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The impact of prenatal alcohol and/or tobacco exposure on brain structure in a large sample of children from a South African birth cohort

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Abstract

Background: Neuroimaging studies have emphasized the impact of prenatal alcohol exposure (PAE) on brain development, traditionally in heavily-exposed participants. However, less is known about how naturally occurring community patterns of PAE (including light to moderate exposure)

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affects brain development, particularly in consideration of commonly occurring concurrent impacts of prenatal tobacco exposure (PTE).

Methods: 332 children (ages 8–12) living in South Africa's Cape Flats townships underwent structural magnetic resonance imaging (MRI). During pregnancy, their mothers reported alcohol and tobacco use, which was used to evaluate PAE and PTE effects on their children's brain structure. Analyses involved main effects of PAE and PTE (and their interaction) and the effects of PAE and PTE quantity on cortical thickness, surface area, and volume.

Results: After false-discovery rate (FDR) correction, PAE was associated with thinner left parahippocampal cortices, while PTE was associated with smaller cortical surface area in the bilateral pericalcarine, left lateral orbitofrontal, right posterior cingulate, right rostral anterior cingulate, left caudal middle frontal, and right caudal anterior cingulate gyri. There were no PAE × PTE interactions nor any associations of PAE and PTE exposure on volumetrics that survived FDR correction.

Conclusion: PAE was associated with reduction in structure of the medial temporal lobe, a brain region critical for learning and memory. PTE had stronger and broader associations, including with regions associated with executive function, reward processing, and emotional regulation, potentially reflecting continued postnatal exposure to tobacco (i.e., second-hand smoke exposure). These differential effects are discussed with respect to reduced PAE quantity in our exposed group versus prior studies within this geographical location, the deep poverty in which participants live, and the consequences of apartheid and the dop system. Longer-term follow-up must determine potential environmental and other moderators of the brain findings here and assess the extent to which they endure over time.

Keywords

Prenatal Exposure Delayed Effects; Neuroimaging; Tobacco Use; Alcohol Use; South Africa

Introduction

Despite public health efforts to prevent teratogenic effects of prenatal alcohol exposure (PAE), the prevalence of individuals affected by PAE steadily remains at 2.4–4.8% of live births in many representative populations in the United States (May et al., 2014). Base rates of PAE vary by region of the world, suggesting that they are at least partially influenced by historical, systemic political, and governmental policies. For example, the prevalence of fetal alcohol spectrum disorders (FASDs) in the wine-producing Cape region of South Africa (i.e., the sample discussed here) is estimated to be 13.6% to 20.9% (May et al., 2013). This is likely due to (1) the historical colonial practice of apartheid that created significant socioeconomic disadvantage among communities historically referred to as indigenous Black African or Cape Coloured, who have resided in Cape Town, South Africa (Jacobs and Jacobs, 2013, May et al., 2019) and (2) a history of racially and economically driven payment practices for wine farm laborers in the Western Cape known as the "dop system" that contributed to heavy drinking in the region (Adebiyi et al., 2021, London, 2000).

Research has consistently shown that PAE can cause dramatic effects on the brain and cognition in developing children (e.g., Astley and Clarren, 2001, Lees et al., 2020a, Mattson

et al., 2019, Riley et al., 2011, Sowell et al., 2001). In animal models, the effects of PAE on brain and behavior vary as a function of quantity, frequency, and timing of exposure (Sulik, 1984, Sulik, 2005, Sulik et al., 1986). Similar effects have been proposed in humans, as large variability has been observed in patterns of deficits in neurocognition, self-regulation, and adaptive functioning (Baer et al., 2003, Hellemans et al., 2010, Lees et al., 2020a). However, while animal studies allow detailed manipulation of quantity, frequency, and timing of exposure, human research is dependent on retrospective maternal reports of alcohol consumption patterns (Moore et al., 2014), which may reduce measurement accuracy and potentially be influenced by social stigma (i.e., reporting less alcohol use during pregnancy than what actually occurred). Further, most studies of FASDs have relied on retrospective data collection (i.e., caregiver report of maternal alcohol consumption during pregnancy in studies often conducted years later), frequently comparing children thought to have heavy exposure compared to individuals with no or minimal exposure (e.g., Donald et al., 2015a, Donald et al., 2015b, Gautam et al., 2015, Lebel et al., 2012). While much has been learned from such research, participants have traditionally been comprised of those with no exposure versus those with more intense PAE-related patterns and/or clinical FASD symptomology. Thus, findings are effectively limited with respect to producing insight into how light or moderate PAE affects neurocognitive development within children who may not be showing clinical levels of symptomology. Further, such research usually does not typically include detailed prospective assessments of other aspects of PAE, such as the quantity, frequency, or timing of exposure. The present study leverages prospective data collection on substance exposures, including alcohol, during pregnancy from biological mothers.

PAE frequently occurs alongside prenatal tobacco exposure (PTE) (Dukes et al., 2017b). Interestingly, while co-exposure has been correlated with increased oxidative stress (Li and Wang, 2004), some animal work has suggested that nicotine exposure (i.e., one component of PTE) only has minimal cumulative effects beyond PAE on its own (Bhattacharya et al., 2020). However, such inconsistencies across animal studies may be due to differences in exposure timing, dosage, and administration (Polli and Kohlmeier, 2020). Further, these relationships may be further impacted by the perinatal and postnatal developmental environments (e.g., family income, parental factors, stress) as shown in several human studies (Roffman et al., 2021, Lees et al., 2020a, Lees et al., 2020b, Wade et al., 2021, Gonzalez et al., 2020). While animal research has offered insight into the mechanistic effects of PAE and PTE, the translational potential is restricted. More specifically, environmental variables that are easily controlled in animal models of prenatal substance exposure do not translate well to the real-world environmental settings that influence human development (e.g., access to enriching resources, nutrition, stress, health care). Further, there is also the issue of variability in substance exposure (i.e., PAE only, PTE only, PTE + PAE) (Dukes et al., 2017b). Accordingly, strategies have been implemented to mitigate this potential confound by recruiting mothers who report alcohol use but no tobacco use, and vice versa. However, in doing so, the corresponding findings may be less reflective of actual behavior in the real world that may result in neurodevelopmental and behavioral deficits (Odendaal et al., 2020), considering that a large proportion of individuals tend to report both PAE and PTE (Oh et al., 2017, Lange et al., 2015, Skagerström et al., 2013, Lange et al., 2018).

Ultimately, potential participants in comparison groups serving as controls are excluded based on PTE, thereby eliminating any possibility of disentangling the effects of PAE and PTE, as well as their interactive teratogenicity.

To address gaps in the literature, the current study enrolled a subsample of children from the Prenatal Alcohol, SIDS and Stillbirth (PASS) Network (Elliott et al., 2020). Between 2007 and 2015, the PASS study recruited 7,060 pregnant women during their first prenatal visit at obstetrical clinics in Cape Town, South Africa; during pregnancy, they reported their drinking and smoking behavior throughout all trimesters (Dukes et al., 2014), thus permitting assessment across a range of alcohol drinking behaviors and quantities consumed, as well as in measures of PTE quantity. Previous neuroimaging analyses of 6-year-old children from the PASS cohort revealed structural differences (after statistical correction) only in the right fusiform gyrus given PAE (Uban et al., 2022), potentially suggesting that any neuroanatomical effects of varying levels of PAE (or PTE) may have not yet emerged at this age. Accordingly, the aim of this study was to evaluate how PAE and PTE relate to brain development during early adolescence, which is a critical developmental period (i.e., when experience-dependent brain plasticity is undergoing changes that impact the brain's structure and function) (Laube et al., 2020). Thus, in contrast to the minimal effects of PAE in 51 6-year-olds within this large cohort, we analyzed the extent to which varying quantities of PAE and/or PTE may be associated with brain development longer after in-utero exposure.

Here, we describe brain structural variation via magnetic resonance imaging (MRI) among 332 children (8- to 12-years-old) recruited from the larger PASS cohort; except for 8 overlapping participants, these children are not the same children from the aforementioned study with 6-year-old children (n = 51). We predicted that brain structure would differ between individuals with and without PAE (statistically controlling for concomitant PTE) and that greater quantities of PAE would be associated with greater brain dysmorphology. As the previous literature has shown large effects of PAE in the brain structure of participants clinically recruited for an FASD diagnosis (Nuñez et al., 2011), we expected the effects of PAE to be more regionally expansive and severe than the effects of PTE (statistically controlling for PAE).

Materials and Methods

Participants

The PASS Network granted permission for this study to approach the existing cohort of children, including those without PAE and those with varying degrees of PAE, from the original PASS sample (Cape Town, South Africa) of over 6,000 participants. Additional detail on this cohort and data collection is available in earlier publications (Elliott et al., 2020, Dukes et al., 2014, Dukes et al., 2017a).

While recruitment into the brain imaging study is ongoing, the current sample in the manuscript consisted of 332 participants (i.e., 220 participants with PAE, 112 participants without PAE), with group differences displayed in Table 1. Figure 1 shows the distribution of individuals with respect to the quantity of PAE and/or PTE. The larger PASS study had their own inclusion and exclusion criteria (Dukes et al., 2014), but for the purposes of the

analyses in the current manuscript, additional inclusion criteria were applied as follows: (1) Children were 8–12 years of age at the time of recruitment, (2) the child was able to give assent, (3) there was no history of traumatic brain injury with loss of consciousness, (4) there was no major medical or central nervous system disorder, and (5) there were no MRI contraindications such as an implant (e.g., metal shunt) or medical condition (e.g., uncontrolled epilepsy) that posed a risk during scanning. Current use of medications with major effects on brain function or blood flow (e.g., antipsychotics, mood stabilizers) and ADHD medications (e.g., stimulants including methylphenidate) were not considered to be exclusionary. Only participants who passed MRI inclusion criteria were included in the analyses (see below).

Procedure

Neuroimaging was collected using a Siemens MAGNETOM Skyra 3T scanner at the Cape Universities Body Imaging Centre (CUBIC). Neuroimaging included a structural T_1w and T_2w scan, diffusion tensor imaging, and a resting state functional MRI (the current manuscript only includes data from the structural sequences, specifically T_1w). Total acquisition time of a typical session was ~45 minutes. The T_{1w} acquisition parameters were acquired single shot, 1×1×1mm voxel size, 176 slices, slice thickness 1.00mm, FOV 230×230, TR=2530ms, TE=1.68, TI=1240ms, flip angle=7.

Neuroimaging Processing

FreeSurfer v7.1.1 recon-all pipeline was used for cortical reconstruction and volumetric segmentation metrics for statistical analysis. The fully-automated directive flag –all was specified for the pipeline which performs all FreeSurfer pipeline stages (autorecon1–3) on the MR images. Briefly, these autorecon stages include motion correction (Reuter et al., 2010), non-uniform intensity normalization (Sled et al., 1998), skull-strip (Ségonne et al., 2004), Talairach transformation and volumetric labeling of cortical and subcortical regions (Fischl et al., 2002, Fischl et al., 2004), tessellation of gray/white matter boundaries for topology correction and cortical surface reconstruction (Fischl et al., 2002, Fischl et al., 2004), parcellation of white and gray matter to the Desikan-Killiany atlas (Regions of Interest or ROI), and derivation of summary statistics for cortical metrics such as volume, thickness, and surface areas for those ROIs. Only T_{1w} scans were used for pial surface creation. All steps are described in greater detail by FreeSurfer: (https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferMethodsCitation.

Statistical Analyses

All statistical analyses were performed in CRAN R v.4.1.

Exposure/No-exposure.—Linear regression was conducted in R using *lm*() in the *stats* package (v4.1.2) to identify associations between prenatal exposure (PAE, PTE) and bilateral regional volumetrics. Measurements of cortical volume, thickness, and surface area of each ROI were regressed on PAE, PTE, and the PAE × PTE interaction. Children's sex, age, and total intracranial volume (ICV) were included as covariates in regression models:

$$Covariates = \{Sex, Age, ICV\},$$

$$BrainStructure \sim b_0 + b_{PAE_E} * PAE_E + b_{PTE_E} * PTE_E + \sum_j^3 b_j * Covariates_j,$$

in which the subscript E refers to "exposure" and b are the unstandardized regression coefficients for each predictor. The Benjamini-Hochberg false-discovery rate (FDR) correction (Benjamini and Hochberg, 1995) was applied within analyzed modality (e.g., cortical volume, thickness, surface area). We describe the main effects and interactions that were statistically significant ($p < .05$), further specifying those that passed FDR correction ($q < .05$). Supplemental Tables 1-8 provide the full model output referring to the relationships between exposure and brain structure (Supporting Information).

Quantity.—To further evaluate how the number of exposures to alcohol and tobacco was associated with brain structure within each exposure group (i.e., PAE, PTE), structural data were regressed (in separate models) on total alcohol consumption (PAE) and total number of cigarettes smoked (PTE). Total grams of alcohol consumed per drink were converted into total standard drinks (i.e., 14 g of alcohol = 1 standard drink); in the current dataset, total alcohol consumption also included total standard drinks around the last menstrual period (LMP) (± 15 days). The total number of cigarettes smoked during pregnancy (beginning at LMP/gestational age 0 days) was estimated by multiplying the participants' reported cigarettes per day by 280 (i.e., 40 weeks * 7 days), with some participants maintaining or decreasing (and others increasing) cigarette use through pregnancy. The PAE-quantity and PTE-quantity analyses only included those participants whose mothers were in their respective exposure groups. The PAE and PTE quantity analyses controlled for PTE and PAE exposure, respectively. As above, sex, age, and ICV were included as covariates in regression models, and the Benjamini-Hochberg FDR correction was applied:

$$BrainStructure \sim b_0 + b_{PAE_Q} * PAE_Q + b_{PTE_E} * PTE_E + \sum_j^3 b_j * Covariates_j,$$

$$BrainStructure \sim b_0 + b_{PTE_Q} * PTE_Q + b_{PAE_E} * PAE_E + \sum_j^3 b_j * Covariates_j,$$

in which the subscript Q refers to "quantity".**Data visualization**. Brain maps highlighting significant associations before and after FDR correction were made using R's *ggseg* package (Mowinckel and Vidal-Piñeiro, 2019). Scatterplots of PAE × PTE interactions and PAE/PTE quantity associations were made using R's *ggplot2* package (Wickham et al., 2016).

Results

Exposure

Cortical structure.—Figure 2 shows both the main effects of and interaction between PAE and PTE on cortical volume, thickness, and surface area across 68 bilateral ROIs.

PAE (statistically controlling for PTE).—After FDR correction, PAE was associated with thinner cortices in the left parahippocampal gyrus, $p < .001$, $q < .05$ (Figure 2). Before correction, PAE was associated with thinner cortices in the right parahippocampal gyrus, $p = .003$, greater surface area of the right precentral gyrus ($p = .024$), smaller volumes of the left parahippocampal ($p = .001$), left entorhinal ($p = .033$), and left lingual gyri ($p = .048$), and greater volume of the right precentral gyrus ($p = .047$; qs > .05).

PTE (statistically controlling for PAE).—After FDR correction, PTE was associated with smaller cortical surface area of the bilateral pericalcarine (p's < .003), left lateral orbitofrontal, $p = .001$, right posterior cingulate, $p < .001$, right rostral anterior cingulate, $p = .003$, left caudal middle frontal, $p = .004$, and right caudal anterior cingulate gyri ($p = .004$, q's < .05) (Figure 2).

There were additional main effects of PTE that did not pass correction. Before correction, PTE was associated with thicker cortices in the right precuneus ($p = .018$), right posterior cingulate ($p = .025$), and right inferior temporal gyri ($p = .026$, q's > .05). PTE was also associated with smaller cortical surface area of 9 other regions: the right lateral orbitofrontal cortex, $p = .012$; right medial orbitofrontal cortex, $p = .012$; left pars orbitalis cortex, $p = .016$; right middle temporal cortex, $p = .027$; right caudal middle frontal cortex, $p = .032$; right lingual cortex, $p = .043$; right paracentral cortex, $p = .048$; left postcentral cortex, $p = .048$; and, the right precentral cortex, $p = .049$. Additionally, before correction for multiple comparisons, PTE was associated with smaller cortical volume of 13 regions: the bilateral middle temporal cortex, ps ≤ .024; bilateral pericalcarine cortex, ps ≤ .030; bilateral lateral orbitofrontal cortex, p's < .004; left caudal middle frontal cortex, $p = .002$; right rostral anterior cingulate cortex, $p = .005$; right caudal anterior cingulate cortex, $p = .008$; right posterior cingulate cortex, $p = .011$; left entorhinal cortex, $p = .016$; left precentral cortex, $p = .025$; and, the left insular cortex, $p = .028$. Again, these latter results did not pass FDR correction.

In addition to these main effects, there were several regions that exhibited significant PTE × PAE interactions (Figures 2–3), albeit none of which passed FDR correction: right cuneus cortical thickness, $p = .023$; right rostral anterior cingulate cortical thickness, $p = .032$; right superior frontal cortical thickness, $p = .037$; right isthmus cingulate cortical surface area, $p = .018$; right lateral occipital cortical surface area, $p = .026$; right pars triangularis cortical surface area, $p = .038$; right posterior cingulate cortical surface area, $p = .039$; right lateral occipital cortical volume, $p = .026$; right pericalcarine cortical volume, $p = .030$; right isthmus cingulate cortical volume, $p = .030$; and, right pars triangularis cortical volume, $p = .034$. As seen in the top row of Figure 3, PTE was associated with reduced thickness in the PAE group but greater thickness in the non-PAE group. In contrast, for cortical surface area and volume, the differences between the PTE and non-PTE groups were more pronounced in the non-PAE than PAE group (Figure 3, middle and bottom rows).

Subcortical structure.—There were no main effects of PAE or PTE (nor interactions) on subcortical volume that passed FDR correction. However, before correction, analysis revealed that PAE was associated with significantly greater volumes of the left caudate, $p = .043$. In contrast, PTE was associated with reduced right hippocampal volume, $p = .030$.

Further, there were significant PAE × PTE interactions on left cerebellar cortical volume, p = .019, and right amygdalar volume, p = .015 (Figures 4–5). For the left cerebellar cortex, the differences in volumes between the PTE and non-PTE groups were more pronounced given PAE versus no PAE (and vice versa for right amygdalar volume).

Quantity

Cortical structure.—In contrast to the analyses comparing the effects of prenatal exposures, there were no cortical volumetrics that passed FDR correction with respect to quantities of prenatal alcohol and/or tobacco exposure. Before correction, PTE quantity was positively associated with cortical thickness in the right lingual gyrus (p = .039) and cortical surface area and volume of the right pars triangularis gyrus (p's ≤ .037) (Figure 6). In contrast, PTE quantity was negatively associated with cortical surface area of the bilateral caudal middle frontal gyri (p's ≤ .028), bilateral precuneus gyri (p's ≤ .044), right superior parietal gyrus (p = .026), left cuneus gyrus (p = .030), and the right transverse temporal gyrus (p = .040), as well as with cortical volume of the right caudal middle frontal gyrus (p = .011). PAE quantity was only associated with a decrease in left lateral occipital cortical volume, p = .049, but this also did not pass FDR correction (Figure 6).

Subcortical structure.—PTE quantity was negatively associated with volumes of both the central corpus callosum, p = .016, and the left thalamus, p = .050, but neither of these associations passed FDR correction (Figure 7). There were no main effects of PAE quantity on subcortical volume.

Discussion

In this report, we describe structural brain MRI data in a prospectively recruited community sample of children (living in the Western Cape region's Cape Flats townships of South Africa) who had varying levels of PAE and PTE (i.e., across the range from no exposure to heavy exposure), which may be more reflective of naturally occurring ranges in exposure patterns at the community level relative to many previous studies. Our findings of brain structural differences between children with PAE (controlling for concomitant PTE) or PTE (controlling for concomitant PAE), relative to their unexposed counterparts, are important because they highlight the potentially greater deleterious effects of PTE as distinct from PAE on later brain development, which, as described below, may emphasize a need to consider the postnatal environment in future studies of PAE and/or PTE.

Alcohol exposure (controlling for tobacco)

Here, we found that PAE was associated with thinner cortices in the parahippocampal gyrus, a medial temporal lobe (MTL) structure important for learning and memory. Despite similarities between the exposed and control participants on extreme environmental adversity (described below), these results suggest that the MTL may be more vulnerable to PAE than other brain structures are, in comparison to previous studies of PAE in the same geographical region of South Africa. Abnormalities of MTL structures have been previously reported in PAE (Moore and Xia, 2021), and neuroimaging analyses of 51 6-year-olds from the PASS cohort also revealed structural differences in the fusiform gyrus given PAE (i.e.,

another structure that spans the MTL) (Uban et al., 2022). Other cortical regions affected by PAE included precentral sulcus and medial occipital cortices as well as the caudate nucleus subcortically, but these effects did not survive correction for multiple comparisons.

Contrary to the literature examining brain structure in children with FASDs (e.g., Moore and Xia, 2021), we did not see large effects of PAE in this community sample (i.e., large effect sizes and wide spatial distribution of brain differences). There could be numerous explanations for the discrepancies, but we highlight three possibilities. First, while most published reports have focused on children with heavy PAE (e.g., Lindinger et al., 2021) or those with FASD diagnoses, our sample was recruited prospectively, and we did not use *quantity* of exposure for inclusion in our exposed group; in other words, we did not design our study to maximize the chances to find differences between PAE and non-PAE groups. Here, we were specifically interested in understanding the extent to which variability in exposure may be translatable to other populations in which PAE is still prevalent, even though quantities of exposure may be below thresholds from most previous studies and among children not specifically recruited with an FASD diagnosis. Indeed, in cohorts of the Cape Coloured community in South Africa, as studied here, past research of (1) newborns who were heavily exposed to alcohol prenatally (Jacobson et al., 2017), (2) children who met criteria for fetal alcohol syndrome (FAS) (De Guio et al., 2014), and (3) young adolescents with FAS or partial FAS (Joseph et al., 2014) exhibited (1) smaller corpus callosum volumes, (2) smaller white and gray matter volumes, and (3) morphological differences in the hippocampus and caudate, respectively, compared to controls. Given these past and our current results, as well as similar white and gray matter volumes in controls and children who were heavily exposed but not syndromal for FAS (De Guio et al., 2014), more moderate PAE may not elicit the same severity of neuroanatomical change observed in individuals with FAS/FASD, especially given the deeply impoverished conditions experienced by the children in this sample.

Secondly, and more specifically, the extremely impoverished postnatal living conditions of the sample recruited may have potentially strong deleterious effects on brain development in those with no prenatal exposure (especially in the context of more moderate exposure, on average, in the PAE group, as seen here), which may then overshadow the known effects of PAE and/or PTE. Third, previous longitudinal studies have shown that observable differences between children with FASDs and unexposed children vary over time through adolescence (Lebel et al., 2012). Thus, it is possible that with the progression of developmental trajectories of brain structure (in the children studied here), differences between PAE groups may become more apparent. Accordingly, longitudinal brain imaging studies in the PASS cohort may shed more light on the age-effects of PAE long after in utero and early postnatal exposure.

While we expected that our results would corroborate previous reports of widespread brain structural abnormalities among children specifically recruited for heavy alcohol exposure within the same region of South Africa (Fan et al., 2016, Miles et al., 2021), this was not the case in our sample. Indeed, even though there were relationships between quantity of PAE and brain structure in the left lateral occipital cortex, these results did not survive FDR correction (Figure 6). Therefore, it is possible that brain biomarkers of PAE are subtler with

less exposure, with no differentiation from their unexposed counterparts when analyses collapse across wide-ranging exposure quantities. Indeed, to our knowledge, the most similar studies of brain imaging research on PAE among participants in similar communities to the PASS cohort state that mothers of participants in their PAE groups "drank heavily (*M*=9 drinks/occasion)" (Lindinger et al., 2021, p. 145). Our PAE participants, none of whom were selected based on quantities of exposure had a mean level of exposure of 0.82 drinks/week, suggesting that there may be ongoing reductions in prevalence of teratogenic patterns of PAE/PTE occurring within this community. Recruitment into the brain imaging study of the PASS cohort is ongoing, and continued research will help determine how both quantities, frequencies, and timings of PAE exposure relate to brain structure.

There is also considerable support for the possibility that PAE in the context of extreme poverty may not be dissociable given the similarity of the environments in which both the PAE and non-PAE participants were raised. It is well established that poverty has deleterious effects on cognitive development (Brooks-Gunn and Duncan, 1997), and more recent work has shown that the effects of poverty on cognition may be rooted in brain structure (Noble et al., 2015, Gonzalez et al., 2020). As previously described, the children included in this sample all reside in the Cape Flats townships in South Africa. The Cape Flats was an apartheid-designated space for people historically referred to as indigenous Black African or Cape Coloured, where generations of residents have historically been and continue to be systematically deprived of governmental resources and opportunities to enhance their collective educational and socioeconomic status (Turok et al., 2021). Indeed, the median monthly household income for our participants was R7,555 ZAR (*IQR* = R8,420 ZAR), which, on 2020 Aug 30 (i.e., approximate midpoint of scanning dates), was equivalent to an annual household income of $5,461 USD. While there have been efforts over time to enhance specific communities within the Cape Flats (Dhupelia-Mesthrie, 2014), many individuals have historically experienced fewer neighborhood health, economic, educational, and social opportunities. At the extreme end, there are areas in the Cape Flats where individuals continue to experience food insecurity and unstable housing (i.e., no indoor plumbing or electricity) (Brink et al., 2020). As the effects of PAE on brain development in our sample were not as extensive as has been previously reported, our data suggest the real possibility that the effect of environmental factors on brain development in our non-PAE or non-PTE group may outweigh that of prenatal exposure given 8–12 years of development in a deleterious environment. Indeed, similar explanations have been proffered in a recent study of executive functioning (EF) in children with PAE in the Saldanha Bay municipality in South Africa, where no effects of PAE on executive functioning were found (Louw et al., 2021). Accordingly, while we did not set out to adequately measure specific environmental factors that could illuminate these possibilities, we believe it is critical to acknowledge this possibility to properly understand the nature of the sample under study.

Tobacco exposure (controlling for alcohol)

Here, the brain structural impact of PTE was greater than that of PAE in terms of the regional expanse and effect sizes observed that passed correction for multiple comparisons. Specifically, PTE was associated with smaller surface areas in several regions associated with executive function (e.g., caudal middle frontal, cingulate), reward processing (e.g.,

orbitofrontal cortex), and emotional regulation (e.g., cingulate). Previous studies have shown that PTE can negatively impact neurodevelopment, including poorer cognitive performance in children (Cornelius and Day, 2009, Cornelius et al., 2001, Ernst et al., 2001, Huizink and Mulder, 2006) and lower total brain volumes among children with PTE (El Marroun et al., 2016, El Marroun et al., 2014). Typically, alcohol exposure ends at birth or after weaning for potential exposure through breast milk, but tobacco exposure does not necessarily end in the same time frame given second-hand smoke exposure in the environment. Previous studies have shown exposure to second-hand smoke is associated with adverse growth outcomes including smaller head circumference (Nadhiroh et al., 2020). Indeed, the Cape Flats neighborhoods experience overcrowding (Wilkinson, 2000), and overcrowded, poorly ventilated conditions may facilitate secondhand smoke exposure (Sabde and Zodpey, 2011, Kraev et al., 2009). The PASS study includes extensive documentation of pregnancy, birth, and early medical and developmental outcomes (Dukes et al., 2014), which can be linked to all children included in this neuroimaging sub-study, which will be the focus of future investigations.

Conclusion

While our results showing that PTE was more broadly associated with brain structure (vs. PAE) were contrary to our hypotheses, our results do illustrate that the patterning of the effects of PAE, PTE, and their interaction on cortical and subcortical brain structure are not simply the sum of PAE and PTE but rather highly complex downstream outcomes that warrant further investigation. Moreover, the structural associations of PAE and PTE quantity reflect the benefit of considering the amount of exposure along with analyses considering simply being exposed or not to such teratogens. Previous studies, including our own, that have focused on children with heavy PAE (and often adopted outside of their culture and biological families) show much larger effects on the brain. The findings described here highlight the need to further investigate quantity and timing of PAE/PTE, as well as individual differences between participants with PAE at any level of exposure, that is, effects that may depend on the age of participants under study. Ultimately, the limited effects of PAE observed here may reflect more universal deficits of socioeconomic disadvantage resulting from historic apartheid policies or the lasting impact of the “dop system” (i.e., in consideration of epigenetic inheritance of health problems related to alcohol) (Chastain and Sarkar, 2017). If secondhand smoke exposure (or other environmental factors) is augmenting the effects of PTE on brain structure, then further, longitudinal neuroimaging research with this cohort is necessary to evaluate the emergence of PAE- and/or PTE-related neurodevelopmental outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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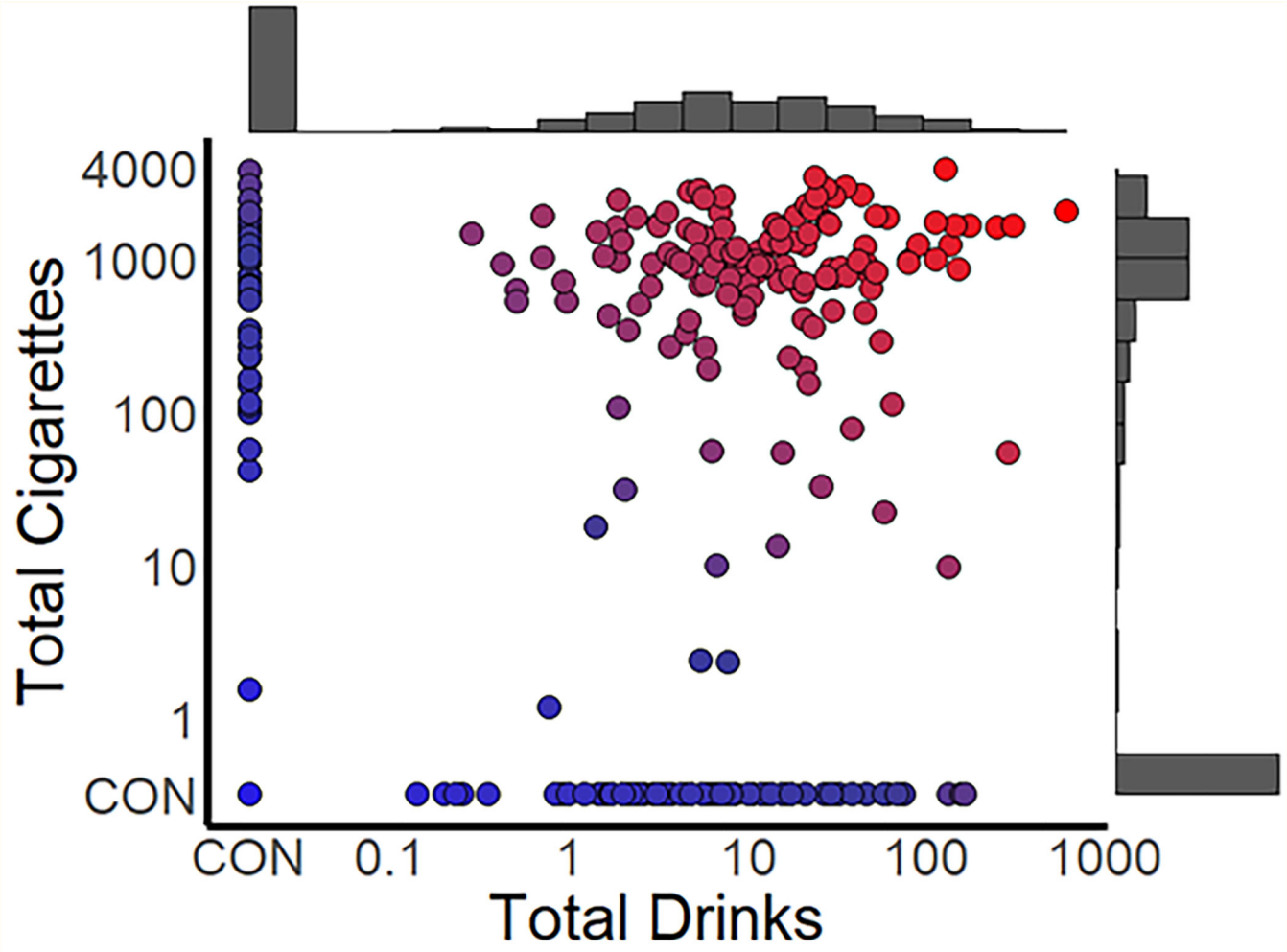

Figure 1.
Distribution of participants per PAE and/or PTE quantity. The abscissa and ordinate are presented on a log10 scale. CON = control group (i.e., no exposure).

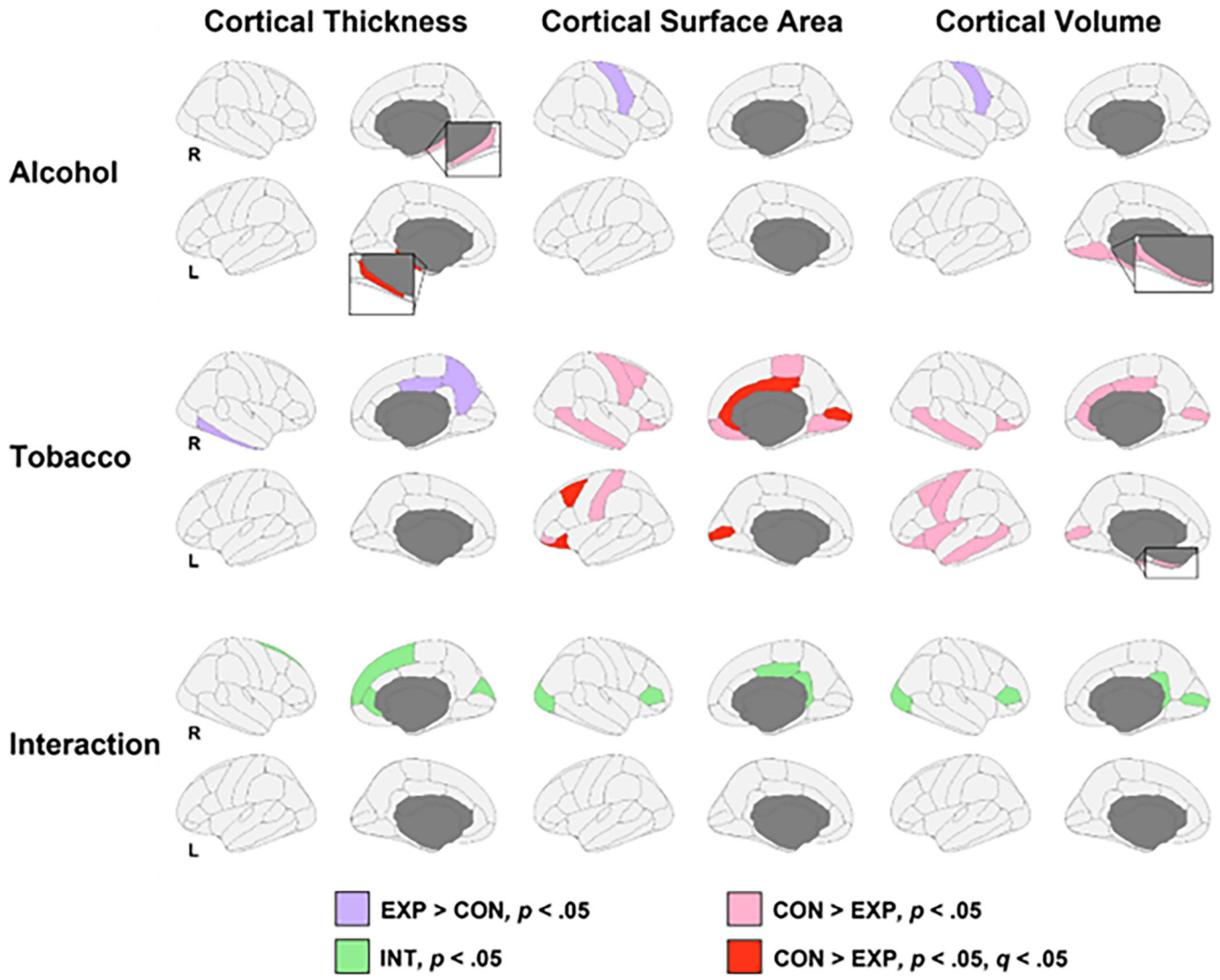

Figure 2.

Brain maps of cortical regions significantly associated with alcohol and tobacco exposure during pregnancy. L = left hemisphere. R = right hemisphere. EXP = Exposed to prenatal alcohol and/or tobacco. CON = control group. INT = interaction.

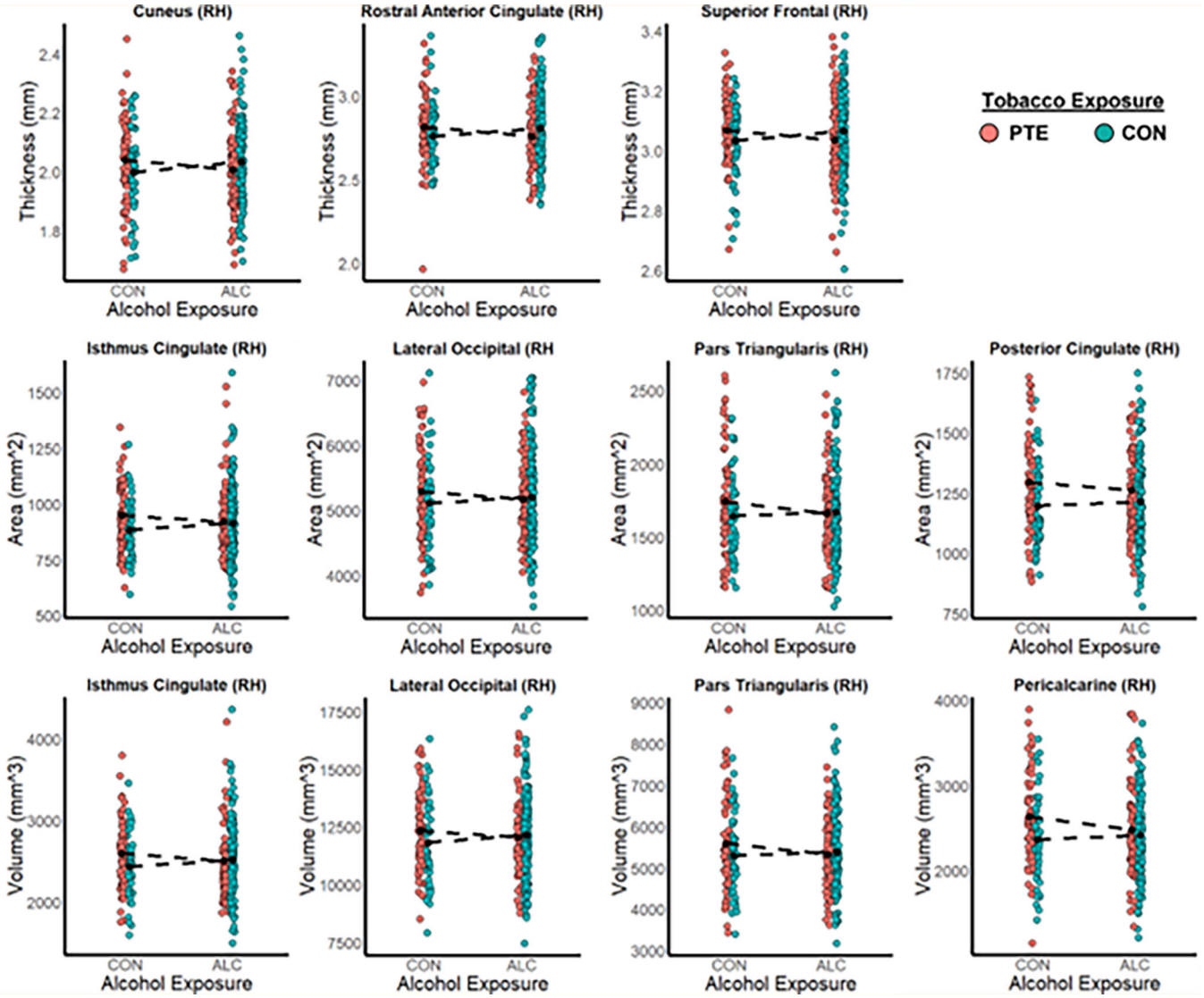

Figure 3.

Cortical regions exhibiting significant interactions between prenatal alcohol exposure (PAE) and prenatal tobacco exposure (PTE). CON = control group. Black data points and dashed lines designate the means of each PAE × PTE subgroup.

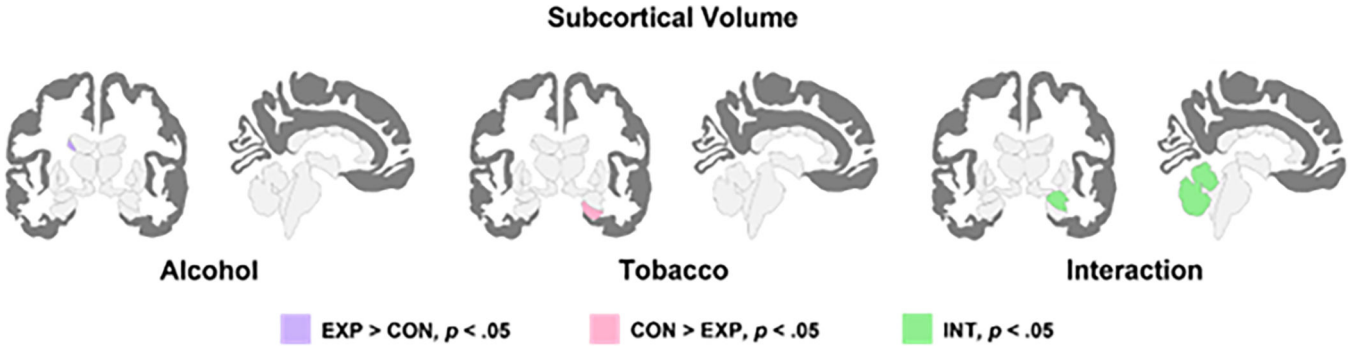

Figure 4.

Brain maps of subcortical regions significantly associated with alcohol and tobacco exposure during pregnancy. L = left hemisphere. R = right hemisphere. EXP = Exposed to prenatal alcohol and/or tobacco. CON = control group. INT = interaction.

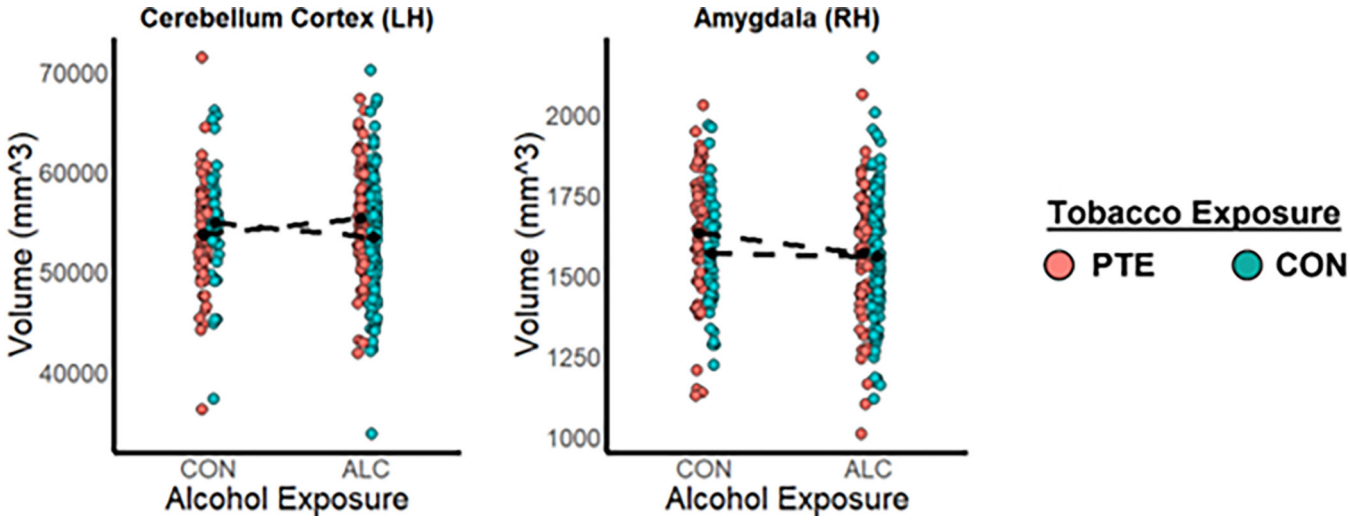

Figure 5.

Subcortical regions exhibiting significant interactions between prenatal alcohol exposure (PAE) and prenatal tobacco exposure (PTE). CON = control group. Black data points and dashed lines designate the means of each PAE × PTE subgroup.

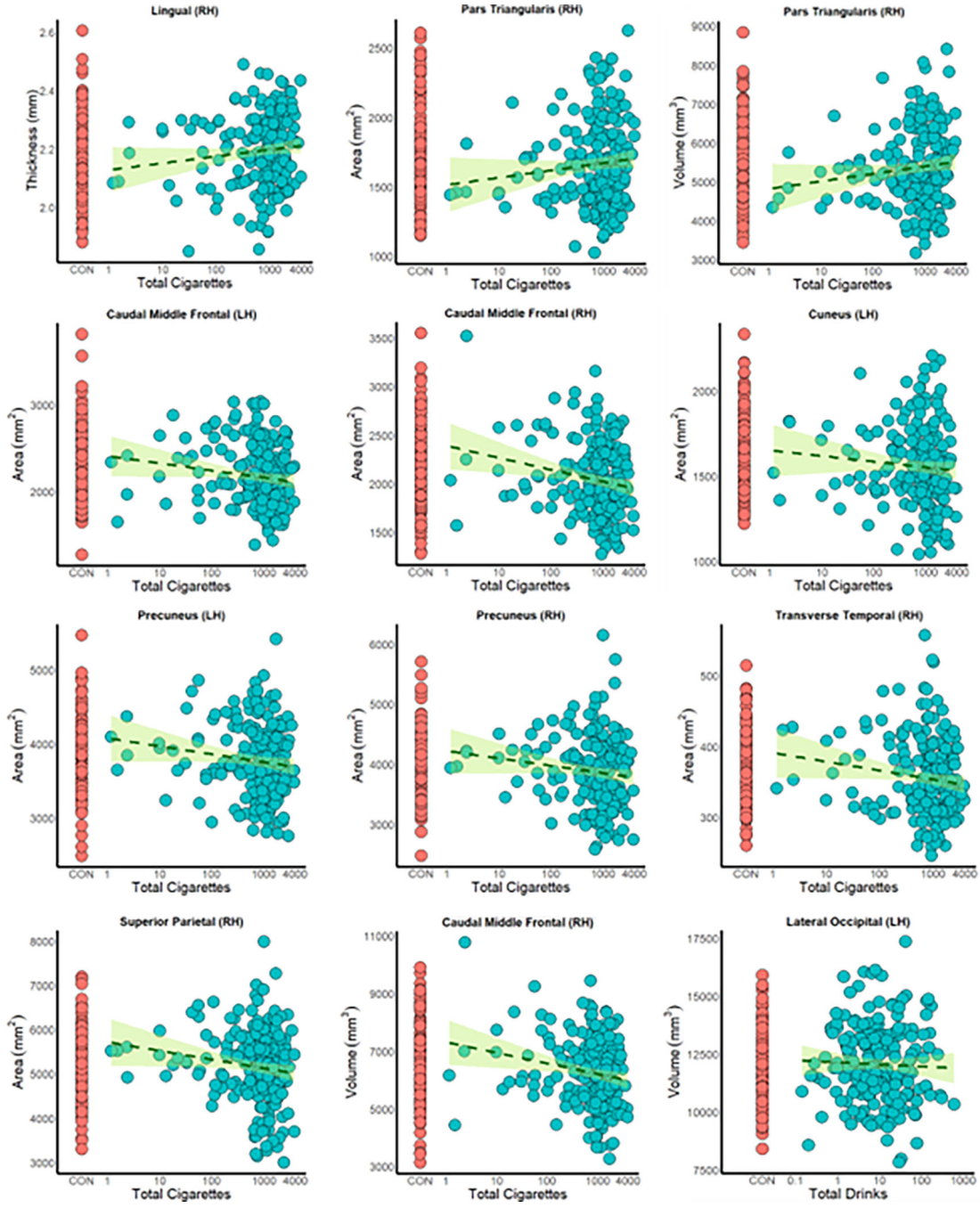

Figure 6.

Cortical regions exhibiting significant (uncorrected) associations with quantity of tobacco or alcohol exposure during pregnancy (i.e., total cigarettes smoked: prenatal tobacco exposure, PTE; total drinks: prenatal alcohol exposure, PAE). Red data points reflect those not exposed to tobacco or alcohol prenatally (i.e., controls; CON). Blue data points are the individuals in the PTE group or PAE group (bottom right panel). The abscissa is presented on a log10 scale, and the dashed line is a best fit, simple regression line to convey directionality of the association. LH = left hemisphere. RH = right hemisphere.

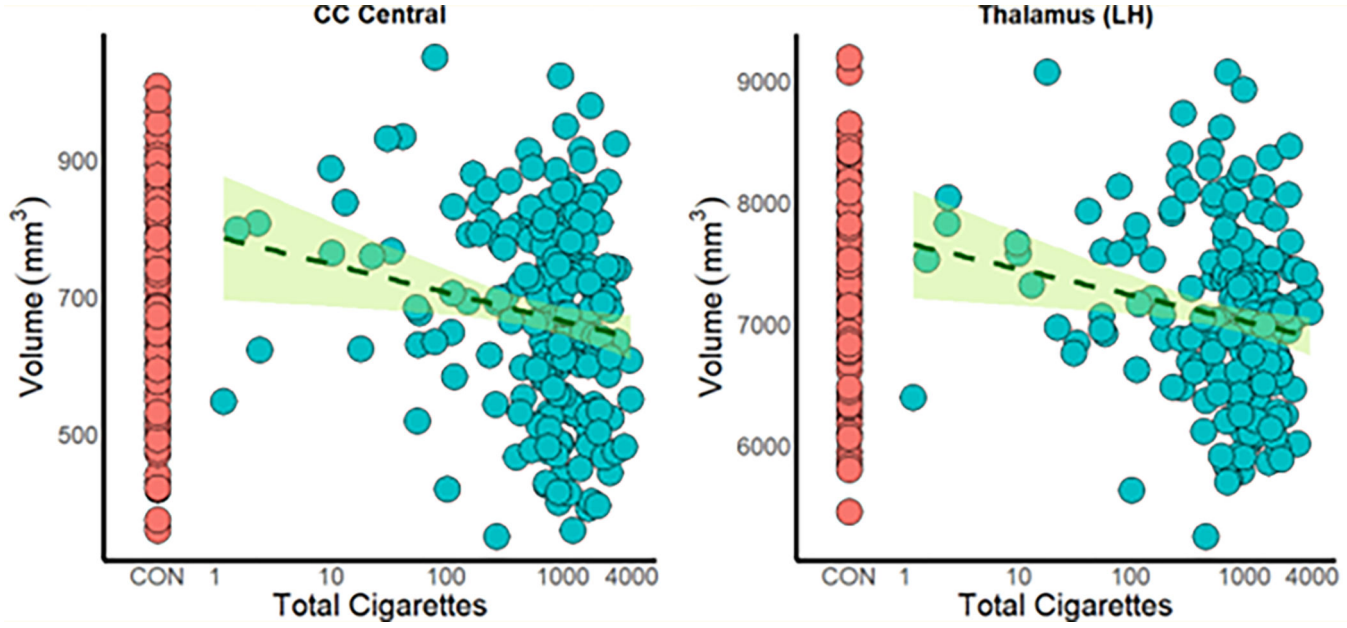

Figure 7.

Subcortical regions exhibiting significant (uncorrected) associations with quantity of tobacco exposure during pregnancy (i.e., total cigarettes smoked: prenatal tobacco exposure, PTE). Red data points reflect those not exposed to tobacco prenatally (i.e., controls; CON). Blue data points are the individuals in the PTE group. The abscissa is presented on a log scale, and the dashed line is a best fit, simple regression line to convey directionality of the association. LH = left hemisphere. CC = corpus callosum.

Table 1.

Participant demographics.

"Total Drinks" and "Total Cigarettes" refer to the total number of standard drinks and cigarettes smoked, respectively, during pregnancy ("Total Drinks" also included alcohol consumption around the last menstrual period [LMP] [± 15 days]; "Total Cigarettes" were estimated by multiplying cigarettes per day since LMP/gestational age 0 days by 280 [40 weeks * 7 days]). PAE = prenatal alcohol exposure. PTE = prenatal tobacco exposure.

	PAE (*N*=220)	No-PAE (*N*=112)
Sex [n (%)]		
Female	124 (56.4%)	53 (47.3%)
Male	96 (43.6%)	59 (51.7%)
Age (Years)		
Mean (SD)	10.3 (1.4)	10.3 (1.3)
Total Drinks		
Missing (*n*)	9	0
Mean (*SD*)	28.7 (60.7)	0 (0)
Prenatal Tobacco Exposure [n (%)]		
No-PTE	70 (31.8%)	63 (56.2%)
PTE	150 (68.2%)	49 (43.8%)
Total Cigarettes		
Mean (*SD*)	741.8 (824.4)	454.2 (751.0)