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Neighborhood disadvantage and longitudinal brain-predicted-age trajectory during adolescence

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ABSTRACT

Neighborhood disadvantage has consistently been linked to alterations in brain structure; however, positive environmental (e.g., positive parenting) and psychological factors (e.g., temperament) may buffer these effects. We aimed to investigate associations between neighborhood disadvantage and deviations from typical neurodevelopmental trajectories during adolescence, and examine the moderating role of positive parenting and temperamental effortful control (EC). Using a large dataset (n = 1313), a normative model of brain morphology was established, which was then used to predict the age of youth from a longitudinal dataset (n = 166, three time-points at age 12, 16, and 19). Using linear mixed models, we investigated whether trajectories of the difference between brain-predicted-age and chronological age (brainAGE) were associated with neighborhood disadvantage, and whether positive parenting (positive behavior during a problem-solving task) and EC moderated these associations. We found that neighborhood disadvantage was associated with positive brainAGE during early adolescence and a deceleration (decreasing brainAGE) thereafter. EC moderated this association such that in disadvantaged adolescents, low EC was associated with delayed development (negative brainAGE) during late adolescence. Findings provide evidence for complex associations between environmental and psychological factors, and brain maturation. They suggest that neighborhood disadvantage may have long-term effects on neurodevelopment during adolescence, but high EC could buffer these effects.

1. Introduction

Early experience of socioeconomic disadvantage is associated with lifelong negative cognitive and mental health outcomes (Forns et al., 2012; Koutra et al., 2012; Packard et al., 2011; Ruijsbroek et al., 2011). While socioeconomic disadvantage can be considered at the household level (e.g., family income), *neighborhood* disadvantage has been shown to have particularly negative effects on the individual, including lower academic achievement and greater physical and mental health problems (Leventhal & Brooks-Gunn, 2000). A disadvantaged neighborhood is one in which people generally have lower levels of income, employment, and education, and can be associated with several risk factors (e.g., inadequate access to healthcare, low resourced schools, and higher pollution and crime) for maladaptive outcomes (Evans, 2004; Santiago

et al., 2011). While much work has been devoted to understanding the neurobiological effects of family-based measures of socioeconomic disadvantage, where studies have demonstrated household socioeconomic disadvantage to be associated with cortical thickness, surface area, and cortical and subcortical volume in adolescents (Hanson et al., 2011, 2015; Lawson et al., 2013; Machlin et al., 2020; Mackey et al., 2015; Noble et al., 2015), less is known about the effects of *neighborhood* disadvantage on the brain. Adolescence is a key developmental period (Dumontheil, 2016; Tamnes et al., 2017) during which brain structure may be vulnerable to effects of socioeconomic disadvantage (Farah, 2018; Lawson et al., 2013, 2017; Whittle et al., 2017). However, there has been little longitudinal work investigating the association between neighborhood disadvantage and brain structural development. Indeed, there is only one study to our knowledge; in the same sample as reported

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here, we previously found that neighborhood disadvantage was associated with increases in thickness/volume of temporal regions and parahippocampus and amygdala in youth (11 to 19 years; Whittle et al., 2017). As such, and given marked neurodevelopment across adolescence (Blakemore, 2012; Foulkes & Blakemore, 2018), further studies are needed to understand whether and how neighborhood disadvantage is associated with deviations from normative neurodevelopmental trajectories, and how these in turn may contribute to negative functional outcomes.

Early experiences play an important role in shaping brain development. For example, it is suggested that resource-rich low-stress environments are conducive to the optimal development of brain systems associated with executive and other types of cognitive function. In contrast, development may be altered in low-resource high-stress environments, such that the development of brain systems that are involved in adapting and reacting to stressful conditions, is potentially prioritized over the development of brain systems supporting executive functioning (Blair & Raver, 2016). Indeed, some developmental models (such as the stress acceleration hypothesis [SAH]; Callaghan & Tottenham, 2016) and life-history theory (Ellis & Del Giudice, 2019), propose that adverse experiences (including those that co-occur with socioeconomic disadvantage) potentially accelerate biological and neurodevelopmental processes to reach 'adult-like' functioning earlier, given that faster development may be advantageous under high stress conditions in an evolutionary context. Although theoretical models of stress-associated acceleration originally considered emotional circuits (Callaghan & Tottenham, 2016), the concept has often been applied more broadly (including in structural neuroimaging studies) suggesting generally accelerated neurobiological aging in response to adversity (e.g., Colich et al., 2020; Gur et al., 2019). Existing research investigating associations between neighborhood disadvantage and adolescent structural gray matter development has found mixed support for these models. For example, while cross-sectional literature has found neighborhood-disadvantage-associated accelerated development (i.e., higher proportions of individuals <18 years misclassified as adults; Gur et al., 2019), our previous longitudinal study (as mentioned above) reported findings that reflect disadvantage-associated maturational lag of temporal, parahippocampal, and subcortical regions (Whittle et al., 2017). Studies investigating other SES indicators have similarly found inconsistent effects (Barch et al., 2020; Hair et al., 2015; Hanson et al., 2013; Lawson et al., 2013; Mackey et al., 2015; Noble et al., 2015; Romeo et al., 2018). Further, longitudinal resting-state functional connectivity work on the same sample as investigated here has also shown that different neural circuits show adversity-associated accelerated versus delayed development (Rakesh et al., 2021a).

Past work, however, has not quantified normative development, and deviations from said development at an *individual* level, which would be beneficial for testing hypotheses about accelerated versus delayed development. Further, despite neighborhood disadvantage having unique effects on childhood behavioral (Leventhal & Brooks-Gunn, 2000) and brain development (Gard et al., 2021; Taylor et al., 2020; Rakesh et al., 2021b), no work to our knowledge has examined neighborhood-disadvantage-associated deviations from typical brain development trajectories at an individual level. Using machine learning models, an individual's *brain age* can be predicted based on neuroimaging data, thus allowing quantification of the extent to which an individual deviates from typical neurodevelopment. This is computed as the difference between an individual's brain-predicted-age and chronological age and is referred to as the *brain age gap estimate* (brainAGE) (Cole & Franke, 2017). brainAGE values close to zero indicate typical development, whereas positive and negative brainAGE values suggest older and younger brains, respectively. To our knowledge, no studies have directly tested hypotheses regarding the association between neighborhood disadvantage and deviations from typical brainAGE developmental trajectories using longitudinal designs. Longitudinal work permits investigation of whether deviations in brainAGE

associated with socioeconomic disadvantage stay constant, or are more pronounced at particular developmental stages (i.e., converge/diverge with development).

Further, while neighborhood disadvantage has been shown to be associated with negative outcomes, positive environmental or psychological factors may attenuate such negative effects. For example, positive caregiving (e.g., higher parental warmth and sensitivity) has been shown to *buffer* the negative effects of disadvantage on socio-emotional outcomes and school readiness (Sheridan et al., 2010). Indeed, it has been previously demonstrated that positive parenting buffers the effects of neighborhood disadvantage on structural (Whittle et al., 2017; Ziegler et al., 2020) and functional (Brody et al., 2019; Rakesh et al., 2021b) neurodevelopment. Further, studies have shown that certain facets of temperament (e.g., effortful control) are also associated with neurodevelopment (Vijayakumar et al., 2014), and mitigate the negative consequences of socioeconomic disadvantage on academic functioning (Wang et al., 2017). Individuals with high effortful control have been shown to possess greater behavioral and emotion regulation, which could contribute to this mitigating effect (Eisenberg et al., 2006). Whether positive factors such as positive parenting and effortful control moderate the association between neighborhood disadvantage and brainAGE is unknown. Given the large number of youth that face neighborhood disadvantage (Annie E. Casey Foundation, 2014), understanding the role of potential moderators such as positive parenting and temperament, is important for targeting prevention efforts.

The aim of the present study was to investigate whether neighborhood disadvantage is associated with accelerated or delayed structural neurodevelopment during adolescence (represented by brainAGE trajectory), and whether positive parenting and/or temperamental effortful control have buffering effects. In order to address these aims, we used a normative model of brain age based on data from the openly available Philadelphia Neurodevelopmental Cohort (PNC) dataset (n = 1313), and applied it to an independent longitudinal dataset (three time-points, n = 166).

Given conflicting findings regarding the association between disadvantage (generally speaking) and accelerated versus delayed adolescent brain development, we did not make specific directional hypotheses. Based on our previous work with this sample, we might expect that neighborhood disadvantage would be associated with decreasing brain age (negative trajectory), and that positive parenting and effortful control would moderate this relationship such that brainAGE would normalize (i.e., be close to zero) in those with a) higher levels of positive parenting, and/or b) higher levels of effortful control. Alternatively, consistent with the SAH, we might expect that high neighborhood disadvantage would be associated with accelerated development (i.e., positive brainAGE trajectory). Exploratory analyses also investigated whether i) positive parenting and effortful control were independently associated with brainAGE trajectories, and ii) given past evidence for male-specific effects of neighborhood disadvantage and positive parenting on brain structure (i.e., dorsal frontal thickness; Whittle et al., 2017), as well as the suggestion that boys may be more vulnerable to effects of neighborhood disadvantage (Chetty & Hendren, 2018), sex would moderate associations.

2. Methods

2.1. Participants and Procedures

2.1.1. Philadelphia Neurodevelopmental Cohort (PNC)

Recruitment procedures and assessment protocols for the original PNC sample can be found in Calkins et al. (2015). The present study included 1313 participants (mean age 14.5 years, SD = 3.43, 659 F) for whom a structural magnetic resonance imaging (MRI) scan was acquired. This sample was obtained after excluding participants on the basis of image quality, medical conditions, and missing data (n = 285; for details see Cropley et al., 2020). Structural MRI scans from this final

PNC sample were used to train the normative brain age model described in subsequent sections.

2.1.2. Orygen Adolescent Development Study (OADS)

Participants were derived from a larger Australian longitudinal cohort of 2453 adolescents, of which 245 agreed to participate in longitudinal research, (see Yap et al. (2011) for details). From this larger sample, 177 community-residing adolescents completed structural MRI scans 1-3 times (average ages = 13 [T1], 17 [T2], and 19 [T3] years). Following exclusions based on missing data and poor image quality, 166 participants were included in the final analysis. For more information see Whittle et al. (2017). Of these, 73 participants (44.0%) had 3 scans, 55 (33.1%) had 2 scans, and 38 (22.9%) had 1 scan. Participants in the current study did not differ from the original sample in key demographic variables at baseline (age, sex, and neighborhood disadvantage; p > 0.5). The research was approved by the human research ethics committee at The University of Melbourne, Australia, and written informed consent was obtained from each child and a parent and/or guardian. IQ was measured using the Wechsler Intelligence Scale for Children IV (WISC IV) (Wechler, 2003) [see SI for details]. See SI for MRI acquisition protocol of the PNC and OADS.

2.2. Measures

2.2.1. Neighborhood Disadvantage

We used the Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-economic Disadvantage (IRSD; Pink, 2008) to operationalize neighborhood disadvantage. The SEIFA-IRSD is a summary measure that characterizes relative disadvantage within neighborhoods based on Australian census data (e.g., percentage of households in the neighborhood that have low income or people that have low skilled occupations). Percentiles were used for analyses, and high-percentile scores indicate relatively greater neighborhood disadvantage.

2.2.2. Positive Parenting

Each mother-child pair completed a Problem Solving Interaction (PSI) task at T1. Five issues for discussion endorsed as occurring frequently and generating the highest intensity of anger (by the mother and the child) were selected based on an Issues Checklist (Prinz et al., 1979). Maternal behavior was coded using the Living in Family Environments (LIFE) micro-coding scheme (Hops et al., 1995), and frequency of maternal expression of positive behavior (rate per minute) was calculated.

2.2.3. Effortful Control

Effortful control was assessed at T1 using participants' responses to the Early Adolescent Temperament Questionnaire-Revised (EATQ-R) (Capaldi & Rothbart, 1992; Ellis & Rothbart, 2001). See Supplementary Information (SI) for details of the measures and distributions.

2.3. Statistical Analyses

2.3.1. MRI processing

Of note, in the OADS, different scanners were used at T1 versus T2 and T3. Steps were taken to ensure that there were no confounds associated with multi-site scanning (see Dennison et al., 2013; Vijayakumar et al., 2016; Whittle et al., 2017). Image processing for both datasets was conducted using automated pipelines in Freesurfer v6.0 (through the longitudinal stream for the OADS). Data was extracted based on the Desikan-Killiany parcellation scheme resulting in 111 measures: 34 cortical regions (each with volume, thickness, and area), seven subcortical volumes (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus), 1 lateral ventricle volume, and intra-cranial volume (ICV).

2.3.2. Prediction of brain age and calculation of brainAGE

Using data from the PNC sample, a support vector regression (SVR) model (using 10-fold cross-validation) was used to predict each individual's age (in the PNC sample) based on the 111 measures listed above (i.e., the normative model; Cropley et al., 2020). All measures were standardized. Model performance within the PNC sample was quantified in a previous study (see Cropley et al., 2020 and Section 3.2 for model performance within the PNC sample). The present study used the previously trained normative model to predict the age of the OADS sample at each time point. brainAGE was calculated by subtracting chronological age from the predicted age. Based on recent recommendations regarding bias associated with 'regression to the mean' (Le et al., 2018), we regressed out the effect of age on brainAGE (across the whole sample with a cross-sectional model including all timepoints). Positive and negative brainAGE values reflect older and younger brains, respectively. Validity of the model was quantified by computing the mean absolute error (MAE) and the Pearson correlation coefficient between the brain-predicted-age and chronological age for the OADS sample. Further, in order to enhance our understanding of the novel brainAGE metric, we examined associations between change in brainAGE and change in brain morphology (thickness, surface area, and volume of 34 regions). See SI for details.

2.3.3. Relationships between brainAGE, and neighborhood disadvantage, positive parenting, and Effortful Control

Linear mixed models (LMM), which permit the use of all available data (Gibbons et al., 2010), were used to examine the relationship between neighborhood disadvantage and brainAGE trajectory (brainAGE predicted by an interaction between chronological age and neighborhood disadvantage). For model equations see SI. Next, we separately examined whether positive parenting and effortful control moderated the effect of neighborhood disadvantage on brainAGE trajectory. We controlled for multiple comparisons using the false discovery rate (P_{FDR} < 0.05). We covaried for sex and IQ in our models.

Given that the study is centered around the salience of the neighborhood context and that recent work has shown unique associations between neighborhood disadvantage (as compared to family indices of SES) and alterations in brain structure (Gard et al., 2021; Hyde et al., 2020; Taylor et al., 2020; Tomlinson et al., 2020; Whittle et al., 2017), we covaried for parent education (assessed using the Australian National University Four scale) as well as the experience of childhood maltreatment (total score on the total score on the Childhood Trauma Questionnaire [CTQ]; Bernstein et al. 1994; see SI for details) in order to test whether effects held when accounting for household SES and other experiences of adversity.

2.3.4. Exploratory analyses

Exploratory analyses were conducted to examine the independent relationships between i) positive parenting and ii) temperamental effortful control, and brainAGE trajectory using LMM. We also explored whether sex moderated all aforementioned associations. For significant longitudinal effects, follow-up analyses were run to examine cross-sectional relationships at each time point using ordinary least squares (OLS) regression. In addition to covariates mentioned above, we also controlled for neighborhood disadvantage in analyses where it was not the variable of interest. P values < 0.05 were considered significant for exploratory analyses.

For main and exploratory analyses, to evaluate the robustness of findings, we evaluated the normality of model residuals, and in cases where these residuals were not normally distributed, we re-ran our models after winsorizing our variables of interest (5th-95th percentile; Liao et al., 2016). If residuals were found to not be normally distributed in the models with winsorized data, we used robust regression/LMM to verify if findings remained significant (using unwinsorized data). Results from these analyses are presented in SI and are described in text below in cases where findings become non-significant with winsorized

data/robust models.

2.3.5. Regional localization of association between brainAGE and neighborhood disadvantage/positive parenting/effortful control

To determine which cerebral loci contributed the most to significant associations, we re-trained the SVR model nine times on the PNC dataset, with specific brain lobes/regions (i.e., frontal/parietal/temporal/occipital/insula/cingulate/subcortical/ICV/ventricles) excluded in each incidence of the training, and then used to the model to compute the brain-predicted-age of the OADS sample. Thereafter, we re-ran LMMs to determine the strength of the relationship between predictors and brainAGE trajectory (computed after a lobe was omitted from the data), and recorded the t-statistic value of the association (i.e., between neighborhood disadvantage/effortful control/positive parenting and brainAGE). Larger decreases in t-statistic values correspond to the lobe being important for the association. If a relatively strong decrease in t-statistic values was found for a lobe, the process was repeated excluding regions within that specific lobe. Of note, the magnitude of decreases in t-stat values chosen was subjective and only to localize the relationships observed in Section 2.5.

2.3.6. Mediation models and functional outcomes

In exploratory analyses we also investigated the mediating role of brainAGE trajectory (obtained as random age slopes from LMM) in the relationship between neighborhood disadvantage and age-19 outcomes [i.e., depression and anxiety symptoms (based on Center for Epidemiologic Studies Depression Scale (Radloff, 1977) and Beck Anxiety Inventory (Beck et al., 1988)) as well as problematic substance use (Rakesh et al., 2020) and academic performance]. See SI for details of methods and results.

3. Results

3.1. Demographic Information

The PNC sample consisted of 1313 youth (659 F; aged 8-21, M = 14.5 ± 5.4 years). Demographic information for the OADS sample can be found in Table 1.

3.2. Brain age prediction based on brain morphology

In a previous study we successfully predicted chronological age from brain structural features with high accuracy in the PNC (Cropley et al.,

Table 1
Demographic information.

OADS Sample Characteristics	
N total (N females)	166 (86 F)
T1 age, y	12.79 (0.425)
T2 age, y	16.70 (0.518)
T3 age, y	19.08 (0.460)
Delay time from T1 to T2, y	3.83 (0.204)
Delay time from T2 to T3, y	2.38 (0.219)
Estimated FSIQ	107.86 (15.60)
IRSD	37.07 (26.69)
Maternal positivity during PSI	1.71 (0.62)
DNCYr12, N/total N (%)	21/127 (16.5)

Unless otherwise stated, values represent mean and standard deviation (in parentheses).
Abbreviations: DNCYr12, did not complete year 12/senior year school; FSIQ, full-scale IQ; IRSD, Index of Relative Socioeconomic Disadvantage (neighborhood disadvantage (scale 1-100, with higher scores indicating relatively more disadvantage)); See Supplementary Figure S1 for the distribution of IRSD; PSI, problem-solving interaction; T1, time 1; T2, time 2; T3, time 3. The sample included in the present study did not differ from the original sample in key demographic characteristics (age [at baseline], sex, and neighborhood disadvantage, $p > .5$)
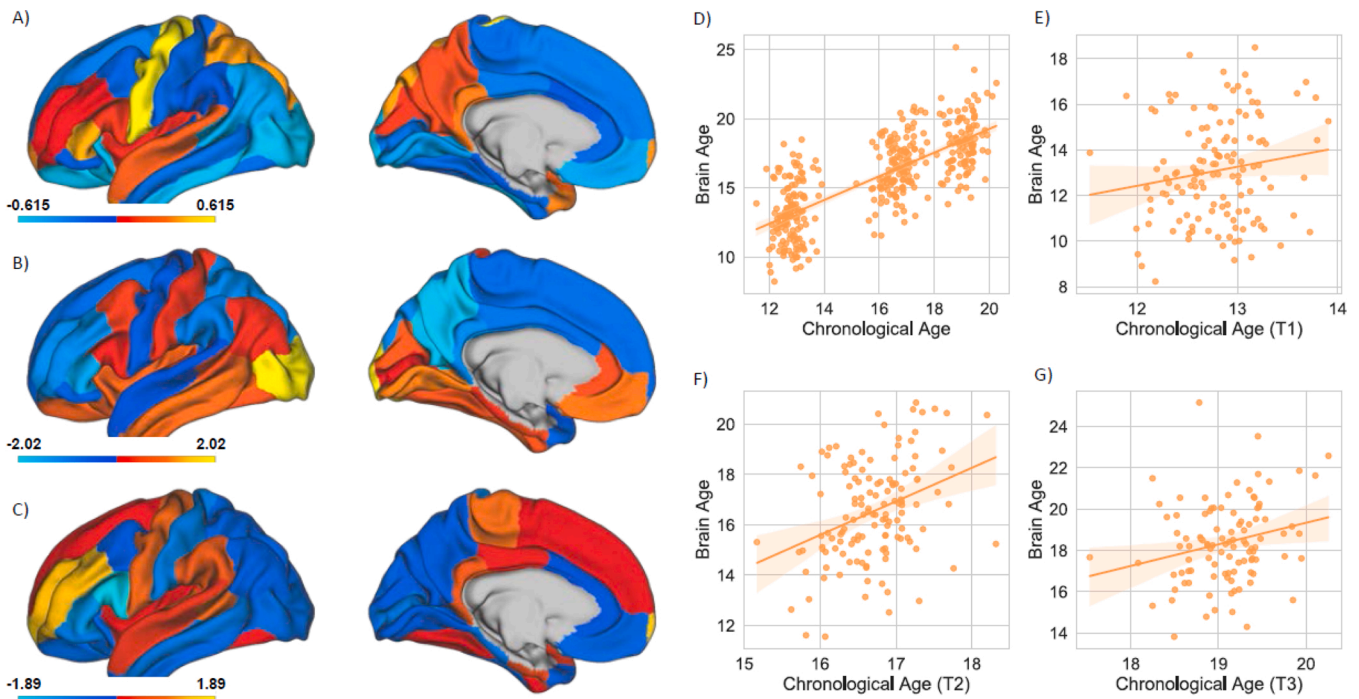
2020). The beta weights for each feature in the age prediction model are depicted in Fig. 1A,B,C. When training the SVR on the whole PNC sample, structural brain measures predicted chronological age with a mean absolute error (MAE) of 1.43 years and a correlation between chronological and predicted age of r = 0.79, p < 0.0001. Applying the trained model on the OADS cohort yielded adequate results with a MAE of 1.64 years (r = 0.74, p < 0.0001; Fig. 1D) across the three time points.

3.3. Relationships between predictor variables and brainAGE

3.3.1. Neighborhood disadvantage

There was a significant effect of neighborhood disadvantage on brainAGE trajectory (t = -2.36, $p = 0.019$; Fig. 2A), whereby higher disadvantage was associated with a decrease in brainAGE across adolescence. Results were also significant when covarying for parent education and childhood maltreatment (t = -2.31, $p = 0.021$). Cross-sectionally, disadvantage was associated with positive brainAGE at T1, but not T2 or T3 (Fig. 3A).

3.3.2. Moderating role of positive parenting and effortful control

Positive parenting did not moderate the relationship between neighborhood disadvantage and brainAGE trajectory (t = 1.92, $p = 0.056$; Fig. 2D,E). Effortful control was found to significantly moderate the relationship between neighborhood disadvantage and brainAGE trajectory (t = 2.19, $p = 0.029$; Fig. 2F,G), whereby disadvantaged individuals with high effortful control did not demonstrate the same negative trajectory of brainAGE as those with low effortful control. Unstandardized residuals were found to not be normally distributed. Results remained significant with winsorized data (p = 0.04). Residuals for models with winsorized outliers were also not normally distributed, and findings were no longer significant with robust LMM (p = 0.082). Cross-sectionally, this relationship was found to be significant at T3, but not T1 or T2 such that in disadvantaged adolescents, low effortful control was related to negative brainAGE values at T3.

3.3.3. Exploratory analyses

We found a significant effect of positive parenting on brainAGE trajectory (t = 2.40, p = 0.017; Fig. 2B), whereby low maternal positivity was associated with a decrease in brainAGE across adolescence. Cross-sectionally, this effect was found to be significant at T1, but not T2 or T3 (Fig. 3B). We also found a significant effect of effortful control on brainAGE trajectory (t = 2.45, p = 0.015; Fig. 2C). Cross-sectionally, this effect was significant at T2, but not T1 or T3.

Sex was not found to moderate the relationship between neighborhood disadvantage and brainAGE trajectory (t = 1.16, p = 0.244). Sex also did not moderate the relationship between neighborhood disadvantage, positive parenting/effortful control and brainAGE trajectory (t = -0.83, p = 0.407; t = .396, p = 0.692).

3.4. Brain regions contributing to the association between environmental variables and brainAGE

The greatest reduction in t-statistic values (and hence greatest contribution) for neighborhood disadvantage was observed with ICV, frontal lobe (particularly Paracentral, Parstriangularis, Precentral, Superiorfrontal regions), and temporal lobe (particularly Inferiortemporal) exclusion (Fig. 4A,B). The greatest reduction in t-statistic values for positive parenting was found when excluding the temporal lobe (Fig. 4C,D). Finally, for the association between effortful control and brainAGE trajectory, the greatest reduction in t-statistic values was observed when excluding the frontal lobe and the cingulate region (Fig. 4E,F). See Table S7-9.

4. Discussion

In a longitudinal sample, we found that neighborhood disadvantage

Fig. 1. The beta weights for each individual cortical region for thickness (A), volume (B), and surface area (C) in the prediction of age have been visualized based on the Desikan-Killiany parcellation scheme. Warmer colors correspond to positive beta weights whereas cooler colors correspond to negative beta weights. Only one hemisphere is shown due to the averaging of left and right hemispheres for each region (see Supplementary Figure S2 for beta weights of subcortical structures, ICV, and ventricles). The correlation between corrected predicted age and chronological age have been depicted for all time points (D), and Time 1, 2, and 3 (E,F,G). Age estimates at individual time-points: T1 = 1.78 years MAE (r = 0.16, p = 0.06; Fig. 1E); T2 = 1.50 years MAE (r = 0.35, p < 0.0001; Fig. 1F); T3 = 1.62 years MAE (r = 0.24, p = 0.01; Fig. 1G).

was associated with brainAGE trajectories from early to late adolescence, whereby high disadvantage was associated with positive brainAGE (reflecting an older brain-predicted-age than chronological age) during early adolescence and a deceleration (i.e., decrease) through to late adolescence. Further, we found that temperamental effortful control moderated the relationship between disadvantage and change in brainAGE, such that low effortful control was associated with a decelerating brainAGE trajectory in disadvantaged individuals and negative brainAGE (younger brain-predicted-age than chronological age) during late adolescence.

Our longitudinal findings suggest that neighborhood disadvantage is associated with a decelerating brainAGE trajectory. This finding could indicate delayed brain development, and is consistent with other work finding neighborhood and other types of disadvantage to be associated with delayed brain maturation (Barch et al., 2020; Hair et al., 2015; Hanson et al., 2013; Whittle et al., 2017), as interpreted by authors. In the only previous longitudinal study to our knowledge (in the same sample of adolescents) we reported that higher neighborhood disadvantage was associated with relative cortical thickening in the para-hippocampal and temporal cortices (Whittle et al., 2017), which we interpreted as delayed development.

Consideration of our cross-sectional findings adds more nuance to this interpretation, however. Disadvantage was associated with positive brainAGE during early adolescence, which appeared to 'normalize' (i.e., was close to zero) by late adolescence. As such, our cross-sectional findings during early adolescence could be interpreted as consistent with the SAH (i.e., positive brainAGE may be interpreted as advanced development; Cole & Franke, 2017; Cropley et al., 2020). Previous cross-sectional work in youth has identified a pattern of neighborhood, and other types of socioeconomic disadvantage to be associated with lower cortical thickness (suggested to be a proxy for advanced brain age/development; Lawson et al., 2013; Mackey et al., 2015; Piccolo et al., 2016). A recent meta-analysis examining the association between

different types of adversity and biological aging in childhood/adolescence reported an association between low SES and accelerated cortical-thinning in frontoparietal, default mode, and visual regions (Colich et al., 2020), again consistent with advanced brain age. As such, our findings highlight that neighborhood disadvantage may not be associated either with advanced or delayed brain development; rather, it may be associated with different patterns across the adolescent period.

While our findings of a significant cross-sectional association between neighborhood disadvantage and advanced brainAGE during early adolescence is consistent with the SAH, stress acceleration does not explain the changes seen in brainAGE trajectories across adolescence. Indeed, recent longitudinal work using brainAGE has shown decelerated/negative trajectories of brainAGE associated with mood disorders (de Nooij et al., 2020); however, with no knowledge of changes that occur after late adolescence, and no relationships with functioning (see SI), it is challenging to comment on the meaning of adversity-related associations with reducing brainAGE trajectories, and interpret them as either adaptive or maladaptive. However, we speculate that this might reflect either: 1) that disadvantaged individuals tend to "normalize" by late adolescence, or 2) disadvantaged individuals may proceed to have decelerated development post late adolescence (indeed, this trend was present during late adolescence for disadvantaged individuals with low effortful control), which could reflect stress-associated early acceleration followed by delays in development. It is possible that development does not follow a simple linear trajectory of stress-associated acceleration of aging processes from adolescence to adulthood (de Nooij et al., 2020). In addition, it is important to acknowledge that positive and negative brainAGE values could also reflect *atypical* developmental patterns, not simply advanced or delayed development (which only implies a temporal shift of normative patterns).

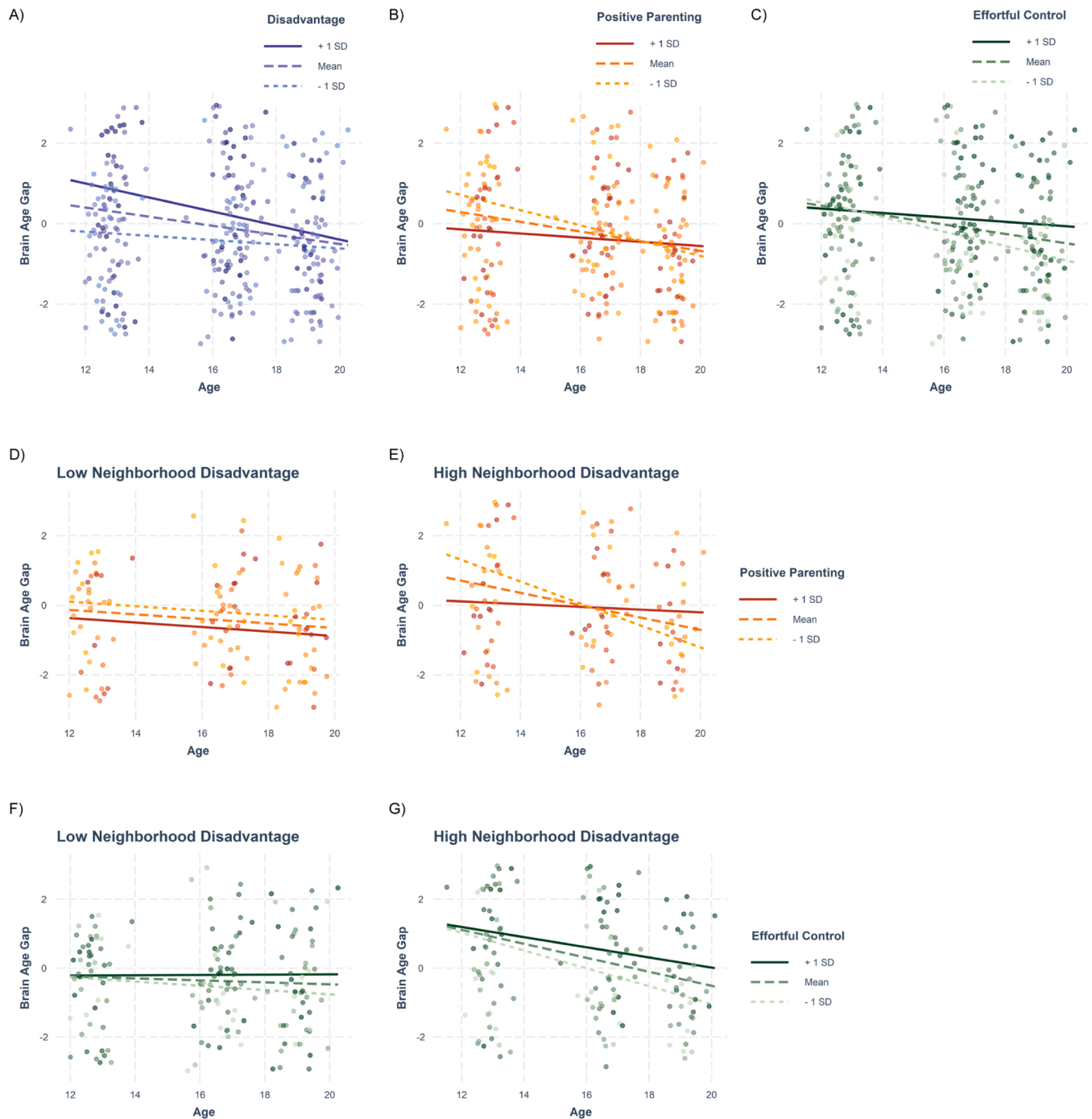Of note, increases in the brainAGE metric were associated with

Fig. 2. Relationships between neighborhood disadvantage, positive parenting, effortful control and brainAGE. Developmental trajectories are represented for the brainAGE for adolescents with relatively high and low (A) neighborhood disadvantage, (B) positive maternal behavior, and (C) effortful control. Effect of positive maternal behavior on brainAGE trajectories in adolescents with relatively high (D) and low neighborhood disadvantage (E) based on a mean ± 1SD for visualization. Effect of effortful control on brainAGE trajectories in adolescents with relatively low (F) and high neighborhood disadvantage (G) based on a median split for visualization. brainAGE = brain age gap estimate. Blue/purple, red/orange, and greens reflect models with neighborhood disadvantage, positive parenting, and effortful control as moderators, respectively.

greater cortical thinning/volumetric loss/surface area reduction (see SI). This lends credence to the notion that cortical thinning (as well change in the other metrics) is associated with advanced aging, and highlights the clinical utility of the brainAGE tool – i.e., its ability to map individual deviations from typical development both cross-sectionally and longitudinally.

Our finding of the association between neighborhood disadvantage and brainAGE trajectory being driven by temporal and frontal lobes is consistent with our previous longitudinal work (Whittle et al., 2017), in

addition to other longitudinal work on family-SES and brain development (Hair et al., 2015). Neighborhood disadvantage has consistently been linked to alterations in cognitive and language development, likely due to a combination of different factors, such as school quality (usually associated with neighborhood income; Leventhal & Brooks-Gunn, 2000), the presence of role models and socializing influences for parents (which in turn would impact parent-child interactions), and lower access to other resources in the community (e.g., parks, libraries) (Kohen et al., 2008). Given the role of temporal and frontal regions in language
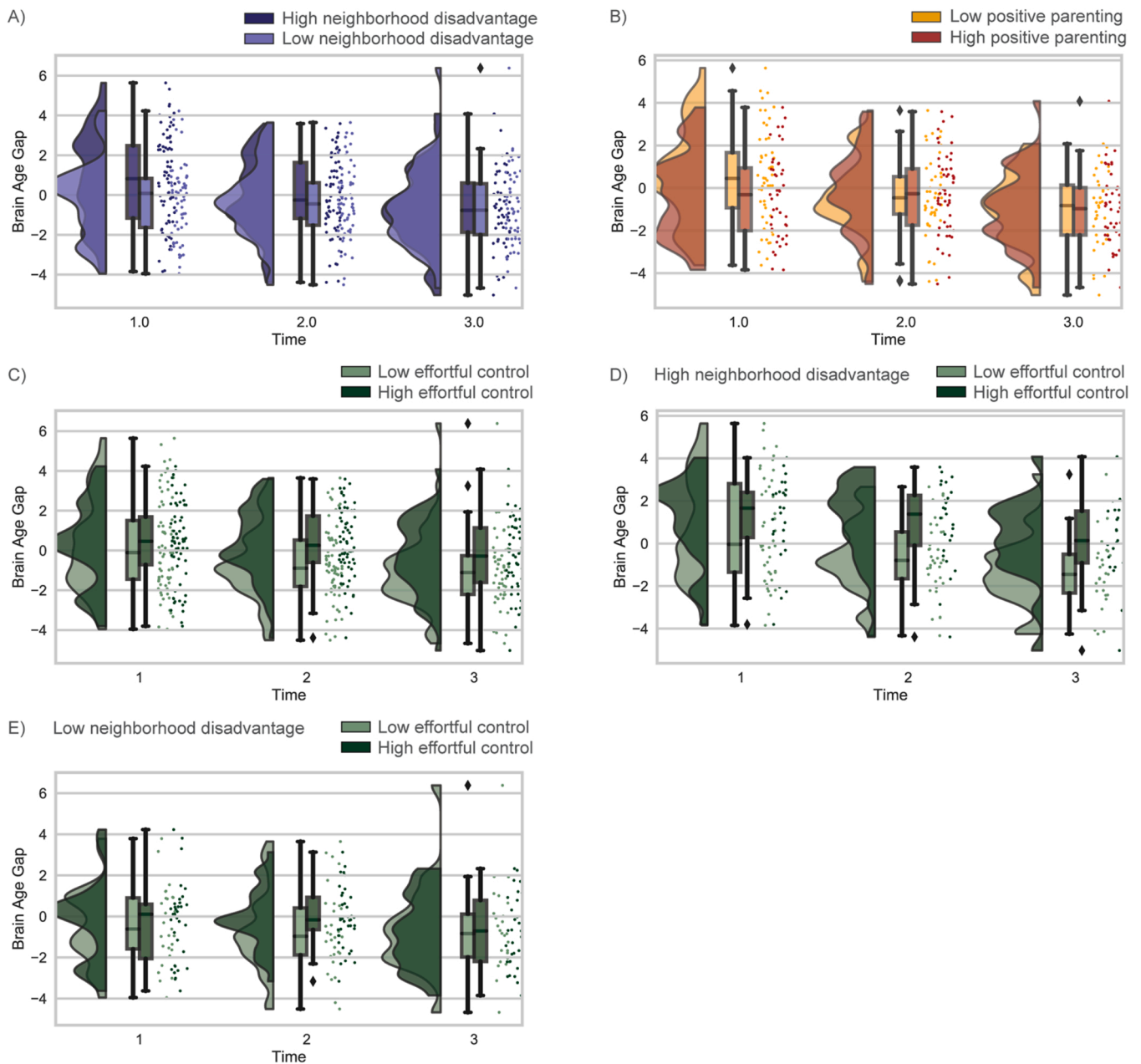
Fig. 3. Cross-sectional differences are represented in raincloud plots at Time 1, 2, and 3 for the brainAGE for adolescents with relatively high and low neighborhood disadvantage (A) positive maternal behavior (B), and effortful control (C) based on a median split of the data for visualization. Effect of effortful control on brainAGE trajectories in adolescents with relatively high (D) and low neighborhood disadvantage (E) at Time 1, 2 and 3. Blue/purple, red/orange, and greens reflect models with neighborhood disadvantage, positive parenting, and effortful control as moderators, respectively.

Cross-sectional relationships: Cross-sectionally, neighborhood disadvantage was associated with positive brainAGE at T1 ($F_{(126,3)} = 5.60$, $R^2 = 0.12$, $p = 0.001$), but not T2 ($F_{(128,3)} = 3.50$, $R^2 = 0.08$, $p = 0.098$) or T3 ($F_{(99,3)} = 0.675$, $R^2 = 0.02$, $p = 0.838$).

Cross-sectionally, the moderating role of effortful control on relationship between neighborhood disadvantage and brainAGE was found to be significant at T3 ($F_{(95,5)} = 1.66$, $R^2 = 0.08$, $p = 0.048$), but not T2 ($F_{(121,5)} = 4.63$, $R^2 = 0.16$, $p = 0.131$), or T1 ($F_{(118,5)} = 3.48$, $R^2 = 0.13$, $p = 0.267$).

Cross-sectionally, the relationship between positive parenting and brainAGE was found to be significant at T1 ($F_{(90,4)} = 5.04$, $R^2 = 0.15$, $p = 0.046$), but not T2 ($F_{(90,4)} = 2.9$, $R^2 = 0.08$, $p = 0.88$) or T3 ($F_{(74,4)} = 1.69$, $R^2 = 0.08$, $p = 0.411$).

Cross-sectionally, the association between effortful control and brainAGE was significant at T2 ($F_{(123,4)} = 4.45$, $R^2 = 0.097$, $p = 0.002$), but not T1 ($F_{(120,4)} = 3.96$, $R^2 = 0.086$, $p = 0.71$) or T3 ($F_{(96,4)} = 1.07$, $R^2 = 0.004$, $p = 0.37$).

Abbreviations: brainAGE=brain age gap estimate. * = $p < 0.05$.

and cognition (Duncan & Owen, 2000; Price, 2010), our findings are consistent with this notion. Although speculative, brainAGE could represent a neural mechanism by which neighborhood disadvantage impacts cognitive and language development.

Importantly, accounting for household SES and other experiences of adversity did not substantially change our findings of neighborhood-

disadvantage-associated change in brainAGE. In line with past work (Gard et al., 2021; Rakesh et al., 2021a; Taylor et al., 2020; Rakesh et al., 2021b), this finding shows that the effects of neighborhood context are above and beyond family-level and other adversities such as parent education and childhood maltreatment, and highlights the salience of the neighborhood environment in shaping brain development. Future
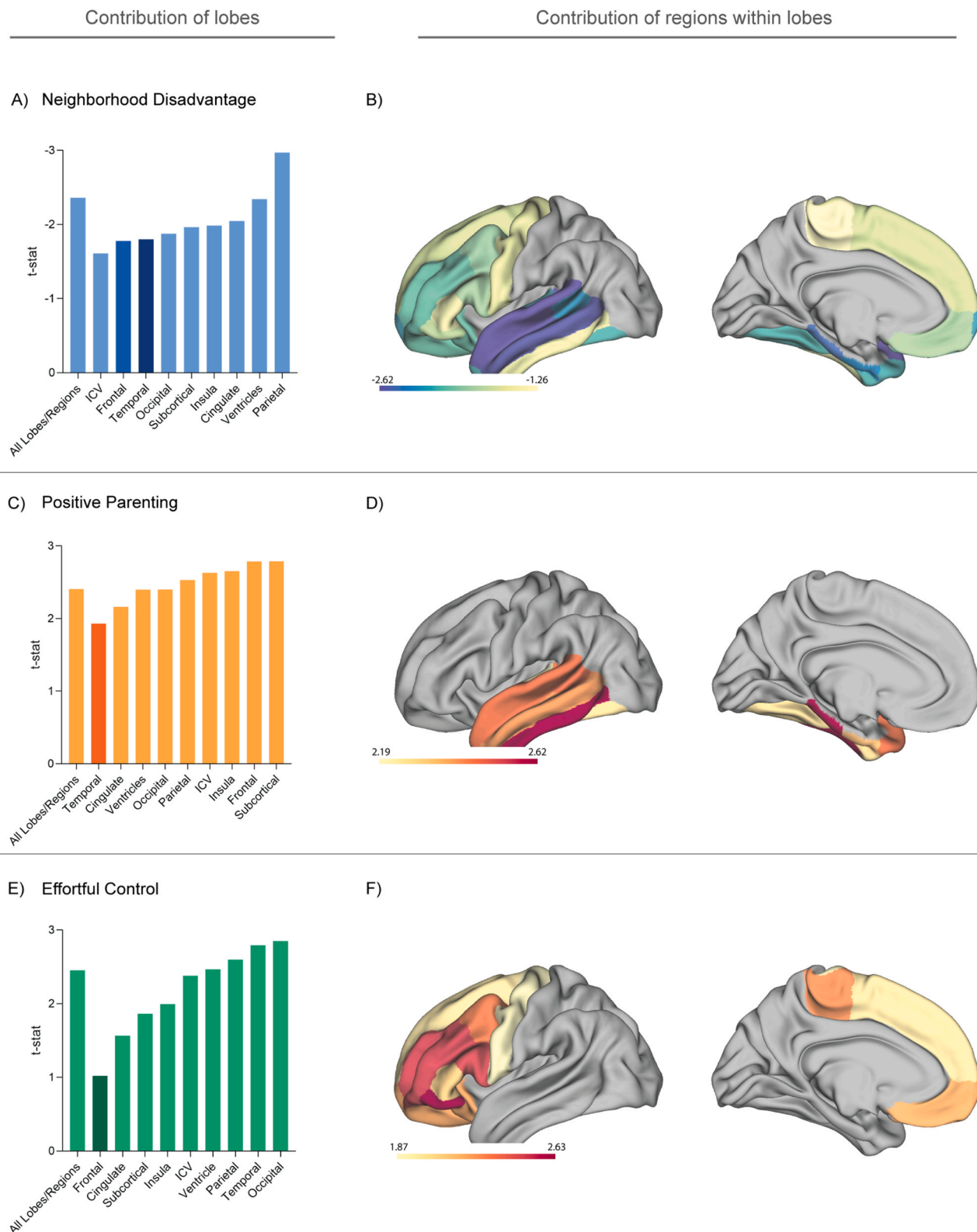
Fig. 4. Brain regions contributing to the association between environmental variables and brainAGE. Cortical renderings of the t statistic values of models for results in 3.3. (A) t stat values for the relationship between neighborhood disadvantage and change in brainAGE with the exclusion of each lobe/region and (B) regions within the frontal and temporal lobes; (C) t stat values for the relationship between positive parenting and change in brainAGE with the exclusion of each lobe/region and (D) regions within the temporal lobe, (E) t stat values for the relationship between temperamental effortful control and change in brainAGE with the exclusion of each lobe and (F) regions within the frontal lobe. Darker colors in the bar plots represent the lobes being depicted in panels B, D, and F. Blue/purple, red/orange, and green in A, C, and E reflect t-stat values from models with neighborhood disadvantage, positive parenting, and effortful control as moderators, respectively. Warm and cool colors in B, D, and F reflect positive and negative t-stat values respectively. See the Supplementary Tables S7-9.
Abbreviations: brainAGE=brain age gap estimate, ICV = Intracranial volume

work should disentangle the specific mechanisms that may be driving these effects (i.e., stress/exposure to violence and/or lower access to resources [e.g., playgrounds, libraries, low-resourced schools]; Hyde et al., 2020).

Contrary to hypotheses, and in contrast to our previous finding from the sample (Whittle et al., 2017), positive parenting did not moderate the association between neighborhood disadvantage and brain development. Contrasting findings could be attributed to the utilization of different metrics (brainAGE based on thickness/area/volume across the whole brain in the present study vs the use thickness and region-specific findings in Whittle et al., 2017). However, we found an independent effect of positive parenting on brainAGE trajectory, whereby less maternal positivity was found to be associated with positive brainAGE during early adolescence and deceleration thereafter. Of note, this relationship was found to be driven by temporal regions. Given the known role of these regions in language and cognitive functions such as social cognition (Price, 2010; Zahn et al., 2007), and other work suggesting that parenting is considered important for both language development (Perkins et al., 2013) and social cognition (Steele et al., 2002), it is possible that temporally shifted patterns of neurodevelopment in cortical temporal regions may have implications for language and cognitive abilities, and/or other aspects of adolescent functioning.

We found that temperamental effortful control moderated the relationship between neighborhood disadvantage and brainAGE trajectory, such that individuals with low effortful control exhibited a deceleration in brainAGE from early- to late adolescence and the brain-predicted-age of individuals was *younger*(i.e., lower) than their actual age in late adolescence. Conversely, individuals with high effortful control exhibited a more stable brainAGE trajectory. The combination of high neighborhood disadvantage and low effortful control may thus be associated with more protracted or delayed development after early adolescence, becoming evident by late adolescence. Conversely, high effortful control may partially buffer the effects of socioeconomic disadvantage on brainAGE. Previous work suggests that effortful control has the capacity to alleviate some of the negative consequences of socioeconomic disadvantage on academic functioning (Wang et al., 2017); however, in the absence of relationships with outcomes in the present study (see SI), it is difficult to interpret whether this relationship with brainAGE trajectory is indeed a *buffering* mechanism. In addition, given that certain model assumptions were not met (i.e., normality of residuals) and findings were not significant with robust LMM, we make our interpretations very cautiously. Further, effortful control was also independently associated with brainAGE trajectory, whereby low effortful control was associated with deceleration in brainAGE. This relationship was found to be driven by frontal and cingulate regions, which is consistent with prior work highlighting the importance of these regions for functions central to effortful control including inhibitory and attentional control (Milham et al., 2001; Vijayakumar et al., 2014) as well as emotion regulation (Etkin et al., 2011; Ochsner et al., 2012).

While our study has strengths, such as the longitudinal design and observational measures of parenting, some limitations must be considered. First, childhood is also considered a sensitive neurodevelopmental period (Giedd et al., 1999); however, we were only able to assess effects from early to late adolescence. Future work should examine effects of socioeconomic disadvantage, and the potential buffering effects of positive parenting and temperamental factors (such as effortful control), on neurodevelopment during childhood. Second, the PNC recruited participants from pediatric clinics in the United States (Calkins et al., 2015), whereas the OADS participants were from the community in Australia. However, the model performed well on the OADS sample, which speaks to the broader utility of the brainAGE metric. However, given our findings of disadvantage-associated alterations in brainAGE trajectories, it is possible that brainAGE models would not perform well across training and test cohorts with drastically different environmental exposures. Training datasets should therefore be chosen that have a large socio-demographically diverse sample. Third, given past associations between puberty and brain development (Blakemore et al., 2010), and disadvantage and pubertal development (Sun et al., 2017), changes in brainAGE could also be associated with changes in pubertal status. Future work should examine associations between brainAGE and pubertal development. Fourth, although in testing the SAH, our assumption is that neighborhood disadvantage is a proxy for stress, we did not directly investigate stress exposure. Future work should include measures of perceived stress to complement analyses. Fifth, we did not examine the association between change in disadvantage/parenting and change in brain age. Future work should account for changes in these time-varying constructs when looking at relationships with brain development using extended longitudinal designs. Further, given that timing of disadvantage also plays a role in brain development (Gard et al., 2021), future work should examine the role of timing of exposure in the relationship between neighborhood disadvantage and brain development. Sixth, given that some variables were not temporally separated, we could not conduct mediation analyses (Maxwell et al., 2011; Maxwell & Cole, 2007). However, based on findings from some past research (Luby et al., 2013), it is possible that parenting behavior acts as a mediator, rather than a moderator, between neighborhood disadvantage and brain development – an open question for future studies. Finally, the data collected for this study utilized two scanners; however, inter-scanner reliability was previously assessed and validated in a robust manner (Dennison et al., 2013; Vijayakumar et al., 2016; Whittle et al., 2017).

In sum, the present study provides evidence for the impact of socioeconomic disadvantage, positive parenting, and temperament, on brain maturational trajectories, whereby higher disadvantage and lower positive parenting were found to be associated with increased brainAGE during early adolescence, and a decrease thereafter, and low effortful control was associated with negative brainAGE in late adolescence in those with high neighborhood disadvantage. Our findings highlight the importance of studying the interplay between neighborhood disadvantage and other environmental and psychological factors, in the prediction of neurodevelopment, in order to advance our understanding of the consequences of socioeconomic disadvantage on long-term functioning and mental health.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2021.101002.

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