Are all threats equal? Associations of childhood exposure to physical attack versus threatened violence with preadolescent brain structure

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ABSTRACT

Background: Neurodevelopmental studies of childhood adversity often define threatening experiences as those involving harm or the threat of harm. Whether effects differ between experiences involving harm ("physical attack") versus the threat of harm alone ("threatened violence") remains underexplored. We hypothesized that while both types of experiences would be associated with smaller preadolescent global and corticolimbic brain volumes, associations with physical attack would be greater.
Methods: Generation R Study researchers (the Netherlands) acquired T1-weighted scans from 2905 preadolescent children, computed brain volumes using FreeSurfer, and asked mothers whether their children ever experienced physical attack (n = 202) or threatened violence (n = 335). Using standardized global (cortical, subcortical, white matter) and corticolimbic (amygdala, hippocampus, anterior cingulate cortex, orbitofrontal cortex) volumes, we fit confounder-adjusted models.
Results: Physical attack was associated with smaller global volumes ($\beta_{cortical}$=−0.14; 95% CI: −0.26, −0.02); $\beta_{white\ matter}$= −0.16; 95% CI: − 0.28, − 0.03) and possibly some corticolimbic volumes, e.g., $\beta_{amygdala/ICV-adjusted}$= −0.10 (95% CI: −0.21, 0.01). We found no evidence of associations between threatened violence and smaller volumes in any outcome; instead, such estimates were small, highly uncertain, and positive in direction.
Conclusions: Experiences of physical attack and threatened violence may have quantitively different neurodevelopmental effects. Thus, differences between types of threatening experiences may be neurodevelopmentally salient.

1. Introduction

Globally, childhood mental disorders and behavior problems impose a substantial burden on population health (Whiteford et al., 2013; Vos et al., 2020). In the United States, for example, they account for more medical spending on children ($13.9 billion in 2012) than any other condition, yet current prevention efforts are hampered by an incomplete understanding of what causes them (Ghandour et al., 2019; Soni, 2001; Bui et al., 2017). Extensive research has documented the role of childhood adversity—i.e., negative experiences that entail either harmful or inadequate input (e.g., abuse or neglect, respectively) and that require

significant adaptation from a typical child—in increasing the risk of child mental disorders and behavior problems (Nelson and Gabard-Durnam, 2020; Berens et al., 201; Humphreys and Zeanah, 2015; McLaughlin et al., 2019). Foundational research exploring mental health effects of childhood adversity generally examined either *qualitative* differences in adverse experiences (i.e., specificity models investigating one adversity at a time) or *quantitative* differences in the number of adversities a child experienced (i.e., cumulative risk models). (Smith and Pollak, 2021; McLaughlin et al., 2021). Cumulative risk models have provided valuable insight over time and continue to guide practice and policy (Lanier et al., 2018). More recently, however, investigators have

proposed "dimensional" models that consider both qualitative and quantitative features of a child's adverse experiences to provide greater insight into neurobiological mechanisms mediating childhood adversity and mental disorders (McLaughlin et al., 2019, 2021).

Most prominently, Sheridan and McLaughlin (2014) proposed the dimensional model of adversity, which maintains that (1) qualitative features of adverse experiences encode multiple underlying dimensions of social experiences that have distinct neurodevelopmental effects, and (2) effects will scale based on quantitative features of the adverse experiences, e.g., the frequency and severity of a child's experience (Sheridan and McLaughlin, 2014; McLaughlin and Sheridan, 2016; McLaughlin et al., 2014). Sheridan and McLaughlin (2014) initially defined two dimensions for their model: (1) experiential deprivation, or the absence of expected cognitive and social input, and (2) threatening experiences. Borrowing from the DSM-5 definition of "traumatic event," they defined threatening experiences as those "characterized by *actual or threatened.* harm to one's physical integrity" (emphasis added) (Sheridan and McLaughlin, 2014). More recently, McLaughlin et al. (2019) defined threats as "experiences involving *harm or threat of harm* to the child" (emphasis added). Thus, the dimensional model of adversity assumes that both (1) experiences involving harm and (2) experiences involving only the threat of harm should cause similar neurodevelopmental effects, perhaps differing only based on the frequency and severity of the experiences.

Subsequent research has generally supported the dimensional model of adversity, but whether experiences involving harm and experiences involving threatened harm alone have similar effects has not yet been directly tested (McLaughlin et al., 2019). While the two types of experiences share many attributes (e.g., they may both induce fear), they may differ in important qualitative ways, and related evidence from both animal models and humans suggests they may lead to somewhat different effects. For example, some rodent models of traumatic stress use foot shock paradigms (possibly mimicking aspects of physically harmful experiences), while others expose rodents to a predator's scent (possibly mimicking experiences of threatened harm alone) (Schöner et al., 2017; Lezak et al., 2017). These paradigms elicit somewhat different biologic responses in rodents, suggesting that while both of them entail physically threatening experiences, they may impact brain function differently.

In humans, neural responses to fear-inducing stimuli partially depend on whether the stimuli cause pain (Biggs et al., 2020). Some neural correlates of pain-inducing and non-pain-inducing stimuli overlap, with the former being greater in magnitude than the latter (i.e., quantitative but not qualitative differences). This suggests neural responses are partly a function of stimulus intensity. However, in other regions of the brain, the two types of stimuli (pain-inducing and non-pain-inducing) may evoke opposing responses, which implies pain-dependent qualitative differences in neural responses independent from those due to stimulus intensity. For example, in the parieto-occipital sulcus, pain-inducing stimuli appear to evoke a positive response, while non-pain-inducing stimuli may evoke a negative response (Biggs et al., 2020). Thus, some short-term neural responses to pain versus the threat of pain may differ. By extension, it is possible that some longer-term responses to "harm" versus the threat of "harm" may also differ.

Other taxonomies of adverse experiences that are based on their presumed effects distinguish between instances of harm versus threat of harm. For example, since at least the 1700s, legal systems (specifically, the common law of intentional torts) have distinguished between threatening experiences where the perpetrator actually strikes the victim (i.e., "battery," hereafter referred to as "physical attack"), and those where the perpetrator threatens but does not actually strike the victim (i.e., "assault," hereafter referred to as "threatened violence") (William Blackstone, 1765). While this legal distinction developed without evidence from modern neuroscience technologies, it is nevertheless premised on defining types of experiences based on their specific

consequences for victims, and it developed over centuries of observation.

Experiences of physical attack and threatened violence are common in the United States, though estimates of prevalence range widely depending on how researchers define violence exposure. Finkelhor et al. (2015) report that prevalence of "any physical assault" (a broad definition that aggregates physical attack, threatened violence, and other types of violence) among American youth aged 0–17 years exceeds 50%. Meanwhile, Kessler et al., 1995 report that 11% of men and 7% of women in the United States experience traumatic physical attack at some point in their lives. Nevertheless, whether these distinct experiences may have similar or different neurodevelopmental consequences has not yet been tested. Our study aims to explore this knowledge gap.

Prior research has generally found that violence exposure (regardless of precise definition) is associated with smaller volumes in both gray matter, particularly in corticolimbic regions, and white matter, particularly in the corpus callosum, but these results have been somewhat inconsistent (McLaughlin et al., 2019; Teicher et al., 2016; Islam and Kaffman, 2021). The corpus callosum is the brain's largest white matter bundle, and it is involved in managing emotional and social responses among many other tasks (Islam and Kaffman, 2021). Separately, the brain's corticolimbic system, including the amygdala, hippocampus, anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC), is involved in threat perception and response (McLaughlin et al., 2019; Teicher et al., 2016; Holz et al., 2020). Smaller volumes in both the corpus callosum and corticolimbic regions have been associated with a spectrum of mental disorders (Teicher et al., 2016; Islam and Kaffman, 2021). Many of these disorders first occur in adolescence, a sensitive period of neurodevelopment marked by exceedingly rapid neural reorganization (Fuhrmann et al., 2015; Solmi et al., 2021). In turn, studying whether and how adverse experiences impact brain structure immediately prior to this period (i.e., in preadolescence) may inform our understanding of why so many mental disorders begin in adolescence.

However, studying possible differences in neurostructural effects of physical attack versus threatened violence is difficult for several reasons. Many neuroimaging studies of childhood violent experiences rely on clinical samples where children have often experienced both types of violence. This inhibits their ability to detect differing effects of co-occurring experiences because they often do not include enough participants exposed to only one of the two experiences. Moreover, these studies are often limited by sample size, further reducing their ability to detect differences between the two types of experiences. To overcome these limitations, this population neuroscience study uses a large sample of children from the general population, some of whom experienced physical attack, threatened violence, both types of violence, and neither type of violence.

This study uses data from the Generation R Study. When children were about ten years old, researchers collected retrospective data from mothers on their child's lifetime experiences with physical attack and threatened violence, and the children completed an MRI brain scan (White et al., 2018). Because human behavior entails coordinated activity across many brain regions, we hypothesized that physical attack and threatened violence experiences would each be associated with global brain differences, namely, smaller (1) cortical gray matter volume, (2) white matter volume, and (3) subcortical gray matter volume. We further hypothesized that physical attack experience would be associated with greater volumetric differences than threatened violence experience. Finally, we postulated that any global cortical or subcortical volume differences would be due, in part, to differences in corticolimbic brain regions, i.e., the amygdala, hippocampus, anterior cingulate cortex, and orbitofrontal cortex.

2. Material and methods

2.1. Participants

This study uses data from the Generation R Study, a population-based birth cohort in Rotterdam, the Netherlands, seeking to identify social, environmental, and genetic factors affecting child development (Jaddoe et al., 2012). The Generation R Study enrolled 9978 new mother-infant dyads living in Rotterdam between 2002 and 2006. After securing written informed consent and assent from participants and their parents when appropriate, researchers have collected data from children and their caregivers at multiple times through the present. All consent forms and study protocols were and are approved by the Medical Ethics Committee of the Erasmus University Medical Center.

When participating children reached preadolescence (mean age 10.1 years, range 8.6–12.0), study researchers interviewed each child's primary caregiver, 96% of whom were mothers, about whether their child had ever experienced physical attack or threatened violence (White et al., 2018). At the same study center visit, staff scanned children with magnetic resonance imaging (MRI) (White et al., 2018). Primary analyses in this study included children with usable MRI data (described below) and reliable violence experience data reported by mothers. Among these children, we excluded those whose mothers reported using cocaine or heroin while pregnant. When twins and triplets were enrolled, we excluded all but one randomly selected sibling to avoid challenges with correlated data. Our final analytic sample included 2905 children. Appendix A.1 provides more sample selection details.

2.2. Measures

2.2.1. Violence experience

This study uses information from two different instruments, each administered at a different timepoint in the participants' childhoods, regarding instances of physically threatening experiences. These instruments, which are described in detail below, include: (1) an in-person maternal interview about their child's experiences with physical attack and / or threatened violence, which we used to derive our primary exposure measure; and (2) a postal questionnaire about corporal punishment practices, which mothers completed when their children were 8.1 years old. The corporal punishment questionnaire, which we used in secondary analyses, assessed disciplinary tactics used by parents that may have involved experiences qualitatively similar to those of physical attack. However, our hypotheses are not confined to parent-perpetrated violence—they relate to all violent experiences regardless of perpetrator—but we use the corporal punishment data in secondary analyses to contextualize our primary analyses based on maternal interview data.

Physical attack and threatened violence. During an in-person study center visit when children were preadolescents, trained study staff interviewed mothers about their child's experiences with stressful life events. The interview adapted items from Kendler's Life Stress Interview and Brown and Harris's Life Event and Difficulty Schedule (White et al., 2018; Amone-P'Olak et al., 2009; Brown and Harris, 1978). In the interview, mothers reported if their child had experienced any of 24 stressful life events at any point in time during his or her childhood (yes, no), including physical attack or threatened violence. English translations of questions asked in Dutch are (1) "Has anyone ever used physical violence against your child, for example, beaten [him / her] up?" (i.e., "physical attack"); and (2) "Has anyone ever threatened to use physical violence against your child, such that it didn't happen but your child was scared?" (i.e., "threatened violence"). Interviewers were trained to clarify that these questions referred to distinct types of non-overlapping experiences by ensuring that a single discrete event in the child's life could not be characterized as both physical attack and threatened violence. However, if a child initially experienced an instance of threatened violence and then, later in time, an instance of physical attack, the child's mother could report exposure to both types

of experiences. Importantly, interviewers were also trained to clarify that the questions were not meant to capture *de minimis* experiences of physical attack or threatened violence, e.g., rough play or playground skirmishes. Interviewers deemed responses from mothers unreliable if language barriers inhibited the mother's question comprehension. We excluded these participants (n = 66).

Corporal Punishment. When children were aged 8.1 years, mothers answered via postal questionnaire two questions regarding how often either slapping or spanking "typically occurs in the home" on a 5-point frequency scale ranging from "never" to "always." (Shelton and Frick, 1996; Essau et al., 2006). We summed these answers to construct a continuous score ranging from 0 to 8 quantifying each participant's corporal punishment experience. Appendix A.2 provides further detail.

2.2.2. Brain imaging

Generation R researchers have described magnetic resonance imaging protocols elsewhere (White et al., 2018). All scans were acquired on a 3 Tesla GE Discovery MR750w scanner (General Electric, Milwaukee, WI, USA) yielding 1 mm isotropic resolution. Study staff processed resulting images in FreeSurfer v6.0.0, which estimated both global volumes and volumes for corticolimbic regions of interest (ROIs) in mm^3 (Fischl, 2012). Study researchers visually inspected each reconstruction and excluded poor quality images. In our primary analyses, we assessed three global volumes: (1) total cortical gray matter (all cortical tissue between the pial and white matter surfaces); (2) total cerebral white matter (white matter tissue inside the white matter surface, excluding cerebellar white matter and the brainstem); and (3) total subcortical gray matter (sum of volumes for the thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and ventral diencephalon). ROIs included the amygdala, hippocampus, rostral and caudal anterior cingulate cortex (ACC), and lateral and medial orbitofrontal cortex (OFC).

2.2.3. Covariates

Researchers retrieved birthdate and sex data from birth records. Parents self-reported the following: their national origin and ethnicity, which we used to categorize child ethnicity as European (excluding Turkish), Turkish, Moroccan, Surinamese, and Other Ethnicity; household income during pregnancy ($<$ or $\geq$ €2200 / month); highest maternal or paternal completed education level at study enrollment (less than high school equivalent; high school or intermediate vocational training; advanced vocational training, bachelor's degree, or higher); maternal and paternal history of psychotic episodes (yes / no for each parent); maternal age at childbirth; maternal smoking during pregnancy (never, until pregnancy known, or through pregnancy); and parental prenatal psychopathology symptoms assessed using the 53-item Brief Symptom Inventory (BSI) (Derogatis and Melisaratos, 1983). We calculated continuous BSI sum scores for each parent.

We imputed missing covariate (but not exposure or outcome) data. The proportion of missing data for most covariates was low ($<$ 2%), except for household income (22%), maternal psychopathology symptoms (23%), partner educational attainment (36%), and partner psychopathology symptoms (38%). We imputed these missing values using the rich auxiliary data collected by Generation R researchers throughout the participants' lives that were predictive of missing covariate data, e. g., other socioeconomic indicators for partner educational attainment and partner history of psychosis for partner psychopathology symptoms (Perkins et al., 2018; Harel et al., 2018). To ensure we sufficiently modeled uncertainty around the imputed values, we created 50 imputed datasets, and we combined resulting estimates using Rubin's Rules (Rubin, 1996). Appendix A.3 includes additional imputation model details. For use in sensitivity analyses, we also calculated inverse probability of attrition weights to account for differential attrition by sociodemographic characteristics. We deemed lost to follow-up any participant enrolled at baseline but excluded from our analytic sample for any reason. Appendix A.4 includes additional details regarding how

these weights were derived.

2.3. Statistical analyses

We excluded participants with global or ROI volumes over four standard deviations from the measure's analysis sample mean because such values are either biologically implausible or so far from the sample means that they likely represent pathology or brain structure abnormality (n = 14 excluded). Because we did not hypothesize hemisphere-specific effects, we averaged hemisphere-specific ROI volumes and standardized all measures. We used *t*-tests to assess sociodemographic differences in exposures. We calculated correlation coefficients between actual and threatened violence exposure and scores for harsh parenting and corporal punishment exposure.

In primary analyses, we used ordinary least squares (OLS)-estimated linear regression models to assess whether physical attack and threatened violence experiences were associated with continuous measures of the three global outcomes. For each outcome, we fit minimally adjusted models adjusting for scan age, sex, and ethnicity, and fully adjusted models incorporating all remaining covariates listed above (hereafter referred to as Primary Models). We additionally adjusted models of subcortical volume for total intracranial volume (ICV) to estimate whether physical attack or threatened violence were associated with subcortical volume differences *over and above* any global effects. Within each type of threatening experience, we adjusted *p*-values and calculated *q*-values for multiple tests via the Benjamini-Hochberg procedure, a method that controls the false discovery rate (FDR) when assuming non-negative correlation among estimates (3 global brain volumes, 3 tests) (Benjamini and Hochberg, 1995; White et al., 2019).

We fit several fully adjusted OLS-estimated sensitivity models to assess whether our results were robust to different sample constructions, model specifications, and modeling strategy assumptions. First, we fit linear models using inverse probability of attrition weights to address possible selection bias from differential attrition by sociodemographic variables (Sensitivity Model 1). Second, we fit a model including covariates for both physical attack and threatened violence exposure simultaneously (Sensitivity Model 2). Third, we fit models in subsamples excluding participants reporting both primary exposures, e.g., in models assessing physical attack, we excluded participants exposed to threatened violence (Sensitivity Model 3). Next, we fit marginal models of both primary exposures using both (1) inverse probability of exposure weights (Marginal Model 1) and (2) standardization via the parametric G-formula (Marginal Model 2) (Hernán and Robins, 2020). These models attempt to estimate population average exposure effects—as opposed to Primary Model effect estimates that are conditional on covariates—and thus require a different set of assumptions. Appendices A.4 and A.5 detail these models more thoroughly. Thereafter, we re-fit Primary Models using a subsample of participants exposed either to physical attack or to threatened violence, but not to both types of experiences (n = 405). By excluding participants who experienced neither or both types of violence, these "Direct Comparison" models attempt to compare brain volumes of children who experienced physical attack only versus threatened violence only. Finally, to gain additional context for our subcortical volume findings, we fit ICV-unadjusted models, which we report in the Appendix, and which explore associations before accounting for global differences in overall head size.

In secondary analyses, we sought to clarify whether corticolimbic ROIs were affected by our primary exposures in ways that were similar to our global measures. Using the same modeling strategy detailed above, we fit ROI-specific models using continuous outcomes. For subcortical ROIs (i.e., amygdala and hippocampal volume), we fit models both adjusted and unadjusted for ICV. For these secondary analyses, we adjusted *p*-values and calculated *q*-values assuming 6 tests (6 brain ROIs) within each type of threatening experience via the Benjamini-Hochberg procedure.

Finally, we conducted secondary analyses assessing both global and ROI-specific associations with continuous corporal punishment scores using fully adjusted OLS-estimated models. We also fit these models additionally adjusting for physical attack exposure to assess whether estimates of either of these experiences (corporal punishment or physical attack) changed when considering the other.

After modeling our data, we interpreted results consistent with the American Statistical Association's guidance to evaluate the strength of statistical evidence based on effect sizes and confidence intervals, effect directions, and continuous p-values (Wasserstein and Lazar, 2016). In doing so, we minimize our reliance on *p*-value cutoffs in null hypothesis significance testing, though we use the language of statistical significance as a heuristic to concisely communicate certain results.

3. Results

3.1. Analytic sample characteristics

Our primary analytic sample differed from the baseline cohort by sociodemographic characteristics. Included versus excluded participants were more likely to have European ethnicity (70% vs. 58%), parents with post-secondary educations (61% vs. 44%), and older mothers (mean maternal age at birth 31.6 vs. 29.8 years).

Of 2905 children in our analytic sample, 202 experienced physical attack (Table 1). Boys were more likely than girls to have been exposed (9.8% vs. 4.1%), as were children with lower versus higher educated parents (8.8% vs. 5.6%). Separately, 335 children experienced threatened violence, with similar patterns of differential exposure across sociodemographic groups to those above (Table 1). 66 children experienced both physical attack and threatened violence. Experiencing physical attack was moderately correlated with experiencing threatened violence (r = 0.19). Neither physical attack nor threatened violence

Table 1

Distribution of primary and secondary exposures by participant characteristics in the primary analytic sample.

	Total n (%)	Physical Attack n (%)	Threatened Violence n (%)	Corporal Punishment $\bar{x}$ (s)
Total sample	2905 (100.0)	202 (7.0)	335 (11.5)	0.6 (1.0)
Sex				
Female	1472 (50.7)	61 (4.1)	122 (8.3)	0.5 (1.0)
Male	1433 (49.3)	141 (9.8)	213 (14.9)	0.7 (1.0)
National origin / ethnicity				
European (non-Turkish)	1985 (69.6)	123 (6.2)	218 (11.0)	0.5 (0.9)
Turkish	148 (5.2)	8 (5.4)	12 (8.1)	0.6 (1.0)
Moroccan	126 (4.4)	8 (6.3)	14 (11.1)	1.3 (1.4)
Surinamese	212 (7.4)	23 (10.8)	30 (14.2)	1.0 (1.1)
Other	382 (13.4)	32 (8.4)	56 (14.7)	1.0 (1.3)
Household education				
Less than high school	116 (4.3)	7 (6.0)	10 (8.6)	0.8 (1.0)
High school equivalent	946 (34.7)	87 (9.2)	142 (15.0)	0.8 (1.1)
More than high school	1666 (61.1)	93 (5.6)	162 (9.7)	0.5 (0.9)
Household income				
€2200 / month or less	1442 (49.6)	126 (8.7)	195 (13.5)	0.8 (1.1)
More than €2200 / month	1463 (50.4)	76 (5.2)	140 (9.6)	0.5 (0.9)

a. This table is based on observed values for each characteristic and does not account for missing data.

b. $\bar{x}$ and s denote sample mean and standard deviation, respectively.

c. Corporal punishment scores were assessed at mean child age 8 years and have a range from 0 to 8.

were correlated with corporal punishment (r = −0.02 and r = 0.02, respectively).

3.2. Global brain volumes, primary and sensitivity analyses

In fully adjusted models, physical attack experience was associated with smaller total cortical gray matter and total white matter volume (Table 2). As illustrated in Fig. 1, these results were robust to sample construction, model specification, and modeling strategy in most sensitivity analyses, though estimates from models excluding participants reporting both actual and threatened violence exposure were attenuated (Fig. 1, Sensitivity Model 3). For example, the Primary Model estimate of the association between physical attack and cortical gray matter volume was $\beta_{physical\ attack/cortical\ volume} = -0.14$ (95% CI: −0.26, −0.02; $p = 0.03$; $q = 0.04$). In sensitivity models, these estimates ranged from $\beta = -0.10$ (95% CI: −0.24, 0.05) in Sensitivity Model 3 to $\beta = -0.16$ (95% CI: −0.32, −0.01) in Marginal Model 1, which used IPWs for exposure. Notably, the interpretation of the former estimate is conditional on included model covariates, while the latter is interpreted as the population average association. Separately, physical attack experience was associated with subcortical volume only *before* ICV adjustment. See Appendix B.7 and E.2. After adjusting for ICV, this relationship was no longer statistically significant: $\beta_{physical\ attack/subcortical\ volume\ (ICV\ adjusted)} = -0.05$ (95% CI: −0.14, 0.03). Because adjusting for ICV attenuated this relationship, we found no statistically significant evidence that physical attack was associated with lower total subcortical volume over and above possible global effects (Table 2, Fig. 1).

We also found no evidence that threatened violence exposure (versus no exposure) was associated with total cortical or white matter volume in primary and sensitivity analyses, e.g., $\beta_{threatened\ violence/cortical\ volume} = 0.04$ (95% CI: −0.06, 0.13) (Table 2, Fig. 1). Compared with estimates for physical attack, those of threatened violence were smaller in magnitude and, in fact, almost uniformly opposite in direction. Standard errors were relatively large, and no estimates were statistically significant at the $p = 0.05$ level. ICV-adjusted estimates of subcortical volume were close to zero with no consistent positive or negative pattern. Appendices B.1 through B.5 report sensitivity model results for global outcomes.

In Direct Comparison models, children who experienced physical attack only (versus threatened violence only) had smaller cortical ($\beta_{cortical} = -0.19$; 95% CI: −0.36, −0.01) and white matter ($\beta_{white\ matter} = -0.21$; 95% CI: −0.39, −0.03) volumes, and possibly smaller subcortical volumes after adjusting for ICV ($\beta_{Subcortical\ /\ ICV\ adjusted} = -0.08$; 95% CI: −0.21, 0.05). See Fig. 1, Fig. 3, and Appendix B.7.

3.3. Corticolimbic brain volumes, primary and sensitivity analyses

Results from fully adjusted ROI analyses suggest physical attack exposure (versus no physical attack exposure) may be associated with smaller amygdala volume after ICV adjustment. While the estimate from the Primary Model, $\beta_{physical\ attack/amygdala\ (ICV\ adjusted)} = -0.10$ (95% CI: −0.21, 0.01) (Table 3, Fig. 2) was not statistically significant ($p = 0.08$, $q = 0.24$), sensitivity model estimates were highly consistent and ranged from $\beta_{physical\ attack/amygdala\ (ICV\ adjusted)} = -0.13$ (95% CI: −0.25, 0.00) in Marginal Model 1 (IPWs for exposure) to $\beta_{physical\ attack/amygdala\ (ICV\ adjusted)} = -0.10$ (95% CI: −0.24, 0.05) in Sensitivity Model 1 (IPWs for attrition) (Appendices C.1-C.5). Results from the Primary Model also suggest a possible relationship between physical attack and smaller lateral OFC volume: $\beta_{physical\ attack/lateral\ OFC} = -0.13$ (95% CI: −0.26, 0.01; $p = 0.06$; $q = 0.24$), with most sensitivity models yielding comparable results. Evidence of a similar relationship between physical attack and smaller medial OFC was comparatively weaker but nonetheless noteworthy in context, e.g., Primary Model $\beta_{physical\ attack/medial\ OFC} = -0.09$ (95% CI: −0.22, 0.04; $p = 0.17$; $q = 0.34$). We found no other evidence suggesting associations between physical attack and any other ROI.

Our results also provide weak evidence of a possible relationship between threatened violence exposure (versus no exposure) and larger medial OFC volume (Table 3, Fig. 2). For example, in the Primary Model, $\beta_{threatened\ violence/medial\ OFC} = 0.10$ (95% CI: −0.00, 0.21; $p = 0.06$; $q = 0.36$), and in Sensitivity Model 2 (modeling both exposures simultaneously), $\beta_{threatened\ violence/medial\ OFC} = 0.12$ (95% CI: 0.01, 0.22; $p = 0.03$; $q = 0.18$). While we found no evidence of associations between threatened violence and any other corticolimbic ROI, results from all such models evinced a pattern in which nearly every estimate was positive (see, e.g., Fig. 2). Appendices C.1 through C.5 report ROI sensitivity model results.

In Direct Comparison models, physical attack exposure (versus threatened violence exposure) was also associated with smaller volumes in the amygdala (both ICV-unadjusted and -adjusted) and medial OFC, with weaker evidence of similar differences in hippocampal and lateral OFC volumes. (Fig. 2, Fig. 3, Appendix C.6, Appendix E.1). These models revealed no evidence of volume differences in either ACC region.

3.4. Secondary analyses

In secondary analyses, a higher corporal punishment score was associated with smaller global (total cortical and white matter) and cortical ROI volumes (rostral and caudal ACC, medial and lateral OFC), but not subcortical ROI volumes (amygdala, hippocampus) after ICV

Table 2
Associations between childhood physical attack exposure, threatened violence exposure, and standardized global brain volumes in preadolescence. n = 2905.

Physical Attack	Minimally adjusted models			Fully adjusted models			
	β	95% CI	p	β	95% CI	p	q
Cortical Gray Matter	-0.18	(−0.31, −0.06)	< 0.01	-0.14	(−0.26, −0.02)	0.03	0.04
White Matter	-0.19	(−0.31, −0.06)	< 0.01	-0.16	(−0.28, −0.03)	0.01	0.04
Subcortical Gray Matter	-0.05	(−0.13, 0.03)	0.23	-0.05	(−0.14, 0.03)	0.22	0.22
Threatened Violence	Minimally adjusted models			Fully adjusted models			
	β	95% CI	p	β	95% CI	p	q
Cortical Gray Matter	-0.01	(−0.11, 0.09)	0.87	0.04	(−0.06, 0.13)	0.45	0.68
White Matter	0.01	(−0.09, 0.11)	0.89	0.04	(−0.06, 0.14)	0.44	0.68
Subcortical Gray Matter	0.01	(−0.06, 0.08)	0.84	0.00	(−0.06, 0.07)	0.91	0.91

a. Minimally adjusted models include covariates for child age, sex, and ethnicity.

b. Fully adjusted models include covariates for child age at MRI scan, sex, and ethnicity; household income at birth; highest parental education level achieved; maternal and paternal history of psychosis; maternal and paternal psychopathology symptoms; maternal age at the child's birth; and child in utero exposure to smoking.

c. Models of subcortical gray matter are additionally adjusted for intracranial volume (ICV). Results from ICV-unadjusted models, which answer a somewhat different but related scientific question, appear in Appendix Table B.3.

d. q-values were calculated given 3 global measures of brain volume within each exposure via the Simes / Benjamini-Hochberg FDR adjustment method. q-values in this context can be conceptualized as "FDR-corrected" p-values. q-values calculated via alternative methods appear in Appendix Tables B.1 & B.2.

e. Physical attack associations with (1) cortical gray matter and (2) white matter remain statistically significant after adjusting for multiple comparisons. No other associations are statistically significant.

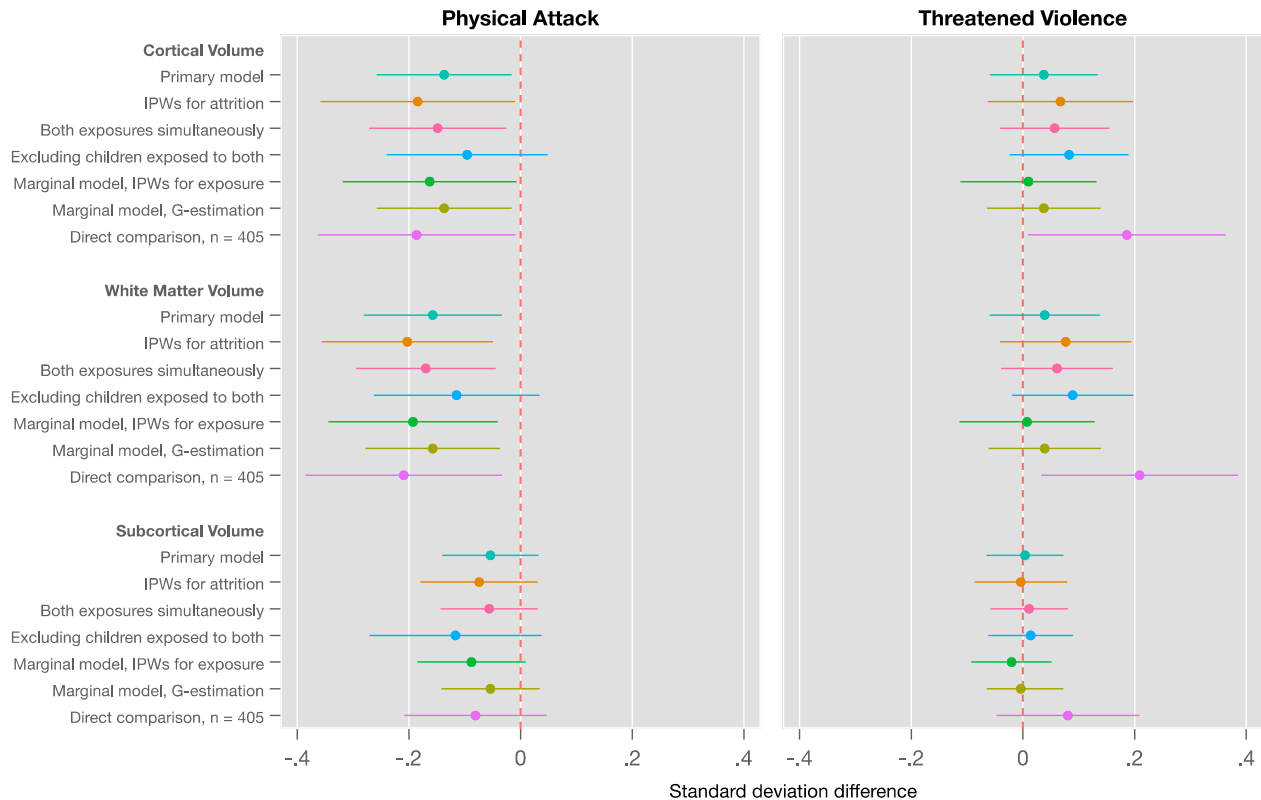## Global Brain Volumes: Primary and Sensitivity Model Estimates

Fig. 1. Associations between physical attack, threatened violence, and standardized global brain volumes using multiple modeling strategies. All models use sample size n = 2905 unless otherwise stated. Primary models are OLS-estimated linear regression models in the full analytic sample. n = 2905. Models using "IPWs for attrition" use inverse probability of attrition weights to account for selection bias (Sensitivity Model 1). Models with "both exposures simultaneously" include covariates for both actual and mere threatened violence exposure simultaneously (Sensitivity Model 2). Models "excluding children exposed to both" exclude participants exposed to both actual and mere threatened violence (Sensitivity Model 3). n = 2570 for physical attack; n = 2703 for threatened violence. Marginal models using "IPWs for exposure" are fit using inverse probability of exposure weights. Marginal models using G-Estimation are fit using standardization via the parametric G-formula. Direct Comparison models use a subsample of participants exposed to either physical attack or threatened violence, but not to both of them. n = 405. Estimates are from fully adjusted models accounting for child scan age, sex, ethnicity, household income, highest parental education level, maternal and paternal history of psychosis, maternal and paternal psychopathology symptoms, maternal age at child's birth, and child in utero exposure to smoking. Models of subcortical volume are additionally adjusted for ICV. Primary model estimates of the associations between (1) physical attack and cortical volume and (2) physical attack and white matter volume remain statistically significant after adjusting for multiple comparisons. See Table 1.

adjustment (Appendix D.1). Adding a covariate for physical attack to models of corporal punishment did not markedly change the corporal punishment estimate for any outcome (Appendix D.2). Similarly, estimates for physical attack were mostly similar with and without additionally adjusting for corporal punishment. The exception was for amygdala volume, e.g., before adjusting for corporal punishment score, $\beta_{\text{physical attack/amygdala (ICV adjusted)}} = -0.10$ (95% CI: -0.21, 0.01); but afterward, $\beta_{\text{physical attack/amygdala (ICV adjusted)}} = -0.20$ (95% CI: -0.34, -0.05).

4. Discussion

This study explored and compared associations between two types of physically threatening experiences—physical attack and threatened violence—and preadolescent brain structure. Despite similarities between these experiences (e.g., both may induce fear), our results suggest physical attack and threatened violence may have quantitatively different effects on both global and corticolimbic brain structure.

Specifically, physical attack experience was associated with smaller total cortical and white matter volume. Follow-up corticolimbic ROI analyses suggested that physical attack may also be associated with smaller amygdala, lateral OFC, and possibly medial OFC volumes, though these results did not reach conventional values of statistical

significance. Consistent estimates of these associations across multiple modeling strategies decreases the likelihood that the results are spurious due to model misspecification or sample construction.

Our measure of physical attack captured a spectrum of experiences—from aggressive fighting to parental physical abuse—while our corporal punishment measure captured a narrower range of parent-perpetrated experiences. Nevertheless, analyses of corporal punishment experience enable a form of replication of our physical attack findings because both experiences entail instances of children being physically struck without their consent, e.g., being spanked, slapped, or beaten up. Thus, results from both measures (physical attack and corporal punishment)—each assessed at a different time and capturing a slightly different set of physically violent experiences—converge on a central finding: on average, physical attack experience in childhood is associated with smaller global and possibly some corticolimbic brain volumes in preadolescence in a population-based sample.

In contrast, we found no evidence that associations between threatened violence experience and smaller brain volumes were similar to those of physical attack experience. None of the threatened violence effect estimates for either global or ROI outcomes were statistically significant after FDR adjustment. Moreover, the direction of nearly all such estimates—though small in magnitude, highly uncertain, and statistically non-significant—was positive, i.e., the estimates were in the

Table 3

Associations between childhood physical attack exposure, threatened violence exposure, and standardized corticolimbic volumes in preadolescence. n = 2905.

Physical Attack	Minimally adjusted models			Fully adjusted models			
	β	95% CI	p	β	95% CI	p	q
Amygdala Volume	-0.09	(−0.21, 0.02)	0.10	-0.10	(−0.21, 0.01)	0.08	0.24
Hippocampus Volume	-0.03	(−0.14, 0.09)	0.63	-0.03	(−0.14, 0.09)	0.64	0.72
Anterior Cingulate Cortex							
Rostral Volume	-0.10	(−0.23, 0.04)	0.16	-0.07	(−0.21, 0.06)	0.30	0.45
Caudal Volume	0.01	(−0.13, 0.15)	0.91	0.03	(−0.12, 0.17)	0.72	0.72
Orbitofrontal Cortex							
Medial Volume	-0.12	(−0.25, −0.01)	0.08	-0.09	(−0.22, 0.04)	0.17	0.34
Lateral Volume	-0.16	(−0.30, −0.03)	0.02	-0.13	(−0.26, 0.01)	0.06	0.24
Threatened Violence	Minimally adjusted models			Fully adjusted models			
	β	95% CI	p	β	95% CI	p	q
Amygdala Volume	0.04	(−0.05, 0.13)	0.43	0.03	(−0.06, 0.12)	0.56	0.62
Hippocampus Volume	0.06	(−0.03, 0.15)	0.16	0.06	(−0.03, 0.15)	0.18	0.54
Anterior Cingulate Cortex							
Rostral Volume	0.02	(−0.08, 0.13)	0.66	0.05	(−0.06, 0.16)	0.40	0.60
Caudal Volume	0.04	(−0.07, 0.15)	0.50	0.05	(−0.06, 0.17)	0.36	0.60
Orbitofrontal Cortex							
Medial Volume	0.07	(−0.03, 0.18)	0.16	0.10	(−0.00, 0.21)	0.06	0.36
Lateral Volume	-0.01	(−0.12, 0.10)	0.86	0.03	(−0.08, 0.13)	0.62	0.62

a. Minimally adjusted models include covariates for child age, sex, and ethnicity.

b. Fully adjusted models include covariates for child age at MRI scan, sex, and ethnicity; household income at birth; highest parental education level achieved; maternal and paternal history of psychosis; maternal and paternal psychopathology symptoms; maternal age at the child's birth; and child in utero exposure to smoking.

c. Models of amygdala and hippocampus volume are additionally adjusted for intracranial volume (ICV). Results from ICV-unadjusted models, which answer a somewhat different but related scientific question, appear in Appendix Table C.3.

d. q-values were calculated given 6 regional measures of brain volume within each exposure via the Simes / Benjamini-Hochberg FDR adjustment method. q-values in this context can be conceptualized as "FDR-corrected" p-values. q-values calculated via alternative methods appear in Appendix Tables C.1 & C.2.

e. Of note, none of the fully adjusted estimates listed in this table are statistically significant at the p = 0.05 level.

opposite direction compared to those of physical attack. Direct Comparison models further suggest that effects of threatened violence differ from those of physical attack, at least in magnitude. Compared directly to children who experienced only threatened violence, children who experienced only physical attack had smaller volumes in most global and corticolimbic outcomes. Thus, results from Direct Comparison models suggest quantitative differences in effects between physical attack and threatened violence.

These results are consistent with a number of possible scenarios. The first scenario is that while experiences of physical attack have a negative effect on some preadolescent brain volumes, those of threatened violence (as they are measured and operationalized in this study) have no enduring effect on brain volumes. A second possibility is that experiences of threatened violence have small negative effects on brain volumes—akin to those of physical attack but smaller in magnitude, which is what we originally hypothesized—but our study was simply unable to detect them. In that case, our population-based sample may have been statistically underpowered to detect these smaller effects, or our measures may have been too imprecise. Under this second scenario, differences in effect magnitudes between the two types of experiences may be due to exposure severity. Both physical attack and threatened violence may affect the same regions of the brain in similar ways, with the latter being a less impactful manifestation of the former. However, if the two types of experiences differed only by severity, we might expect that at least some effect estimates for both experiences would have shared directionality (if not magnitude), but this was not the case. In any event, whether the first scenario (threatened violence has no effects) or the second scenario (threatened violence has negative effects but we did not detect them) is correct, our results suggest quantitative differences in effects between experiences of physical attack and threatened violence.

There is also a third—albeit less likely—scenario that we cannot rule out and that may warrant further investigation in future research. Namely, the near-uniform pattern in which effect estimates for physical attack versus threatened violence are in opposite directions hints at possible *qualitative* differences in effects. It is worth considering whether physical attack may lead to some smaller brain volumes, while

threatened violence may lead to some larger volumes. Differences in effect direction (i.e., qualitative differences) could arise from allostatic processes. Models of allostasis, i.e., stress-responsive biologic processes that interact in nonlinear ways to maintain homeostasis, posit differing neuronal effects depending on stressor severity and chronicity (McEwen et al., 2015; Hanson and Nacewicz, 2021). Notably, while possible qualitative differences in neural effects of physical attack and threatened violence are not easily explained by existing models of adversity, similar differences may not be without precedent: as reviewed above, some neural correlates of fear-inducing stimuli appear to depend on the presence or absence of pain (Biggs et al., 2020). Nevertheless, while this scenario may warrant additional investigation, it remains an unlikely possibility. Threatened violence effect sizes were exceedingly small for all outcomes, none were statistically significant after FDR correction, and all of them were based on responses to a single interview question posed to mothers. Moreover, none of this evidence should be construed to suggest that experiences of threatened violence confer "positive" effects on children.

Our study reflects some aspects of specificity models of childhood adversity because it independently tested effects of qualitatively different experiences. However, our study was also informed by the dimensional model of adversity, and our findings bear on aspects of it in two ways. First, the dimensional model argues that effects of adversity scale based on experience frequency and severity. In practice, studies exploring this aspect of the dimensional model (at least as it relates to threat) have created threat "severity scores" by summing the discrete types threatening experiences to which a child has been exposed (McLaughlin et al., 2016; Weissman et al., 2020). Implicit in this practice is that different types of threatening experiences will have additive effects, much the same way cumulative risk models sum exposures to all types of adversity. Our findings suggest that the effect magnitude of some threats may be different than that of others, such that creating severity scores in this way may not accurately reflect the underlying severity of a child's overall exposure. Second, in contrast to the dimensional model, our study hints at the possibility that experiences of physical attack and threatened violence may have some qualitatively different effects. Additional research in population-based samples large

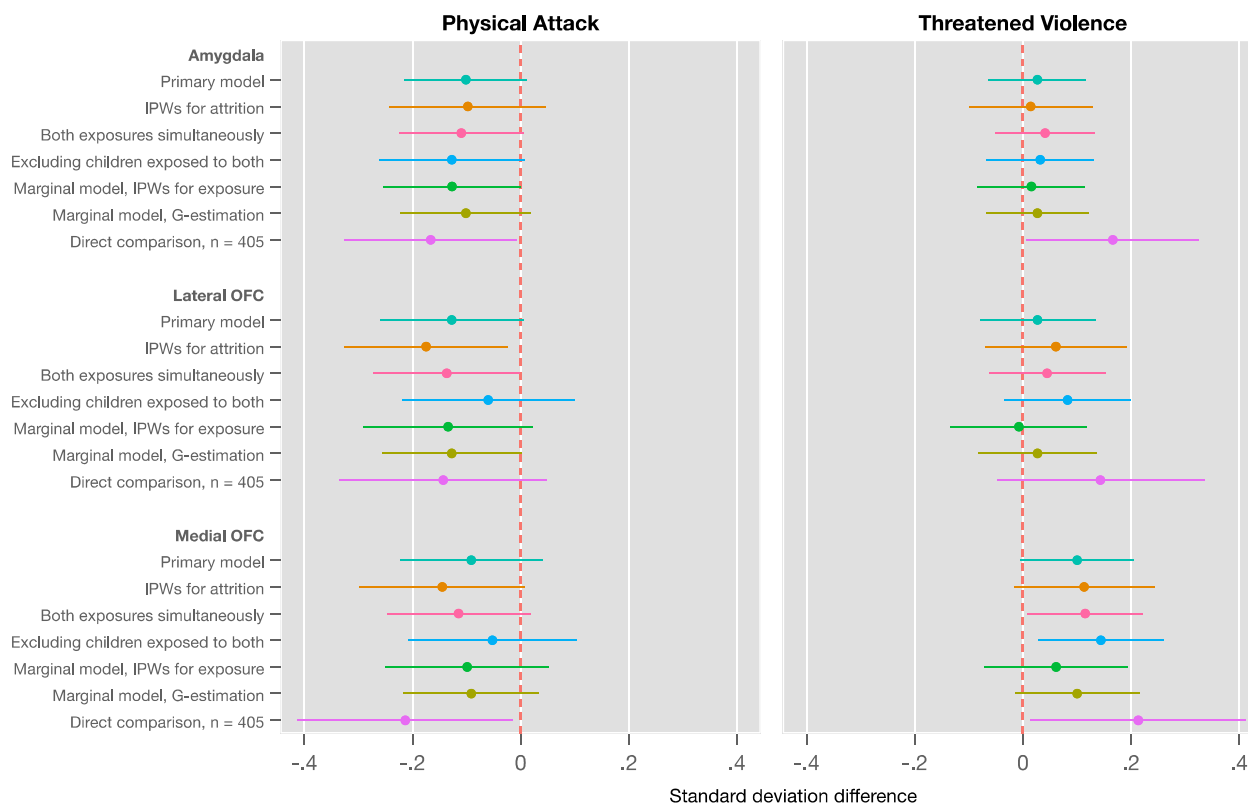## Selected Corticolimbic Volumes: Primary and Sensitivity Model Estimates

Fig. 2. Associations between physical attack, threatened violence, and selected standardized corticolimbic volumes using multiple modeling strategies. All models use sample size n = 2905 unless otherwise stated. Primary models are OLS-estimated linear regression models in the full analytic sample. n = 2905. Models using "IPWs for attrition" use inverse probability of attrition weights to account for selection bias (Sensitivity Model 1). Models with "both exposures simultaneously" include covariates for both actual and mere threatened violence exposure simultaneously (Sensitivity Model 2). Models "excluding children exposed to both" exclude participants exposed to both actual and mere threatened violence (Sensitivity Model 3). n = 2570 for physical attack; n = 2703 for threatened violence. Marginal models using "IPWs for exposure" are fit using inverse probability of exposure weights. Marginal models using G-Estimation are fit using standardization via the parametric G-formula. Direct Comparison models use a subsample of participants exposed to either physical attack or threatened violence, but not to both of them. n = 405. Estimates are from fully adjusted models accounting for child scan age, sex, ethnicity, household income at birth, highest parental education level achieved, maternal and paternal history of psychosis, maternal and paternal psychopathology symptoms, maternal age at child's birth, and child in utero exposure to smoking. Models of amygdala volume are additionally adjusted for ICV. Notably, none of the fully adjusted primary model estimates above are statistically at the $p = 0.05$ level before or after adjusting for multiple comparisons.

enough to isolate effects of specific types of threatening experiences on specific brain regions may clarify this question.

Identifying possible differences in neurodevelopmental effects of physical attack and threatened violence also has public health significance. Gaining a greater understanding of the neural mechanisms mediating relationships between specific types of violence exposure and child mental wellbeing can clarify how the brain changes in response to specific types of adversity. Ultimately, this type of research may help provide insight into understanding what types of interventions may enable children facing adversity to reach their full potential. Moreover, explanatory models of childhood adversity—including the dimensional model of childhood adversity—can be exceedingly useful in guiding policy and mobilizing public health resources, but only if they are premised on scientifically sound assumptions. It is therefore important to test these assumptions to ensure the model's translational impact.

Our study has some limitations. Because data for our primary exposures and outcomes were collected at the same time, our study is cross-sectional. We used retrospective maternal reports of violent experiences because Generation R did not collect child-report data on them. Mothers may not have known about, remembered, or wanted to report all instances of the two types of experiences. They also may have been less likely to know about or recall threatened violence experiences than physical attack experiences because instances of the latter may

have led to injury or seemed more impactful. Mothers also may not have viewed corporal punishment as physical attack, particularly because "physical attack" was defined in Generation R as "beat[ing] up" the child. This may explain why corporal punishment scores were not correlated with physical attack. We partially addressed some these concerns by testing corporal punishment exposure separately, which was assessed prospectively at a different age. Neither our hypotheses nor our models account for experience timing, i.e., the age when children were exposed. Emerging research suggests timing of adversity exposure may impact the effects of it (Nelson and Gabard-Durnam, 2020; Dunn et al., 2019; Gabard-Durnam and McLaughlin, 2019). Our models also do not account for experience frequency or severity; thus, we are unable to test directly whether effects scale based on frequency and severity. Our study does not account for possible differences in pubertal status of our participants, though we included both age at MRI scan and sex as covariates, which may partially account for these differences. Differential attrition in the cohort by sociodemographic characteristics limits the study's generalizability, but our use of inverse probability of attrition weights reduces concerns about selection bias. Finally, as with all observational studies, confounding and reverse causation may have biased our results.

Our study also has significant strengths. Trained Generation R researchers collected our primary exposure data via in-person maternal

Selected Global and Cortical Volumes: Comparison of Selected Effect Estimates
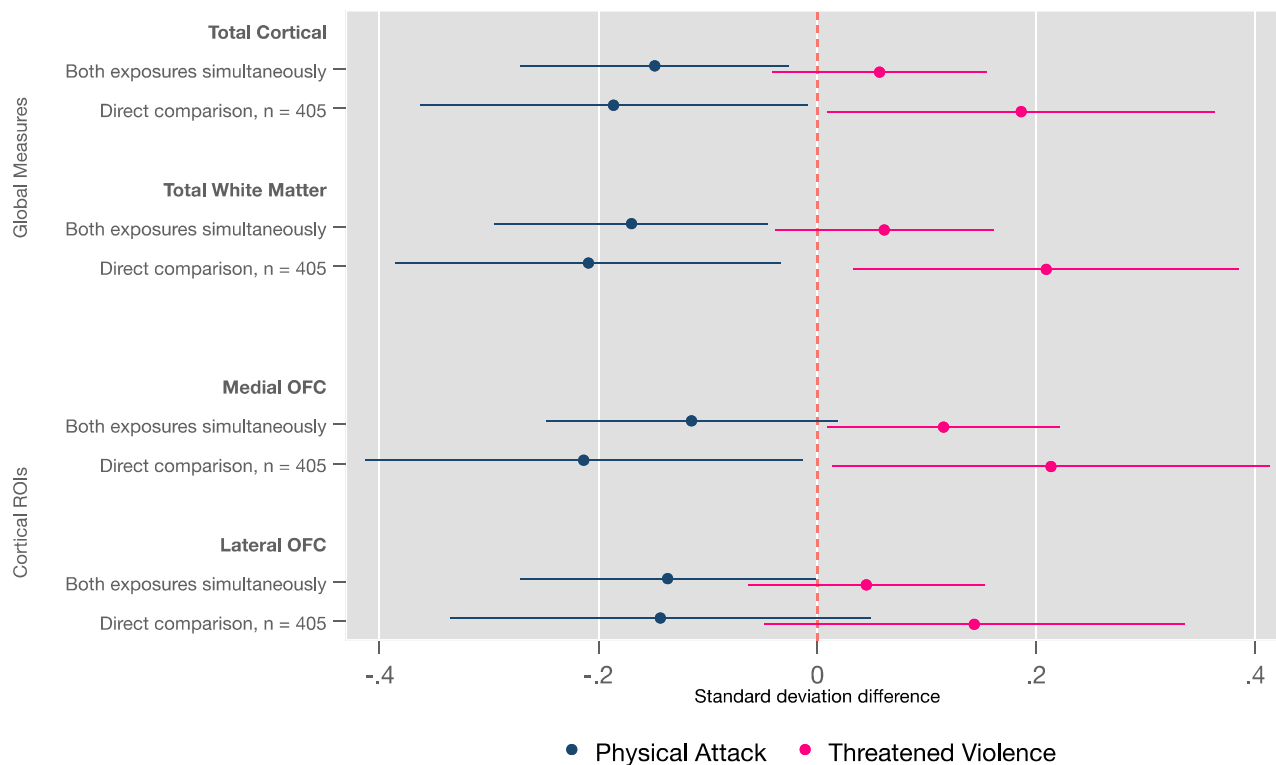

Fig. 3. Associations between physical attack (navy), threatened violence (pink), and selected standardized brain volumes in selected sensitivity models. Models with "both exposures simultaneously" include covariates for both actual and mere threatened violence exposure simultaneously (Sensitivity Model 2). n = 2905. Direct Comparison models use a subsample of participants exposed to either physical attack or threatened violence, but not to both of them. n = 405. Because all participants in this subsample experienced one or the other type of violence, effect estimates mirror each other. Estimates are from fully adjusted models accounting for child scan age, sex, ethnicity, household income at birth, highest parental education level achieved, maternal and paternal history of psychosis, maternal and paternal psychopathology symptoms, maternal age at child's birth, and child in utero exposure to smoking.

interviews, which enabled researchers to clarify mothers' questions about what specific types of experiences constituted physical attack versus threatened violence. Similarly, our sample was large enough to investigate two frequently co-occurring experiences and to isolate their possible effects. Our sample was also more likely to capture less severe forms of these experiences than samples in which violence-exposed children are specifically recruited. Moreover, we were able to partially replicate findings using an independent measure (corporal punishment), which was assessed at a different timepoint in the participants' lives. Finally, we employed a variety of modeling strategies to assess the robustness of our results.

5. Conclusions

In our population-based sample of 2905 children, experiences of physical attack—but not of threatened violence—were associated with smaller preadolescent global brain and some corticolimbic volumes. These results suggest that two types of threatening experiences may have quantitatively—and perhaps qualitatively—different neuro-developmental consequences. Future studies in population-based samples large enough to isolate effects of frequently co-occurring experiences may confirm or refine aspects of dimensional models of adversity.

More broadly, our study contributes to research exploring how threatening experiences may affect brain development, which has important public health consequences. Prior studies suggest differences in corticolimbic function mediate associations between violent experiences and child mental disorders and behavior problems, while our findings suggest different types of violence exposure may have different

effects on corticolimbic phenotype (McLaughlin and Lambert, 2017). In turn, our study provides additional context when untangling the complex neurodevelopmental and behavioral response to childhood violence exposure and adversity.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2021.101033.

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