophrenia. We found suggestive associations between schizophrenia genetic liability and multiple adjacent frontal area measures, particularly for rostral middle frontal and pars orbitalis area and to a lesser extent, pars opercularis and lateral orbitofrontal area. These findings are partially consistent with one prior study which demonstrated an association between schizophrenia genetic liability and both frontal and parietal area measures before peak age of schizophrenia onset (Prasad et al., 2010), but not with two other previous similarly-sized studies (Harms et al., 2010; Li et al., 2012), which showed no significant associations with any regional area measures during this period. Instead, we additionally found an association between schizophrenia genetic liability and a cingulate area measure (insula area). Thus, we replicated findings supporting schizophrenia early genetic effects on frontal areas and additionally observed schizophrenia genetic effects on insula area before peak age of schizophrenia onset, suggesting the possible importance of early schizophrenia genetic effects on surface area expansion in these regions.

Overall, early neurodevelopmental effects were observed in regional measures of surface area but not in regional measures of cortical thickness. Despite the limited power to detect early neurodevelopmental effects in this study, the early neurodevelopmental effects observed in this

study were largely consistent with those observed in prior studies, including a general lack of support for early neurodevelopmental effects on regional cortical thickness (Byun et al., 2012; Harms et al., 2010; Karnik-Henry et al., 2012; Li et al., 2012; Prasad et al., 2010; Sprooten et al., 2013) and converging support for early neurodevelopmental effects on frontal area (Prasad et al., 2010). Early neurodevelopmental effects on parietal area were not supported in this study, despite some suggestive evidence from a prior study (Prasad et al., 2010). In addition, the current study also found early neurodevelopmental effects for cingulate area.

4.1.3 Summary of Evidence for Late Schizophrenia Neurodevelopmental Effects

Late schizophrenia genetic effects were observed for only one global cortical measure: mean thickness. Thus, although schizophrenia genetic effects may not influence cortical thickness immediately before schizophrenia onset, schizophrenia genetic effects may broadly influence cortical thickness immediately after schizophrenia onset. This result is consistent with findings from the largest prior study, which suggested that, after early adulthood before age 40, schizophrenia genetic liability is associated with decreases in cortical thickness across all lobes (Goldman et al., 2009). Total surface area was not associated with late neurodevelopmental schizophrenia effects, despite some suggestive evidence of increased total surface area with greater schizophrenia liability in a small study (Goghari et al., 2007). Schizophrenia genetic liability may therefore show little effect on mean thickness before peak age of onset but may begin to decrease mean thickness immediately after peak age of schizophrenia onset, whereas schizophrenia genetic liability may consistently show little effect on total surface area before and immediately after peak age of schizophrenia onset.

In line with prior findings of schizophrenia genetic effects on widespread decreases in cortical thickness immediately after peak age of schizophrenia onset (Goldman et al., 2009), we found limited to moderate evidence for late schizophrenia genetic effects on cortical thickness across all lobes except for the occipital lobe. The most robust findings in the current study were observed for late schizophrenia genetic effects on multiple temporal thickness measures, ranging from superior temporal to medial temporal regions, and on cingulate thickness measures, including rostral anterior and isthmus cingulate thickness. More limited findings were observed for late schizophrenia genetic effects on frontal thickness, with pars orbitalis thickness showing the strongest evidence of all frontal thickness measures, and parietal thickness, with inferior parietal thickness showing the strongest evidence of all parietal thickness measures. Thus, our findings are consistent with the largest prior study by far (Goldman et al., 2009) and emphasize late schizophrenia neurodevelopmental effects on cortical thickness, particularly for temporal and cingulate regions, and to a lesser extent, frontal and parietal regions.

In comparison to the multitude of cortical thickness measures that appear to be influenced by late schizophrenia genetic effects, we found less evidence for late schizophrenia genetic effects on cortical surface area measures. In particular, we found limited evidence that late schizophrenia genetic effects were associated with frontal, parietal, temporal, and occipital area. However, this pattern of developmental genetic effects was also found in depression for one frontal area measure and two parietal area measures. Thus, diagnostically specific late schizophrenia effects were observed only for selected parietal, temporal, and occipital area measures. This pattern is partially consistent with the only one of two studies to examine effects of schizophrenia liability on cortical surface area immediately after peak age of schizophrenia onset (Goghari et al., 2007), which suggested that schizophrenia liability was associated with decreases in temporal and cingulate area.

Thus, late schizophrenia genetic effects may influence most robustly parietal and temporal area, and to a lesser extent, occipital area.

Taken together, late neurodevelopmental effects particularly influence both global and regional cortical thickness, with especially robust evidence on temporal and cingulate thickness, and somewhat more limited evidence for frontal and parietal thickness. In contrast, late neurodevelopmental effects do not appear to influence global cortical surface area but regionally influence parietal and temporal area, and to a lesser extent, occipital area.

4.1.4 Summary of Evidence for Schizophrenia Neurodegenerative Effects

Neurodegenerative schizophrenia genetic effects were not observed for any global cortical measure, consistent with the only study to examine schizophrenia genetic liability on global cortical thickness (Yang et al., 2010). Thus, to the extent that neurodegenerative schizophrenia genetic effects influence cortical thickness or cortical surface area, these genetic effects do not appear to be widespread.

We found limited evidence supporting neurodegenerative schizophrenia effects on frontal thickness, particularly orbitofrontal and precentral thickness. This finding is consistent with the sparse literature to date, which indicates that individuals with schizophrenia show normative age-related declines in cortical thickness after age 40 except for perhaps larger age-related decreases for left frontal thickness, particularly of the left prefrontal cortex (Kuperberg et al., 2003; Nesvag et al., 2008; Zhang et al., 2015). In addition, we also found evidence of neurodegenerative schizophrenia effects on a temporal thickness measure, entorhinal thickness. Our findings provide new evidence to suggest that, in relatives who have passed the peak age of schizophrenia onset,

schizophrenia genetic liability may have neurodegenerative effects for temporal and frontal thickness.

There was no evidence in the current study to suggest neurodegenerative schizophrenia genetic effects on cortical surface area, as neurodegenerative effects on inferior parietal area were not diagnostically specific to schizophrenia and were also found in depression. This is in line with the only study to our knowledge suggesting that individuals with schizophrenia show normative age-related decreases in cortical surface area, at least for frontal and temporal regions, after peak age of schizophrenia onset (Cobia et al., 2012).

Taken together, these findings suggest that schizophrenia genetic effects may influence cortical thickness development past the peak age of schizophrenia onset and through the plateau age of schizophrenia onset, with possible neurodegenerative effects being observed for temporal thickness and to a lesser extent, frontal thickness.

4.2 IMPLICATIONS

This is the first study to our knowledge to directly test early neurodevelopmental, late neurodevelopmental, and neurodegenerative models of schizophrenia and to demonstrate that schizophrenia genetic effects on cortical thickness and cortical surface area may show changes across age of risk that are compatible with each of these models of schizophrenia. The developmental patterns in genetic correlations between schizophrenia and cortical measures suggest that schizophrenia genetic risk variants may overlap with or interact with gene variants that influence brain development.

Overall genetic effects on cortical traits appeared be consistent with those observed in studies of normative development and were relatively high, stable, and pleiotropic. However, the relationships between these overall genetic effects on cortical traits and schizophrenia genetic effects was anything but constant, appearing to undergo dynamic changes depending on the cortical region and age period. Importantly, schizophrenia genetic effects varied in localization and were more apparent for specific brain regions rather than across the brain. This pattern suggests that schizophrenia genetic effects differentially affect neurodevelopment of certain brain regions, perhaps more than contributing to common developmental factors that are found across brain regions.

Schizophrenia genetic effects on the brain also varied in developmental timing. Building upon the finding that cortical thickness and cortical surface area are influenced by largely independent genetic effects in normative development (Panizzon et al., 2009), we found that these independent developmental neurogenetic effects also show distinct relationships with schizophrenia genetic effects. Not only did schizophrenia developmental neurogenetic influences show differential effects across cortical regions, they differed between cortical thickness and cortical surface area, such that schizophrenia genetic effects on cortical thickness of a given region was rarely (only three times, for inferior parietal, inferior temporal, and fusiform regions) accompanied by schizophrenia genetic effects on cortical surface for the region, and vice versa. This finding suggests that future studies examining schizophrenia developmental neurogenetic effects on the brain may benefit from examining both cortical thickness and cortical surface area rather than only probing either cortical trait for a given region.

In particular, cortical surface area appears to be influenced earlier, before peak age of onset, by schizophrenia genetic liability whereas cortical thickness appears to be influenced later, through

plateau age of onset, by schizophrenia genetic liability. Before the ages at which individuals are most likely to develop schizophrenia, schizophrenia genetic risk variants may contribute to limiting or decreasing the growth of frontal and cingulate surface area. Immediately after the age at which individuals are most likely to develop schizophrenia, schizophrenia genetic risk variants have far-reaching effects on the brain, contributing to decreases in frontal, parietal, temporal, and cingulate thickness as well as temporal, occipital, and cingulate surface area. Subsequently, during the age at which individuals are least likely to develop schizophrenia, schizophrenia genetic risk variants may contribute to declines in frontal and temporal thickness.

The findings of the current study suggest a possibly greater influence of early schizophrenia genetic effects on cortical surface area than on cortical thickness, potential influence of late schizophrenia genetic effects on both cortical thickness and surface area, and a greater influence of neurodegenerative schizophrenia genetic effects on cortical thickness than on cortical surface area. Interestingly, the regional surface area measures that are influenced by schizophrenia genetic effects during early development do not overlap with those that are influenced by schizophrenia genetic effects during late development. Indeed, early schizophrenia genetic effects appear to influence only surface area for frontal and cingulate regions, whereas widespread late schizophrenia genetic effects appear to influence surface area for all regions except frontal and cingulate regions. Furthermore, schizophrenia genetic effects appear to only influence cortical thickness measures after peak age of schizophrenia onset and are much more restricted during plateau age of schizophrenia onset.

Taken together, each of these findings provides a working hypothesis from which to follow up using phenomic, genomic, and transcriptomic approaches. For example, given that early schizophrenia genetic effects appear to influence only surface area for frontal and cingulate regions

and not cortical thickness for any region, the integration of multiple brain and behavior phenotypes using phenomics approaches may be informed by examining frontal surface area along with behavioral traits that may be related to cortical surface area expansion for frontal regions, such as working memory and attention (e.g., Doan et al., 2017; Tadayon, Pascual-Leone, & Santarnecchi, 2019). Furthermore, in focusing a genome-wide search for schizophrenia gene variants on individuals who have not yet reached the peak age of schizophrenia onset, a working hypothesis could entail examining the subset of neurodevelopmental gene variants that are thought to be involved in neuronal specialization and are evidently associated with decreases in surface area for specific frontal and/or cingulate regions in normative cortical development based on genomic brain atlases. Gene expression profiles for this subset of neurodevelopmental genes could be corroborated against gene expression profiles for putative schizophrenia risk variants that are expressed before adolescence or young adulthood, to determine the extent to which the RNA sequencing profiles may show greater similarities than otherwise expected. The overlapping genes which show similar expression profiles may become genes of interest for following up using functional genomics approaches.

The potential utility of these findings for developing novel hypotheses is supported by comparing imaging genetic studies that collapse across schizophrenia age of risk against studies that have more restricted age ranges. To our knowledge, only four studies to date have examined associations between schizophrenia polygenic risk and cortical thickness and/or cortical surface area (Alnaes et al., 2019; French et al., 2015; Neilson et al., 2019; Voineskos et al., 2016). Of these studies, the study that collapsed across age of risk for schizophrenia (N = 565; age range = 8-86 years) found no associations between schizophrenia polygenic risk and frontal and temporal thickness (Voineskos et al., 2016), which contrasts with our findings of late neurodevelopmental

and neurodegenerative effects on frontal thickness and late neurodevelopmental effects on temporal thickness. In contrast, a larger study in adolescents and young adults who are approaching the peak age of risk for schizophrenia (N = 1,577, age range = 12-22 years) found an association between schizophrenia polygenic risk and mean cortical thickness only in cannabis users but not in non-users, which is in line with our findings of a lack of early schizophrenia neurodevelopmental effects on mean cortical thickness. The largest study of individuals in the general population who are generally in the plateau age of risk for schizophrenia (N = 12,490, mean (s.d.) age = 55.9 (7.9) years), schizophrenia polygenic risk was associated with decreased frontal and temporal thickness (Alnaes et al., 2019), which is at least partially consistent with our findings of neurodegenerative effects on frontal thickness. This sample was completely overlapping with a smaller study (N=2,856) (Neilson et al., 2019). Taken together with the current findings, the extant literature suggests that developmental effects are well worth consideration in investigating the relationships between schizophrenia genetic risk and structural brain features.

This study thus provides a proof of concept for demonstrating that, just as genetic risk profiles that combine cortical traits may not be sensitive to schizophrenia genetic effects for specific cortical traits, schizophrenia genetic risk profiles that collapse across schizophrenia age of risk may not be sensitive to schizophrenia genetic effects that are most apparent only at certain developmental timepoints for specific cortical traits, thereby yielding few associations (e.g., Voineskos et al., 2016). Associations between schizophrenia genetic risk profiles and cortical structures may be informed by focusing on gene variants that have been functionally linked to neurodevelopment (e.g., Forsyth et al., 2019; Spalthoff et al., 2019). Targets may be similarly refined for genome-wide searches for schizophrenia neurodevelopmental risk variants by examining subsets of gene networks that are enriched for neuronal specialization within regions

rather than neuronal growth factors in general. Indeed, targets may be even further refined by examining schizophrenia developmental changes in gene expression levels for selected brain regions from the current study. Our findings therefore emphasize the rationale for examining expression levels of schizophrenia risk variants that have been identified in genome-wide association studies during the critical neurodevelopmental period of late adolescence and early adulthood, as this may provide a window into the putative neurodevelopmental mechanisms that may precipitate schizophrenia onset.

4.3 CONSIDERATIONS

To our knowledge, this is the first study to directly test early and late neurodevelopmental models of schizophrenia. The large, extended-pedigree design of this study was well suited particularly for examining late neurodevelopmental and neurodegenerative models of schizophrenia. Other strengths of this study include the examination of both cortical thickness and cortical surface area within our sample, allowing for comparisons of these different features of cortical development in the same individuals. Our analyses further distinguished between genetic effects in general compared to those that are correlated with schizophrenia, by examining the heritability of a given cortical measure and the genetic correlation between schizophrenia and the cortical measure, respectively. In addition, we were able to examine the diagnostic specificity of any observed effects to schizophrenia compared to depression.

Despite these strengths, certain limitations should be noted. In particular, relatives under 12 years of age did not undergo neuroimaging, thereby constraining our ability to test early neurodevelopmental models. In addition, although a total of 506 individuals provided quality MRI

data, sample sizes were relatively modest, especially for the early period. These power considerations may have also contributed the overall relatively low level of support for developmental effects. Furthermore, although we aimed to control alpha error using standard False Discovery Rate corrections, the number of regions and age periods examined may nevertheless still have had effects of increasing false positive findings. This was also a cross-sectional study not longitudinal, thus any age observed effects may also reflect cohort effects. Given the cross-sectional nature of this study, we cannot infer the directionality of schizophrenia genetic effects and genetic effects on the brain from a significant genetic correlation between schizophrenia and cortical structures during a given developmental period. Thus, we cannot distinguish whether schizophrenia genetic effects modify cortical structures during this developmental period, whether genetic effects on cortical structures alter liability for schizophrenia during this developmental period, or whether genetic effects influence both schizophrenia and cortical structures during this developmental period. These factors along with the novelty of this study suggest that these findings may be better considered in the context of hypothesis generation rather than hypothesis testing.

The ethnically homogenous sample may limit the generalizability of our findings for individuals who are not Caucasian. The multiplex design of this study may also limit the generalizability of our study to individuals with schizophrenia who do not have a family history of schizophrenia. The findings for depression may also not be representative as the relatives with depression are related to a schizophrenia proband. However, this would likely bias against our findings of diagnostic specificity, as individuals with schizophrenia are also related to a relative with schizophrenia as well. Although the extended pedigree design enables computation of genetic estimates on linear predictions across a wide range of kinship relationships, from first- to fourth-

degree of relation in this study, genetic effects may be overestimated in cases where the resemblance of environmental effects also vary linearly with degree of kinship. However, developmental neurogenetic effects did not span across relatives with different diagnoses of schizophrenia and depression, suggesting that shared environmental effects contributed little to these effects in schizophrenia.

4.4 CONCLUSIONS

To our knowledge, this is the first study to directly test early neurodevelopmental, late neurodevelopmental, and neurodegenerative models of schizophrenia, showing that the effects of schizophrenia genetic risk influence different aspects of brain structure before and after schizophrenia peak age of onset. Overall genetic effects on cortical thickness and cortical surface area are generally stable and overlapping across age of risk. Early schizophrenia genetic effects influence regional surface area, particularly for frontal and cingulate regions, whereas late schizophrenia genetic effects are more widespread and influence both regional thickness (across frontal, parietal, temporal, and cingulate regions) and regional surface area (across parietal, temporal, occipital, and cingulate regions). Furthermore, neurodegenerative schizophrenia genetic effects influence regional cortical thickness, particularly for frontal and temporal regions.

Given that gene variants that influence cortical surface area may show greatest effects before and during peak age of schizophrenia onset whereas gene variants that influence cortical thickness may show greatest effects during and after peak age of schizophrenia onset, our findings bear important implications across multiple levels of systems genetic approaches: 1) for phenomic investigations, instead of examining only cortical thickness or cortical surface area, cortical

thickness and cortical surface area may be investigated together with relevant behavioral traits to more fully elucidate the individual-wide changes associated with schizophrenia genetic liability; 2) for genomic investigations, targets of genome-wide searches for schizophrenia genetic risk variants may be refined by examining specific cortical measures depending on the subjects' age relative to peak age of schizophrenia onset; and 3) for transcriptomic investigations, examining changes in the expression of schizophrenia genetic risk variants across neurodevelopment of specific cortical regions may provide mechanistic insights into the development of schizophrenia. Overall, our findings emphasize the utility of using developmental approaches to inform genetic investigations of schizophrenia.

APPENDIX: SUPPLEMENTARY TABLES

Appendix Table 1. Comparisons of genetic effects on global cortical measures between age-risk periods, with basic covariates.

		Genetic Correlations Between Age-Risk Periods						Heritability × Age Interaction		
		Rise/Peak		Peak/Plateau		Rise/Plateau		Rise/Peak	Peak/Plateau	Rise/Plateau
Lobe	Region	R_G	p-value	R_G	*p*-value	R_G	*p*-value	*p-value*	*p-value*	*p-value*
Global	Intracranial Volume	0.109	(1.000)	-0.621	(1.000)	1.000	(1.000)	(0.419)	(0.978)	(1.000)
	Lateral Ventricle Volume	1.000	(1.000)	0.235	(1.000)	1.000	(1.000)	(0.414)	(0.275)	(1.000)
	Mean Thickness	1.000	(1.000)	-0.576	(1.000)	1.000	(1.000)	(0.414)	(0.978)	(1.000)
	Total Surface Area	NA	(1.000)	-0.455	(1.000)	0.906	(1.000)	(NA)	(0.978)	(1.000)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted excluding all schizophrenia participants (N=123, N=30 with cortical data). Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 2. Phenotypic correlations between schizophrenia and global cortical measures with basic covariates.

		Phenotypic Correlations Within Age-Risk Periods						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_P	*p*-value	R_P	*p*-value	R_P	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Global	Intracranial Volume	-0.600	(NA)	-0.402	(NA)	-0.245	(NA)	-2.116	(0.046*)	-1.908	(0.075)	-3.576	(0.001*)
	Lateral Ventricle Volume	-0.011	(0.919)	0.207	(0.105)	0.278	(0.001*)	-1.747	(0.081)	-0.823	(0.411)	-2.391	(0.022*)
	Mean Thickness	-0.139	(0.365)	-0.458	(0.009*)	-0.293	(0.001*)	2.814	(0.017*)	-2.095	(0.075)	1.299	(0.194)
	Total Surface Area	-0.735	(NA)	-0.542	(0.000*)	-0.406	(0.000*)	-2.630	(0.017*)	-1.911	(0.075)	-4.101	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all schizophrenia participants (N=123, N=30 with cortical data). Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 3. Phenotypic correlations between schizophrenia and global cortical measures with conservative covariates.

		Phenotypic Correlations Within Age-Risk Periods						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_P	*p*-value	R_P	*p*-value	R_P	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Global	Intracranial Volume	-0.631	(NA)	-0.287	(0.042*)	-0.190	(0.078)	-3.543	(0.001*)	-1.107	(0.537)	-4.426	(0.000*)
	Lateral Ventricle Volume	0.150	(0.365)	0.302	(0.003*)	0.338	(0.000*)	-1.265	(0.274)	-0.434	(0.665)	-1.609	(0.143)
	Mean Thickness	-0.322	(0.558)	-0.227	(0.018*)	-0.175	(0.078)	-0.815	(0.415)	-0.583	(0.665)	-1.264	(0.206)
	Total Surface Area	-0.768	(NA)	-0.485	(0.003*)	-0.376	(0.000*)	-3.854	(0.000*)	-1.449	(0.537)	-4.998	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all schizophrenia participants (N=123, N=30 with cortical data).
Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 4. Phenotypic correlations between depression and global cortical measures with basic covariates.

		Phenotypic Correlations Within Age-Risk Periods						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_P	*p*-value	R_P	*p*-value	R_P	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Global	Intracranial Volume	-0.171	(0.349)	-0.156	(0.444)	0.115	(0.292)	-0.111	(0.912)	-2.405	(0.032*)	-2.139	(0.065)
	Lateral Ventricle Volume	-0.138	(0.349)	-0.270	(NA)	0.195	(0.282)	0.961	(0.449)	-4.218	(0.000*)	-2.471	(0.054)
	Mean Thickness	-0.236	(0.349)	0.006	(0.975)	-0.080	(0.485)	-1.708	(0.254)	0.758	(0.449)	-1.181	(0.317)
	Total Surface Area	0.165	(0.349)	-0.053	(0.959)	0.055	(0.525)	1.527	(0.254)	-0.965	(0.446)	0.818	(0.413)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all depression participants (N=137, N=38 with cortical data).
Covariates included age, age^2, sex, site, and schizophrenia for all analyses.

Appendix Table 5. Phenotypic correlations between depression and global cortical measures with conservative covariates.

		Phenotypic Correlations Within Age-Risk Periods						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_P	*p*-value	R_P	*p*-value	R_P	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Global	Intracranial Volume	-0.194	(0.302)	-0.162	(0.531)	0.124	(0.255)	-0.228	(0.820)	-2.561	(0.021*)	-2.358	(0.073)
	Lateral Ventricle Volume	0.026	(0.774)	-0.101	(0.661)	0.234	(0.039*)	0.884	(0.502)	-3.014	(0.010*)	-1.557	(0.159)
	Mean Thickness	-0.197	(0.302)	-0.038	(0.661)	-0.031	(0.707)	-1.120	(0.502)	-0.061	(0.951)	-1.236	(0.216)
	Total Surface Area	0.191	(0.302)	0.050	(0.661)	-0.091	(0.383)	0.999	(0.502)	1.253	(0.280)	2.094	(0.073)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all depression participants (N=137, N=38 with cortical data).
Covariates included age, age^2, sex, site, and schizophrenia for all analyses.

Appendix Table 6. Environmental correlations between schizophrenia and global cortical measures with basic covariates.

		Environmental Correlations						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_E	*p*-value	R_E	*p*-value	R_E	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Global	Intracranial Volume	-0.900	(NA)	-0.471	(NA)	-0.900	(NA)	-7.620	(0.000*)	10.387	(0.000*)	0.000	(1.000)
	Lateral Ventricle Volume	-0.349	(0.714)	0.900	(0.228)	0.900	(0.007*)	-14.558	(0.000*)	-0.001	(1.000)	-14.808	(0.000*)
	Mean Thickness	-0.900	(0.714)	-1.000	(0.085)	-1.000	(0.007*)	54.970	(0.000*)	0.000	(1.000)	55.908	(0.000*)
	Total Surface Area	0.900	(NA)	0.220	(0.905)	-0.900	(0.293)	9.899	(0.000*)	18.329	(0.000*)	23.743	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all schizophrenia participants (N=123, N=30 with cortical data).
Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 7. Environmental correlations between schizophrenia and global cortical measures with conservative covariates.

		Environmental Correlations						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_E	*p*-value	R_E	*p*-value	R_E	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Global	Intracranial Volume	-0.900	(NA)	0.061	(1.000)	0.358	(0.875)	-12.151	(0.000*)	-3.373	(0.001*)	-14.864	(0.000*)
	Lateral Ventricle Volume	0.186	(1.000)	0.900	(0.116)	0.900	(0.038*)	-10.170	(0.000*)	0.000	(1.000)	-10.328	(0.000*)
	Mean Thickness	-0.900	(0.426)	-0.415	(1.000)	-0.900	(0.309)	-8.167	(0.000*)	11.085	(0.000*)	0.000	(1.000)
	Total Surface Area	-0.179	(NA)	0.180	(1.000)	-0.900	(0.214)	-2.882	(0.004*)	17.793	(0.000*)	10.387	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all schizophrenia participants (N=123, N=30 with cortical data).
Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 8. Environmental correlations between depression and global cortical measures with basic covariates.

		Environmental Correlations						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_E	*p*-value	R_E	*p*-value	R_E	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Global	Intracranial Volume	-0.304	(0.659)	-0.015	(0.956)	0.390	(0.436)	-2.095	(0.048*)	-3.774	(0.000*)	-5.395	(0.000*)
	Lateral Ventricle Volume	-0.883	(0.231)	-0.900	(NA)	0.282	(0.436)	0.568	(0.570)	-15.640	(0.000*)	-12.333	(0.000*)
	Mean Thickness	-0.287	(0.659)	0.347	(0.956)	-0.266	(0.436)	-4.561	(0.000*)	5.636	(0.000*)	-0.166	(0.868)
	Total Surface Area	0.900	(0.231)	0.101	(0.956)	-0.022	(0.926)	9.505	(0.000*)	1.092	(0.275)	10.963	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all depression participants (N=137, N=38 with cortical data).
Covariates included age, age^2, sex, site, and schizophrenia for all analyses.

Appendix Table 9. Environmental correlations between depression and global cortical measures with conservative covariates.

		Environmental Correlations						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_E	*p*-value	R_E	*p*-value	R_E	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Global	Intracranial Volume	-0.354	(0.555)	-0.156	(0.886)	0.328	(0.396)	-1.471	(0.188)	-4.418	(0.000*)	-5.210	(0.000*)
	Lateral Ventricle Volume	-0.570	(0.429)	-0.112	(0.886)	0.230	(0.396)	-3.706	(0.000*)	-3.082	(0.004*)	-6.471	(0.000*)
	Mean Thickness	-0.508	(0.394)	-0.548	(0.540)	-0.337	(0.566)	0.384	(0.701)	-2.346	(0.025*)	-1.533	(0.125)
	Total Surface Area	0.900	(0.394)	-0.063	(0.886)	-0.261	(0.396)	10.646	(0.000*)	1.812	(0.070)	12.764	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all depression participants (N=137, N=38 with cortical data).
Covariates included age, age^2, sex, site, and schizophrenia for all analyses.

Appendix Table 10. Comparisons of genetic effects on cortical thickness between age-risk periods, with basic covariates.

		Genetic Correlations Between Age-Risk Periods						Heritability × Age Interaction		
		Rise/Peak		Peak/Plateau		Rise/Plateau		Rise/Peak	Peak/Plateau	Rise/Plateau
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	*p-value*	*p-value*	*p-value*
Frontal	Frontal Pole	0.186	(NA)	-1.000	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
	Superior Frontal	0.677	(1.000)	-0.488	(1.000)	0.935	(1.000)	(0.911)	(0.974)	(1.000)
	Rostral Middle Frontal	1.000	(1.000)	-0.246	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)
	Caudal Middle Frontal	0.766	(1.000)	-0.536	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)
	Pars Opercularis	0.350	(1.000)	-1.000	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)
	Pars Triangularis	1.000	(1.000)	-0.110	(1.000)	1.000	(1.000)	(0.980)	(0.974)	(1.000)
	Pars Orbitalis	1.000	(1.000)	-0.250	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)
	Lateral Orbitofrontal	1.000	(1.000)	-0.450	(1.000)	0.916	(1.000)	(0.911)	(0.974)	(1.000)
	Medial Orbitofrontal	0.444	(1.000)	-0.186	(1.000)	0.429	(1.000)	(0.911)	(0.974)	(1.000)
	Precentral	1.000	(1.000)	-0.293	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)
	Paracentral	NA	(NA)	-0.805	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
Parietal	Superior Parietal	0.444	(NA)	0.121	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
	Inferior Parietal	0.165	(1.000)	0.603	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)
	Supramarginal	-0.260	(1.000)	0.138	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)
	Postcentral	0.192	(NA)	0.324	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
	Precuneus	1.000	(NA)	0.598	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
Temporal	Superior Temporal	-1.000	(1.000)	0.647	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)
	Superior Temporal Sulcus	1.000	(1.000)	1.000	(1.000)	0.907	(1.000)	(0.911)	(0.974)	(1.000)
	Middle Temporal	-1.000	(1.000)	-0.163	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)
	Inferior Temporal	0.086	(1.000)	-1.000	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)
	Fusiform	0.310	(1.000)	-1.000	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)
	Transverse Temporal	0.100	(NA)	-1.000	(NA)	0.709	(NA)	(NA)	(NA)	(NA)
	Entorhinal	0.123	(1.000)	-0.437	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)
	Temporal Pole	0.120	(NA)	-0.240	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
	Parahippocampal	-0.079	(1.000)	0.216	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)
Occipital	Lateral Occipital	1.000	(NA)	0.142	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
	Lingual	0.473	(1.000)	0.442	(1.000)	0.707	(1.000)	(0.980)	(0.974)	(1.000)
	Cuneus	1.000	(NA)	-0.486	(NA)	0.775	(NA)	(NA)	(NA)	(NA)
	Pericalcarine	0.338	(NA)	1.000	(NA)	0.964	(NA)	(NA)	(NA)	(NA)
Cingulate	Rostral Anterior Cingulate	0.378	(1.000)	-0.808	(1.000)	0.853	(1.000)	(0.911)	(0.974)	(1.000)
	Caudal Anterior Cingulate	0.354	(NA)	0.279	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
	Posterior Cingulate	1.000	(1.000)	0.454	(1.000)	0.789	(1.000)	(0.911)	(0.974)	(1.000)
	Isthmus Cingulate	1.000	(1.000)	1.000	(1.000)	0.032	(1.000)	(0.911)	(0.974)	(1.000)
	Insula	1.000	(1.000)	-0.669	(1.000)	1.000	(1.000)	(0.911)	(0.974)	(1.000)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted excluding all schizophrenia participants (N=123, N=30 with cortical data). Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 11. Phenotypic correlations between schizophrenia and cortical thickness with basic covariates.

		Phenotypic Correlations Within Age-Risk Periods						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_P	*p*-value	R_P	*p*-value	R_P	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	0.518	(NA)	0.073	(NA)	0.042	(NA)	3.966	(NA)	0.328	(NA)	4.279	(NA)
	Superior Frontal	-0.353	(0.746)	-0.431	(0.000*)	-0.263	(NA)	0.733	(0.533)	-2.074	(0.097)	-0.802	(0.540)
	Rostral Middle Frontal	-0.066	(0.899)	-0.458	(NA)	-0.227	(0.013*)	3.404	(0.002*)	-2.856	(0.020*)	1.331	(0.281)
	Caudal Middle Frontal	-0.311	(0.799)	-0.478	(0.005*)	-0.239	(0.007*)	1.574	(0.156)	-2.988	(0.016*)	-0.628	(0.618)
	Pars Opercularis	-0.763	(0.010*)	-0.641	(0.000*)	-0.403	(0.000*)	-1.924	(0.083)	-3.595	(0.007*)	-4.639	(0.000*)
	Pars Triangularis	-0.357	(0.799)	-0.476	(0.005*)	-0.291	(0.006*)	1.145	(0.305)	-2.352	(0.061)	-0.590	(0.618)
	Pars Orbitalis	0.152	(0.746)	-0.220	(NA)	-0.248	(0.013*)	2.991	(0.006*)	0.313	(0.799)	3.275	(0.002*)
	Lateral Orbitofrontal	0.003	(1.000)	-0.178	(0.088)	-0.256	(0.017*)	1.449	(0.188)	0.883	(0.510)	2.132	(0.058)
	Medial Orbitofrontal	0.469	(0.570)	-0.177	(0.151)	-0.138	(0.173)	5.451	(0.000*)	-0.434	(0.764)	5.220	(0.000*)
	Precentral	0.053	(1.000)	-0.168	(NA)	-0.232	(0.018*)	1.764	(0.112)	0.722	(0.569)	2.333	(0.041*)
	Paracentral	0.063	(NA)	-0.119	(NA)	0.044	(NA)	1.446	(NA)	-1.767	(NA)	0.153	(NA)
Parietal	Superior Parietal	0.007	(NA)	-0.109	(NA)	-0.128	(NA)	0.923	(NA)	0.214	(NA)	1.099	(NA)
	Inferior Parietal	0.392	(0.899)	-0.233	(0.036*)	-0.241	(0.012*)	5.169	(0.000*)	0.090	(0.928)	5.324	(0.000*)
	Supramarginal	-0.048	(1.000)	-0.486	(0.005*)	-0.216	(0.025*)	3.830	(0.000*)	-3.370	(0.009*)	1.382	(0.274)
	Postcentral	0.411	(NA)	-0.222	(NA)	-0.134	(NA)	5.256	(NA)	-0.986	(NA)	4.609	(NA)
	Precuneus	-0.152	(NA)	-0.149	(NA)	-0.143	(NA)	-0.022	(NA)	-0.071	(NA)	-0.076	(NA)
Temporal	Superior Temporal	-0.105	(0.799)	-0.429	(0.006*)	-0.175	(0.052)	2.805	(0.010*)	-3.052	(0.016*)	0.576	(0.618)
	Superior Temporal Sulcus	-0.168	(1.000)	-0.441	(0.000*)	-0.294	(0.003*)	2.411	(0.028*)	-1.850	(0.135)	1.072	(0.408)
	Middle Temporal	0.183	(0.837)	-0.394	(NA)	-0.269	(0.006*)	4.771	(0.000*)	-1.525	(0.244)	3.715	(0.001*)
	Inferior Temporal	0.326	(1.000)	-0.502	(NA)	-0.357	(0.006*)	7.060	(0.000*)	-1.930	(0.123)	5.741	(0.000*)
	Fusiform	0.373	(1.000)	-0.461	(0.005*)	-0.376	(0.000*)	7.061	(0.000*)	-1.120	(0.431)	6.345	(0.000*)
	Transverse Temporal	-0.426	(NA)	-0.370	(NA)	-0.049	(NA)	-0.521	(NA)	-3.675	(NA)	-3.272	(NA)
	Entorhinal	-0.329	(0.440)	-0.262	(0.028*)	-0.236	(0.025*)	-0.585	(0.601)	-0.299	(0.799)	-0.818	(0.540)
	Temporal Pole	0.431	(NA)	-0.179	(NA)	-0.234	(NA)	5.088	(NA)	0.625	(NA)	5.641	(NA)
	Parahippocampal	0.177	(0.899)	-0.112	(0.463)	-0.335	(0.006*)	2.307	(0.035*)	2.547	(0.042*)	4.247	(0.000*)
Occipital	Lateral Occipital	0.201	(NA)	-0.191	(NA)	-0.091	(NA)	3.151	(NA)	-1.102	(NA)	2.383	(NA)
	Lingual	-0.290	(1.000)	-0.224	(0.088)	-0.290	(0.009*)	-0.560	(0.601)	0.760	(0.569)	-0.003	(0.998)
	Cuneus	-0.471	(NA)	-0.126	(NA)	-0.002	(NA)	-3.042	(NA)	-1.356	(NA)	-4.106	(NA)
	Pericalcarine	-0.688	(NA)	0.049	(NA)	0.117	(NA)	-7.081	(NA)	-0.742	(NA)	-7.756	(NA)
Cingulate	Rostral Anterior Cingulate	0.428	(0.746)	-0.103	(NA)	-0.185	(0.066)	4.443	(0.000*)	0.898	(0.510)	5.189	(0.000*)
	Caudal Anterior Cingulate	0.014	(NA)	-0.096	(NA)	-0.180	(NA)	0.874	(NA)	0.929	(NA)	1.582	(NA)
	Posterior Cingulate	-0.238	(0.067)	-0.292	(0.040*)	-0.208	(0.020*)	0.462	(0.644)	-0.969	(0.510)	-0.253	(0.837)
	Isthmus Cingulate	0.479	(0.440)	-0.334	(0.028*)	-0.136	(0.172)	6.890	(0.000*)	-2.268	(0.067)	5.315	(0.000*)
	Insula	0.066	(0.899)	-0.302	(0.008*)	-0.198	(0.052)	2.996	(0.006*)	-1.204	(0.405)	2.149	(0.058)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all schizophrenia participants (N=123, N=30 with cortical data).
Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 12. Phenotypic correlations between schizophrenia and cortical thickness with conservative covariates.

		Phenotypic Correlations Within Age-Risk Periods						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_P	*p*-value	R_P	*p*-value	R_P	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	0.367	(NA)	0.114	(NA)	0.050	(NA)	2.144	(NA)	0.694	(NA)	2.696	(NA)
	Superior Frontal	-0.450	(0.447)	-0.369	(0.002*)	-0.223	(0.039*)	-0.778	(0.591)	-1.723	(0.195)	-2.079	(0.072)
	Rostral Middle Frontal	-0.169	(0.502)	-0.351	(NA)	-0.181	(0.089)	1.552	(0.198)	-1.977	(0.158)	0.097	(0.965)
	Caudal Middle Frontal	-0.289	(0.502)	-0.339	(0.002*)	-0.175	(0.089)	0.447	(0.723)	-1.903	(0.158)	-0.970	(0.449)
	Pars Opercularis	-0.732	(0.012*)	-0.568	(0.000*)	-0.377	(0.003*)	-2.288	(0.057)	-2.667	(0.059)	-4.319	(0.000*)
	Pars Triangularis	-0.504	(0.447)	-0.461	(0.009*)	-0.276	(0.012*)	-0.440	(0.723)	-2.316	(0.079)	-2.180	(0.067)
	Pars Orbitalis	-0.050	(0.980)	-0.137	(0.436)	-0.218	(0.044*)	0.690	(0.626)	0.904	(0.495)	1.377	(0.258)
	Lateral Orbitofrontal	-0.156	(0.980)	-0.163	(0.182)	-0.290	(0.014*)	0.060	(0.952)	1.447	(0.257)	1.144	(0.363)
	Medial Orbitofrontal	0.173	(0.447)	-0.169	(0.219)	-0.164	(0.115)	2.736	(0.023*)	-0.052	(0.958)	2.739	(0.018*)
	Precentral	0.083	(0.980)	-0.032	(0.581)	-0.156	(0.120)	0.919	(0.515)	1.347	(0.273)	1.941	(0.092)
	Paracentral	0.029	(NA)	-0.010	(NA)	0.041	(NA)	0.312	(NA)	-0.550	(NA)	-0.095	(NA)
Parietal	Superior Parietal	0.115	(NA)	0.048	(NA)	-0.067	(NA)	0.530	(NA)	1.242	(NA)	1.467	(NA)
	Inferior Parietal	0.232	(0.980)	-0.098	(0.226)	-0.157	(0.089)	2.645	(0.023*)	0.646	(0.596)	3.170	(0.005*)
	Supramarginal	-0.155	(0.522)	-0.374	(0.002*)	-0.154	(0.120)	1.878	(0.111)	-2.557	(0.061)	-0.005	(0.996)
	Postcentral	0.336	(NA)	-0.076	(NA)	-0.060	(NA)	3.369	(NA)	-0.169	(NA)	3.295	(NA)
	Precuneus	-0.118	(NA)	-0.191	(NA)	-0.108	(NA)	0.590	(NA)	-0.909	(NA)	-0.080	(NA)
Temporal	Superior Temporal	-0.191	(0.447)	-0.344	(0.077)	-0.137	(0.221)	1.313	(0.290)	-2.376	(0.079)	-0.444	(0.720)
	Superior Temporal Sulcus	-0.171	(1.000)	-0.396	(0.000*)	-0.279	(0.005*)	1.953	(0.106)	-1.417	(0.257)	0.922	(0.455)
	Middle Temporal	0.035	(1.000)	-0.326	(NA)	-0.225	(0.038*)	2.953	(0.014*)	-1.173	(0.346)	2.121	(0.071)
	Inferior Temporal	0.184	(0.817)	-0.387	(NA)	-0.317	(0.003*)	4.715	(0.000*)	-0.858	(0.499)	4.146	(0.000*)
	Fusiform	0.204	(0.817)	-0.320	(0.016*)	-0.384	(0.001*)	4.263	(0.000*)	0.781	(0.526)	4.914	(0.000*)
	Transverse Temporal	-0.457	(NA)	-0.248	(NA)	0.012	(NA)	-1.902	(NA)	-2.855	(NA)	-4.067	(NA)
	Entorhinal	-0.464	(0.308)	-0.233	(0.081)	-0.224	(0.089)	-2.091	(0.084)	-0.108	(0.956)	-2.205	(0.067)
	Temporal Pole	0.007	(NA)	-0.203	(NA)	-0.236	(NA)	1.692	(NA)	0.374	(NA)	1.999	(NA)
	Parahippocampal	0.107	(0.817)	-0.127	(0.436)	-0.359	(0.001*)	1.862	(0.111)	2.668	(0.059)	3.887	(0.000*)
Occipital	Lateral Occipital	-0.396	(NA)	-0.133	(NA)	-0.048	(NA)	-2.253	(NA)	-0.925	(NA)	-2.980	(NA)
	Lingual	-0.152	(0.817)	-0.072	(0.581)	-0.241	(0.038*)	-0.639	(0.633)	1.866	(0.158)	0.747	(0.523)
	Cuneus	-0.062	(NA)	0.025	(NA)	0.006	(NA)	-0.693	(NA)	0.212	(NA)	-0.545	(NA)
	Pericalcarine	-0.737	(NA)	0.140	(NA)	0.162	(NA)	-8.585	(NA)	-0.246	(NA)	-8.903	(NA)
Cingulate	Rostral Anterior Cingulate	0.244	(0.817)	-0.219	(0.216)	-0.242	(0.037*)	3.736	(0.001*)	0.264	(0.867)	3.991	(0.000*)
	Caudal Anterior Cingulate	-0.188	(NA)	-0.227	(NA)	-0.242	(NA)	0.318	(NA)	0.173	(NA)	0.453	(NA)
	Posterior Cingulate	-0.276	(0.012*)	-0.317	(0.081)	-0.179	(0.089)	0.363	(0.749)	-1.590	(0.234)	-0.821	(0.498)
	Isthmus Cingulate	0.347	(0.817)	-0.450	(NA)	-0.213	(0.052)	6.712	(0.000*)	-2.891	(0.059)	4.653	(0.000*)
	Insula	-0.003	(1.000)	-0.327	(0.059)	-0.203	(0.089)	2.663	(0.023*)	-1.440	(0.257)	1.627	(0.170)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all schizophrenia participants (N=123, N=30 with cortical data).
Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 13. Phenotypic correlations between depression and cortical thickness with basic covariates.

		Phenotypic Correlations Within Age-Risk Periods						Proportion of Phenotypic Covariance					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_P	*p*-value	R_P	*p*-value	R_P	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	-0.373	(NA)	-0.082	(NA)	-0.122	(NA)	-2.147	(NA)	0.357	(NA)	-1.977	(NA)
	Superior Frontal	-0.228	(NA)	0.062	(1.000)	-0.063	(0.635)	-2.044	(0.172)	1.117	(0.497)	-1.239	(0.723)
	Rostral Middle Frontal	-0.124	(0.366)	0.058	(1.000)	-0.092	(0.517)	-1.265	(0.364)	1.331	(0.497)	-0.238	(0.891)
	Caudal Middle Frontal	-0.116	(0.366)	0.069	(1.000)	-0.084	(0.517)	-1.288	(0.364)	1.363	(0.497)	-0.236	(0.891)
	Pars Opercularis	-0.348	(NA)	-0.099	(1.000)	-0.171	(0.256)	-1.832	(0.220)	0.650	(0.624)	-1.401	(0.723)
	Pars Triangularis	-0.177	(0.407)	-0.035	(1.000)	-0.169	(0.309)	-0.999	(0.457)	1.199	(0.497)	-0.066	(0.951)
	Pars Orbitalis	-0.226	(0.366)	0.002	(1.000)	-0.117	(0.351)	-1.611	(0.274)	1.063	(0.497)	-0.826	(0.723)
	Lateral Orbitofrontal	-0.146	(0.459)	-0.070	(1.000)	-0.188	(0.256)	-0.535	(0.649)	1.066	(0.497)	0.315	(0.891)
	Medial Orbitofrontal	-0.330	(0.277)	-0.110	(1.000)	-0.237	(0.219)	-1.615	(0.274)	1.165	(0.497)	-0.746	(0.748)
	Precentral	-0.107	(0.378)	-0.021	(1.000)	0.023	(0.874)	-0.600	(0.631)	-0.390	(0.801)	-0.957	(0.723)
	Paracentral	-0.142	(NA)	0.011	(NA)	-0.087	(NA)	-1.068	(NA)	0.869	(NA)	-0.412	(NA)
Parietal	Superior Parietal	-0.168	(NA)	0.178	(NA)	0.113	(NA)	-2.421	(NA)	0.585	(NA)	-2.078	(NA)
	Inferior Parietal	-0.285	(0.366)	0.054	(1.000)	-0.073	(0.601)	-2.408	(0.172)	1.124	(0.497)	-1.619	(0.723)
	Supramarginal	-0.079	(0.686)	0.026	(1.000)	-0.160	(0.312)	-0.733	(0.592)	1.665	(0.497)	0.601	(0.840)
	Postcentral	-0.011	(NA)	0.102	(NA)	0.058	(NA)	-0.786	(NA)	0.392	(NA)	-0.508	(NA)
	Precuneus	-0.333	(NA)	0.050	(NA)	0.008	(NA)	-2.746	(NA)	0.372	(NA)	-2.598	(NA)
Temporal	Superior Temporal	-0.131	(0.492)	0.004	(1.000)	-0.086	(0.517)	-0.937	(0.472)	0.800	(0.591)	-0.330	(0.891)
	Superior Temporal Sulcus	-0.198	(0.366)	0.089	(1.000)	-0.034	(0.856)	-2.006	(0.172)	1.094	(0.497)	-1.218	(0.723)
	Middle Temporal	-0.138	(0.476)	0.059	(1.000)	-0.024	(0.874)	-1.373	(0.355)	0.737	(0.591)	-0.844	(0.723)
	Inferior Temporal	-0.365	(0.277)	-0.039	(1.000)	-0.033	(0.856)	-2.381	(0.172)	-0.054	(0.957)	-2.565	(0.237)
	Fusiform	-0.325	(0.277)	-0.032	(1.000)	-0.147	(0.331)	-2.120	(0.172)	1.031	(0.497)	-1.391	(0.723)
	Transverse Temporal	-0.107	(NA)	-0.012	(NA)	-0.023	(NA)	-0.660	(NA)	0.098	(NA)	-0.617	(NA)
	Entorhinal	0.115	(0.366)	0.107	(1.000)	-0.013	(0.923)	0.055	(0.956)	1.066	(0.497)	0.940	(0.723)
	Temporal Pole	-0.407	(NA)	-0.163	(NA)	-0.147	(NA)	-1.857	(NA)	-0.145	(NA)	-2.085	(NA)
	Parahippocampal	-0.307	(0.299)	-0.159	(1.000)	-0.178	(0.219)	-1.092	(0.422)	0.180	(0.905)	-1.006	(0.723)
Occipital	Lateral Occipital	-0.154	(NA)	0.095	(NA)	-0.045	(NA)	-1.741	(NA)	1.243	(NA)	-0.815	(NA)
	Lingual	-0.313	(0.277)	-0.111	(1.000)	-0.257	(NA)	-1.473	(0.324)	1.343	(0.497)	-0.448	(0.885)
	Cuneus	-0.345	(NA)	-0.008	(NA)	0.075	(NA)	-2.439	(NA)	-0.741	(NA)	-3.194	(NA)
	Pericalcarine	-0.228	(NA)	-0.042	(NA)	-0.026	(NA)	-1.312	(NA)	-0.144	(NA)	-1.507	(NA)
Cingulate	Rostral Anterior Cingulate	-0.161	(0.407)	-0.138	(1.000)	-0.275	(0.201)	-0.165	(0.908)	1.279	(0.497)	0.883	(0.723)
	Caudal Anterior Cingulate	-0.155	(NA)	0.018	(NA)	0.092	(NA)	-1.210	(NA)	-0.663	(NA)	-1.829	(NA)
	Posterior Cingulate	-0.302	(0.277)	-0.019	(1.000)	0.000	(1.000)	-2.031	(0.172)	-0.169	(0.905)	-2.289	(0.254)
	Isthmus Cingulate	-0.237	(0.366)	-0.070	(1.000)	-0.168	(0.309)	-1.185	(0.388)	0.877	(0.584)	-0.529	(0.858)
	Insula	-0.237	(0.277)	-0.149	(1.000)	-0.229	(0.219)	-0.632	(0.631)	0.735	(0.591)	-0.061	(0.951)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all depression participants (N=137, N=38 with cortical data).
Covariates included age, age^2, sex, site, and schizophrenia for all analyses.

Appendix Table 14. Phenotypic correlations between depression and cortical thickness with conservative covariates.

		Phenotypic Correlations Within Age-Risk Periods						Proportion of Phenotypic Covariance					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_P	*p*-value	R_P	*p*-value	R_P	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	-0.431	(NA)	-0.145	(NA)	-0.104	(NA)	-2.182	(NA)	-0.367	(NA)	-2.613	(NA)
	Superior Frontal	-0.197	(0.332)	0.035	(0.973)	-0.035	(0.848)	-1.630	(0.329)	0.622	(0.927)	-1.211	(0.520)
	Rostral Middle Frontal	-0.201	(0.332)	0.031	(1.000)	-0.067	(0.745)	-1.624	(0.329)	0.866	(0.927)	-1.003	(0.606)
	Caudal Middle Frontal	-0.112	(0.400)	0.070	(1.000)	-0.071	(0.722)	-1.272	(0.390)	1.261	(0.927)	-0.303	(0.874)
	Pars Opercularis	-0.156	(0.351)	-0.112	(0.825)	-0.162	(0.369)	-0.313	(0.826)	0.458	(0.927)	0.047	(0.962)
	Pars Triangularis	-0.229	(0.332)	-0.073	(0.887)	-0.144	(0.431)	-1.111	(0.440)	0.642	(0.927)	-0.646	(0.745)
	Pars Orbitalis	-0.258	(0.274)	-0.055	(0.901)	-0.096	(0.542)	-1.454	(0.336)	0.365	(0.927)	-1.236	(0.520)
	Lateral Orbitofrontal	-0.194	(0.332)	-0.114	(0.825)	-0.145	(0.431)	-0.570	(0.654)	0.275	(0.927)	-0.375	(0.857)
	Medial Orbitofrontal	-0.341	(0.274)	-0.136	(0.825)	-0.228	(0.255)	-1.519	(0.329)	0.852	(0.927)	-0.903	(0.648)
	Precentral	-0.173	(0.332)	-0.031	(0.971)	0.045	(0.848)	-0.998	(0.440)	-0.678	(0.927)	-1.617	(0.406)
	Paracentral	-0.140	(NA)	-0.018	(NA)	-0.056	(NA)	-0.847	(NA)	0.338	(NA)	-0.617	(NA)
Parietal	Superior Parietal	-0.226	(NA)	0.126	(NA)	0.118	(NA)	-2.470	(NA)	0.073	(NA)	-2.554	(NA)
	Inferior Parietal	-0.372	(0.274)	-0.012	(0.973)	-0.046	(0.848)	-2.625	(0.100)	0.304	(0.927)	-2.527	(0.132)
	Supramarginal	-0.159	(0.376)	-0.020	(0.973)	-0.124	(0.532)	-0.972	(0.440)	0.934	(0.927)	-0.256	(0.874)
	Postcentral	-0.007	(NA)	0.092	(NA)	0.064	(NA)	-0.689	(NA)	0.248	(NA)	-0.524	(NA)
	Precuneus	-0.412	(NA)	0.033	(NA)	0.017	(NA)	-3.270	(NA)	0.139	(NA)	-3.346	(NA)
Temporal	Superior Temporal	-0.189	(0.351)	-0.055	(0.901)	-0.049	(0.848)	-0.945	(0.440)	-0.049	(0.961)	-1.041	(0.606)
	Superior Temporal Sulcus	-0.187	(0.351)	0.088	(0.887)	-0.022	(0.885)	-1.928	(0.309)	0.981	(0.927)	-1.229	(0.520)
	Middle Temporal	-0.237	(0.330)	0.023	(0.973)	0.002	(0.991)	-1.831	(0.309)	0.181	(0.938)	-1.788	(0.339)
	Inferior Temporal	-0.491	(0.121)	-0.087	(0.874)	-0.001	(0.991)	-3.123	(0.041*)	-0.768	(0.927)	-3.940	(0.002*)
	Fusiform	-0.351	(0.274)	-0.050	(0.901)	-0.108	(0.556)	-2.194	(0.216)	0.514	(0.927)	-1.897	(0.332)
	Transverse Temporal	-0.126	(NA)	-0.001	(NA)	-0.017	(NA)	-0.872	(NA)	0.143	(NA)	-0.804	(NA)
	Entorhinal	0.056	(0.553)	0.060	(0.901)	0.032	(0.848)	-0.027	(0.979)	0.245	(0.927)	0.175	(0.900)
	Temporal Pole	-0.443	(NA)	-0.211	(NA)	-0.104	(NA)	-1.811	(NA)	-0.977	(NA)	-2.724	(NA)
	Parahippocampal	-0.331	(0.296)	-0.188	(0.825)	-0.176	(0.387)	-1.063	(0.440)	-0.110	(0.954)	-1.215	(0.520)
Occipital	Lateral Occipital	-0.239	(NA)	0.043	(NA)	-0.023	(NA)	-1.991	(NA)	0.593	(NA)	-1.617	(NA)
	Lingual	-0.303	(0.296)	-0.112	(0.874)	-0.255	(0.119)	-1.389	(0.345)	1.311	(0.927)	-0.385	(0.857)
	Cuneus	-0.467	(NA)	-0.027	(NA)	0.093	(NA)	-3.329	(NA)	-1.070	(NA)	-4.407	(NA)
	Pericalcarine	-0.271	(NA)	-0.048	(NA)	-0.014	(NA)	-1.594	(NA)	-0.303	(NA)	-1.938	(NA)
Cingulate	Rostral Anterior Cingulate	-0.144	(0.400)	-0.151	(0.825)	-0.251	(0.096)	0.053	(0.979)	0.927	(0.927)	0.823	(0.675)
	Caudal Anterior Cingulate	-0.259	(NA)	-0.055	(NA)	0.131	(NA)	-1.457	(NA)	-1.660	(NA)	-2.915	(NA)
	Posterior Cingulate	-0.265	(0.296)	-0.046	(0.901)	0.025	(0.885)	-1.561	(0.329)	-0.633	(0.927)	-2.176	(0.227)
	Isthmus Cingulate	-0.247	(0.332)	-0.101	(0.840)	-0.151	(0.431)	-1.045	(0.440)	0.455	(0.927)	-0.730	(0.714)
	Insula	-0.266	(0.330)	-0.157	(0.825)	-0.202	(0.324)	-0.791	(0.519)	0.413	(0.927)	-0.496	(0.839)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all depression participants (N=137, N=38 with cortical data).
Covariates included age, age^2, sex, site, and schizophrenia for all analyses.

Appendix Table 15. Environmental correlations between schizophrenia and cortical thickness with basic covariates.

		Environmental Correlations						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_E	*p*-value	R_E	*p*-value	R_E	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	0.900	(NA)	-0.625	(NA)	-0.861	(NA)	17.479	(NA)	6.086	(NA)	22.318	(NA)
	Superior Frontal	-0.900	(0.770)	-1.000	(0.036*)	-0.900	(NA)	54.970	(0.000*)	-74.932	(0.000*)	0.001	(1.000)
	Rostral Middle Frontal	-0.900	(0.770)	-0.900	(NA)	-1.000	(0.014*)	0.000	(1.000)	74.932	(0.000*)	55.908	(0.000*)
	Caudal Middle Frontal	-0.900	(0.770)	-1.000	(0.060)	-0.900	(0.028*)	54.970	(0.000*)	-74.931	(0.000*)	0.001	(1.000)
	Pars Opercularis	-1.000	(0.770)	-0.900	(0.177)	-0.900	(0.014*)	-54.970	(0.000*)	0.001	(1.000)	-55.907	(0.000*)
	Pars Triangularis	-0.389	(0.821)	-0.900	(0.122)	-0.900	(0.257)	8.420	(0.000*)	-0.008	(1.000)	8.557	(0.000*)
	Pars Orbitalis	-0.900	(0.821)	-0.900	(NA)	-0.900	(0.257)	0.001	(1.000)	-0.002	(1.000)	0.000	(1.000)
	Lateral Orbitofrontal	0.015	(0.978)	-0.900	(0.241)	-0.850	(0.358)	11.789	(0.000*)	-2.343	(0.031*)	10.243	(0.000*)
	Medial Orbitofrontal	0.900	(0.868)	-0.690	(0.454)	-0.012	(0.987)	18.411	(0.000*)	-9.036	(0.000*)	11.983	(0.000*)
	Precentral	-0.811	(0.868)	-0.900	(NA)	-0.900	(0.106)	2.712	(0.009*)	0.000	(1.000)	2.758	(0.008*)
	Paracentral	0.403	(NA)	-0.775	(NA)	-0.900	(NA)	11.581	(NA)	4.745	(NA)	15.318	(NA)
Parietal	Superior Parietal	0.021	(NA)	-0.900	(NA)	-0.900	(NA)	11.839	(NA)	0.000	(NA)	12.041	(NA)
	Inferior Parietal	-1.000	(0.770)	-0.900	(0.122)	-1.000	(0.014*)	-54.970	(0.000*)	74.933	(0.000*)	0.000	(1.000)
	Supramarginal	-0.900	(0.821)	-0.900	(0.454)	-0.900	(0.106)	0.000	(1.000)	0.000	(1.000)	0.000	(1.000)
	Postcentral	-0.360	(NA)	-0.497	(NA)	-0.900	(NA)	1.339	(NA)	10.018	(NA)	8.836	(NA)
	Precuneus	-0.811	(NA)	-0.202	(NA)	-0.480	(NA)	-7.342	(NA)	3.446	(NA)	-4.897	(NA)
Temporal	Superior Temporal	-0.639	(0.868)	-0.900	(0.102)	-0.900	(0.151)	5.674	(0.000*)	0.000	(1.000)	5.771	(0.000*)
	Superior Temporal Sulcus	-0.900	(0.770)	-1.000	(0.102)	-0.900	(0.014*)	54.970	(0.000*)	-74.932	(0.000*)	0.000	(1.000)
	Middle Temporal	-0.900	(0.770)	-1.000	(NA)	-1.000	(0.027*)	54.970	(0.000*)	0.000	(1.000)	55.908	(0.000*)
	Inferior Temporal	-0.900	(0.821)	-0.900	(NA)	-1.000	(0.039*)	0.000	(1.000)	74.933	(0.000*)	55.908	(0.000*)
	Fusiform	-0.900	(0.770)	-1.000	(0.153)	-0.900	(0.062)	54.970	(0.000*)	-74.933	(0.000*)	0.000	(1.000)
	Transverse Temporal	-0.900	(NA)	-0.900	(NA)	-0.900	(NA)	0.000	(NA)	0.000	(NA)	0.000	(NA)
	Entorhinal	-0.900	(0.770)	-0.118	(0.901)	-0.021	(0.987)	-10.735	(0.000*)	-1.051	(0.449)	-11.703	(0.000*)
	Temporal Pole	-1.000	(NA)	-1.000	(NA)	-0.856	(NA)	0.000	(NA)	-77.013	(NA)	-57.460	(NA)
	Parahippocampal	-0.900	(0.868)	0.900	(0.607)	-0.589	(0.852)	NA	(0.000*)	23.225	(0.000*)	-6.414	(0.000*)
Occipital	Lateral Occipital	-0.900	(NA)	-1.000	(NA)	-0.900	(NA)	54.970	(NA)	-74.933	(NA)	0.000	(NA)
	Lingual	0.900	(0.821)	0.725	(0.757)	-0.840	(0.606)	4.397	(0.000*)	23.129	(0.000*)	21.728	(0.000*)
	Cuneus	-0.246	(NA)	-0.707	(NA)	-0.002	(NA)	4.996	(NA)	-9.506	(NA)	-2.011	(NA)
	Pericalcarine	-0.950	(NA)	0.247	(NA)	-0.900	(NA)	-16.539	(NA)	18.639	(NA)	-2.915	(NA)
Cingulate	Rostral Anterior Cingulate	-0.900	(0.770)	-0.900	(NA)	-0.270	(0.852)	0.000	(1.000)	-12.919	(0.000*)	-9.639	(0.000*)
	Caudal Anterior Cingulate	-0.900	(NA)	-0.900	(NA)	-0.656	(NA)	0.000	(NA)	-7.418	(NA)	-5.535	(NA)
	Posterior Cingulate	-1.000	(0.770)	-0.900	(0.262)	-0.900	(0.062)	-54.970	(0.000*)	0.000	(1.000)	-55.908	(0.000*)
	Isthmus Cingulate	0.900	(0.821)	0.900	(0.449)	-0.491	(0.612)	0.000	(1.000)	21.720	(0.000*)	16.206	(0.000*)
	Insula	0.383	(0.821)	-0.900	(0.449)	-0.157	(0.947)	14.875	(0.000*)	-14.204	(0.000*)	4.531	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all schizophrenia participants (N=123, N=30 with cortical data).
Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 16. Environmental correlations between schizophrenia and cortical thickness with conservative covariates.

		Environmental Correlations						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_E	*p*-value	R_E	*p*-value	R_E	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	0.900	(NA)	-0.600	(NA)	0.299	(NA)	17.155	(NA)	-10.769	(NA)	9.364	(NA)
	Superior Frontal	-0.900	(0.783)	-1.000	(0.013*)	-1.000	(0.234)	54.934	(0.000*)	0.000	(1.000)	55.789	(0.000*)
	Rostral Middle Frontal	-0.895	(0.783)	-0.900	(NA)	-0.900	(0.376)	0.197	(1.000)	-0.001	(1.000)	0.200	(1.000)
	Caudal Middle Frontal	-0.900	(0.783)	-1.000	(0.013*)	-1.000	(0.290)	54.934	(0.000*)	0.000	(1.000)	55.789	(0.000*)
	Pars Opercularis	-0.900	(0.800)	-1.000	(0.025*)	-1.000	(0.055)	54.933	(0.000*)	0.000	(1.000)	55.788	(0.000*)
	Pars Triangularis	-0.539	(1.000)	-0.900	(0.127)	-0.829	(0.709)	6.894	(0.000*)	-3.076	(0.004*)	4.699	(0.000*)
	Pars Orbitalis	-0.900	(0.783)	-0.900	(0.734)	-0.146	(0.963)	0.000	(1.000)	-14.256	(0.000*)	-10.667	(0.000*)
	Lateral Orbitofrontal	-0.900	(0.783)	-0.900	(0.399)	-0.483	(0.709)	0.000	(1.000)	-10.160	(0.000*)	-7.603	(0.000*)
	Medial Orbitofrontal	0.900	(0.783)	-0.900	(0.407)	0.211	(0.963)	23.334	(0.000*)	-18.133	(0.000*)	10.129	(0.000*)
	Precentral	-0.533	(0.800)	-0.900	(0.151)	-0.782	(0.643)	6.957	(0.000*)	-4.532	(0.000*)	3.674	(0.000*)
	Paracentral	0.900	(NA)	-0.874	(NA)	-0.706	(NA)	22.348	(NA)	-5.051	(NA)	18.916	(NA)
Parietal	Superior Parietal	0.671	(NA)	-0.900	(NA)	-0.900	(NA)	18.099	(NA)	0.000	(NA)	18.380	(NA)
	Inferior Parietal	-0.900	(0.783)	-0.900	(0.127)	-0.900	(0.238)	0.000	(1.000)	0.000	(1.000)	0.000	(1.000)
	Supramarginal	-0.533	(0.783)	-0.900	(0.249)	-0.900	(0.643)	6.950	(0.000*)	0.000	(1.000)	7.059	(0.000*)
	Postcentral	-0.426	(NA)	-0.549	(NA)	-0.529	(NA)	1.278	(NA)	-0.298	(NA)	1.076	(NA)
	Precuneus	-0.678	(NA)	-0.900	(NA)	-0.900	(NA)	5.128	(NA)	0.000	(NA)	5.207	(NA)
Temporal	Superior Temporal	-0.363	(0.902)	-0.900	(0.205)	-0.873	(0.709)	8.648	(0.000*)	-1.345	(0.316)	7.776	(0.000*)
	Superior Temporal Sulcus	-0.900	(0.783)	-1.000	(0.082)	-0.900	(0.084)	54.931	(0.000*)	-74.558	(0.000*)	-0.003	(1.000)
	Middle Temporal	-0.900	(0.783)	-1.000	(NA)	-0.900	(0.356)	54.934	(0.000*)	-74.558	(0.000*)	0.000	(1.000)
	Inferior Temporal	-0.900	(0.813)	-0.900	(NA)	-0.900	(0.129)	0.000	(1.000)	0.000	(1.000)	0.000	(1.000)
	Fusiform	-0.900	(0.783)	-0.900	(0.031*)	-0.900	(0.290)	0.000	(1.000)	0.000	(1.000)	0.000	(1.000)
	Transverse Temporal	-0.900	(NA)	-0.900	(NA)	-0.190	(NA)	0.000	(NA)	-13.761	(NA)	-10.297	(NA)
	Entorhinal	-0.900	(0.783)	-0.128	(0.940)	0.257	(0.798)	-10.647	(0.000*)	-4.216	(0.000*)	-13.967	(0.000*)
	Temporal Pole	-1.000	(NA)	-0.900	(NA)	-0.548	(NA)	-54.934	(NA)	-9.213	(NA)	-62.683	(NA)
	Parahippocampal	-0.768	(0.978)	0.900	(0.674)	-0.460	(0.742)	-19.716	(0.000*)	21.178	(0.000*)	-4.177	(0.000*)
Occipital	Lateral Occipital	-0.900	(NA)	-1.000	(NA)	-0.900	(NA)	54.934	(NA)	-74.558	(NA)	0.000	(NA)
	Lingual	0.900	(0.800)	0.001	(0.994)	-0.097	(0.963)	11.658	(0.000*)	1.052	(0.481)	12.626	(0.000*)
	Cuneus	-0.359	(NA)	-0.900	(NA)	-0.900	(NA)	8.687	(NA)	0.001	(NA)	8.823	(NA)
	Pericalcarine	-1.000	(NA)	0.809	(NA)	-0.812	(NA)	-75.502	(NA)	24.279	(NA)	-58.511	(NA)
Cingulate	Rostral Anterior Cingulate	-0.900	(0.783)	-0.900	(0.674)	-0.596	(0.674)	0.000	(1.000)	-8.439	(0.000*)	-6.315	(0.000*)
	Caudal Anterior Cingulate	-0.900	(NA)	-0.900	(NA)	-0.900	(NA)	0.000	(NA)	0.000	(NA)	0.000	(NA)
	Posterior Cingulate	-1.000	(0.783)	-0.900	(0.335)	-0.900	(0.436)	-54.934	(0.000*)	0.000	(1.000)	-55.789	(0.000*)
	Isthmus Cingulate	0.900	(0.783)	0.900	(NA)	-0.695	(0.624)	0.000	(1.000)	25.044	(0.000*)	18.739	(0.000*)
	Insula	-0.016	(1.000)	-0.900	(0.544)	0.031	(0.973)	11.538	(0.000*)	-16.167	(0.000*)	-0.380	(0.953)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all schizophrenia participants (N=123, N=30 with cortical data).
Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 17. Environmental correlations between depression and cortical thickness with basic covariates.

		Environmental Correlations						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_E	*p*-value	R_E	*p*-value	R_E	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	-0.900	(NA)	-0.536	(NA)	-1.000	(NA)	-6.057	(NA)	69.279	(NA)	50.881	(NA)
	Superior Frontal	-0.900	(NA)	-0.900	(0.753)	-0.787	(0.818)	0.000	(1.000)	-3.637	(0.001*)	-3.007	(0.007*)
	Rostral Middle Frontal	-0.515	(0.808)	-0.492	(0.753)	-0.620	(0.818)	-0.222	(0.902)	1.660	(0.131)	1.137	(0.294)
	Caudal Middle Frontal	-0.835	(0.808)	-0.900	(0.753)	-0.084	(0.818)	1.854	(0.100)	-12.321	(0.000*)	-8.227	(0.000*)
	Pars Opercularis	-0.886	(NA)	-0.513	(0.753)	-0.226	(0.818)	-5.791	(0.000*)	-2.993	(0.005*)	-8.603	(0.000*)
	Pars Triangularis	-0.260	(0.808)	-0.073	(0.995)	-0.093	(0.818)	-1.340	(0.237)	0.178	(0.859)	-1.271	(0.260)
	Pars Orbitalis	-0.601	(0.808)	0.900	(0.753)	-0.182	(0.818)	-15.027	(0.000*)	14.697	(0.000*)	-3.749	(0.001*)
	Lateral Orbitofrontal	-0.249	(0.808)	0.405	(0.753)	-0.116	(0.818)	-4.736	(0.000*)	4.845	(0.000*)	-1.005	(0.329)
	Medial Orbitofrontal	-0.756	(0.422)	-0.335	(0.753)	-0.546	(0.818)	-4.430	(0.000*)	2.340	(0.030*)	-2.753	(0.014*)
	Precentral	-0.065	(0.914)	0.900	(0.753)	0.123	(0.818)	-10.663	(0.000*)	11.964	(0.000*)	-1.390	(0.223)
	Paracentral	-0.900	(NA)	-0.375	(NA)	-0.788	(NA)	-7.472	(NA)	5.956	(NA)	-2.982	(NA)
Parietal	Superior Parietal	-0.476	(NA)	0.217	(NA)	0.259	(NA)	-5.116	(NA)	-0.392	(NA)	-5.739	(NA)
	Inferior Parietal	-0.210	(0.821)	0.448	(0.753)	-0.075	(0.818)	-4.822	(0.000*)	4.949	(0.000*)	-1.010	(0.329)
	Supramarginal	-0.025	(1.000)	-0.114	(0.995)	-0.232	(0.818)	0.618	(0.617)	1.080	(0.322)	1.547	(0.175)
	Postcentral	-0.900	(NA)	0.083	(NA)	-0.147	(NA)	-10.789	(NA)	2.059	(NA)	-9.716	(NA)
	Precuneus	-0.415	(NA)	0.239	(NA)	-0.056	(NA)	-4.751	(NA)	2.660	(NA)	-2.828	(NA)
Temporal	Superior Temporal	-0.343	(0.808)	0.384	(0.753)	-0.373	(0.818)	-5.282	(0.000*)	7.067	(0.000*)	0.254	(0.800)
	Superior Temporal Sulcus	0.261	(0.808)	0.002	(1.000)	0.038	(0.862)	1.845	(0.100)	-0.320	(0.783)	1.687	(0.162)
	Middle Temporal	-0.220	(0.808)	0.069	(0.995)	-0.010	(0.958)	-2.034	(0.074)	0.704	(0.527)	-1.570	(0.175)
	Inferior Temporal	-0.317	(0.808)	0.071	(0.995)	-0.069	(0.818)	-2.765	(0.011*)	1.242	(0.274)	-1.899	(0.110)
	Fusiform	-0.381	(0.808)	0.111	(0.995)	-0.177	(0.818)	-3.557	(0.001*)	2.579	(0.016*)	-1.631	(0.169)
	Transverse Temporal	0.900	(NA)	0.116	(NA)	0.010	(NA)	9.402	(NA)	0.948	(NA)	10.733	(NA)
	Entorhinal	0.209	(0.808)	0.356	(0.753)	0.057	(0.818)	-1.111	(0.323)	2.799	(0.009*)	1.139	(0.294)
	Temporal Pole	-0.675	(NA)	0.286	(NA)	-0.097	(NA)	-7.718	(NA)	3.471	(NA)	-5.298	(NA)
	Parahippocampal	-0.529	(0.699)	-0.052	(0.995)	-0.174	(0.818)	-3.721	(0.000*)	1.098	(0.322)	-3.030	(0.007*)
Occipital	Lateral Occipital	0.818	(NA)	0.212	(NA)	0.195	(NA)	6.477	(NA)	0.154	(NA)	6.982	(NA)
	Lingual	-0.277	(0.821)	-0.443	(0.753)	-0.746	(NA)	1.324	(0.237)	4.331	(0.000*)	4.983	(0.000*)
	Cuneus	-0.747	(NA)	-0.176	(NA)	0.195	(NA)	-5.468	(NA)	-3.331	(NA)	-8.541	(NA)
	Pericalcarine	-0.115	(NA)	0.900	(NA)	-0.171	(NA)	-11.013	(NA)	14.596	(NA)	0.416	(NA)
Cingulate	Rostral Anterior Cingulate	-0.367	(0.808)	-0.524	(0.753)	0.151	(0.818)	1.370	(0.237)	-6.517	(0.000*)	-3.939	(0.000*)
	Caudal Anterior Cingulate	-1.000	(NA)	-0.495	(NA)	0.083	(NA)	-54.522	(NA)	-5.561	(NA)	-62.297	(NA)
	Posterior Cingulate	-1.000	(0.422)	-0.653	(1.000)	0.268	(0.818)	-52.881	(0.000*)	-9.362	(0.000*)	-63.704	(0.000*)
	Isthmus Cingulate	-0.838	(0.808)	-0.258	(0.753)	0.103	(0.818)	-6.592	(0.000*)	-3.260	(0.002*)	-9.672	(0.000*)
	Insula	-0.406	(0.808)	-0.394	(0.790)	-0.156	(0.818)	-0.098	(0.964)	-2.303	(0.031*)	-2.009	(0.093)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all depression participants (N=137, N=38 with cortical data).
Covariates included age, age^2, sex, site, and schizophrenia for all analyses.

Appendix Table 18. Environmental correlations between depression and cortical thickness with conservative covariates.

		Environmental Correlations						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_E	*p*-value	R_E	*p*-value	R_E	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	-0.900	(NA)	-0.794	(NA)	-0.369	(NA)	-2.706	(NA)	-6.165	(NA)	-7.963	(NA)
	Superior Frontal	-0.512	(0.494)	-0.900	(0.649)	-0.731	(0.892)	6.286	(0.000*)	-4.812	(0.000*)	2.673	(0.011*)
	Rostral Middle Frontal	-1.000	(0.372)	-0.900	(0.649)	-0.788	(0.715)	-48.079	(0.000*)	-3.601	(0.001*)	-53.858	(0.000*)
	Caudal Middle Frontal	-0.900	(0.464)	-0.900	(0.649)	-0.163	(0.892)	0.000	(1.000)	-11.606	(0.000*)	-9.598	(0.000*)
	Pars Opercularis	-0.401	(0.520)	-0.900	(0.649)	-0.280	(0.892)	7.266	(0.000*)	-10.516	(0.000*)	-1.006	(0.328)
	Pars Triangularis	-0.582	(0.522)	-0.832	(0.649)	-0.087	(0.892)	3.672	(0.000*)	-9.831	(0.000*)	-4.244	(0.000*)
	Pars Orbitalis	-0.900	(0.372)	-0.014	(1.000)	-0.097	(0.892)	-10.123	(0.000*)	0.741	(0.502)	-10.100	(0.000*)
	Lateral Orbitofrontal	-0.332	(0.522)	0.146	(0.905)	-0.124	(0.892)	-3.410	(0.001*)	2.411	(0.026*)	-1.616	(0.128)
	Medial Orbitofrontal	-0.836	(0.372)	-0.421	(0.649)	-0.606	(0.715)	-5.260	(0.000*)	2.250	(0.037*)	-3.706	(0.000*)
	Precentral	-0.851	(0.742)	-0.165	(0.905)	0.124	(0.892)	-7.581	(0.000*)	-2.586	(0.017*)	-10.162	(0.000*)
	Paracentral	-0.352	(NA)	-0.900	(NA)	-0.900	(NA)	7.661	(NA)	0.000	(NA)	8.108	(NA)
Parietal	Superior Parietal	-0.770	(NA)	-0.215	(NA)	0.251	(NA)	-5.565	(NA)	-4.214	(NA)	-9.374	(NA)
	Inferior Parietal	-0.556	(0.522)	-0.063	(0.905)	-0.078	(0.892)	-3.917	(0.000*)	0.140	(0.889)	-4.030	(0.000*)
	Supramarginal	-0.900	(0.681)	-0.900	(0.649)	-0.459	(0.892)	0.000	(1.000)	-8.661	(0.000*)	-7.162	(0.000*)
	Postcentral	-0.900	(NA)	-0.711	(NA)	-0.224	(NA)	-4.049	(NA)	-5.861	(NA)	-9.132	(NA)
	Precuneus	-0.851	(NA)	-0.900	(NA)	-0.169	(NA)	1.484	(NA)	-11.549	(NA)	-7.980	(NA)
Temporal	Superior Temporal	-0.529	(0.522)	0.016	(0.984)	-0.383	(0.892)	-4.198	(0.000*)	3.731	(0.001*)	-1.358	(0.201)
	Superior Temporal Sulcus	0.161	(0.810)	-0.072	(0.905)	0.014	(0.982)	1.624	(0.133)	-0.756	(0.502)	1.093	(0.300)
	Middle Temporal	-0.569	(0.494)	-0.359	(0.790)	-0.003	(0.988)	-1.879	(0.081)	-3.300	(0.002*)	-4.718	(0.000*)
	Inferior Temporal	-0.664	(0.464)	-0.211	(0.649)	-0.047	(0.982)	-4.061	(0.000*)	-1.487	(0.186)	-5.527	(0.000*)
	Fusiform	-0.649	(0.464)	-0.087	(0.905)	-0.198	(0.892)	-4.760	(0.000*)	1.005	(0.381)	-4.206	(0.000*)
	Transverse Temporal	0.485	(NA)	-0.089	(NA)	0.028	(NA)	4.292	(NA)	-1.039	(NA)	3.683	(NA)
	Entorhinal	0.038	(0.817)	0.129	(0.905)	0.011	(0.982)	-0.632	(0.607)	1.052	(0.374)	0.201	(0.840)
	Temporal Pole	-0.737	(NA)	0.078	(NA)	-0.029	(NA)	-7.092	(NA)	0.948	(NA)	-6.721	(NA)
	Parahippocampal	-0.572	(0.372)	-0.163	(0.905)	-0.184	(0.892)	-3.369	(0.001*)	0.193	(0.885)	-3.406	(0.001*)
Occipital	Lateral Occipital	0.401	(NA)	-0.141	(NA)	0.198	(NA)	3.933	(NA)	-3.037	(NA)	1.651	(NA)
	Lingual	-0.454	(0.715)	-0.893	(0.649)	-0.801	(0.715)	6.572	(0.000*)	-2.974	(0.006*)	4.496	(0.000*)
	Cuneus	-0.862	(NA)	-0.457	(NA)	0.180	(NA)	-5.606	(NA)	-5.994	(NA)	-10.889	(NA)
	Pericalcarine	-0.246	(NA)	0.073	(NA)	-0.182	(NA)	-2.253	(NA)	2.283	(NA)	-0.497	(NA)
Cingulate	Rostral Anterior Cingulate	-0.179	(0.742)	-0.499	(0.649)	0.070	(0.892)	2.550	(0.016*)	-5.489	(0.000*)	-1.841	(0.084)
	Caudal Anterior Cingulate	-1.000	(NA)	-0.563	(NA)	0.081	(NA)	-53.872	(NA)	-6.369	(NA)	-62.278	(NA)
	Posterior Cingulate	-0.753	(0.372)	-0.820	(0.649)	0.365	(0.892)	1.238	(0.261)	-13.671	(0.000*)	-9.995	(0.000*)
	Isthmus Cingulate	-0.595	(0.494)	-0.076	(0.905)	0.160	(0.892)	-4.223	(0.000*)	-2.111	(0.050)	-6.215	(0.000*)
	Insula	-0.459	(0.450)	-0.481	(0.790)	-0.149	(0.892)	0.196	(0.925)	-3.316	(0.002*)	-2.534	(0.015*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all depression participants (N=137, N=38 with cortical data).
Covariates included age, age^2, sex, site, and schizophrenia for all analyses.

Appendix Table 19. Comparisons of genetic effects on cortical surface area between age-risk periods, with basic covariates.

		Genetic Correlations Between Age-Risk Periods						Heritability × Age Interaction		
		Rise/Peak		Peak/Plateau		Rise/Plateau		Rise/Peak	Peak/Plateau	Rise/Plateau
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	*p-value*	*p-value*	*p-value*
Frontal	Frontal Pole	0.867	(1.000)	0.054	(1.000)	0.863	(1.000)	(0.547)	(0.980)	(1.000)
	Superior Frontal	1.000	(1.000)	-0.241	(1.000)	0.903	(1.000)	(0.658)	(1.000)	(1.000)
	Rostral Middle Frontal	1.000	(1.000)	0.694	(1.000)	0.920	(1.000)	(0.658)	(0.980)	(1.000)
	Caudal Middle Frontal	1.000	(1.000)	-0.712	(1.000)	0.715	(1.000)	(0.658)	(0.995)	(1.000)
	Pars Opercularis	NA	(1.000)	0.174	(1.000)	1.000	(1.000)	(NA)	(0.980)	(1.000)
	Pars Triangularis	-1.000	(NA)	-0.444	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
	Pars Orbitalis	NA	(1.000)	1.000	(1.000)	1.000	(1.000)	(NA)	(0.980)	(1.000)
	Lateral Orbitofrontal	1.000	(1.000)	-0.049	(1.000)	0.860	(1.000)	(0.764)	(0.980)	(1.000)
	Medial Orbitofrontal	0.136	(1.000)	-0.448	(1.000)	0.946	(1.000)	(0.925)	(0.980)	(1.000)
	Precentral	-0.528	(NA)	-0.716	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
	Paracentral	NA	(NA)	0.816	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
Parietal	Superior Parietal	0.431	(1.000)	-0.581	(1.000)	0.830	(1.000)	(0.951)	(0.980)	(1.000)
	Inferior Parietal	0.746	(1.000)	0.696	(1.000)	1.000	(1.000)	(0.764)	(0.980)	(1.000)
	Supramarginal	NA	(1.000)	0.684	(1.000)	1.000	(1.000)	(NA)	(1.000)	(1.000)
	Postcentral	0.599	(1.000)	-0.072	(1.000)	0.979	(1.000)	(0.764)	(1.000)	(1.000)
	Precuneus	NA	(1.000)	-0.323	(1.000)	0.798	(1.000)	(NA)	(1.000)	(1.000)
Temporal	Superior Temporal	1.000	(NA)	0.067	(NA)	0.950	(NA)	(NA)	(NA)	(NA)
	Superior Temporal Sulcus	NA	(1.000)	-0.471	(1.000)	1.000	(1.000)	(NA)	(0.980)	(1.000)
	Middle Temporal	NA	(1.000)	0.084	(1.000)	0.774	(1.000)	(NA)	(1.000)	(1.000)
	Inferior Temporal	1.000	(1.000)	-0.133	(1.000)	NA	(1.000)	(0.885)	(0.995)	(1.000)
	Fusiform	0.110	(1.000)	-0.739	(1.000)	1.000	(1.000)	(0.547)	(1.000)	(1.000)
	Transverse Temporal	-0.275	(1.000)	-1.000	(1.000)	0.790	(1.000)	(0.764)	(0.980)	(1.000)
	Entorhinal	0.107	(1.000)	-0.869	(1.000)	1.000	(1.000)	(0.547)	(0.980)	(1.000)
	Temporal Pole	1.000	(NA)	-0.978	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
	Parahippocampal	-1.000	(1.000)	-0.030	(1.000)	0.688	(1.000)	(0.658)	(0.995)	(1.000)
Occipital	Lateral Occipital	0.407	(1.000)	-0.249	(1.000)	0.912	(1.000)	(0.776)	(0.980)	(1.000)
	Lingual	0.732	(1.000)	0.478	(1.000)	0.324	(1.000)	(0.925)	(0.995)	(1.000)
	Cuneus	0.339	(NA)	1.000	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
	Pericalcarine	1.000	(1.000)	1.000	(1.000)	1.000	(1.000)	(0.788)	(0.995)	(1.000)
Cingulate	Rostral Anterior Cingulate	NA	(NA)	-1.000	(NA)	-1.000	(NA)	(NA)	(NA)	(NA)
	Caudal Anterior Cingulate	NA	(NA)	0.624	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
	Posterior Cingulate	1.000	(NA)	1.000	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
	Isthmus Cingulate	1.000	(NA)	-0.661	(NA)	1.000	(NA)	(NA)	(NA)	(NA)
	Insula	-0.323	(1.000)	-0.594	(1.000)	NA	(1.000)	(0.896)	(0.980)	(1.000)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted excluding all schizophrenia participants (N=123, N=30 with cortical data). Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 20. Phenotypic correlations between schizophrenia and cortical surface area with basic covariates.

		Phenotypic Correlations Within Age-Risk Periods						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_P	*p*-value	R_P	*p*-value	R_P	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	-0.057	(1.000)	-0.196	(0.140)	-0.197	(0.057)	1.123	(0.369)	0.005	(0.996)	1.145	(0.318)
	Superior Frontal	-0.726	(NA)	-0.459	(NA)	-0.351	(NA)	-3.364	(0.004*)	-1.402	(0.276)	-4.467	(0.000*)
	Rostral Middle Frontal	-0.917	(NA)	-0.566	(0.002*)	-0.346	(0.003*)	-7.358	(0.000*)	-3.030	(0.020*)	-9.745	(0.000*)
	Caudal Middle Frontal	-0.601	(0.329)	-0.383	(0.047*)	-0.364	(0.000*)	-2.313	(0.045*)	-0.233	(0.933)	-2.526	(0.021*)
	Pars Opercularis	-0.516	(0.093)	-0.365	(0.002*)	-0.296	(0.007*)	-1.488	(0.205)	-0.835	(0.583)	-2.137	(0.049*)
	Pars Triangularis	-0.704	(NA)	-0.458	(NA)	-0.204	(NA)	-3.005	(NA)	-3.115	(NA)	-5.380	(NA)
	Pars Orbitalis	-0.626	(NA)	-0.407	(0.002*)	-0.293	(0.009*)	-2.393	(0.040*)	-1.417	(0.276)	-3.491	(0.001*)
	Lateral Orbitofrontal	-0.718	(0.059)	-0.444	(0.006*)	-0.324	(0.004*)	-3.381	(0.004*)	-1.523	(0.255)	-4.575	(0.000*)
	Medial Orbitofrontal	-0.824	(NA)	-0.610	(0.001*)	-0.380	(0.000*)	-3.657	(0.003*)	-3.339	(0.010*)	-6.211	(0.000*)
	Precentral	-0.721	(NA)	-0.470	(NA)	-0.210	(NA)	-3.161	(NA)	-3.218	(NA)	-5.615	(NA)
	Paracentral	-0.439	(NA)	-0.328	(NA)	-0.129	(NA)	-1.035	(NA)	-2.281	(NA)	-2.754	(NA)
Parietal	Superior Parietal	-0.444	(0.218)	-0.383	(0.002*)	-0.386	(0.001*)	-0.586	(0.638)	0.042	(0.996)	-0.565	(0.597)
	Inferior Parietal	-0.625	(0.071)	-0.451	(0.006*)	-0.084	(NA)	-1.955	(0.087)	-4.352	(0.000*)	-5.235	(0.000*)
	Supramarginal	-0.633	(NA)	-0.315	(0.007*)	-0.319	(0.004*)	-3.326	(0.004*)	0.053	(0.996)	-3.344	(0.002*)
	Postcentral	-0.630	(0.092)	-0.473	(0.004*)	-0.303	(0.007*)	-1.798	(0.115)	-2.172	(0.090)	-3.449	(0.001*)
	Precuneus	-0.667	(0.065)	-0.344	(0.035*)	-0.391	(NA)	-3.539	(0.003*)	0.579	(0.675)	-3.167	(0.003*)
Temporal	Superior Temporal	-0.613	(NA)	-0.213	(NA)	-0.201	(NA)	-3.945	(NA)	-0.134	(NA)	-4.112	(NA)
	Superior Temporal Sulcus	-0.559	(0.076)	-0.357	(0.019*)	-0.171	(0.060)	-2.046	(0.076)	-2.171	(0.090)	-3.701	(0.001*)
	Middle Temporal	-0.575	(NA)	-0.504	(0.002*)	-0.318	(0.004*)	-0.797	(0.521)	-2.429	(0.083)	-2.622	(0.017*)
	Inferior Temporal	-0.626	(0.144)	-0.355	(0.035*)	-0.407	(0.000*)	-2.881	(0.014*)	0.656	(0.647)	-2.441	(0.025*)
	Fusiform	-0.340	(0.406)	-0.444	(0.006*)	-0.251	(0.009*)	0.976	(0.439)	-2.381	(0.083)	-0.784	(0.495)
	Transverse Temporal	-0.458	(NA)	-0.232	(0.084)	-0.293	(0.003*)	-2.044	(0.076)	0.705	(0.641)	-1.553	(0.170)
	Entorhinal	-0.327	(0.609)	-0.273	(0.041*)	-0.341	(0.001*)	-0.473	(0.694)	0.819	(0.583)	0.130	(0.897)
	Temporal Pole	-0.178	(NA)	0.045	(NA)	-0.142	(NA)	-1.790	(NA)	2.036	(NA)	-0.301	(NA)
	Parahippocampal	-0.457	(0.106)	-0.169	(0.002*)	-0.328	(0.008*)	-2.558	(0.028*)	1.836	(0.159)	-1.231	(0.291)
Occipital	Lateral Occipital	-0.449	(0.171)	-0.474	(0.002*)	-0.352	(0.003*)	0.255	(0.834)	-1.603	(0.238)	-0.937	(0.419)
	Lingual	-0.482	(0.144)	-0.403	(0.006*)	-0.248	(0.021*)	-0.782	(0.521)	-1.883	(0.159)	-2.201	(0.044*)
	Cuneus	-0.543	(NA)	-0.327	(NA)	-0.232	(NA)	-2.138	(NA)	-1.111	(NA)	-3.003	(NA)
	Pericalcarine	-0.335	(0.320)	-0.333	(0.035*)	-0.251	(NA)	-0.025	(0.980)	-0.966	(0.535)	-0.747	(0.497)
Cingulate	Rostral Anterior Cingulate	-0.575	(NA)	-0.227	(NA)	-0.177	(NA)	-3.359	(NA)	-0.572	(NA)	-3.843	(NA)
	Caudal Anterior Cingulate	-0.486	(NA)	-0.301	(NA)	-0.214	(NA)	-1.739	(NA)	-1.015	(NA)	-2.526	(NA)
	Posterior Cingulate	-0.541	(NA)	-0.275	(NA)	-0.191	(NA)	-2.567	(NA)	-0.968	(NA)	-3.333	(NA)
	Isthmus Cingulate	-0.673	(NA)	-0.210	(NA)	-0.182	(NA)	-4.771	(NA)	-0.314	(NA)	-5.087	(NA)
	Insula	-0.665	(NA)	-0.438	(NA)	-0.258	(NA)	-2.632	(0.025*)	-2.223	(0.090)	-4.335	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all schizophrenia participants (N=123, N=30 with cortical data).
Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 21. Phenotypic correlations between schizophrenia and cortical surface area with conservative covariates.

		Phenotypic Correlations Within Age-Risk Periods						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_P	*p*-value	R_P	*p*-value	R_P	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	0.162	(0.263)	-0.124	(0.426)	-0.173	(0.109)	2.289	(0.066)	0.536	(0.726)	2.725	(0.015*)
	Superior Frontal	-0.638	(NA)	-0.369	(0.043*)	-0.278	(NA)	-2.910	(0.022*)	-1.098	(0.544)	-3.777	(0.001*)
	Rostral Middle Frontal	-0.823	(0.010*)	-0.523	(0.000*)	-0.311	(0.007*)	-4.653	(0.000*)	-2.781	(0.101)	-6.806	(0.000*)
	Caudal Middle Frontal	0.071	(0.473)	-0.183	(0.364)	-0.308	(0.003*)	2.027	(0.085)	1.442	(0.473)	3.138	(0.006*)
	Pars Opercularis	-0.439	(0.231)	-0.271	(0.105)	-0.274	(0.006*)	-1.531	(0.168)	0.038	(0.970)	-1.527	(0.217)
	Pars Triangularis	-0.603	(NA)	-0.320	(NA)	-0.139	(NA)	-2.906	(NA)	-2.055	(NA)	-4.490	(NA)
	Pars Orbitalis	-0.527	(0.158)	-0.344	(0.079)	-0.246	(0.020*)	-1.801	(0.112)	-1.157	(0.540)	-2.694	(0.015*)
	Lateral Orbitofrontal	-0.679	(0.139)	-0.380	(0.048*)	-0.255	(0.006*)	-3.374	(0.006*)	-1.503	(0.473)	-4.552	(0.000*)
	Medial Orbitofrontal	-0.581	(0.139)	-0.464	(0.001*)	-0.272	(0.007*)	-1.278	(0.230)	-2.395	(0.133)	-3.090	(0.006*)
	Precentral	-0.532	(NA)	-0.407	(NA)	-0.147	(NA)	-1.269	(NA)	-3.051	(NA)	-3.572	(NA)
	Paracentral	-0.290	(NA)	-0.219	(NA)	-0.045	(NA)	-0.597	(NA)	-1.916	(NA)	-2.040	(NA)
Parietal	Superior Parietal	-0.284	(0.473)	-0.336	(0.035*)	-0.373	(0.001*)	0.452	(0.680)	0.461	(0.737)	0.804	(0.506)
	Inferior Parietal	-0.384	(NA)	-0.203	(0.184)	-0.283	(0.020*)	-1.572	(0.164)	0.907	(0.547)	-0.918	(0.453)
	Supramarginal	-0.492	(0.139)	-0.236	(0.076)	-0.259	(0.020*)	-2.358	(0.063)	0.260	(0.832)	-2.200	(0.051)
	Postcentral	-0.158	(0.394)	-0.394	(0.043*)	-0.244	(0.021*)	2.040	(0.085)	-1.805	(0.426)	0.721	(0.538)
	Precuneus	-0.615	(0.139)	-0.259	(0.174)	-0.343	(0.005*)	-3.581	(0.004*)	0.989	(0.547)	-2.897	(0.010*)
Temporal	Superior Temporal	-0.367	(NA)	0.020	(NA)	-0.094	(NA)	-3.208	(NA)	1.228	(NA)	-2.339	(NA)
	Superior Temporal Sulcus	-0.478	(0.139)	-0.238	(0.048*)	-0.086	(0.342)	-2.202	(0.074)	-1.678	(0.448)	-3.492	(0.002*)
	Middle Temporal	-0.276	(1.000)	-0.363	(0.043*)	-0.249	(0.011*)	0.763	(0.486)	-1.349	(0.473)	-0.235	(0.815)
	Inferior Temporal	0.018	(0.263)	-0.236	(0.184)	-0.354	(0.001*)	2.052	(0.085)	1.389	(0.473)	3.123	(0.006*)
	Fusiform	0.036	(0.374)	-0.206	(0.239)	-0.128	(0.196)	1.937	(0.090)	-0.862	(0.549)	1.322	(0.278)
	Transverse Temporal	-0.404	(0.139)	-0.180	(0.247)	-0.262	(0.021*)	-1.951	(0.090)	0.922	(0.547)	-1.291	(0.278)
	Entorhinal	0.010	(0.848)	-0.282	(0.105)	-0.304	(0.006*)	2.379	(0.063)	0.257	(0.832)	2.608	(0.018*)
	Temporal Pole	-0.103	(NA)	0.176	(NA)	-0.100	(NA)	-2.228	(NA)	2.990	(NA)	-0.026	(NA)
	Parahippocampal	-0.287	(0.263)	-0.436	(0.014*)	-0.219	(0.040*)	1.357	(0.216)	-2.634	(0.101)	-0.593	(0.604)
Occipital	Lateral Occipital	-0.208	(0.180)	-0.362	(0.043*)	-0.315	(0.003*)	1.340	(0.216)	-0.582	(0.726)	0.926	(0.453)
	Lingual	-0.263	(0.407)	-0.290	(0.043*)	-0.199	(0.040*)	0.237	(0.813)	-1.042	(0.547)	-0.539	(0.615)
	Cuneus	-0.394	(NA)	-0.262	(NA)	-0.201	(NA)	-1.182	(NA)	-0.690	(NA)	-1.717	(NA)
	Pericalcarine	-0.050	(0.263)	-0.268	(0.114)	-0.223	(NA)	1.782	(0.112)	-0.517	(0.726)	1.422	(0.248)
Cingulate	Rostral Anterior Cingulate	-0.223	(NA)	0.037	(NA)	-0.066	(NA)	-2.097	(NA)	1.116	(NA)	-1.295	(NA)
	Caudal Anterior Cingulate	-0.322	(NA)	-0.004	(NA)	-0.109	(NA)	-2.611	(NA)	1.130	(NA)	-1.806	(NA)
	Posterior Cingulate	-0.242	(NA)	-0.140	(NA)	-0.075	(NA)	-0.833	(NA)	-0.717	(NA)	-1.382	(NA)
	Isthmus Cingulate	-0.626	(NA)	-0.029	(NA)	-0.044	(NA)	-5.593	(NA)	0.160	(NA)	-5.561	(NA)
	Insula	-0.559	(0.139)	-0.270	(0.105)	-0.160	(0.126)	-2.801	(0.024*)	-1.243	(0.513)	-3.775	(0.001*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all schizophrenia participants (N=123, N=30 with cortical data).
Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 22. Phenotypic correlations between depression and cortical surface area with basic covariates.

		Phenotypic Correlations Within Age-Risk Periods						Proportion of Phenotypic Covariance					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_P	*p*-value	R_P	*p*-value	R_P	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	0.049	(0.801)	-0.037	(0.976)	0.042	(0.843)	0.600	(0.794)	-0.702	(0.724)	0.054	(0.957)
	Superior Frontal	-0.100	(1.000)	-0.106	(0.976)	0.122	(0.645)	0.045	(0.964)	-2.035	(0.290)	-1.635	(0.292)
	Rostral Middle Frontal	0.049	(0.526)	-0.016	(0.976)	-0.047	(0.843)	0.451	(0.794)	0.270	(0.900)	0.701	(0.683)
	Caudal Middle Frontal	-0.111	(0.753)	-0.053	(0.976)	-0.010	(0.953)	-0.408	(0.794)	-0.383	(0.900)	-0.748	(0.683)
	Pars Opercularis	0.267	(0.526)	-0.133	(0.976)	0.002	(0.982)	2.822	(0.057)	-1.201	(0.499)	1.993	(0.250)
	Pars Triangularis	0.151	(NA)	-0.068	(NA)	-0.021	(NA)	1.532	(NA)	-0.419	(NA)	1.274	(NA)
	Pars Orbitalis	-0.009	(1.000)	-0.105	(0.976)	0.114	(0.834)	0.663	(0.794)	-1.945	(0.290)	-0.907	(0.625)
	Lateral Orbitofrontal	0.100	(0.526)	-0.098	(0.976)	0.039	(NA)	1.378	(0.367)	-1.212	(0.499)	0.456	(0.819)
	Medial Orbitofrontal	0.222	(0.526)	-0.012	(0.976)	0.190	(0.411)	1.645	(0.240)	-1.814	(0.290)	0.241	(0.883)
	Precentral	0.085	(NA)	-0.030	(NA)	0.065	(NA)	0.802	(NA)	-0.843	(NA)	0.152	(NA)
	Paracentral	-0.142	(NA)	-0.012	(NA)	0.109	(NA)	-0.905	(NA)	-1.078	(NA)	-1.849	(NA)
Parietal	Superior Parietal	0.371	(NA)	0.008	(0.976)	-0.024	(0.914)	2.644	(0.062)	0.287	(0.900)	3.035	(0.058)
	Inferior Parietal	0.116	(0.474)	-0.070	(0.976)	-0.133	(0.645)	1.291	(0.394)	0.568	(0.805)	1.835	(0.250)
	Supramarginal	0.196	(0.474)	0.136	(0.976)	0.113	(0.843)	0.434	(0.794)	0.199	(0.918)	0.625	(0.710)
	Postcentral	0.283	(0.474)	0.041	(0.976)	0.047	(0.843)	1.734	(0.221)	-0.051	(0.960)	1.793	(0.250)
	Precuneus	0.241	(0.474)	0.076	(0.976)	-0.054	(0.843)	1.179	(0.440)	1.152	(0.499)	2.201	(0.250)
Temporal	Superior Temporal	0.086	(NA)	-0.122	(NA)	0.097	(NA)	1.447	(NA)	-1.947	(NA)	-0.079	(NA)
	Superior Temporal Sulcus	-0.061	(0.753)	0.004	(0.976)	0.216	(0.248)	-0.454	(0.794)	-1.909	(0.290)	-2.059	(0.250)
	Middle Temporal	0.310	(NA)	-0.045	(0.976)	0.069	(0.843)	2.535	(0.062)	-1.021	(0.527)	1.839	(0.250)
	Inferior Temporal	0.312	(NA)	-0.097	(0.976)	0.105	(0.843)	2.916	(0.057)	-1.796	(0.290)	1.601	(0.292)
	Fusiform	0.186	(0.526)	-0.062	(0.976)	0.053	(0.843)	1.740	(0.221)	-1.025	(0.527)	0.994	(0.591)
	Transverse Temporal	-0.013	(1.000)	-0.046	(0.976)	-0.051	(0.843)	0.225	(0.858)	0.050	(0.960)	0.279	(0.883)
	Entorhinal	-0.170	(0.526)	-0.283	(0.217)	-0.012	(0.953)	0.828	(0.699)	-2.476	(0.290)	-1.171	(0.483)
	Temporal Pole	-0.031	(NA)	-0.014	(NA)	0.011	(NA)	-0.120	(NA)	-0.218	(NA)	-0.308	(NA)
	Parahippocampal	0.205	(0.526)	-0.118	(0.976)	0.046	(0.843)	2.262	(0.095)	-1.456	(0.390)	1.189	(0.483)
Occipital	Lateral Occipital	0.329	(0.474)	-0.017	(0.976)	0.156	(0.645)	2.488	(0.062)	-1.550	(0.390)	1.351	(0.424)
	Lingual	-0.017	(1.000)	-0.061	(0.976)	0.035	(0.843)	0.302	(0.832)	-0.854	(0.629)	-0.386	(0.839)
	Cuneus	0.195	(NA)	0.107	(NA)	-0.074	(NA)	0.623	(NA)	1.614	(NA)	1.994	(NA)
	Pericalcarine	0.064	(0.881)	0.007	(0.976)	0.042	(0.843)	0.393	(0.794)	-0.314	(0.900)	0.156	(0.914)
Cingulate	Rostral Anterior Cingulate	0.360	(NA)	0.033	(NA)	0.222	(NA)	2.384	(NA)	-1.715	(NA)	1.104	(NA)
	Caudal Anterior Cingulate	0.053	(NA)	-0.025	(NA)	0.081	(NA)	0.539	(NA)	-0.940	(NA)	-0.207	(NA)
	Posterior Cingulate	0.093	(NA)	0.014	(NA)	0.081	(NA)	0.551	(NA)	-0.602	(NA)	0.086	(NA)
	Isthmus Cingulate	0.231	(NA)	0.125	(NA)	0.146	(NA)	0.760	(NA)	-0.182	(NA)	0.653	(NA)
	Insula	0.150	(0.526)	-0.113	(0.976)	0.051	(0.843)	1.834	(0.221)	-1.453	(0.390)	0.739	(0.683)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all depression participants (N=137, N=38 with cortical data).
Covariates included age, age^2, sex, site, and schizophrenia for all analyses.

Appendix Table 23. Phenotypic correlations between depression and cortical surface area conservative covariates.

		Phenotypic Correlations Within Age-Risk Periods						Proportion of Phenotypic Covariance					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_P	*p*-value	R_P	*p*-value	R_P	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	0.162	(0.526)	0.032	(0.975)	-0.002	(0.985)	0.907	(0.583)	0.301	(0.990)	1.208	(0.363)
	Superior Frontal	-0.045	(0.312)	-0.028	(0.975)	0.036	(0.972)	-0.117	(0.936)	-0.563	(0.917)	-0.589	(0.635)
	Rostral Middle Frontal	0.020	(1.000)	0.050	(0.975)	-0.160	(0.565)	-0.210	(0.936)	1.879	(0.362)	1.332	(0.338)
	Caudal Middle Frontal	-0.015	(1.000)	0.043	(0.975)	-0.062	(0.972)	-0.401	(0.876)	0.938	(0.836)	0.352	(0.756)
	Pars Opercularis	0.305	(0.262)	-0.051	(0.975)	-0.052	(0.972)	2.537	(0.134)	0.012	(0.990)	2.695	(0.028*)
	Pars Triangularis	0.197	(NA)	-0.013	(NA)	-0.084	(NA)	1.476	(NA)	0.635	(NA)	2.088	(NA)
	Pars Orbitalis	-0.011	(1.000)	-0.053	(0.975)	0.032	(0.972)	0.288	(0.928)	-0.758	(0.897)	-0.322	(0.756)
	Lateral Orbitofrontal	0.156	(0.526)	-0.025	(0.975)	-0.094	(0.851)	1.264	(0.495)	0.616	(0.917)	1.847	(0.173)
	Medial Orbitofrontal	0.269	(0.309)	0.088	(0.975)	0.130	(0.842)	1.306	(0.495)	-0.380	(0.990)	1.068	(0.428)
	Precentral	0.203	(NA)	0.071	(NA)	-0.025	(NA)	0.937	(NA)	0.851	(NA)	1.695	(NA)
	Paracentral	-0.032	(NA)	0.081	(NA)	0.059	(NA)	-0.784	(NA)	0.197	(NA)	-0.666	(NA)
Parietal	Superior Parietal	0.405	(0.104)	0.113	(0.975)	-0.115	(0.851)	2.191	(0.137)	2.036	(0.334)	4.002	(0.001*)
	Inferior Parietal	0.200	(0.346)	0.039	(0.975)	-0.229	(0.565)	1.139	(0.501)	2.409	(0.192)	3.198	(0.008*)
	Supramarginal	0.270	(0.063)	0.217	(0.614)	0.037	(0.972)	0.394	(0.876)	1.627	(0.415)	1.763	(0.187)
	Postcentral	0.239	(0.309)	0.085	(0.975)	-0.058	(0.972)	1.100	(0.501)	1.273	(0.696)	2.217	(0.091)
	Precuneus	0.363	(0.133)	0.191	(0.767)	-0.155	(0.565)	1.296	(0.495)	3.102	(0.046*)	3.937	(0.001*)
Temporal	Superior Temporal	0.081	(NA)	-0.020	(NA)	-0.005	(NA)	0.705	(NA)	-0.135	(NA)	0.634	(NA)
	Superior Temporal Sulcus	0.094	(0.697)	0.154	(0.975)	0.173	(0.565)	-0.423	(0.876)	-0.176	(0.990)	-0.593	(0.635)
	Middle Temporal	0.376	(NA)	0.073	(0.975)	-0.017	(0.972)	2.231	(0.137)	0.806	(0.897)	3.027	(0.012*)
	Inferior Temporal	0.463	(0.063)	0.036	(0.975)	0.031	(0.972)	3.225	(0.030*)	0.042	(0.990)	3.447	(0.005*)
	Fusiform	0.159	(0.309)	-0.003	(0.987)	-0.013	(0.972)	1.132	(0.501)	0.091	(0.990)	1.274	(0.347)
	Transverse Temporal	-0.004	(1.000)	-0.016	(0.975)	-0.133	(0.842)	0.080	(0.936)	1.044	(0.832)	0.948	(0.447)
	Entorhinal	-0.104	(0.526)	-0.241	(0.604)	-0.062	(0.972)	0.981	(0.560)	-1.632	(0.415)	-0.311	(0.756)
	Temporal Pole	-0.051	(NA)	-0.026	(NA)	-0.025	(NA)	-0.174	(NA)	-0.004	(NA)	-0.188	(NA)
	Parahippocampal	0.213	(0.104)	-0.026	(0.975)	0.012	(0.972)	1.680	(0.372)	-0.340	(0.990)	1.496	(0.269)
Occipital	Lateral Occipital	0.332	(0.207)	0.010	(0.987)	0.083	(0.933)	2.323	(0.137)	-0.652	(0.917)	1.920	(0.165)
	Lingual	0.123	(0.676)	0.001	(0.987)	-0.003	(0.985)	0.846	(0.596)	0.039	(0.990)	0.927	(0.447)
	Cuneus	0.181	(NA)	0.154	(NA)	-0.141	(NA)	0.190	(NA)	2.638	(NA)	2.383	(NA)
	Pericalcarine	0.113	(0.676)	0.090	(0.975)	-0.023	(0.972)	0.160	(0.936)	1.011	(0.832)	1.005	(0.444)
Cingulate	Rostral Anterior Cingulate	0.372	(NA)	0.112	(NA)	0.195	(NA)	1.934	(NA)	-0.758	(NA)	1.419	(NA)
	Caudal Anterior Cingulate	0.106	(NA)	0.065	(NA)	0.065	(NA)	0.287	(NA)	-0.004	(NA)	0.301	(NA)
	Posterior Cingulate	0.210	(NA)	0.105	(NA)	0.003	(NA)	0.750	(NA)	0.904	(NA)	1.541	(NA)
	Isthmus Cingulate	0.277	(NA)	0.195	(NA)	0.079	(NA)	0.605	(NA)	1.047	(NA)	1.506	(NA)
	Insula	0.177	(0.488)	-0.042	(0.975)	-0.033	(0.972)	1.526	(0.435)	-0.080	(0.990)	1.549	(0.265)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all depression participants (N=137, N=38 with cortical data).
Covariates included age, age^2, sex, site, and schizophrenia for all analyses.

Appendix Table 24. Environmental correlations between schizophrenia and cortical surface area with basic covariates.

		Environmental Correlations						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_E	*p*-value	R_E	*p*-value	R_E	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	0.900	(0.656)	0.900	(0.848)	0.900	(0.547)	0.000	(1.000)	0.000	(1.000)	0.000	(1.000)
	Superior Frontal	-0.443	(NA)	1.000	(NA)	-0.900	(NA)	-70.412	(0.000*)	106.760	(0.000*)	8.041	(0.000*)
	Rostral Middle Frontal	-0.898	(NA)	-0.357	(1.000)	-0.900	(0.549)	-8.640	(0.000*)	11.878	(0.000*)	0.075	(1.000)
	Caudal Middle Frontal	0.900	(0.656)	0.900	(0.836)	-0.900	(0.037*)	-0.001	(1.000)	31.824	(0.000*)	23.743	(0.000*)
	Pars Opercularis	1.000	(0.656)	0.900	(0.860)	-0.900	(0.549)	54.970	(0.000*)	NA	(0.000*)	79.650	(0.000*)
	Pars Triangularis	-0.017	(NA)	0.900	(NA)	-0.900	(NA)	-11.805	(NA)	31.822	(NA)	11.736	(NA)
	Pars Orbitalis	1.000	(NA)	-0.196	(1.000)	-0.707	(0.678)	68.219	(0.000*)	7.374	(0.000*)	74.884	(0.000*)
	Lateral Orbitofrontal	0.463	(0.964)	0.900	(1.000)	-0.900	(0.547)	-7.697	(0.000*)	31.822	(0.000*)	15.914	(0.000*)
	Medial Orbitofrontal	0.900	(NA)	0.211	(1.000)	-0.898	(0.750)	9.976	(0.000*)	18.122	(0.000*)	23.667	(0.000*)
	Precentral	-0.900	(NA)	-0.900	(NA)	-0.436	(NA)	0.000	(NA)	-10.864	(NA)	-8.105	(NA)
	Paracentral	0.900	(NA)	0.186	(NA)	-0.893	(NA)	10.177	(NA)	17.545	(NA)	23.441	(NA)
Parietal	Superior Parietal	1.000	(0.699)	0.900	(0.860)	0.024	(1.000)	54.970	(0.000*)	15.648	(0.000*)	67.583	(0.000*)
	Inferior Parietal	-0.900	(0.850)	-0.900	(0.836)	-0.173	(NA)	0.000	(1.000)	-14.019	(0.000*)	-10.459	(0.000*)
	Supramarginal	-0.900	(NA)	0.900	(1.000)	-0.900	(0.547)	-23.344	(0.000*)	NA	(0.000*)	0.000	(1.000)
	Postcentral	-0.900	(0.850)	-0.900	(0.860)	-0.626	(0.549)	0.000	(1.000)	-7.975	(0.000*)	-5.950	(0.000*)
	Precuneus	-0.900	(0.699)	-0.177	(1.000)	-0.900	(NA)	-10.254	(0.000*)	13.977	(0.000*)	0.000	(1.000)
Temporal	Superior Temporal	0.900	(NA)	0.355	(NA)	-0.424	(NA)	8.730	(NA)	8.906	(NA)	15.524	(NA)
	Superior Temporal Sulcus	-0.900	(0.699)	-0.900	(0.836)	-0.900	(0.377)	0.000	(1.000)	0.000	(1.000)	0.000	(1.000)
	Middle Temporal	1.000	(NA)	0.411	(1.000)	-0.213	(0.950)	63.178	(0.000*)	7.058	(0.000*)	69.522	(0.000*)
	Inferior Temporal	-0.783	(0.964)	0.688	(1.000)	-0.692	(0.547)	-15.034	(0.000*)	18.316	(0.000*)	-1.625	(0.139)
	Fusiform	0.900	(0.656)	1.000	(0.836)	-0.290	(0.950)	-54.970	(0.000*)	94.072	(0.000*)	14.280	(0.000*)
	Transverse Temporal	-0.649	(NA)	-0.210	(1.000)	-0.900	(0.547)	-4.450	(0.000*)	13.608	(0.000*)	5.627	(0.000*)
	Entorhinal	0.900	(0.615)	-0.538	(1.000)	-0.712	(0.549)	16.436	(0.000*)	3.146	(0.002*)	19.064	(0.000*)
	Temporal Pole	0.900	(NA)	0.900	(NA)	0.717	(NA)	0.000	(NA)	6.167	(NA)	4.601	(NA)
	Parahippocampal	-1.000	(0.656)	-0.195	(1.000)	-0.551	(1.000)	-65.077	(0.000*)	4.567	(0.000*)	-62.780	(0.000*)
Occipital	Lateral Occipital	-0.768	(0.964)	0.714	(1.000)	-0.350	(0.950)	-15.143	(0.000*)	13.622	(0.000*)	-5.239	(0.000*)
	Lingual	-0.743	(1.000)	1.000	(0.836)	-0.900	(0.549)	-74.238	(0.000*)	106.755	(0.000*)	4.145	(0.000*)
	Cuneus	-1.000	(NA)	-0.900	(NA)	-0.196	(NA)	-54.970	(NA)	-13.771	(NA)	-66.182	(NA)
	Pericalcarine	-0.900	(0.964)	0.863	(0.860)	-0.900	(NA)	-22.013	(0.000*)	30.020	(0.000*)	0.009	(1.000)
Cingulate	Rostral Anterior Cingulate	-0.900	(NA)	0.504	(NA)	-0.900	(NA)	-16.073	(NA)	21.910	(NA)	0.000	(NA)
	Caudal Anterior Cingulate	-0.148	(NA)	-0.900	(NA)	-0.900	(NA)	10.494	(NA)	0.000	(NA)	10.673	(NA)
	Posterior Cingulate	0.900	(NA)	-0.572	(NA)	-0.900	(NA)	16.833	(NA)	8.876	(NA)	23.743	(NA)
	Isthmus Cingulate	-0.907	(NA)	-0.873	(NA)	-0.900	(NA)	-1.324	(NA)	1.366	(NA)	-0.327	(NA)
	Insula	-0.900	(NA)	-0.900	(NA)	-1.000	(NA)	0.000	(1.000)	74.932	(0.000*)	55.908	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all schizophrenia participants (N=123, N=30 with cortical data).
Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 25. Environmental correlations between schizophrenia and cortical surface area with conservative covariates.

		Environmental Correlations						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_E	*p*-value	R_E	*p*-value	R_E	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	0.900	(0.681)	0.900	(0.470)	0.900	(0.401)	0.000	(1.000)	0.000	(1.000)	0.000	(1.000)
	Superior Frontal	1.000	(NA)	0.900	(0.419)	-0.900	(NA)	54.934	(0.000*)	31.663	(0.000*)	79.481	(0.000*)
	Rostral Middle Frontal	-0.898	(0.907)	-0.584	(0.807)	-0.900	(0.378)	-6.289	(0.000*)	8.637	(0.000*)	0.076	(1.000)
	Caudal Middle Frontal	1.000	(0.394)	0.900	(0.419)	-1.000	(0.013*)	54.933	(0.000*)	106.222	(0.000*)	NA	(0.000*)
	Pars Opercularis	1.000	(0.681)	1.000	(0.693)	-0.900	(0.378)	0.000	(1.000)	106.220	(0.000*)	79.481	(0.000*)
	Pars Triangularis	0.650	(NA)	0.328	(NA)	-0.900	(NA)	3.441	(NA)	19.497	(NA)	18.084	(NA)
	Pars Orbitalis	0.900	(0.885)	-0.421	(0.892)	-0.711	(0.421)	15.226	(0.000*)	4.731	(0.000*)	19.003	(0.000*)
	Lateral Orbitofrontal	-0.737	(0.907)	-0.245	(0.956)	-0.900	(0.285)	-5.493	(0.000*)	13.141	(0.000*)	4.254	(0.000*)
	Medial Orbitofrontal	0.900	(0.885)	0.506	(0.892)	0.078	(0.968)	7.248	(0.000*)	5.151	(0.000*)	11.215	(0.000*)
	Precentral	-0.142	(NA)	-0.350	(NA)	-0.482	(NA)	1.769	(NA)	1.721	(NA)	3.084	(NA)
	Paracentral	0.900	(NA)	0.607	(NA)	-0.900	(NA)	6.085	(NA)	23.410	(NA)	23.697	(NA)
Parietal	Superior Parietal	0.900	(0.681)	0.900	(0.419)	0.026	(0.968)	0.000	(1.000)	15.551	(0.000*)	11.637	(0.000*)
	Inferior Parietal	-0.900	(NA)	-0.900	(0.548)	-0.900	(0.285)	0.000	(1.000)	0.000	(1.000)	0.000	(1.000)
	Supramarginal	0.377	(1.000)	0.431	(0.892)	-0.900	(0.339)	-0.512	(0.859)	20.792	(0.000*)	15.038	(0.000*)
	Postcentral	-0.900	(0.681)	-0.900	(0.807)	-0.753	(0.378)	0.000	(1.000)	-5.290	(0.000*)	-3.958	(0.000*)
	Precuneus	-0.900	(0.742)	-0.536	(0.892)	-0.900	(0.285)	-6.924	(0.000*)	9.397	(0.000*)	0.000	(1.000)
Temporal	Superior Temporal	0.900	(NA)	0.058	(NA)	-0.008	(NA)	11.201	(NA)	0.719	(NA)	11.914	(NA)
	Superior Temporal Sulcus	-0.900	(0.907)	-0.839	(0.470)	-0.900	(0.285)	-2.009	(0.067)	2.727	(0.008*)	0.000	(1.000)
	Middle Temporal	1.000	(0.630)	-0.123	(1.000)	-0.108	(0.968)	67.581	(0.000*)	-0.163	(0.995)	68.511	(0.000*)
	Inferior Temporal	0.105	(0.907)	0.484	(0.892)	-0.900	(0.285)	-3.352	(0.001*)	21.516	(0.000*)	12.696	(0.000*)
	Fusiform	0.186	(1.000)	1.000	(0.419)	0.030	(0.968)	-65.107	(0.000*)	90.068	(0.000*)	1.274	(0.286)
	Transverse Temporal	-0.900	(1.000)	-0.438	(0.892)	-0.900	(0.378)	-7.943	(0.000*)	10.780	(0.000*)	0.000	(1.000)
	Entorhinal	0.900	(0.394)	0.900	(0.892)	-0.621	(0.698)	0.000	(1.000)	23.639	(0.000*)	17.688	(0.000*)
	Temporal Pole	0.900	(NA)	0.900	(NA)	0.900	(NA)	0.000	(NA)	0.000	(NA)	0.000	(NA)
	Parahippocampal	-0.900	(0.630)	-0.900	(0.693)	-0.900	(0.339)	0.000	(1.000)	0.000	(1.000)	0.000	(1.000)
Occipital	Lateral Occipital	-0.032	(1.000)	0.302	(0.892)	-0.605	(0.630)	-2.726	(0.010*)	10.890	(0.000*)	5.381	(0.000*)
	Lingual	-0.349	(1.000)	0.900	(0.419)	-0.900	(0.378)	-14.549	(0.000*)	NA	(0.000*)	8.917	(0.000*)
	Cuneus	-0.900	(NA)	-0.900	(NA)	-0.119	(NA)	0.000	(NA)	-14.550	(NA)	-10.888	(NA)
	Pericalcarine	-0.313	(0.907)	0.228	(0.892)	-0.900	(NA)	-4.409	(0.000*)	18.331	(0.000*)	9.239	(0.000*)
Cingulate	Rostral Anterior Cingulate	0.145	(NA)	0.588	(NA)	-0.528	(NA)	-4.191	(NA)	13.577	(NA)	5.903	(NA)
	Caudal Anterior Cingulate	-0.400	(NA)	-0.004	(NA)	-0.900	(NA)	-3.324	(NA)	15.786	(NA)	8.436	(NA)
	Posterior Cingulate	0.900	(NA)	-0.411	(NA)	-0.715	(NA)	15.126	(NA)	4.944	(NA)	19.061	(NA)
	Isthmus Cingulate	-0.900	(NA)	-0.900	(NA)	-0.343	(NA)	0.000	(NA)	-11.984	(NA)	-8.967	(NA)
	Insula	-0.900	(0.885)	-0.784	(0.892)	-1.000	(0.339)	-3.292	(0.002*)	79.025	(0.000*)	55.789	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all schizophrenia participants (N=123, N=30 with cortical data).
Covariates included age, age^2, sex, and site for all analyses.

Appendix Table 26. Environmental correlations between depression and cortical surface area with basic covariates.

		Environmental Correlations						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_E	*p*-value	R_E	*p*-value	R_E	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	0.282	(0.552)	0.378	(0.865)	0.357	(0.778)	-0.750	(0.453)	0.211	(0.869)	-0.619	(0.536)
	Superior Frontal	1.000	(0.422)	0.900	(0.789)	-0.900	(0.778)	48.079	(0.000*)	NA	(0.000*)	72.488	(0.000*)
	Rostral Middle Frontal	0.900	(0.389)	0.032	(0.932)	-0.159	(0.778)	9.987	(0.000*)	1.712	(0.130)	11.984	(0.000*)
	Caudal Middle Frontal	0.136	(0.957)	0.786	(0.789)	-0.017	(0.978)	-6.418	(0.000*)	9.572	(0.000*)	1.123	(0.285)
	Pars Opercularis	0.900	(0.284)	-0.730	(0.789)	-0.197	(0.778)	16.647	(0.000*)	-6.472	(0.000*)	12.265	(0.000*)
	Pars Triangularis	0.900	(NA)	-0.154	(NA)	0.186	(NA)	11.284	(NA)	-3.042	(NA)	9.426	(NA)
	Pars Orbitalis	0.852	(0.596)	-0.815	(0.789)	-0.098	(0.786)	16.673	(0.000*)	-9.254	(0.000*)	9.992	(0.000*)
	Lateral Orbitofrontal	1.000	(0.284)	0.900	(0.789)	-0.015	(NA)	48.079	(0.000*)	13.202	(0.000*)	61.798	(0.000*)
	Medial Orbitofrontal	0.900	(0.552)	0.485	(0.789)	0.005	(0.978)	6.534	(0.000*)	4.655	(0.000*)	10.764	(0.000*)
	Precentral	1.000	(NA)	0.900	(NA)	0.303	(NA)	48.079	(NA)	10.291	(NA)	59.391	(NA)
	Paracentral	-0.900	(NA)	-0.072	(NA)	-0.170	(NA)	-9.712	(NA)	0.890	(NA)	-9.541	(NA)
Parietal	Superior Parietal	0.900	(NA)	-0.347	(0.878)	-0.118	(0.778)	12.721	(0.000*)	-2.159	(0.053)	11.677	(0.000*)
	Inferior Parietal	0.900	(0.422)	-0.167	(0.900)	-0.257	(0.778)	11.378	(0.000*)	0.841	(0.480)	12.737	(0.000*)
	Supramarginal	0.900	(0.284)	0.164	(0.865)	0.190	(0.778)	9.060	(0.000*)	-0.235	(0.869)	9.393	(0.000*)
	Postcentral	0.892	(0.389)	-0.160	(0.900)	-0.166	(0.778)	11.047	(0.000*)	0.048	(0.962)	11.731	(0.000*)
	Precuneus	0.900	(0.389)	0.302	(0.900)	0.077	(0.902)	8.045	(0.000*)	2.084	(0.059)	10.238	(0.000*)
Temporal	Superior Temporal	0.900	(NA)	-0.015	(NA)	-0.092	(NA)	10.312	(NA)	0.685	(NA)	11.479	(NA)
	Superior Temporal Sulcus	0.006	(0.987)	-0.228	(0.789)	-0.347	(0.778)	1.654	(0.107)	1.146	(0.318)	2.698	(0.008*)
	Middle Temporal	0.900	(NA)	-0.594	(0.789)	-0.339	(0.778)	14.951	(0.000*)	-2.933	(0.006*)	13.397	(0.000*)
	Inferior Temporal	1.000	(NA)	0.235	(0.900)	-0.142	(0.778)	56.624	(0.000*)	3.396	(0.001*)	62.732	(0.000*)
	Fusiform	0.451	(0.596)	0.064	(0.900)	-0.091	(0.778)	2.919	(0.004*)	1.383	(0.222)	4.233	(0.000*)
	Transverse Temporal	0.049	(0.957)	0.207	(0.900)	0.615	(0.778)	-1.112	(0.278)	-4.495	(0.000*)	-4.894	(0.000*)
	Entorhinal	-0.238	(0.552)	0.588	(0.878)	0.106	(0.778)	-6.355	(0.000*)	5.036	(0.000*)	-2.560	(0.012*)
	Temporal Pole	0.900	(NA)	0.373	(NA)	0.583	(NA)	7.489	(NA)	-2.434	(NA)	5.913	(NA)
	Parahippocampal	0.900	(0.284)	-0.551	(0.932)	0.314	(0.778)	14.502	(0.000*)	-8.374	(0.000*)	8.422	(0.000*)
Occipital	Lateral Occipital	0.238	(0.609)	-0.635	(0.789)	0.372	(0.778)	6.887	(0.000*)	-10.120	(0.000*)	-1.081	(0.292)
	Lingual	0.798	(0.284)	-0.160	(0.900)	0.008	(0.978)	8.707	(0.000*)	-1.501	(0.188)	7.973	(0.000*)
	Cuneus	0.157	(NA)	-0.299	(NA)	-0.585	(NA)	3.240	(NA)	3.211	(NA)	6.084	(NA)
	Pericalcarine	0.823	(0.552)	-0.077	(0.932)	-0.387	(0.778)	8.616	(0.000*)	2.942	(0.006*)	11.550	(0.000*)
Cingulate	Rostral Anterior Cingulate	0.900	(NA)	0.430	(NA)	0.900	(NA)	7.017	(NA)	-8.980	(NA)	0.000	(NA)
	Caudal Anterior Cingulate	0.391	(NA)	0.070	(NA)	0.301	(NA)	2.382	(NA)	-2.139	(NA)	0.752	(NA)
	Posterior Cingulate	0.900	(NA)	0.900	(NA)	0.341	(NA)	0.000	(NA)	9.914	(NA)	8.198	(NA)
	Isthmus Cingulate	1.000	(NA)	0.900	(NA)	0.437	(NA)	48.079	(NA)	8.907	(NA)	58.246	(NA)
	Insula	0.900	(0.284)	0.269	(0.789)	0.236	(0.778)	8.294	(0.000*)	0.317	(0.858)	9.040	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all depression participants (N=137, N=38 with cortical data).
Covariates included age, age^2, sex, site, and schizophrenia for all analyses.

Appendix Table 27. Environmental correlations between depression and cortical surface area with conservative covariates.

		Environmental Correlations						Comparisons Across Age-Risk Periods					
		Rise		Peak		Plateau		Rise/Peak		Peak/Plateau		Rise/Plateau	
Lobe	Region	R_E	*p*-value	R_E	*p*-value	R_E	*p*-value	*z*	*p*-value	*z*	*p*-value	*z*	*p*-value
Frontal	Frontal Pole	0.619	(0.538)	0.439	(0.997)	0.319	(0.712)	1.754	(0.091)	1.249	(0.282)	2.889	(0.005*)
	Superior Frontal	0.900	(0.128)	0.595	(0.997)	-0.888	(0.092)	5.454	(0.000*)	18.640	(0.000*)	21.185	(0.000*)
	Rostral Middle Frontal	1.000	(0.251)	0.080	(0.997)	-0.213	(0.712)	57.729	(0.000*)	2.637	(0.015*)	63.274	(0.000*)
	Caudal Middle Frontal	-0.025	(0.937)	0.416	(0.997)	-0.050	(0.785)	-3.248	(0.002*)	4.375	(0.000*)	0.181	(0.856)
	Pars Opercularis	0.900	(0.251)	-0.327	(0.997)	-0.156	(0.712)	12.564	(0.000*)	-1.622	(0.179)	11.955	(0.000*)
	Pars Triangularis	0.574	(NA)	-0.113	(NA)	0.194	(NA)	5.313	(NA)	-2.753	(NA)	3.346	(NA)
	Pars Orbitalis	0.249	(0.634)	-0.524	(0.997)	-0.269	(0.726)	5.804	(0.000*)	-2.719	(0.013*)	3.893	(0.000*)
	Lateral Orbitofrontal	0.874	(0.340)	0.504	(0.997)	-0.169	(0.712)	5.512	(0.000*)	6.435	(0.000*)	11.154	(0.000*)
	Medial Orbitofrontal	0.293	(0.725)	0.082	(0.997)	-0.062	(0.785)	1.517	(0.141)	1.285	(0.280)	2.669	(0.010*)
	Precentral	0.761	(NA)	0.900	(NA)	0.201	(NA)	-3.279	(NA)	11.259	(NA)	5.840	(NA)
	Paracentral	-0.430	(NA)	0.649	(NA)	-0.285	(NA)	-8.550	(NA)	9.466	(NA)	-1.221	(NA)
Parietal	Superior Parietal	0.478	(0.423)	-0.203	(0.997)	-0.144	(0.785)	5.039	(0.000*)	-0.538	(0.645)	4.889	(0.000*)
	Inferior Parietal	0.900	(0.340)	-0.037	(0.997)	-0.393	(0.712)	10.469	(0.000*)	3.355	(0.002*)	13.853	(0.000*)
	Supramarginal	0.474	(0.340)	0.095	(0.997)	0.201	(0.726)	2.906	(0.005*)	-0.963	(0.403)	2.278	(0.026*)
	Postcentral	0.348	(0.538)	-0.154	(0.997)	-0.128	(0.785)	3.593	(0.000*)	-0.229	(0.819)	3.613	(0.000*)
	Precuneus	0.527	(0.423)	0.060	(0.997)	-0.070	(0.785)	3.650	(0.000*)	1.155	(0.314)	4.817	(0.000*)
Temporal	Superior Temporal	0.239	(NA)	-0.031	(NA)	-0.175	(NA)	1.909	(NA)	1.288	(NA)	3.085	(NA)
	Superior Temporal Sulcus	0.391	(0.746)	-0.056	(0.997)	-0.539	(0.076)	3.250	(0.002*)	4.850	(0.000*)	7.450	(0.000*)
	Middle Temporal	0.900	(NA)	-0.473	(0.997)	-0.449	(0.092)	13.770	(0.000*)	-0.266	(0.819)	14.353	(0.000*)
	Inferior Temporal	0.900	(0.285)	0.209	(0.997)	-0.325	(0.712)	8.736	(0.000*)	4.880	(0.000*)	13.280	(0.000*)
	Fusiform	0.195	(0.538)	0.000	(0.997)	-0.162	(0.712)	1.375	(0.176)	1.443	(0.238)	2.649	(0.010*)
	Transverse Temporal	0.126	(0.778)	0.144	(0.997)	0.492	(0.076)	-0.128	(0.898)	-3.489	(0.001*)	-3.021	(0.004*)
	Entorhinal	-0.192	(0.641)	0.655	(0.997)	0.179	(0.785)	-6.784	(0.000*)	5.351	(0.000*)	-2.755	(0.008*)
	Temporal Pole	0.900	(NA)	0.262	(NA)	0.768	(NA)	8.351	(NA)	-6.624	(NA)	3.361	(NA)
	Parahippocampal	0.900	(0.251)	0.001	(0.997)	0.423	(0.712)	10.202	(0.000*)	-3.993	(0.000*)	7.494	(0.000*)
Occipital	Lateral Occipital	0.188	(0.630)	-0.377	(0.997)	0.399	(0.643)	4.069	(0.000*)	-7.268	(0.000*)	-1.704	(0.092)
	Lingual	0.209	(0.659)	-0.138	(0.997)	-0.042	(0.844)	2.432	(0.018*)	-0.854	(0.449)	1.868	(0.067)
	Cuneus	0.460	(NA)	-0.284	(NA)	-0.634	(NA)	5.469	(NA)	4.054	(NA)	9.139	(NA)
	Pericalcarine	0.555	(0.565)	-0.108	(0.997)	-0.574	(0.641)	5.089	(0.000*)	4.835	(0.000*)	9.384	(0.000*)
Cingulate	Rostral Anterior Cingulate	0.636	(NA)	0.191	(NA)	0.652	(NA)	3.869	(NA)	-5.193	(NA)	-0.199	(NA)
	Caudal Anterior Cingulate	0.183	(NA)	0.111	(NA)	0.203	(NA)	0.506	(NA)	-0.832	(NA)	-0.152	(NA)
	Posterior Cingulate	0.900	(NA)	0.128	(NA)	0.247	(NA)	9.319	(NA)	-1.097	(NA)	8.954	(NA)
	Isthmus Cingulate	0.900	(NA)	0.831	(NA)	0.265	(NA)	1.939	(NA)	8.179	(NA)	8.816	(NA)
	Insula	0.900	(0.251)	0.118	(0.997)	0.264	(0.726)	9.389	(0.000*)	-1.350	(0.266)	8.819	(0.000*)

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Analyses conducted including all depression participants (N=137, N=38 with cortical data).
Covariates included age, age^2, sex, site, and schizophrenia for all analyses

Appendix Table 28. Genetic correlations between depression and global cortical measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Global	Intracranial Volume	-0.105	(0.988)	-0.221	(0.858)	0.047	(0.827)	-0.099	(1.000)	-0.167	(0.839)	0.046	(0.940)
	Lateral Ventricle Volume	0.406	(0.551)	-0.030	(NA)	0.142	(0.827)	0.479	(0.524)	-0.132	(0.839)	0.239	(0.940)
	Mean Thickness	-0.208	(0.551)	-0.060	(0.858)	0.031	(0.827)	0.071	(1.000)	0.129	(0.839)	0.079	(0.940)
	Total Surface Area	-0.078	(1.000)	-0.123	(0.858)	0.103	(0.827)	-0.271	(0.524)	0.168	(0.839)	0.022	(0.940)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*Z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Global	Intracranial Volume	0.835	(0.538)	Stable	-2.406	(0.065)	Stable	0.480	(0.682)	Stable	-1.908	(0.113)	Stable
	Lateral Ventricle Volume	-3.200	(0.005*)	Decrease	1.543	(0.164)	Stable	-4.543	(0.000*)	Decrease	3.343	(0.003*)	Increase
	Mean Thickness	-1.045	(0.538)	Stable	-0.809	(0.419)	Stable	-0.410	(0.682)	Stable	0.452	(0.651)	Stable
	Total Surface Area	0.311	(0.756)	Stable	-2.011	(0.089)	Stable	-3.104	(0.004*)	Decrease	1.315	(0.251)	Stable

		Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
		Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
		0.0%	75.0%	25.0%	0.0%	100.0%	0.0%	0.0%	50.0%	50.0%	25.0%	75.0%	0.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all depression participants (N=38 with cortical data) and additionally covarying schizophrenia. Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0), Depression (scored Depression group = 1, not in Depression group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume (except for intracranial volume, for which conservative adjustments additionally included only parental education and scan quality).

For comparisons across age-risk periods, genetic correlations between depression and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).

As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period. This comparison applies to all cortical measures except lateral ventricle volume, for which genetic correlations are expected to be positive rather than negative; here, "increase" indicates a significantly more positive genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less positive genetic correlation from the earlier to the later age-risk period.

Appendix Table 29. Genetic correlations between depression and frontal thickness measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Frontal	Frontal Pole	0.357	(NA)	0.181	(NA)	0.396	(NA)	0.325	(NA)	0.275	(NA)	0.075	(NA)
	Superior Frontal	-0.131	(NC)	0.228	(0.962)	0.125	(0.890)	0.048	(1.000)	0.272	(0.998)	0.177	(0.971)
	Rostral Middle Frontal	0.149	(1.000)	0.194	(0.962)	0.239	(0.890)	0.239	(1.000)	0.290	(0.998)	0.331	(0.971)
	Caudal Middle Frontal	0.095	(1.000)	0.227	(0.962)	-0.084	(0.890)	0.155	(1.000)	0.332	(0.998)	-0.028	(0.971)
	Pars Opercularis	-0.131	(NC)	0.066	(0.962)	-0.134	(0.890)	0.059	(1.000)	0.149	(0.998)	-0.086	(0.971)
	Pars Triangularis	-0.124	(1.000)	-0.020	(0.962)	-0.222	(0.890)	-0.065	(1.000)	0.027	(1.000)	-0.186	(0.971)
	Pars Orbitalis	-0.049	(1.000)	-0.290	(0.962)	-0.092	(0.890)	0.069	(1.000)	-0.069	(1.000)	-0.095	(0.971)
	Lateral Orbitofrontal	-0.073	(1.000)	-0.557	(0.962)	-0.282	(0.890)	-0.050	(1.000)	-0.435	(0.998)	-0.179	(0.971)
	Medial Orbitofrontal	0.900	(1.000)	0.099	(0.962)	0.118	(1.000)	0.900	(1.000)	0.119	(1.000)	0.182	(0.971)
	Precentral	-0.124	(1.000)	-0.189	(0.962)	-0.058	(0.890)	-0.109	(1.000)	-0.013	(1.000)	-0.006	(0.971)
	Paracentral	-0.063	(NA)	0.190	(NA)	0.110	(NA)	0.035	(NA)	0.333	(NA)	0.078	(NA)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Frontal	Frontal Pole	1.321	(NA)	-	-2.089	(NA)	-	0.381	(NA)	-	1.841	(NA)	-
	Superior Frontal	-2.529	(0.044*)	Decrease	0.947	(0.439)	Stable	-1.606	(0.226)	Stable	0.893	(0.570)	Stable
	Rostral Middle Frontal	-0.327	(0.762)	Stable	-0.418	(0.706)	Stable	-0.385	(0.732)	Stable	-0.401	(0.863)	Stable
	Caudal Middle Frontal	-0.937	(0.534)	Stable	2.799	(0.017*)	Increase	-1.315	(0.362)	Stable	3.314	(0.004*)	Increase
	Pars Opercularis	-1.372	(0.355)	Stable	1.783	(0.156)	Stable	-0.629	(0.609)	Stable	2.100	(0.069)	Stable
	Pars Triangularis	-0.721	(0.591)	Stable	1.822	(0.156)	Stable	-0.639	(0.609)	Stable	1.914	(0.091)	Stable
	Pars Orbitalis	1.732	(0.191)	Stable	-1.835	(0.156)	Stable	0.964	(0.514)	Stable	0.232	(0.939)	Stable
	Lateral Orbitofrontal	3.852	(0.001*)	Increase	-3.011	(0.010*)	Decrease	2.881	(0.019*)	Increase	-2.527	(0.038*)	Decrease
	Medial Orbitofrontal	9.520	(0.000*)	Increase	-0.172	(0.863)	Stable	9.383	(0.000*)	Increase	-0.577	(0.811)	Stable
	Precentral	0.464	(0.708)	Stable	-1.176	(0.370)	Stable	-0.670	(0.609)	Stable	-0.064	(0.962)	Stable
	Paracentral	-1.774	(NA)	-	0.726	(NA)	-	-2.158	(NA)	-	2.379	(NA)	-

	Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
	Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
	22.2%	66.7%	11.1%	11.1%	77.8%	11.1%	22.2%	77.8%	0.0%	11.1%	77.8%	11.1%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all depression participants (N=38 with cortical data) and additionally covarying schizophrenia. Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0), Depression (scored Depression group = 1, not in Depression group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments. NC indicates that the significance of the parameter was not computable.

For comparisons across age-risk periods, genetic correlations between depression and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).
As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Appendix Table 30. Genetic correlations between depression and parietal thickness measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Parietal	Superior Parietal	0.029	(NA)	0.163	(NA)	-0.028	(NA)	0.109	(NA)	0.294	(NA)	0.032	(NA)
	Inferior Parietal	-0.355	(1.000)	-0.184	(0.962)	-0.075	(0.890)	-0.267	(1.000)	0.015	(1.000)	-0.026	(0.971)
	Supramarginal	-0.104	(1.000)	0.076	(0.962)	-0.108	(0.890)	-0.040	(1.000)	0.263	(0.998)	0.029	(0.971)
	Postcentral	0.102	(NA)	0.140	(NA)	0.180	(NA)	0.123	(NA)	0.443	(NA)	0.221	(NA)
	Precuneus	-0.281	(NA)	0.026	(NA)	0.072	(NA)	-0.124	(NA)	0.178	(NA)	0.102	(NA)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Parietal	Superior Parietal	-0.938	(NA)	-	1.705	(NA)	-	-1.348	(NA)	-	2.405	(NA)	-
	Inferior Parietal	-1.278	(0.372)	Stable	-0.984	(0.439)	Stable	-2.000	(0.139)	Stable	0.368	(0.863)	Stable
	Supramarginal	-1.252	(0.372)	Stable	1.638	(0.194)	Stable	-2.145	(0.123)	Stable	2.132	(0.069)	Stable
	Postcentral	-0.263	(NA)	-	-0.364	(NA)	-	-2.448	(NA)	-	2.234	(NA)	-
	Precuneus	-2.183	(NA)	-	-0.407	(NA)	-	-2.111	(NA)	-	0.686	(NA)	-

		Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
		Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
		0.0%	100.0%	0.0%	0.0%	100.0%	0.0%	0.0%	100.0%	0.0%	0.0%	100.0%	0.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all depression participants (N=38 with cortical data) and additionally covarying schizophrenia. Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0), Depression (scored Depression group = 1, not in Depression group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.
For comparisons across age-risk periods, genetic correlations between depression and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).
As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Appendix Table 31. Genetic correlations between depression and temporal thickness measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Temporal	Superior Temporal	0.003	(1.000)	-0.271	(0.962)	0.131	(0.890)	0.018	(1.000)	-0.107	(0.998)	0.182	(0.971)
	Superior Temporal Sulcus	-0.485	(1.000)	0.247	(0.962)	-0.131	(0.890)	-0.404	(1.000)	0.300	(0.998)	-0.070	(0.971)
	Middle Temporal	-0.072	(1.000)	0.055	(0.962)	-0.035	(0.912)	0.043	(1.000)	0.272	(0.998)	0.006	(0.971)
	Inferior Temporal	-0.412	(1.000)	-0.131	(0.962)	-0.004	(1.000)	-0.379	(1.000)	0.014	(1.000)	0.030	(0.971)
	Fusiform	-0.314	(1.000)	-0.219	(0.962)	-0.148	(0.890)	-0.071	(1.000)	-0.007	(1.000)	-0.012	(0.971)
	Transverse Temporal	-0.386	(NA)	-0.082	(NA)	-0.044	(NA)	-0.306	(NA)	0.043	(NA)	-0.048	(NA)
	Entorhinal	-0.011	(1.000)	-0.111	(0.962)	-0.237	(0.890)	0.148	(1.000)	0.002	(1.000)	0.258	(0.971)
	Temporal Pole	-0.119	(NA)	-0.900	(NA)	-0.282	(NA)	-0.230	(NA)	-0.900	(NA)	-0.254	(NA)
	Parahippocampal	0.020	(1.000)	-0.239	(0.962)	-0.182	(0.890)	0.018	(1.000)	-0.218	(0.998)	-0.173	(0.971)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Temporal	Superior Temporal	1.947	(0.148)	Stable	-3.642	(0.002*)	Decrease	0.872	(0.551)	Stable	-2.589	(0.037*)	Decrease
	Superior Temporal Sulcus	-5.417	(0.000*)	Decrease	3.410	(0.003*)	Increase	-5.121	(0.000*)	Decrease	3.370	(0.004*)	Increase
	Middle Temporal	-0.886	(0.540)	Stable	0.804	(0.510)	Stable	-1.636	(0.226)	Stable	2.425	(0.044*)	Increase
	Inferior Temporal	-2.121	(0.111)	Stable	-1.133	(0.370)	Stable	-2.860	(0.019*)	Decrease	-0.140	(0.962)	Stable
	Fusiform	-0.703	(0.591)	Stable	-0.655	(0.589)	Stable	-0.446	(0.718)	Stable	0.048	(0.962)	Stable
	Transverse Temporal	-2.255	(NA)	-	-0.338	(NA)	-	-2.490	(NA)	-	0.810	(NA)	-
	Entorhinal	0.693	(0.591)	Stable	1.154	(0.370)	Stable	1.018	(0.507)	Stable	-2.324	(0.051)	Stable
	Temporal Pole	9.378	(NA)	-	-10.491	(NA)	-	8.586	(NA)	-	-10.759	(NA)	-
	Parahippocampal	1.832	(0.171)	Stable	-0.534	(0.650)	Stable	1.656	(0.226)	Stable	-0.410	(0.863)	Stable

		Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
		Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
		0.0%	85.7%	14.3%	14.3%	71.4%	14.3%	0.0%	71.4%	28.6%	28.6%	57.1%	14.3%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all depression participants (N=38 with cortical data) and additionally covarying schizophrenia. Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0), Depression (scored Depression group = 1, not in Depression group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.
For comparisons across age-risk periods, genetic correlations between depression and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).

As indicated by comparisons across age-risk periods, “increase” indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, “stable” indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and “decrease” indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Appendix Table 32. Genetic correlations between depression and occipital thickness measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Occipital	Lateral Occipital	-0.296	(NA)	0.045	(NA)	-0.225	(NA)	-0.350	(NA)	0.146	(NA)	-0.158	(NA)
	Lingual	-0.329	(1.000)	0.111	(0.962)	-0.024	(NA)	-0.243	(1.000)	0.280	(0.998)	0.033	(0.971)
	Cuneus	0.112	(NA)	0.169	(NA)	-0.040	(NA)	-0.098	(NA)	0.331	(NA)	0.031	(NA)
	Pericalcarine	-0.335	(NA)	-0.166	(NA)	0.120	(NA)	-0.322	(NA)	-0.069	(NA)	0.165	(NA)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Occipital	Lateral Occipital	-2.433	(NA)	-	2.433	(NA)	-	-3.551	(NA)	-	2.717	(NA)	-
	Lingual	-3.145	(0.010*)	Decrease	1.205	(0.370)	Stable	-3.714	(0.002*)	Decrease	2.252	(0.056)	Stable
	Cuneus	-0.400	(NA)	-	1.866	(NA)	-	-3.063	(NA)	-	2.777	(NA)	-
	Pericalcarine	-1.250	(NA)	-	-2.560	(NA)	-	-1.839	(NA)	-	-2.094	(NA)	-

		Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
		Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
		0.0%	0.0%	100.0%	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%	0.0%	100.0%	0.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all depression participants (N=38 with cortical data) and additionally covarying schizophrenia. Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0), Depression (scored Depression group = 1, not in Depression group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.
For comparisons across age-risk periods, genetic correlations between depression and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).
As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Appendix Table 33. Genetic correlations between depression and cingulate thickness measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Cingulate	Rostral Anterior Cingulate	0.082	(1.000)	0.147	(0.962)	-0.586	(0.890)	-0.180	(1.000)	0.102	(1.000)	-0.564	(0.971)
	Caudal Anterior Cingulate	1.000	(NA)	0.825	(NA)	0.188	(NA)	1.000	(NA)	0.797	(NA)	0.519	(NA)
	Posterior Cingulate	0.055	(1.000)	0.423	(1.000)	-0.194	(0.890)	0.280	(1.000)	0.369	(0.998)	-0.139	(0.971)
	Isthmus Cingulate	0.164	(1.000)	-0.004	(1.000)	-0.457	(0.890)	0.043	(1.000)	-0.112	(1.000)	-0.511	(0.971)
	Insula	-0.073	(1.000)	-0.029	(0.962)	-0.288	(0.890)	0.012	(1.000)	-0.020	(1.000)	-0.243	(0.971)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Cingulate	Rostral Anterior Cingulate	-0.459	(0.708)	Stable	7.273	(0.000*)	Increase	-1.975	(0.139)	Stable	6.579	(0.000*)	Increase
	Caudal Anterior Cingulate	50.153	(NA)	-	8.722	(NA)	-	50.732	(NA)	-	4.564	(NA)	-
	Posterior Cingulate	-2.754	(0.027*)	Decrease	5.754	(0.000*)	Increase	-0.694	(0.609)	Stable	4.678	(0.000*)	Increase
	Isthmus Cingulate	1.179	(0.391)	Stable	4.338	(0.000*)	Increase	1.076	(0.498)	Stable	4.011	(0.000*)	Increase
	Insula	-0.303	(0.762)	Stable	2.369	(0.051)	Stable	0.226	(0.822)	Stable	2.020	(0.077)	Stable

		Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
		Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
		0.0%	75.0%	25.0%	75.0%	25.0%	0.0%	0.0%	100.0%	0.0%	75.0%	25.0%	0.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all depression participants (N=38 with cortical data) and additionally covarying schizophrenia. Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0), Depression (scored Depression group = 1, not in Depression group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.
For comparisons across age-risk periods, genetic correlations between depression and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).
As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Appendix Table 34. Genetic correlations between depression and frontal area measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Frontal	Frontal Pole	-0.059	(0.902)	-0.391	(0.827)	-0.200	(0.909)	-0.098	(1.000)	-0.620	(0.667)	-0.295	(0.901)
	Superior Frontal	-0.345	(0.801)	-0.243	(0.827)	0.413	(0.321)	-0.399	(0.937)	-0.285	(0.667)	0.342	(0.901)
	Rostral Middle Frontal	-0.141	(0.902)	-0.038	(0.972)	0.015	(1.000)	-0.359	(0.937)	0.026	(0.976)	-0.129	(0.901)
	Caudal Middle Frontal	-0.156	(0.902)	-0.583	(0.827)	-0.003	(1.000)	-0.014	(1.000)	-0.900	(0.667)	-0.117	(0.901)
	Pars Opercularis	-0.444	(0.888)	0.068	(0.827)	0.164	(0.909)	-0.633	(1.000)	0.231	(0.667)	0.037	(0.901)
	Pars Triangularis	-0.120	(NA)	0.035	(NA)	-0.227	(NA)	-0.074	(NA)	0.900	(NA)	-0.400	(NA)
	Pars Orbitalis	-0.120	(0.902)	0.107	(0.827)	0.277	(0.909)	-0.112	(1.000)	0.131	(0.830)	0.263	(0.901)
	Lateral Orbitofrontal	-0.343	(0.801)	-0.235	(0.827)	0.075	(NA)	-0.562	(1.000)	-0.268	(0.667)	-0.040	(0.901)
	Medial Orbitofrontal	0.163	(0.902)	-0.144	(0.827)	0.340	(0.909)	0.261	(1.000)	0.097	(0.922)	0.409	(0.901)
	Precentral	0.014	(NA)	-0.199	(NA)	-0.072	(NA)	-0.070	(NA)	-0.225	(NA)	-0.205	(NA)
	Paracentral	-0.063	(NA)	-0.006	(NA)	0.277	(NA)	0.162	(NA)	0.004	(NA)	0.316	(NA)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Frontal	Frontal Pole	2.455	(0.038*)	Increase	-1.867	(0.114)	Stable	4.345	(0.000*)	Increase	-3.742	(0.000*)	Decrease
	Superior Frontal	-0.774	(0.555)	Stable	-6.105	(0.000*)	Decrease	-0.895	(0.445)	Stable	-5.768	(0.000*)	Decrease
	Rostral Middle Frontal	-0.726	(0.562)	Stable	-0.464	(0.650)	Stable	-2.786	(0.013*)	Decrease	1.384	(0.224)	Stable
	Caudal Middle Frontal	3.538	(0.002*)	Increase	-5.889	(0.000*)	Decrease	10.110	(0.000*)	Increase	-12.018	(0.000*)	Decrease
	Pars Opercularis	-3.778	(0.001*)	Decrease	-0.863	(0.540)	Stable	-6.807	(0.000*)	Decrease	1.760	(0.118)	Stable
	Pars Triangularis	-1.076	(NA)	-	2.359	(NA)	-	-10.726	(NA)	-	16.821	(NA)	-
	Pars Orbitalis	-1.576	(0.197)	Stable	-1.571	(0.199)	Stable	-1.696	(0.135)	Stable	-1.226	(0.264)	Stable
	Lateral Orbitofrontal	-0.819	(0.550)	Stable	-2.798	(0.011*)	Decrease	-2.507	(0.021*)	Decrease	-2.079	(0.060)	Stable
	Medial Orbitofrontal	2.144	(0.070)	Stable	-4.423	(0.000*)	Decrease	1.182	(0.300)	Stable	-2.992	(0.005*)	Decrease
	Precentral	1.490	(NA)	-	-1.148	(NA)	-	1.107	(NA)	-	-0.193	(NA)	-
	Paracentral	-0.394	(NA)	-	-2.581	(NA)	-	1.102	(NA)	-	-2.865	(NA)	-

	Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
	Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
	25.0%	62.5%	12.5%	0.0%	50.0%	50.0%	25.0%	37.5%	37.5%	0.0%	50.0%	50.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all depression participants (N=38 with cortical data) and additionally covarying schizophrenia. Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0), Depression (scored Depression group = 1, not in Depression group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.

For comparisons across age-risk periods, genetic correlations between depression and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).
As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Appendix Table 35. Genetic correlations between depression and parietal area measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Parietal	Superior Parietal	0.071	(NC)	0.270	(0.827)	0.057	(0.909)	0.900	(1.000)	0.801	(0.667)	-0.098	(0.901)
	Inferior Parietal	-0.071	(0.902)	0.063	(0.927)	-0.065	(0.909)	-0.146	(1.000)	0.235	(0.922)	-0.106	(0.901)
	Supramarginal	-0.460	(0.801)	0.121	(0.827)	0.044	(1.000)	0.008	(1.000)	0.519	(0.667)	-0.380	(0.901)
	Postcentral	-0.097	(0.902)	0.157	(0.827)	0.590	(0.909)	0.900	(1.000)	0.379	(0.667)	0.044	(0.901)
	Precuneus	-0.056	(0.902)	-0.007	(0.998)	-0.114	(0.909)	0.327	(1.000)	0.356	(0.668)	-0.218	(0.901)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Parietal	Superior Parietal	-1.426	(0.246)	Stable	1.952	(0.102)	Stable	2.566	(0.020*)	Increase	10.657	(0.000*)	Increase
	Inferior Parietal	-0.934	(0.494)	Stable	1.137	(0.409)	Stable	-2.685	(0.016*)	Decrease	3.077	(0.004*)	Increase
	Supramarginal	-4.292	(0.000*)	Decrease	0.682	(0.540)	Stable	-3.937	(0.000*)	Decrease	8.658	(0.000*)	Increase
	Postcentral	-1.771	(0.141)	Stable	-4.616	(0.000*)	Decrease	7.442	(0.000*)	Increase	3.153	(0.003*)	Increase
	Precuneus	-0.341	(0.838)	Stable	0.953	(0.511)	Stable	-0.223	(0.826)	Stable	5.271	(0.000*)	Increase

Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
0.0%	80.0%	20.0%	0.0%	80.0%	20.0%	40.0%	20.0%	40.0%	100.0%	0.0%	0.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all depression participants (N=38 with cortical data) and additionally covarying schizophrenia. Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0), Depression (scored Depression group = 1, not in Depression group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NC indicates that the significance of the parameter was not computable.
For comparisons across age-risk periods, genetic correlations between depression and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).
As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Appendix Table 36. Genetic correlations between depression and temporal area measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Temporal	Superior Temporal	-0.173	(NA)	-0.192	(NA)	0.268	(NA)	-0.123	(NA)	-0.011	(NA)	0.509	(NA)
	Superior Temporal Sulcus	-0.084	(0.902)	0.900	(0.827)	0.710	(0.321)	-0.007	(1.000)	0.900	(0.667)	0.777	(0.236)
	Middle Temporal	0.077	(NC)	0.371	(0.827)	0.438	(0.909)	0.043	(NC)	1.000	(0.667)	0.411	(0.901)
	Inferior Temporal	0.094	(NC)	-0.170	(0.827)	0.326	(0.909)	0.068	(1.000)	-0.102	(0.922)	0.316	(0.901)
	Fusiform	0.000	(1.000)	-0.193	(0.827)	0.242	(0.909)	0.158	(1.000)	-0.014	(0.976)	0.126	(0.901)
	Transverse Temporal	-0.076	(0.902)	-0.574	(0.827)	-0.519	(0.467)	-0.183	(1.000)	-0.900	(0.667)	-0.888	(0.236)
	Entorhinal	-0.133	(0.902)	-0.519	(0.729)	-0.168	(0.909)	-0.059	(1.000)	-0.404	(0.667)	-0.297	(0.901)
	Temporal Pole	-0.198	(NA)	-0.389	(NA)	-0.697	(NA)	-0.190	(NA)	-0.357	(NA)	-0.776	(NA)
	Parahippocampal	-0.105	(0.902)	-0.078	(0.853)	-0.156	(0.909)	-0.150	(1.000)	-0.037	(0.964)	-0.190	(0.901)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Temporal	Superior Temporal	0.140	(NA)	-	-4.160	(NA)	-	-0.786	(NA)	-	-5.072	(NA)	-
	Superior Temporal Sulcus	-10.791	(0.000*)	Decrease	5.196	(0.000*)	Increase	-10.259	(0.000*)	Decrease	3.855	(0.000*)	Increase
	Middle Temporal	-2.170	(0.070)	Stable	-0.709	(0.540)	Stable	-57.991	(0.000*)	Decrease	70.712	(0.000*)	Increase
	Inferior Temporal	1.844	(0.130)	Stable	-4.521	(0.000*)	Decrease	1.185	(0.300)	Stable	-3.808	(0.000*)	Decrease
	Fusiform	1.352	(0.265)	Stable	-3.923	(0.000*)	Decrease	1.201	(0.300)	Stable	-1.240	(0.264)	Stable
	Transverse Temporal	4.005	(0.000*)	Increase	-0.697	(0.540)	Stable	8.923	(0.000*)	Increase	-0.512	(0.659)	Stable
	Entorhinal	3.056	(0.008*)	Increase	-3.590	(0.001*)	Decrease	2.557	(0.020*)	Increase	-1.077	(0.321)	Stable
	Temporal Pole	1.449	(NA)	-	4.011	(NA)	-	1.254	(NA)	-	5.878	(NA)	-
	Parahippocampal	-0.193	(0.884)	Stable	0.703	(0.540)	Stable	-0.790	(0.491)	Stable	1.378	(0.224)	Stable

		Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
		Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
		28.6%	57.1%	14.3%	14.3%	42.9%	42.9%	28.6%	42.9%	28.6%	28.6%	57.1%	14.3%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all depression participants (N=38 with cortical data) and additionally covarying schizophrenia. Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0), Depression (scored Depression group = 1, not in Depression group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.
For comparisons across age-risk periods, genetic correlations between depression and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).

As indicated by comparisons across age-risk periods, “increase” indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, “stable” indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and “decrease” indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Appendix Table 37. Genetic correlations between depression and occipital area measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Occipital	Lateral Occipital	0.369	(0.801)	0.331	(0.827)	0.022	(1.000)	0.434	(1.000)	0.408	(0.667)	-0.077	(0.901)
	Lingual	-0.494	(0.801)	0.000	(1.000)	0.051	(0.909)	0.020	(1.000)	0.080	(0.822)	0.026	(0.901)
	Cuneus	0.317	(NA)	0.900	(NA)	0.325	(NA)	-0.028	(NA)	0.900	(NA)	0.252	(NA)
	Pericalcarine	-0.284	(0.902)	0.088	(0.827)	0.170	(0.909)	-0.269	(1.000)	0.648	(0.667)	0.136	(0.901)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Occipital	Lateral Occipital	0.294	(0.839)	Stable	2.860	(0.010*)	Increase	0.219	(0.826)	Stable	4.525	(0.000*)	Increase
	Lingual	-3.757	(0.001*)	Decrease	-0.454	(0.650)	Stable	-0.422	(0.734)	Stable	0.479	(0.659)	Stable
	Cuneus	-7.930	(NA)	-	10.070	(NA)	-	-10.404	(NA)	-	10.783	(NA)	-
	Pericalcarine	-2.639	(0.025*)	Decrease	-0.736	(0.540)	Stable	-7.262	(0.000*)	Decrease	5.625	(0.000*)	Increase

	Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
	Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
	0.0%	33.3%	66.7%	33.3%	66.7%	0.0%	0.0%	66.7%	33.3%	66.7%	33.3%	0.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all depression participants (N=38 with cortical data) and additionally covarying schizophrenia. Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0), Depression (scored Depression group = 1, not in Depression group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.
For comparisons across age-risk periods, genetic correlations between depression and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).
As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Appendix Table 38. Genetic correlations between depression and cingulate area measures.

		Genetic Correlations with Basic Adjustments						Genetic Correlations with Conservative Adjustments					
		Rise		Peak		Plateau		Rise		Peak		Plateau	
Lobe	Region	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value	R_G	*p*-value
Cingulate	Rostral Anterior Cingulate	-0.309	(NA)	-0.900	(NA)	-0.039	(NA)	0.090	(NA)	0.040	(NA)	-0.229	(NA)
	Caudal Anterior Cingulate	-0.231	(NA)	-0.125	(NA)	-0.088	(NA)	-0.228	(NA)	0.075	(NA)	-0.115	(NA)
	Posterior Cingulate	-0.367	(NA)	-0.120	(NA)	-0.072	(NA)	-0.478	(NA)	0.091	(NA)	-0.219	(NA)
	Isthmus Cingulate	-0.316	(NA)	-0.195	(NA)	-0.038	(NA)	-0.330	(NA)	-0.204	(NA)	-0.095	(NA)
	Insula	-0.368	(0.801)	-0.372	(0.827)	-0.049	(0.909)	-0.488	(1.000)	-0.240	(0.822)	-0.208	(0.901)

		Comparisons Across Age-Risk Periods with Basic Adjustments						Comparisons Across Age-Risk Periods with Conservative Adjustments					
		Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
Lobe	Region	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change	*z*	*p*-value	Change
Cingulate	Rostral Anterior Cingulate	7.990	(NA)	-	-12.719	(NA)	-	0.348	(NA)	-	2.422	(NA)	-
	Caudal Anterior Cingulate	-0.758	(NA)	-	-0.338	(NA)	-	-2.126	(NA)	-	1.692	(NA)	-
	Posterior Cingulate	-1.834	(NA)	-	-0.426	(NA)	-	-4.241	(NA)	-	2.782	(NA)	-
	Isthmus Cingulate	-0.897	(NA)	-	-1.415	(NA)	-	-0.940	(NA)	-	-0.994	(NA)	-
	Insula	0.029	(0.977)	Stable	-3.034	(0.006*)	Decrease	-1.995	(0.074)	Stable	-0.308	(0.758)	Decrease

	Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Basic Adjustments						Proportions of Genetic Correlation Comparisons Showing Changes Across Age-Risk Periods with Conservative Adjustments					
	Rise/Peak			Peak/Plateau			Rise/Peak			Peak/Plateau		
	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
Cingulate	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%

Note. * indicates False Discovery Rate correction at $p<0.05$. Analyses were conducted on inverse-normalized scores and were robustly estimated using the t-distribution. Genetic correlations were estimated including all depression participants (N=38 with cortical data) and additionally covarying schizophrenia. Schizophrenia (scored Schizophrenia group = 1, not in Schizophrenia group = 0), Depression (scored Depression group = 1, not in Depression group = 0). Basic adjustments included site, age, age^2, sex, and handedness whereas conservative adjustments additionally included parental education, scan quality, and intracranial volume. NA indicates that the significance of the parameter was not tested as this measure did not show significant group differences between schizophrenia and controls, with or without key demographic adjustments.
For comparisons across age-risk periods, genetic correlations between depression and cortical measures were computed separately for each age-risk group and compared using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003).
As indicated by comparisons across age-risk periods, "increase" indicates a significantly more negative genetic correlation from the earlier to the later age-risk period, "stable" indicates a nonsignificant change in the genetic correlation from the earlier to the later age-risk period, and "decrease" indicates a significantly less negative genetic correlation from the earlier to the later age-risk period.

Appendix Table 39. Summary of significant overall genetic effects on cortical measures within each age-risk period.

Lobe (*k*)	Cortical Measures with Significant Heritability During Rise Period	Cortical Measures with Significant Heritability During Peak Period	Cortical Measures with Significant Heritability During Plateau Period
Global (4)		intracranial volume (1.00/0.97) mean thickness (0.76/0.87) total surface area (0.83/n.s.)	intracranial volume (0.98/0.92) lateral ventricle volume (0.56/0.55) mean thickness (0.66/0.88) total surface area (0.76/0.65)
TH Frontal (9)		precentral (0.82/n.s.)	superior frontal (0.76/0.75) rostral middle frontal (0.56/0.63) caudal middle frontal (0.67/0.74) pars opercularis (0.55/0.60) pars triangularis (0.59/0.58) lateral orbitofrontal (0.46/0.51) medial orbitofrontal (n.s./0.40) precentral (0.49/0.59)
TH Parietal (2)			inferior parietal (0.36/0.60) supramarginal (0.42/0.79)
TH Temporal (7)		middle temporal (1.00/0.96) inferior temporal (0.97/0.98) parahippocampal (0.79/0.76)	superior temporal (0.55/0.61) superior temporal sulcus (0.38/0.37) middle temporal (0.58/0.78) inferior temporal (0.36/0.53) fusiform (0.42/0.43) parahippocampal (0.61/0.58)
TH Occipital (1)			lingual (0.72/0.66)
TH Cingulate (4)		rostral anterior cingulate (0.85/0.78) isthmus cingulate (n.s./0.78) insula (n.s./0.75)	rostral anterior cingulate (0.54/0.47) posterior cingulate (0.53/0.71) isthmus cingulate (0.35/0.35) insula (0.62/0.66)
SA Frontal (8)		superior frontal (1.00/n.s.) rostral middle frontal (0.47/n.s.) pars opercularis (0.62/n.s.) pars orbitalis (0.57/n.s.) lateral orbitofrontal (1.00/n.s.) medial orbitofrontal (0.80/n.s.)	frontal pole (0.60/0.53) superior frontal (0.99/0.86) rostral middle frontal (0.70/0.61) caudal middle frontal (0.40/n.s.) pars opercularis (0.66/0.73) pars orbitalis (0.49/0.52) lateral orbitofrontal (0.63/0.72) medial orbitofrontal (0.5/0.33)
SA Parietal (5)		superior parietal (0.84/n.s.) supramarginal (0.95/n.s.) postcentral (0.58/n.s.) precuneus (0.86/n.s.)	superior parietal (0.55/0.50) inferior parietal (0.65/0.51) supramarginal (0.47/n.s.) precuneus (0.81/0.59)
SA Temporal (7)		middle temporal (0.68/n.s.) inferior temporal (0.83/n.s.) transverse temporal (0.53/n.s.) entorhinal (1.00/n.s.) parahippocampal (0.84/n.s.)	superior temporal sulcus (0.33/n.s.) middle temporal (0.63/0.53) inferior temporal (0.49/0.58) fusiform (n.s./0.40) transverse temporal (0.67/n.s.) parahippocampal (0.51/0.61)

SA Occipital (3)	pericalcarine (0.59/n.s.)	lateral occipital (0.55/0.60) lingual (0.73/0.50) pericalcarine (0.97/0.91)
SA Cingulate (1)	insula (0.72/n.s.)	insula (0.83/0.82)

Note. k indicates number of cortical measures examined within a given lobe. TH indicates thickness and SA indicates surface area. For each measure, heritability is presented as follows: ("heritability estimated with basic adjustments" / "heritability estimated with conservative adjustments").

Appendix Table 40. Summary of genetic correlations between depression and cortical measures within and across age-risk periods.

Lobe	Region	Significant Difference SZ vs. HC	Significant Rise R_G	Rise/Peak R_G Comparison	Significant Peak R_G	Peak/Plateau R_G Comparison	Significant Plateau R_G	Evidence for Early Neurodevelopmental Effects	Evidence for Late Neurodevelopmental Effects	Evidence for Neurodegenerative Effects
Global	Intracranial Volume									
	Lateral Ventricle Volume									
	Mean Thickness	X		– / –	*(n.s.)* / *(n.s.)*				– / –	
	Total Surface Area									
TH Frontal	Frontal Pole									
	Superior Frontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Rostral Middle Frontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Caudal Middle Frontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	– / –	+ / +
	Pars Opercularis	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Pars Triangularis	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Pars Orbitalis	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Lateral Orbitofrontal	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Medial Orbitofrontal	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Precentral	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Paracentral									
TH Parietal	Superior Parietal									
	Inferior Parietal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Supramarginal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Postcentral									
	Precuneus									
TH Temporal	Superior Temporal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Superior Temporal Sulcus	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	+ / –	*(n.s.)* / *(n.s.)*	– / –	– / –	+ / –
	Middle Temporal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	– / –	– / +
	Inferior Temporal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	– / –	– / +
	Fusiform	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Transverse Temporal									
	Entorhinal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Temporal Pole									
	Parahippocampal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
TH Occipital	Lateral Occipital									
	Lingual	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Cuneus									
	Pericalcarine									
TH Cingulate	Rostral Anterior Cingulate	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	– / –	+ / +
	Caudal Anterior Cingulate									
	Posterior Cingulate	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	– / –	+ / +
	Isthmus Cingulate	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	– / –	+ / +

	Insula	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
SA Frontal	Frontal Pole	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Superior Frontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Rostral Middle Frontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Caudal Middle Frontal	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Pars Opercularis	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Pars Triangularis									
	Pars Orbitalis	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Lateral Orbitofrontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Medial Orbitofrontal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Precentral									
	Paracentral									
SA Parietal	Superior Parietal	X	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	– / +	– / +
	Inferior Parietal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	– / –	– / +
	Supramarginal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	– / –	– / +
	Postcentral	X	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	– / +	– / +
	Precuneus	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	– / –	– / +
SA Temporal	Superior Temporal									
	Superior Temporal Sulcus	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	– / –	+ / +
	Middle Temporal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	– / –	– / +
	Inferior Temporal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Fusiform	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Transverse Temporal	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Entorhinal	X	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	+ / +	– / –
	Temporal Pole									
	Parahippocampal	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
SA Occipital	Lateral Occipital	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	+ / +	*(n.s.)* / *(n.s.)*	– / –	– / –	+ / +
	Lingual	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –
	Cuneus									
	Pericalcarine	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / +	*(n.s.)* / *(n.s.)*	– / –	– / –	– / +
SA Cingulate	Rostral Anterior Cingulate									
	Caudal Anterior Cingulate									
	Posterior Cingulate									
	Isthmus Cingulate									
	Insula	X	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	*(n.s.)* / *(n.s.)*	– / –	– / –	– / –

Note. SZ indicates schizophrenia and HC indicates healthy control. TH indicates thickness and SA indicates surface area. An 'X' for significant group difference indicates that the cortical measure was examined because it showed a significant group difference between schizophrenia and controls. Significant R_G indicates that the significant genetic correlation between depression and the cortical measure for the given age-risk period was presented. Genetic correlations are presented only when significant and are indicated with '*(n.s.)*' when nonsignificant or when the significance could not be computed.

For each measure, results are first presented for analyses with basic adjustments (age, age^2, sex, and site) then presented for analyses with conservative adjustments (age, age^2, sex, site, parental education, scan quality, and intracranial volume), separated by '/'. i.e. analysis with basic adjustments / analysis with conservative adjustments.

For the R_G comparison across age-risk periods using two-tailed Fisher's z-tests (Kashiani & Saleh, 2010; Kominakis, 2003), a '+' (increase) indicates that there is a significantly more negative genetic correlation from the earlier to the later age-risk period, whereas a '–' (decrease) indicates a significantly less negative or nonsignificant genetic correlation from the earlier to the later age-risk period.

Evidence for each effect is indicated as follows: '+ +' indicates strong evidence supporting the effect, '+' indicates suggestive evidence supporting the effect, and '–' indicates no evidence supporting the effect.

Evidence supporting early neurodevelopmental effects is present if the genetic correlation is significant during the Rise period; a nonsignificant genetic correlation during the Rise period does not construe evidence against early neurodevelopmental effects due to the relatively small sample size for the Rise period.

Evidence supporting late neurodevelopmental effects is suggestive if there is a significantly more negative genetic correlation from the Rise to the Peak period (i.e. '+' in the Rise/Peak R_G Comparison) and strong if the genetic correlation is additionally significant during the Peak period.

Similarly, evidence supporting neurodegenerative effects is suggestive if there is a significantly more negative genetic correlation from the Peak to the Plateau period (i.e. '+' in the Peak/Plateau R_G Comparison) and strong if the genetic correlation is additionally significant during the Plateau period.

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