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The associations between area-level residential instability and gray matter volumes from the North American Prodrome Longitudinal Study (NAPLS) consortium

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Abstract

Introduction: Area-level residential instability (ARI), an index of social fragmentation, has been shown to explain the association between urbanicity and psychosis. Urban upbringing has been shown to be associated with reduced gray matter volumes (GMV)s of brain regions corresponding to the right caudal middle frontal gyrus (CMFG) and rostral anterior cingulate cortex (rACC). We hypothesize that greater ARI will be associated with reduced right CMFG and rACC GMVs.

Methods: Data were collected at baseline as part of the North American Prodrome Longitudinal Study Phase 2. Counties where participants resided during childhood were geographically coded using the US Census to area-level factors. ARI was defined as the percentage of residents living in a different house five years ago. Generalized linear mixed models tested associations between ARI and GMVs.

Results: This study included 29 HC and 64 CHR-P individuals who were aged 12 to 24 years, had remained in their baseline residential area, and had magnetic resonance imaging scans. ARI was associated with reduced right CMFG (adjusted $\beta = -0.258$; 95% CI = −0.502 – −0.015) and right rACC volumes (adjusted $\beta = -0.318$; 95% CI = −0.612 – −0.023). The interaction term (ARI-by-diagnostic group) in the prediction of both brain regions was not significant, indicating that the relationships between ARI and regional brain volumes held for both CHR-P and HCs.

Conclusions: ARI may adversely impact similar brain regions as urban upbringing. Further investigation into the potential mechanisms of the relationship between ARI and neurobiology, including social stress, is needed.

Keywords

clinical high risk for psychosis; caudal middle frontal gyrus; rostral anterior cingulate cortex; residential instability; schizophrenia

1. Introduction

Geographic areas with greater residential instability, defined as the percentage of people who moved in an area, have higher rates of mental illnesses, including depression and schizophrenia (Ku et al., 2021b; Silver et al., 2002). It has been shown that individual-level residential instability (defined as number of moves) during childhood and adolescence has been associated with increased risk for psychosis (Price et al., 2018). However, this research is limited because other characteristics such as familial socioeconomic status (SES) and history of mental illnesses might be partial determinants of a youth's exposure to residential relocation (Eriksson et al., 2018). In contrast, area-level characteristics are more a distal feature and reflect environmental exposures that are less likely to be affected by a participant's characteristics such as familial SES and history of mental illnesses. In fact, greater area-level residential instability (ARI), defined as percentage of people in an area living in a different house, has been linked to an earlier age at onset of psychosis and higher likelihood of conversion to psychosis (Ku et al., 2021a, 2020b). The most supported explanation of the relationship between residential instability and psychosis is that changes

in residence, at either individual or area levels, disrupt an individual's ability to form and maintain social connections with other individuals in the wider community, predisposing one to social stress and increasing vulnerability to the impact of life stressors on mental health (Ku et al., 2021b; Price et al., 2018).

ARI has been commonly viewed as an index of social fragmentation, which has been shown to explain the association between urbanicity and psychosis (Zammit et al., 2010). Urbanicity at birth or upbringing is one of the most well-established environmental risk factors for schizophrenia (March et al., 2008; McGrath et al., 2004). Although the mechanisms mediating the relation of urbanicity with psychosis are still not fully understood, neuroimaging studies have suggested that the social stress of urban upbringing is likely one mediator of this association. Recent studies of healthy adults have found that urban upbringing was specifically associated with increased stress-induced activation of the perigenual anterior cingulate cortex (pACC) (Lederbogen et al., 2011), a key region for regulation of amygdala activity, negative affect (Pezawas et al., 2005), and social stress processing (Diorio et al., 1993). Urban upbringing among healthy individuals was also shown to be negatively correlated with gray matter volumes (GMV) of the right posterior dorsolateral prefrontal cortex (DLPFC) and perigenual anterior cingulate cortex in males (pACC) (Haddad et al., 2015).

The DLPFC also regulates affective processing (Zwanzger et al., 2014) and is also highly sensitive to stress (Luethi, 2008). It is well established that individuals with schizophrenia have lower pACC (Fornito et al., 2009) and DLPFC gray matter volumes (GMV)s when compared to healthy controls (HC) (Volpe et al., 2012). In fact, structural volumetric reductions of these two brain regions have been shown to predict conversion to psychosis among youth at clinical high risk of developing psychosis (CHR-P) (Pantelis et al., 2003).

Although researchers have found urban upbringing to be linked with functional and structural characteristics of specific brain regions involved in social stress processing, the specific aspects of the urban environment that may contribute to neurobiological changes linked to schizophrenia and other psychosis are still unclear. It may be that population size or density per se does not increase psychosis risk, but that early urban exposure is a proxy measure for other risk-increasing attributes of the environment (Haddad et al., 2015). For example, social fragmentation, resulting from residential instability, may mediate the association of urban upbringing and psychosis (Zammit et al., 2010). Further, ARI might be related with similar brain regions as urban upbringing.

To date, no studies have investigated the relation of ARI with brain characteristics. In this study, we test the hypothesis that growing up in places with greater ARI will, like urbanicity, be specifically associated with smaller GMVs of brain regions that correspond to the right posterior DLPFC and pACC among both youth at CHR-P and HC: the caudal middle frontal gyrus (CMFG) and rostral anterior cingulate cortex (rACC), respectively (Reber and Tranel, 2019; Swick and Turken, 2002).

Findings from past research suggests that the relation of adverse environmental factors with the brain regions of interest (ROI) would not be diagnostically specific, but rather would

be observed in both healthy and clinical populations (Aberizk et al., 2021; Haddad et al., 2015). In this case, ARI would represent one of numerous environmental factors that may cumulatively contribute to risk for psychosis. However, it is also possible that youth at CHR-P are more sensitive to adverse effects of ARI. Thus, given that gray matter reductions in the prefrontal cortex and cingulate cortex have been implicated in the development of psychosis (Ellis et al., 2020), we conducted analyses to determine whether ARI had a stronger relation with gray matter volumes in youth at CHR-P compared to healthy controls. We also hypothesize that there would be greater reductions in the right ROI based on recent research from animal models and human studies suggesting that early-life environmental stressors appear to have a greater impact on the right hemisphere (Esteves et al., 2020).

Because previous research has shown that a range of environmental and individual-level factors are associated with both brain volumetric reductions and residential instability, analyses were conducted with the inclusion of multiple, potential confounders. These include individual-level factors that would likely be associated with residential instability and/or brain morphology: family history of mental illnesses, race, second-generation migrant status, childhood poverty, education levels of participant and their parents, and life event stress (Aberizk et al., 2021; Akdeniz et al., 2017b; Assari, 2020; Lawson et al., 2013; Lee et al., 2017; LoPilato et al., 2019; Steffener, 2021). Potential area-level confounders include: unemployment, owner-occupied housing, and minority status (Hackman et al., 2021; Ku et al., 2020a; Vargas et al., 2020). To control for exposure to ARI, we limited our sample to only individuals who never moved in their lifetime up to baseline assessment because we did not have data regarding when, or how often, or where individuals moved in the past.

2. Methods

2.1 Subjects

Data were collected at baseline as part of the second phase of the North American Prodrome Longitudinal Study (NAPLS2), a multi-site, longitudinal study that aimed to enhance the prediction of psychosis among help-seeking participants at CHR-P recruited from November 18th, 2008 to March 11th, 2013 with baseline assessments conducted during this time (Addington et al., 2012). Because the focus of the present analysis is on early ARI, we included only participants who: 1) had not moved during their lifetime prior to baseline assessment, 2) had available data on childhood residence (cities/towns) suitable for geo-coding, and 3) had undergone an MRI at baseline.

The Structured Interview for Psychosis-Risk Syndromes (SIPS) determined CHR-P status. This study included a subset of HCs (n=29) and individuals at CHR-P (n=64) who were born between 1985 and 2000. The study protocol and consent form were reviewed and approved by the Institutional Review Boards at all sites, and all procedures complied with the ethical standards of the relevant committees. From the 729 participants who had available cities/towns in the USA to be geocoded to area-level characteristics, 631 had life event stress data, 422 had neuroimaging data, and 93 had never moved in their lifetime.

2.2 Instruments

Sociodemographic and clinical variables were obtained from self-report and interview-based measures at the time of baseline assessment, and included age, sex, second-generation migrant status, race, family history of mental illnesses, childhood poverty, education levels of participant and parents, life events data, and city or town in which the participant lived.

The Structured Interview for Psychosis-Risk Syndromes (SIPS) was administered by experienced clinicians who had undergone specific training. Second-generation migrant status was coded as 1 if they were born in the USA and one or both parents were born abroad and 0 if otherwise. The Family Interview for Genetics Studies was used to obtain family history of mental illnesses, which was coded as 1 if any first- or second-degree family members had depression, bipolar disorder, psychosis, or schizophrenia and 0 when there is no known such mental illnesses among first- or second-degree family members (FIGS NIMH Genetics Initiative: Family Interview for Genetic Studies (FIGS), 1992; Georgopoulos et al., 2019). Childhood poverty was dichotomized as 1 when the income of the individual's family of origin was below the 2014 US Census poverty line for a family of their size and 0 when the family income was above the poverty line (LoPilato et al., 2020). Education level index was an average of *z* scores of highest education levels among the participant, mother, and father. Life events stress (LES) score was derived from a modified version of the Life Events Scale, a 59-item self-report measure of events encountered during their lifetime (e.g., being a victim of a crime) obtained at baseline; participants rated the degree of stressfulness of each event on a scale of 0 to 7 (Trotman et al., 2014). The total LES score ranged from 0 to 364 for the present sample. Never having moved in lifetime was derived from an item on the Life Events Scale and also verified using demographic characteristics (e.g., being born in the USA and not being a first-generation immigrant), which were provided by both participants and parents in the case of minors. We included only those who never moved to capture the cumulative environmental exposure because data on previous and subsequent addresses were not obtained.

2.3 Area-Level Variables

Area-level characteristics, including residential instability, were derived from county-level data from the 1990 and 2000 U.S. Decennial Censuses (U.S. Census Bureau, 2002). Cities/towns where individuals spent the majority of their childhood were linked to the primary county 5-digit Federal Information Processing Standards codes ("United States Cities Database," 2020). Then, 1990 and 2000 county-level characteristics were linked to those codes for participants born between 1985 and 1994, and between 1995 and 2000, respectively. There were 30 unique counties included in this study. Censuses from these two time periods were chosen to capture the area (county) characteristics during childhood. ARI was defined as the percentage of people in the county who reported not living in the same house five years ago. Area-level unemployment was defined as the percentage of people aged 16 or above in the civilian labor force who were unemployed. Area-level owner-occupied housing indicated the owner-occupied units as a percentage of all-occupied housing units. Area-level minority status was defined as percentage of all races other than white among all individuals in a county. Area-level urbanicity was defined as in prior

literature (Haddad et al., 2015): metropolitan area with more than 250,000 inhabitants (coded as 3), town with 20,000 or more inhabitants (coded as 2), and rural area (coded as 1).

2.4 Imaging data acquisition and processing

Magnetic resonance imaging (MRI) was performed at eight sites. Five sites (University of California, Los Angeles; Emory University; Harvard University; University of North Carolina; and Yale University) used Siemens scanners, three sites (Zucker Hillside Hospital; University of California, San Diego; and University of Calgary) used GE scanners. The magnetic field strength of all scanners was 3 Tesla. Siemens sites all used a 12-channel head coil and GE sites all used an 8-channel head coil. Sequence parameters were optimized for each scanner manufacturer, software version and coil configuration according to the ADNI protocol ("ADNI | MRI Analysis," n.d.). Scans were all acquired in the sagittal plane with a 1mm × 1mm in-plane resolution and 1.2mm slice thickness. Siemens scanners used an MPRAGE sequence with a 256 (axial) × 240 (sagittal) × 176 (coronal) mm field of view, TR/TE/TI ¼ 2300/2.91/900 ms and a 9-degree flip angle, while GE scanners used an IR-SPGR sequence with a 26cm field of view, TR/TE/TI ¼ 7.0/minimum full/400 and an 8-degree flip angle (Cannon et al., 2014).

Automated surface based cortical reconstruction, cortical parcellation and subcortical segmentation were performed using the Freesurfer software suite version 5.3 (Dale et al., 1999; Fischl, 2004). Regional parcels for GMVs were extracted using a gyral and sulcal pattern based Desikan atlas with 34 parcels in each hemisphere (Desikan et al., 2006). To improve between-site reliability, cortical and subcortical volumes were adjusted for study site, magnetic resonance imaging magnetic manufacturer (GE versus Siemens), and intracranial volume. Neuroimaging achieved within- and between-site reliabilities of 0.95 or greater for gray matter density in the majority of voxels in the prefrontal and temporal cortical surfaces as well as for the volumes of most subcortical structures (Cannon et al., 2014). A priori defined ROI included the rACC and CMFG of the left and right hemispheres as parcellated by the Freesurfer software and the AAL116 brain atlas coordinates.

2.5 Data Analysis

We first calculated the correlations between ARI, other demographic characteristics, and the ROI to rule out multicollinearity. Then, each significant association between ARI and ROI was tested using a generalized linear mixed (GLM) model with the inclusion of covariates. Fixed factors included baseline age, sex, diagnostic group (HC vs CHR-P), family history of mental illnesses, race, second-generation migrant status, childhood poverty, education level index, life event stress, and area-level variables including residential instability, unemployment, owner-occupied housing, and minority status. We did not control for area-level urbanicity (March et al., 2008) because there was limited variability in this sample. Because individuals were nested in counties, county was treated as a random factor for each neuroanatomical measure.

Each significant association between ARI and ROI was further tested with interaction terms in the GLM models. Since youth at CHR-P and males both have increased schizophrenia risk and may be more impacted by environmental stressors, moderating effects of diagnostic

group and sex were tested. For each significant brain region as the dependent variable, the following were entered as fixed factors: ARI, covariate of interest (diagnostic group or sex), and ARI-by-covariate of interest interaction term.

We conducted ROI analyses in four a priori defined anatomical regions; namely, the right and left hemisphere posterior CMFG and rACC. In line with established neuroimaging standards, structural effects outside these pre-hypothesized anatomical regions were only considered significant if they survived stringent multiple comparisons correction across the whole brain, a highly conservative statistical threshold allowing for the reporting of association findings anywhere in the brain and in the absence of a prespecified regional hypothesis. In all analyses, statistical significance was assumed at a threshold of $P < .05$ after either ROI or Holm-Bonferroni adjustment for multiple comparisons.

The IBM SPSS 24.0.0 statistical software package was used for all analyses.

3. Results

3.1 Sample Characteristics

This study included 29 HC and 64 CHR-P participants. The age range was 12 to 24 years and there were 59 males and 34 females. The average area-level residential instability among HC and CHR-P youth was not significantly different (HC: 42.11%; CHR-P: 44.34%; p=0.353). Other demographic characteristics of the sample are summarized in Table 1. Comparison of sociodemographic and neuroimaging characteristics of subjects with and without geocoding data available is shown in Supplementary Table S1.

3.2 Correlations of ARI with ROI

Bivariate correlations showed that ARI was inversely associated with the left CMFG ($r = -0.285$; $p = 0.006$), right CMFG ($r = -0.268$; $p = 0.009$), and right rACC ($r = -0.240$; $p = 0.020$), but not associated with left rACC ($r = 0.024$; $p = 0.823$) (Table 2). This effect was relatively specific to these areas, as no other brain regions were significantly correlated as shown in Supplementary Table S2. Right rACC volume was only moderately correlated with left rACC volume ($r = 0.407$; $p < 0.001$), indicating lateral asymmetry in the factors that influence rACC volume. Right CMFG was highly correlated with left CMFG ($r = 0.781$; $p < 0.001$). Correlations among predictor variables are shown in Supplementary Table S3.

3.3 Main effect on left CMFG

In the GLM model, the association between ARI and left CMFG was no longer significant after controlling for covariates (adjusted $\beta = -0.232$; 95% CI = −0.473 – 0.010; $p = 0.060$) (Table 3). Age (adjusted $\beta = -0.342$; 95% CI = −0.600 – −0.085; $p = 0.010$) and female sex (adjusted $\beta = -0.268$; 95% CI = −0.467 – −0.069; $p = 0.009$) were significantly associated with reduced left CMFG.

3.4 Main effect on right CMFG

ARI was significantly associated with reduced right CMFG (unadjusted $\beta = -0.268$; 95% CI = −0.469 – −0.068; $p = 0.009$), even after adjusting for individual-level (adjusted $\beta =$

−0.252; 95% CI = −0.462 – −0.041; p = 0.020) and area-level covariates (adjusted β = −0.258; 95% CI = −0.502 – −0.015; p = 0.038) (Table 4). Female sex remained significantly associated with reduced right CMFG in the adjusted model (adjusted β = −0.318; 95% CI = −0.519 – −0.117; p = 0.002).

3.5 Main effect on right rACC

ARI remained significantly associated with reduced right rACC (unadjusted β = −0.240; 95% CI = −0.443 – −0.038; p = 0.020) after adjusting for individual-level (adjusted β = −0.238; 95% CI = −0.473 – −0.003; p = 0.047) and area-level covariates (adjusted β = −0.318; 95% CI = −0.612 – −0.023; p = 0.035) (Table 5). Female sex was associated with reduced right rACC volume even after adjusting for potential confounders (adjusted β = −0.359; 95% CI = −0.551 – −0.166; p < 0.001). Life events stress was also associated with reduced right rACC volume (unadjusted β = −0.236; 95% CI = −0.439 – −0.034; p = 0.023), but this association was no longer significant after adjusting for covariates (adjusted β = −0.199; 95% CI = −0.427 – 0.030; p = 0.087).

3.6 Interaction terms

There were no significant interaction effects seen in the left CMFG, right CMFG, or right rACC for residential instability by diagnostic group or residential instability by sex interaction terms (Supplementary Table S4). These results indicate that the relation between residential instability and both CMFG and rACC volumes holds for both diagnostic groups and sexes.

4. Discussion

In this study, we show that living in areas with greater ARI, an index of social fragmentation, is associated with reduced GM volume in the CMFG and rACC of the right hemisphere. These findings are consistent with prior research showing that urban upbringing is associated with reduced GMVs of brain regions corresponding to the right CMFC and rACC (in males) (Haddad et al., 2015). However, in this study, ARI is not associated with the left rACC, but only associated with the right rACC, which held for both male and females, and for both HCs and youth at CHR-P.

The DLPFC, which lies in the CMFG, is highly susceptible to stress exposure (Luethi, 2008) and structural changes of this region have been shown in individuals with schizophrenia (Volpe et al., 2012). Moreover, threat-evoked anxiety and behavioral inhibition predicts the activation of the right posterior DLPFC (Shackman et al., 2009). Perhaps being brought up in neighborhoods with high residential instability, which has been associated with a lack of social integration (Faris and Dunham, 1939; Silver et al., 2002) and violent crimes (Boggess and Hipp, 2010), leads to heightened vigilance for perceived social threat. Chronic hyperactivation of this brain region from this hypervigilance may eventually lead to dendritic shrinkage and GMV loss of the CMFG (McEwen and Morrison, 2013).

Similarly, the rACC is also vulnerable to social stress (Lederbogen et al., 2011) and is another region where structural changes are seen in schizophrenia (Takahashi et al., 2003). Furthermore, smaller rACC has also been seen in those exposed to environmental stressors

such as low subjective social status (Gianaros et al., 2007), hypoxia (Schmitt et al., 2013), urban violence (Rocha-Rego et al., 2012), urbanicity (Lederbogen et al., 2011), and second-generation migrant status (Akdeniz et al., 2017a). Interestingly, having less family support (Bratis et al., 2009) and lower levels of social contact (Fukunishi and Rahe, 1995) are predictors of higher alexithymia score (indicating greater difficulties in identifying and verbally describing feelings), which is associated with lower right rACC volume (Paradiso et al., 2008). Perhaps, living in areas with higher residential instability may lead to greater social stress and difficulties with emotional processing, which may be associated with reduced right rACC.

The fact that residential instability likely impacts these two brain regions in both youth at CHR-P and HC indicates that this detrimental environmental factor's adverse effects are generalized and may not be specific in the development of psychosis. In fact, reduced GMVs of the DLPFC and ACC have also been seen in depression (Grieve et al., 2013). While those at CHR-P are more likely than HC to develop psychosis, they manifest a range of psychiatric symptoms and syndromes, including mood disorders, at both baseline and follow-up. Those with CHR-P who are at risk for other mental illnesses, such as depression, might be more likely to develop pathology or have worse outcomes if they live in residentially unstable neighborhoods. Indeed, areas with higher residential instability and social fragmentation have higher rates of depression (Silver et al., 2002) and suicide (Steelesmith et al., 2019). Thus, adverse neighborhood characteristics likely represent one of many factors that cumulatively contribute to vulnerability to psychosis.

In our study, volumetric reductions of CMFG and rACC are in the right hemisphere, which aligns with prior research showing that the right hemisphere may be more susceptible to early life environmental stress (Esteves et al., 2020). It could be that the lack of social engagement in residentially unstable neighborhoods during early life may more negatively impact the subcortical areas of the right hemisphere.

In contrast to the previous study (Haddad et al., 2015), our study had some notable differences in study population and methodology. Our study consisted not only of HC, but also included youth at CHR-P. In addition, participants in this study had never moved during their lifetime, which allowed us to control for socioenvironmental exposure. Haddad et al. controlled for this exposure by obtaining details about each participant's place(s) of residence from birth to age 15 (Haddad et al., 2015). By examining a subset of youth who never moved, we eliminated the potential impact of individual-level residential instability on psychosis (Price et al., 2018).

For methodology, our study accounted for county-level variance and controlled for various potential confounders including lifetime stress, which was also associated with lower right rACC in univariate analysis. We also controlled for second-generation migrant status, which was found to be associated with smaller rACC and most of the youth included in this study lived in urban counties. Even with the differences between our study and the prior one (Haddad et al., 2015), we found the same two regions of the brain, CMFG and rACC, had lower volumes associated with early life environmental exposure, which suggests that similar to urban upbringing, ARI may be an important socioenvironmental characteristic that

adversely impacts neurobiology, and when occurring in concert with other risk factors, can contribute to vulnerability to psychosis.

This study has several limitations. First, it is not clear at which developmental period these brain regions may be most susceptible to the impact of residential instability—the area-level factors examined in this study reflected characteristics during childhood or adolescence, but we did not examine whether environmental exposure in utero may also impact the same brain regions. Second, the area-level characteristics were derived at the county level, which was aimed as a proxy for the individual's living environment during childhood. However, the geographic size of the area may be large and not precisely measure one's socioenvironmental exposure. Future studies should aim to assess not only more granular neighborhood-level characteristics, but also subjective experiences of living in one's neighborhood. Third, the directionality and causal mechanisms of the association between ARI and regional GMV changes was not assessed. Although it is more likely that ARI may lead to reduced GMVs instead of changes in brain volumes leading to environmental differences, it could be possible that genetic predisposition to schizophrenia may lead families to live in more residentially unstable areas. In addition, these participants may also have other characteristics that prevents them from moving, which may contribute to regional brain volume changes and risk for psychosis.

Another limitation of this study is the modest sample size. By including only subjects who had never moved, the present sample excludes a large proportion of the total NAPLS sample. This biased sample has implications for the representativeness of the HC and CHR-P sample as well as statistical power to detect the impact of ARI on other brain areas outside our pre-specified ROI. Even though we did not find associations between ARI and other brain regions, it may be the case that other brain regions may be involved but that this study was not highly powered to detect these associations. We focused on the CMFG and rACC due to results from prior literature (Haddad et al., 2015) and hypothesized their relationships with ARI. However, replication of these results in larger sample sizes is needed to establish the impact of ARI on brain morphology and whether ARI differentially impacts those at CHR-P status or not. Finally, this study was limited in determining predictors of conversion to psychosis and testing whether GMV changes may be a mediator between ARI and psychosis. Nonetheless, power was sufficient to detect previously reported relations of area-level characteristics with specific ROI.

Understanding how residential instability of a community impacts the neurobiology of youth not only contributes to knowledge in neuroscience and psychiatry, but also has public health implications. Geographic identification of at-risk groups could be a priority for allocating mental health resources to areas with greater risk for psychosis or other mental illnesses and to target early intervention. Furthermore, future research can investigate area-level characteristics that may promote social cohesion and moderate the detrimental mental health and neurobiological impacts of residential instability. These finding may allow for public policy and public health interventions to be developed to mitigate the environmental risk associated with serious mental illnesses including schizophrenia.

5. Conclusions

These findings provide further convergent evidence for an impact of the socioenvironmental risk factors linked to schizophrenia on the CMFG and rACC. We show that ARI during childhood predicts a greater reduction in CMFG and rACC GMVs in the right hemispheres of both HCs and youth at clinical high risk for psychosis. Perhaps, the social disruption of living in communities with high residential instability during childhood may adversely impact these brain regions. Further investigation into the potential mechanisms of the relationship between ARI and neurobiology, including social stress, is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

Dr. Cannon has served as a consultant for Boehringer-Ingelheim Pharmaceuticals and Lundbeck A/S. Dr. Mathalon has served as a consultant for Aptinyx, Boehringer-Ingelheim Pharmaceuticals, Cadent Therapeutics, and Greenwich Biosciences. Dr. Perkins has served as a consultant for Sunovion and Alkermes, has received research support from Boehringer-Ingelheim, and has received royalties from American Psychiatric Association Publishing. Dr. Woods has received investigator-initiated research support from Pfizer and sponsor-initiated research support from Auspex and Teva; he has served as a consultant for Biomedisyn (unpaid), Boehringer-Ingelheim, and Merck and as an unpaid consultant to DSM-5; he has been granted a patent for a method of treating prodromal schizophrenia with glycine; and he has received royalties from Oxford University Press. The other authors report no financial relationships with commercial interests.

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Table 1.

Sociodemographic characteristics

		n (%)
Age		
	12.0 to 16.0	47 (50.5)
	16.1 to 20.0	28 (30.1)
	20.1 to 24.0	18 (19.4)
Sex		
	Male	59 (63.4)
	Female	34 (36.6)
Diagnostic category	Clinical high risk for psychosis	64 (68.8)
	Healthy Controls	29 (31.2)
Second generation migrant status	Yes	16 (17.2)
	No	77 (82.8)
White race		
	Yes	55 (59.1)
	No	38 (40.9)
Family history of mental illnesses	Yes	55 (59.1)
	No	38 (40.9)
Childhood Poverty	Yes	8 (8.6)
	No	85 (91.4)
Either parent completed college/technical school/undergraduate		
	Yes	62 (66.7)
	No	31 (33.3)
Area-level Urbanicity		
	1	1 (1.1)
	2	2 (2.2)
	3	90 (96.8)

	Mean (SD)
Average number of years of education completed by participant	10.6 (2.8)
Life Event Stress	51.0 (47.9)
Area-level Residential instability	43.6 (10.0)
Area-level Unemployment	6.0 (1.9)
Area-level Minority	36.4 (19.2)
Area-level Owner-occupied housing	59.0 (14.9)

Table 2.

Correlations between sociodemographic characteristics and CMFG and rACC gray matter volumes

	Left CMFG	Right CMFG	Left rACC	Right rACC
Age	−.236*	−0.149	−0.168	−0.164
Sex	−.240*	−.293**	−.245*	−.325**
CHR-P status	0.032	−0.049	−0.137	−0.027
Second generation migrant status	−0.155	−0.131	−.226*	−0.122
White race	.253*	0.158	0.107	0.139
Family history of mental illnesses	0.003	−0.048	−0.055	−0.045
Childhood poverty	−.224*	−0.059	0.156	−0.032
Education level index	−0.031	−0.001	−0.029	−0.105
Life event stress	−0.073	−0.171	−0.069	−.236*
Area-level urbanicity	0.126	0.099	0.149	0.104
Area-level unemployment	−0.147	−0.163	0.101	−0.14
Area-level minority status	−0.134	−0.166	0.041	−0.146
Area-level owner-occupied housing	0.137	0.176	−0.111	0.089
Area-level residential instability	−.285**	−.268**	0.024	−.240*

Abbreviations: CHR-P, clinical high risk for psychosis; CMFG, caudal middle frontal gyrus; rACC, rostral anterior cingulate.

* = Correlation is significant at p<.05

** = Correlation is significant at p<.01

Table 3.

Generalized linear mixed model predicting left caudal middle frontal gyrus gray matter volume

	Univariate			Model A			Model B			Model C		
	β	**95% CI**	***P***	**β**	**95% CI**	***P***	**β**	**95% CI**	***P***	**β**	**95% CI**	***P***
Age	**−0.237**	**−0.438–−0.036**	**0.021**	**−0.343**	**−0.586–−0.101**	**0.006**				**−0.342**	**−0.600–−0.085**	**0.010**
Sex	**−0.234**	**−0.434–−0.034**	**0.023**	**−0.268**	**−0.462–−0.074**	**0.007**				**−0.268**	**−0.467–−0.069**	**0.009**
CHR-P status	0.045	−0.161–0.251	0.665	0.043	−0.171–0.256	0.693				0.039	−0.179–0.257	0.723
Second-generation migrant status	−0.166	−0.373–0.041	0.114	−0.054	−0.291–0.183	0.651				−0.059	−0.305–0.188	0.636
White race	**0.248**	**0.046–0.450**	**0.017**	0.157	−0.076–0.390	0.185				0.154	−0.087–0.396	0.206
Family history of mental illnesses	0.023	−0.184–0.230	0.824	−0.117	−0.331–0.097	0.280				−0.116	−0.334–0.102	0.291
Childhood poverty	**−0.217**	**−0.419–−0.015**	**0.036**	−0.080	−0.289–0.128	0.446				−0.077	−0.290–0.136	0.473
Education level index	−0.038	−0.337–0.262	0.803	0.240	−0.108–0.589	0.174				0.254	−0.105–0.612	0.163
Life events stress	−0.078	−0.285–0.129	0.455	−0.008	−0.231–0.215	0.942				−0.014	−0.243–0.215	0.902
Area-level unemployment	−0.138	−0.359–0.083	0.218				−0.256	−0.72–0.207	0.275	−0.052	−0.515–0.412	0.825
Area-level minority status	−0.126	−0.339–0.088	0.245				0.040	−0.335–0.415	0.832	−0.061	−0.425–0.303	0.740
Area-level owner-occupied housing	0.126	−0.102–0.353	0.277				−0.173	−0.591–0.244	0.411	−0.123	−0.528–0.282	0.547
Area-level residential instability	**−0.285**	**−0.485–−0.086**	**0.006**	**−0.210**	**−0.419–−0.001**	**0.048**	**−0.310**	**−0.543–−0.077**	**0.010**	−0.232	−0.473–0.010	0.060
Variance					82.2%			94.0%			84.8%	

Note: All models in this table used generalized linear mixed models with the left caudal middle frontal gyrus gray matter volume as the dependent variable and county as the random factor.

Model A included all the individual-level variables shown and area-level residential instability as fixed factors.

Model B included all the area-level variables shown including residential instability as fixed factors.

Model C included all the individual- and area-level variables shown as fixed factors.

All significant associations ($p < 0.05$) are shown in bold.

Table 4.

Generalized linear mixed model predicting right caudal middle frontal gyrus gray matter volume

	Univariate			Model D			Model E			Model F		
	β	**95% CI**	***P***	**β**	**95% CI**	***P***	**β**	**95% CI**	***P***	**β**	**95% CI**	***P***
Age	−0.154	−0.359–0.052	0.141	−0.228	−0.473–0.017	0.068				−0.226	−0.485–0.034	0.088
Sex	**−0.293**	**−0.492–−0.094**	**0.004**	**−0.325**	**−0.521–−0.130**	**0.001**				**−0.318**	**−0.519–−0.117**	**0.002**
CHR-P status	−0.049	−0.257–0.159	0.639	0.030	−0.186–0.245	0.784				0.029	−0.191–0.249	0.792
Second-generation migrant status	−0.134	−0.341–0.073	0.202	−0.153	−0.392–0.086	0.206				−0.154	−0.402–0.095	0.222
White race	0.158	−0.047–0.364	0.129	0.082	−0.154–0.317	0.493				0.070	−0.174–0.313	0.571
Family history of mental illnesses	−0.048	−0.256–0.160	0.646	−0.147	−0.363–0.070	0.181				−0.147	−0.367–0.073	0.187
Childhood poverty	−0.059	−0.266–0.149	0.577	0.108	−0.102–0.319	0.309				0.110	−0.105–0.324	0.313
Education level index	−0.002	−0.302–0.298	0.989	0.330	−0.022–0.682	0.066				0.334	−0.027–0.695	0.069
Life events stress	−0.173	−0.379–0.032	0.096	−0.149	−0.373–0.076	0.192				−0.160	−0.391–0.071	0.173
Area-level unemployment	−0.163	−0.369–0.042	0.117				−0.128	−0.590–0.335	0.585	−0.088	−0.555–0.380	0.710
Area-level minority status	−0.166	−0.371–0.039	0.111				−0.032	−0.401–0.338	0.865	−0.053	−0.420–0.314	0.776
Area-level owner-occupied housing	0.176	−0.029–0.381	0.091				−0.057	−0.471–0.357	0.786	−0.100	−0.508–0.309	0.629
Area-level residential instability	**−0.268**	**−0.469–−0.068**	**0.009**	**−0.252**	**−0.462–−0.041**	**0.020**	**−0.253**	**−0.482–−0.025**	**0.030**	**−0.258**	**−0.502–−0.015**	**0.038**
Variance					83.7%			95.8%			86.2%	

Note: All models in this table used generalized linear mixed models with the right caudal middle frontal gyrus gray matter volume as the dependent variable and county as the random factor.

Model D included all the individual-level variables shown and area-level residential instability as fixed factors.

Model E included all the area-level variables shown including residential instability as fixed factors.

Model F included all the individual- and area-level variables shown as fixed factors.

All significant associations ($p < 0.05$) are shown in bold.

Table 5.

Generalized linear mixed model predicting right rostral anterior cingulate cortical gray matter volume

	Univariate			Model G			Model H			Model I		
	β	**95% CI**	***P***	**β**	**95% CI**	***P***	**β**	**95% CI**	***P***	**β**	**95% CI**	***P***
Age	−0.164	−0.369–0.042	0.116	−0.157	−0.400–0.087	0.204				−0.163	−0.418–0.091	0.205
Sex	**−0.325**	**−0.522–−0.128**	**0.001**	**−0.354**	**−0.548–−0.160**	**<0.001**				**−0.359**	**−0.551–−0.166**	**<0.001**
CHR-P status	−0.027	−0.235–0.182	0.800	0.065	−0.150–0.279	0.550				0.047	−0.166–0.259	0.664
Second-generation migrant status	−0.122	−0.329–0.084	0.242	−0.125	−0.363–0.113	0.298				−0.132	−0.369–0.105	0.271
White race	0.139	−0.067–0.345	0.184	0.109	−0.126–0.344	0.358				0.102	−0.138–0.341	0.402
Family history of mental illnesses	−0.045	−0.253–0.163	0.667	−0.151	−0.367–0.064	0.166				−0.160	−0.373–0.053	0.138
Childhood poverty	−0.032	−0.241–0.176	0.757	0.119	−0.088–0.327	0.257				0.134	−0.070–0.338	0.195
Education level index	−0.152	−0.450–0.147	0.315	0.136	−0.213–0.485	0.442				0.148	−0.199–0.495	0.398
Life events stress	**−0.236**	**−0.439–−0.034**	**0.023**	−0.197	−0.423–0.028	0.086				−0.199	−0.427–0.030	0.087
Area-level unemployment	−0.140	−0.346–0.066	0.180				−0.308	−0.790–0.174	0.207	−0.225	−0.735–0.285	0.382
Area-level minority status	−0.146	−0.352–0.060	0.163				−0.090	−0.496–0.316	0.660	−0.187	−0.626–0.253	0.401
Area-level owner-occupied housing	0.089	−0.119–0.296	0.398				−0.349	−0.792–0.094	0.121	−0.390	−0.845–0.066	0.093
Area-level residential instability	**−0.240**	**−0.443–−0.038**	**0.020**	**−0.238**	**−0.473–−0.003**	**0.047**	**−0.322**	**−0.580–−0.064**	**0.015**	**−0.318**	**−0.612–−0.023**	**0.035**
Variance					80.5%			91.9%			75.5%	

All models in this table used generalized linear mixed models with the right rostral anterior cingulate cortical gray matter volume as the dependent variable and county as the random factor.

Model G included all the individual-level variables shown and area-level residential instability as fixed factors.

Model H included all the area-level variables shown including residential instability as fixed factors.

Model I included all the individual- and area-level variables shown as fixed factors.

All significant associations ($p < 0.05$) are shown in bold.