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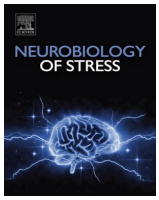

Sensitive periods for the link between childhood maltreatment and brain aging during adulthood

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ABSTRACT

Background: Childhood maltreatment (CM) is associated with the early onset of psychopathology and accelerated biological aging. However, outcomes vary widely among individuals with CM history. This variability may, in part, be explained by differences in age of exposure to CM. In this study, we examined whether CM was associated with accelerated brain aging, depending on the timing of exposure (i.e., 'sensitive periods').
Method: A machine learning algorithm of brain age trained prior to the current study in 3377 healthy individuals was employed in a CM dataset of 150 adult postnatal women, 92 of whom provided MRI data. CM history was retrospectively assessed from birth to age 18 years. Brain-predicted age was calculated from T1-weighted MRI scans. Brain age gap (BAG) was quantified as the disparity between brain-predicted age, relative to chronological age. Sensitive periods were identified using random forest regression with conditional inference trees.
Results: CM severity was associated with greater BAG ($\beta = 0.34$, $p < 0.001$). The most robust type/time risk factors for greater BAG were parental verbal abuse between ages 7 and 15 years, parental physical abuse between ages 4 and 6 years, witnessing sibling violence between ages 4 and 15 years, and sexual abuse between ages 4–6. Parental verbal abuse (7–15 years) and parental physical abuse (4–6) were the variables that were the most important predictors above and beyond duration, multiplicity (number of exposures), and cumulative maltreatment severity.
Conclusion: These findings suggest a link between CM and accelerated brain aging, with certain developmental periods appearing more sensitive to these effects. To the best of our knowledge, this study is the first to identify sensitive periods for the link between CM and brain aging in adults, and the first to examine the link between CM and brain aging in postnatal women. Together, these results suggest that CM's association with brain development is complex and warrants nuanced approaches to investigating the possible mechanisms underlying its effects.

1. Introduction

Early life experiences significantly impact nervous system structure, development, and function, leading to profound impacts on health and disease (Caspi and Moffitt, 2006; Hunter, 2005; Rogers et al., 2019). Negative experiences in particular, like childhood maltreatment (CM), can have severely detrimental and chronically persistent consequences (Hunter, 2005; Lupien et al., 2009). The US Centers for Disease Control and Prevention (CDC) have reported that childhood maltreatment accounts for a large proportion of the risk for drug addiction (64 %) (Dube et al., 2003a), depression (54 %) (Dube et al., 2003b), and suicide attempts (67 %) (Dube et al., 2003b). Moreover, CM is associated with a reduction in life span of as great as 20 years (Brown et al., 2009). These markedly adverse outcomes in psychiatric health and mortality have

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created a need to prevent and reverse the detrimental effects of CM. However, a fundamental understanding of the factors contributing to differential outcomes among maltreated individuals is still needed.

One long-term effect of early life adversity is an overall acceleration in development and aging (Belsky, 2019; Colich and McLaughlin, 2022). This association is thought to be due to increased allostatic load, i.e., the aggregated wear and tear of adverse experiences on the body (Finlay et al., 2022). Biological aging measures, such as "brain age" (Cole et al., 2018; Franke and Gaser, 2019), allow for the quantification of these cumulative effects. Brain age uses age-associated structural features across the brain to derive the apparent "age" of the brain. The difference between an individual's brain age and chronological age, referred to as brain age gap (BAG) or "brain aging", predicts mortality, with accelerated brain aging associated with increased mortality risk (Cole et al., 2018). Previous work suggests that pediatric brain aging is also linked to experiences of early life adversity (Drobinin et al., 2022; Keding et al., 2021; Stenson and Jovanovic, 2021). However, the relationship between childhood maltreatment and brain aging in adulthood is not well understood.

Evidence suggests that the age at which childhood maltreatment is experienced may significantly influence its effects on mental health symptoms (Andersen and Teicher, 2008; Kaplow and Widom, 2007; Schaefer et al., 2022). This phenomenon mirrors other developmental processes with "sensitive periods," during which the brain's susceptibility to environmental influences is heightened (Knudsen, 2004). Current literature suggests that the timing of maltreatment exposure is particularly important when examining its effects on neurobiology (Andersen et al., 2008; Baker et al., 2013; Malhi et al., 2023; Pechtel et al., 2014; Teicher et al., 2018; Zhu et al., 2023). For example, sensitive periods for the effects of maltreatment have been identified for emotional circuitry regions in the brain (Andersen et al., 2008; Pechtel et al., 2014; Teicher et al., 2018). The hippocampus shows peak sensitivity to abuse during early life (~3–7 years), with a second peak during adolescence (10–16 years) (Andersen et al., 2008; Teicher et al., 2018). Increased amygdala volume is associated with childhood maltreatment during preadolescence (10–11 years) (Pechtel et al., 2014). Sensitive periods for the function of these structures have also been identified, with hyperactive responses to threatening stimuli associated with maltreatment exposure during the teenage years, and hypoactive responses linked to exposure during early childhood (Zhu et al., 2023). Still, it remains unclear how childhood maltreatment, and specifically the timing of exposure, impacts cumulative measures of brain development, such as brain age. Moreover, the long-term impact of childhood maltreatment on brain aging into adulthood is not known.

Throughout the CM literature, three primary approaches are typically employed to identify sensitive periods: indirect comparison, direct comparison, and the competing hypotheses approach (Schaefer et al., 2022). The *indirect comparison* approach relies on describing, rather than statistically testing, timing-related differences in outcomes following CM exposure. The *direct comparison* approach strengthens this design by statistically contrasting the effects of CM across developmental periods. Although more robust than indirect comparisons, it remains less powerful than the competing hypotheses approach, which is widely regarded as the most rigorous. In the *competing hypotheses* approach, timing-specific effects are tested directly and evaluated against alternative explanations grounded in broader features of maltreatment, including chronicity (duration of exposure), multiplicity (number of maltreatment types), and cumulative severity. Guided by this framework, we defined sensitive periods using the competing hypotheses approach in order to test whether the timing of CM exposure is specifically linked to accelerated brain aging.

In the present study, we aimed to investigate the association between childhood maltreatment and brain aging by measuring BAG and childhood maltreatment using data from a sample of adult, postnatal women. Using random forest regression, we further examined whether any observed associations were shaped by sensitive periods of exposure. In doing so, we aimed to better understand the relations between childhood maltreatment and brain development while also expanding our knowledge of how different windows of neuroplasticity may influence later outcomes associated with early life adversity.

2. Methods

2.1. Study participants

Participants were drawn from the Mother-Infant Neurobiological Development (MIND) study, designed to assess the impact of maternal childhood maltreatment on maternal and infant neurobiological and behavioral outcomes. Recruitment was conducted via community flyers, prenatal classes, and local birth records. Participants were stratified using the Adverse Childhood Experiences questionnaire (Felitti et al., 1998) such that approximately half of the sample had experienced one or more forms of childhood maltreatment. Exclusion criteria for the main study were: a) English not a primary language spoken at home, b) maternal age over 44 years at the time of infant birth, c) infant born before 36 weeks gestation and/or weighing less than 2500 g, and d) infant congenital disorder/condition. Mothers with a history of head trauma or loss of consciousness lasting more than 20 min, those with concussions and standard MRI exclusions (e.g. – metal implant), were not included in the neuroimaging protocol. Because functional MRI data were also collected (not described here), participants were also required to abstain from alcohol, drugs, or medications (except contraceptives) for at least two weeks prior to scanning and to have had no history of psychotropic medication use before age 18.

Out of 150 participants from the parent study, a total of 92 provided MRI scanning data. 19 of the original 150 never returned calls or emails, 18 indicated that they were not interested in receiving an MRI, typically because of work schedule or childcare responsibilities, and 5 were disqualified based on MRI exclusion criteria. Hence, 108 participants were invited for scanning. Six participants canceled and did not reschedule despite multiple attempts. Three failed to show and did not reschedule, and 3 had complications (panic attack, nausea, or claustrophobia) that precluded scanning. Of the 96 participants who completed scan sessions, 4 scans were unusable due to excessive motion or artifacts. High-quality scans were obtained on $N = 92$ participants (mean age $= 32.38$ (± 4.27) years, details in Table 1). This yielded a sample size comparable to other studies demonstrating evidence of sensitive periods for the link between maltreatment and brain imaging metrics (Andersen and Teicher, 2008; Herzog et al., 2020; McCrory et al., 2013; Pechtel et al., 2022). All study procedures were carried out under the Institutional Review Board of the McLean/Mass General Brigham Healthcare system (IRB Protocol #: 2014P002522).

2.2. Maltreatment history assessment

The Maltreatment and Abuse Chronology of Exposure (MACE) Scale (Teicher and Parigger, 2015) was used to retrospectively assess the timing and severity of maltreatment. The MACE consists of 75 items, and participants were instructed to indicate whether they experienced a given event and, if so, to indicate the ages at which the event occurred (Teicher and Parigger, 2015). Rasch-based severity scores (ranging from 0 to 10) were provided for ten types of maltreatment across age, including parental physical abuse, parental verbal abuse, nonverbal emotional abuse, sexual abuse, emotional neglect, physical neglect, witnessing interparental violence, witnessing violence towards siblings, peer emotional abuse, and peer physical bullying. Scores were also provided for each maltreatment category based on the items endorsed regardless of age (percent case breakdown in Supplemental Fig. S1), as well as an overall composite severity score that summed each of the maltreatment types (range 0–100). For multiplicity scores, the presence/absence of each maltreatment subtype was operationally defined using thresholds (see supplement) for subtype severity scores

Table 1
Characteristics of research participants.

	Finding (n = 92)	% (N)
Age		
mean	32.38	–
sd	4.27	–
Ethnicity		
Hispanic	10	10.9 %
Non-Hispanic	78	84.8 %
Other	4	4.3 %
Race		
Asian American	7	7.6 %
Biracial/Multiracial	8	8.7 %
Black/African American	6	6.5 %
Caucasian/White	70	76.1 %
Native Hawaiian/Pacific Islander	1	1.1 %
Education		
Associate degree	6	6.5 %
Bachelor's Degree	22	23.9 %
Doctoral Degree	17	18.5 %
High school graduate	11	12.0 %
Master's Degree	34	37.0 %
not a high school graduate	1	1.1 %
unspecified	1	1.1 %
Smoking status		
non-smoker	73	79.3 %
smoker	10	10.9 %
unspecified	9	9.8 %
Annual Family Income		
0 to $15,000	7	7.6 %
$16,000 t0 $25,000	7	7.6 %
$26,000 to $50,000	10	10.9 %
$51,000 to $75,000	12	13.0 %
$76,000 to $100,000	16	17.4 %
$101,000 to $150,000	26	28.3 %
$151,000 to $200,000	11	12.0 %
$201,000 or more	3	3.3 %
Multiplicity of Maltreatment Exposure (MACE)		
0, No exposure	43	46.7 %
1, Exposure to 1 types	23	25.0 %
2, Exposure to 2 types	9	9.8 %
≥3, Exposure to ≥3 types	17	18.5 %
≥1, Exposure to ≥1 type	49	53.3 %
Postnatal Depression (EPDS score)		
mean	5.54	
sd	4.57	
PTSD symptoms (PCL score)		
mean	5.69	
sd	10.40	
Total Gray Matter Volume (mm^3)		
mean	609501.35	
sd	40623.26	

Abbreviation: MACE, Maltreatment and Abuse Chronology of Exposure.

established in the original creation of the MACE scale (Teicher and Parigger, 2015). The MACE has excellent test-retest reliability across all ages and each maltreatment subtype (r = 0.91) (Teicher and Parigger, 2015) and has been used to demonstrate sensitive periods for associations of maltreatment exposure with psychopathology (Khan et al., 2015; Schalinski et al., 2016; Inga Schalinski et al., 2019) and with brain structure (Pechtel et al., 2014; Teicher et al., 2018) and function (Zhu et al., 2019, 2023).

2.3. Psychiatric clinical history

In addition to childhood maltreatment history, participants were also assessed for psychiatric conditions related to CM history and postnatal status (i.e. – post-traumatic stress disorder (PTSD) and postnatal depression). PTSD, assessed using the PTSD Checklist for DSM-5 (PCL-5), was characterized using standard thresholds for clinical levels of PTSD (PCL score threshold = 31) (Bovin et al., 2016). Postnatal depression was assessed with the Edinburgh Postnatal Depression Scale (EPDS) using the standard threshold score of 11 (Levis et al., 2020).

2.4. MRI data collection

Neuroimaging was performed on a Siemens Magnetom Prisma (3T; Siemens AG, Siemens Medical Solutions) using a 64-element phased-array radiofrequency reception coil. A high-resolution 3D T1-weighted sequence was acquired for anatomical registration (TR = 2530 ms, TEs = 1.69–7.27 ms, flip angle = 7°, TI = 1100 ms, voxel size = 1.0 × 1.0 × 1.0 mm). Head motion for each T1-weighted scan was quality checked at the scanner. Participants with excessive head motion (4 in total) were excluded from the analysis.

2.5. Brain age calculation

MRI data processing was performed using a combination of software packages, including R version 4.3.1, MATLAB version 2023a, SPM12, and FSL 6.0.6.5. 8. Following pre-processing that included normalization and segmentation of gray matter, white matter, and cerebrospinal fluid, brain-predicted age was calculated using a previously published machine learning model (Cole et al., 2015, 2018) implemented in R. The method utilizes a model based on Gaussian process regression to predict brain age using structural features from T1-weighted MRI images. This validated approach has a demonstrated high prediction accuracy and low mean absolute error, making it a reliable tool for assessing individual brain aging and detecting subtle neurodegenerative changes (Cole et al., 2015, 2018). The algorithm was originally trained on 3377 healthy individuals (ages 18–92 years, mean age = 40.6 years, SD = 21.4), and tested on 857 individuals (18–90 years of age, mean age = 40.1 years, SD = 21). Here, we quantified brain aging by determining the brain age gap (BAG), or the disparity between brain-predicted age and chronological age (see details in *Statistical Analysis* section).

2.6. Brain age model validation

Following the calculation of brain age, we confirmed the overall prediction accuracy of the model in our dataset by calculating the mean absolute error. This was done to ensure that the brain age model could be accurately applied to the CM dataset of adult women. Here, we obtained mean absolute error values comparable to other large datasets, including the UK Biobank (Jonsson et al., 2019) and data originally used for the validation of the brain age algorithm (Cole et al., 2018) (see Results section).

2.7. Statistical analysis

To calculate brain age gap (BAG), we took the residual values from regressing brain-predicted age on chronological age in line with similar studies of biological aging (Horvath, 2013; Le et al., 2018). This approach enables the examination of residual variations in brain age, independent of chronological age, and is an important adjustment necessary to avoid the potential overestimation of age in younger brains and underestimation of age in older brains (Jain et al., 2022; Le et al., 2018; Liang et al., 2019). Missing data values were imputed using the k-nearest neighbors (KNN) algorithm, implemented through the *impute.knn* function from the *impute* package (version 1.74.1) in R. Overall, 1.25 % of all values were missing. 16.30 % of cases had at least one missing value, and the average percent missing per variable was 1.25 %.

A linear regression was then used to assess the relationship between BAG and cumulative MACE severity scores. Follow-up sensitivity analyses were conducted by adding covariates (household income, age, age-squared, total cortical volume, PTSD, postnatal depression, and smoking status) based on their previously documented associations with brain aging (Busby et al., 2023; Hafkemeijer et al., 2014; Linli et al., 2022). Here, the age and age-squared terms were included in order to avoid spurious interpretations due to the non-linear tendency for biological aging to sometimes be overestimated in young adults and

underestimated in older adults (Jain et al., 2022; Le et al., 2018; Liang et al., 2019; Shireby et al., 2020).

A random forest regression with conditional inference trees was conducted to determine whether the severity of exposure to specific types of childhood maltreatment at specific ages is associated with greater BAG in adulthood. This technique was chosen because it does not assume a linear relation between the response and predictor variables (Breiman, 2001), can handle larger numbers of predictor variables with high levels of collinearity (e.g. – multiple timepoints of a given measure), and has higher performance compared to similar approaches (e.g., support vector machines, neural networks, and gradient boosted machines) in accurately identifying the most important predictors of neuropsychiatric outcomes (Khan et al., 2015; I Schalinski et al., 2019; Teicher et al., 2018). Here, we implemented random forest regression analysis using in-house code written in *R* (*version 4.3.1*) based on the *cforest* function from the *party* R package, version 1.3.13 http://party.r-forge.rproject.org/).

In each model, for each maltreatment subtype, the severity score and age of occurrence were used to predict BAG with the same covariates used in the linear regression model. Developmental windows of 3-year increments were used to reduce data dimensionality. These windows were selected to 1) maintain the highest level of temporal detail without overfitting the model (i.e. – having a total number of predictors that exceeded our sample size), and 2) yield windows similar to those described in other work (Dunn et al., 2013, 2016; Kaplow and Widom, 2007). Each regressor in the model was assessed for its overall variable importance (VI). When a variable is important, its random shuffling leads to a large increase in mean square error, calculated as the average squared difference between actual and predicted values. If the variable is unimportant, the effect of its permutation is negligible. To assess the importance of each variable, we independently permuted its values, retrained the random forest regression model, and quantified the effect on the mean squared error of the fit to the test set. The random forest regression model was trained using 63.3 % of the dataset and evaluated in the remaining 36.7 % of the data. The variable importance procedure was then repeated using a total of 50 different random samplings of training and testing sets from the larger dataset in order to generate the mean variable importance for each variable. Chance mean and SD importance levels were then calculated by reshuffling the outcome data 500 times and re-running the analysis to derive chance variable importance measures. Chance variable importance is a metric that shows how much a variable would look important just by random chance, in order to determine whether a variable is truly meaningful or not. The statistical significance for the difference between mean variable importance and random chance variable importance was then derived by Z-test. P-values were adjusted using Bonferroni correction to control

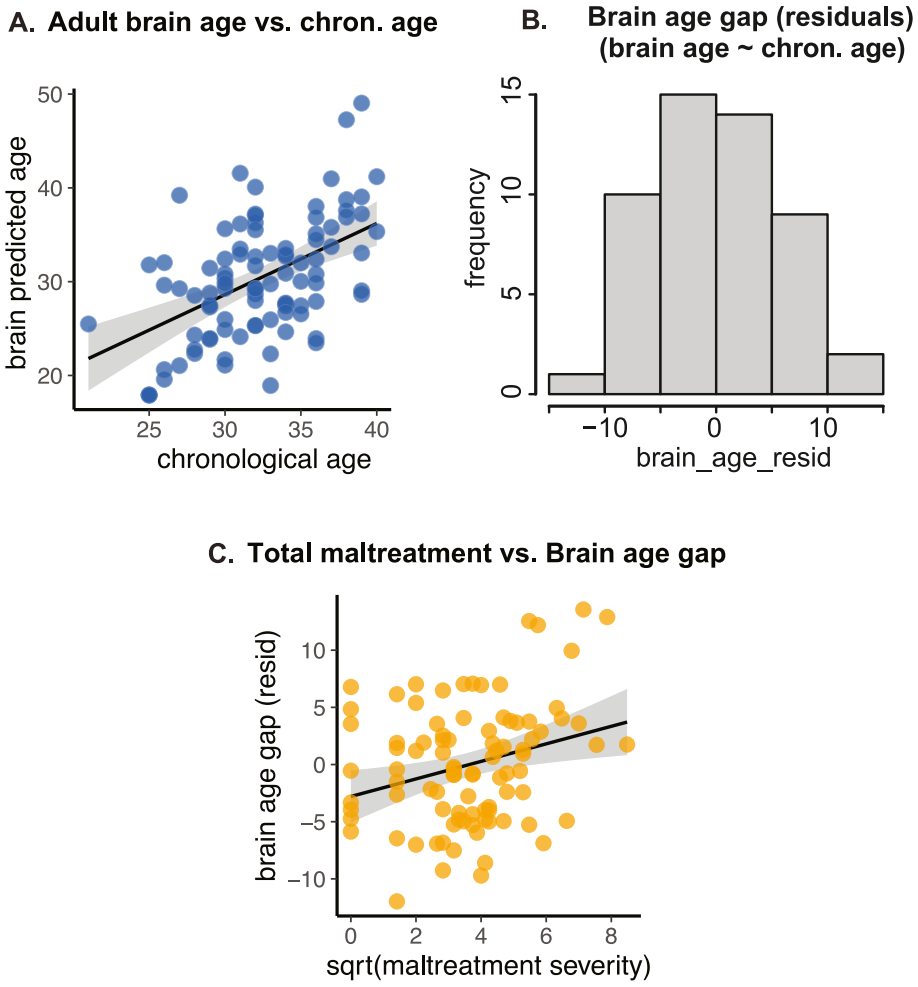

Fig. 1. Childhood trauma and brain age acceleration in adulthood. The accuracy of the brain age metric was confirmed by calculating the mean absolute error (MAE) of the brain age r model in our dataset. We obtained good model fit as demonstrated by low MAE values (4.68 ± 3.37 years) and a significant correlation between brain and chronological age (Pearson's R = 0.52, $p < 0.0001$) (panel A). The distribution of the brain age gap values is shown as a histogram in panel B. The association between composite maltreatment severity and brain age was also assessed and is shown in panel C. The regression model revealed that greater maltreatment severity was significantly associated with larger brain age gap before ($\beta = 0.34$, $p < 0.001$) and after controlling for covariates of income, age, age-squared, total cortical volume, PTSD, postnatal depression, and smoking status ($\beta = 0.27$, $p < 0.05$).

for multiple comparisons (total number of variables in the model). To determine directionality, we used the saved random forests and modified the exposure for each predictor variable from zero to maximum while holding all other predictors constant at their modal value in the model (Teicher et al., 2018; Zhu et al., 2019).

3. Results

3.1. Brain age acceleration and cumulative childhood maltreatment

We first assessed the general accuracy of the brain age metric by calculating the mean absolute error (MAE) of the brain age model in our dataset (Fig. 1A). We obtained MAE values (4.68 ± 3.37 years) comparable to those obtained in the analysis of other datasets, including the UK Biobank (Jonsson et al., 2019) (MAE range: 4.6–5.5 years) and data originally used in the validation of the brain age algorithm (Cole et al., 2018) (MAE = 5.02 years). Additionally, brain-predicted age showed a significant correlation with chronological age ($R = 0.52$, $p < 0.0001$). Brain age gap (BAG) was quantified by taking the residuals from modeling brain age on chronological age as described in the Methods section (Fig. 1B). We then assessed the association between total childhood maltreatment exposure severity and BAG (Fig. 1C). We observed an overall positive association between the composite severity score and BAG (β=*0.34,* $p < 0.001$). A plot of the association between BAG and total childhood maltreatment is shown in Fig. 1C. A follow-up sensitivity analysis was then performed to test whether the results were maintained after controlling for the covariates described above. In these analyses, the main results held, with the overall severity of childhood maltreatment still associated with greater BAG ($\beta = 0.27$, $p < 0.05$).

3.2. Sensitive periods for effects of maltreatment on brain aging

Next, we tested for the presence of sensitive periods during which the effects of childhood maltreatment on BAG were most prominent. We implemented a random forest regression model with conditional inference trees to detect the effects of age of exposure and maltreatment subtype on BAG. This model included age, household income, total cortical volume, PTSD, postnatal depression, and smoking status. In accordance with earlier studies of sensitive periods, the model also included MACE total duration of exposure, maltreatment subtype exposure count (multiplicity), and cumulative maltreatment severity (Hutson et al., 2024; Khan et al., 2015; Pechtel et al., 2014), Both total gray matter volume and smoking status emerged as significant predictors of BAG (Table 2). Consistent with the results from Fig. 1C, cumulative maltreatment severity was a significant predictor of BAG (variable importance [VI] = 0.91, adjusted $p < 0.001$). Neither duration nor multiplicity emerged as significant predictors of BAG. Overall, four subtypes of maltreatment were shown to be significant predictors of BAG: parental verbal abuse, parental physical abuse, witnessing sibling violence, and sexual abuse (Fig. 2, Table 2, Supplemental Table S1). Parental verbal abuse was associated with BAG from ages 7–15 years (max variable importance [VI] = 1.95, $p < 0.0001$). Parental physical abuse in the 4–6 year range was significantly associated with BAG (variable importance [VI] = 1.06, adjusted $p < 0.05$). Witnessing violence towards siblings showed significant associations with BAG for occurrences during the 4–15 year age range (max variable importance [VI] = 0.83, $p < 0.0001$). Lastly, sexual abuse significantly predicted BAG between ages 4–6 years (variable importance [VI] = 0.13, $p < 0.001$). The most important predictors were parental verbal abuse (7–15 years) and parental physical abuse (4–6), which predicted BAG above and beyond duration, maltreatment subtype exposure count (multiplicity), and cumulative maltreatment severity.

We then used the results of the random forest models to determine the directionality of effects at each significant time/type of maltreatment (Fig. 3). Greater exposure to each maltreatment subtype was associated with greater BAG at each time window, with the exception of parental physical abuse at ages 4–6 years, which showed a negative association between BAG and abuse exposure severity.

4. Discussion

The goal of the present study was to determine if exposure to childhood maltreatment is associated with accelerated brain aging in adulthood and whether the timing of exposure relates to differential outcomes in brain aging. In a cohort of adult, postnatal women, we observed that brain aging, measured as BAG, was related to the composite severity of maltreatment. Furthermore, we observed significant associations between BAG and exposure to parental verbal abuse (7–15 years), parental physical abuse (4–6 years), witnessing sibling violence (4–15 years), and sexual abuse (4–6 years), However, only parental verbal abuse and parental physical abuse significantly predicted BAG above and beyond duration, multiplicity and cumulative severity of maltreatment, consistent with the *competing hypotheses* definition of sensitive periods. Overall, greater severity of maltreatment for each subtype was associated with accelerated brain aging (greater BAG), with the exception of physical abuse, which showed a negative association with BAG from age 4–6 years. These results suggest that brain changes, initiated during specific time windows in childhood, induce long-term changes that are evident in adulthood. To the best of our knowledge, no previous studies have investigated sensitive periods linking childhood maltreatment to brain aging during adulthood.

Table 2
Significant factors impacting brain age acceleration.

predictor	variable importance (VI)	sd	z_test	perm_prob	p_adj	p_raw
MACE_PVA_7_9	**1.952**	**0.319**	**7.925**	**0.002**	**1.55E-13**	**2.28E-15**
MACE_PVA_10_12	**1.384**	**0.178**	**5.086**	**0.004**	**2.49E-05**	**3.66E-07**
MACE_PVA_13_15	**0.919**	**0.212**	**3.664**	**0.014**	**0.017**	**2.48E-04**
MACE_PPhysM_4_6	**1.063**	**0.153**	**3.458**	**0.012**	**0.037**	**5.45E-04**
MACE_WSibA_4_6	0.221	0.096	4.928	0.002	5.66E-05	8.33E-07
MACE_WSibA_7_9	0.826	0.161	6.197	0	3.91E-08	5.75E-10
MACE_WSibA_10_12	0.511	0.13	5.799	0.002	4.53E-07	6.65E-09
MACE_WSibA_13_15	0.206	0.099	3.485	0.012	0.033	4.93E-04
MACE_SexAb_4_6	0.128	0.077	4.262	0.008	0.001	2.03E-05
TotalGrayVol	5.958	0.467	14.513	0	6.84E-46	1.01E-47
Smoking Status	1.825	0.309	8.807	0.002	8.71E-17	1.28E-18
MACE cumulative severity	0.908	0.223	4.266	0.006	0.001	1.99E-05
MACE duration	0.454	0.148	1.952	0.046	1	0.051
MACE multiplicity	0.391	0.189	1.588	0.052	1	0.112

Note. PVA = parental verbal abuse; PPhys = parental physical abuse; WSIB = witnessing violence toward siblings; SexAb = sexual abuse.
Note: Items in **bold** indicate variable important greater than the three global maltreatment metrics (cumulative severity, duration, multiplicity).

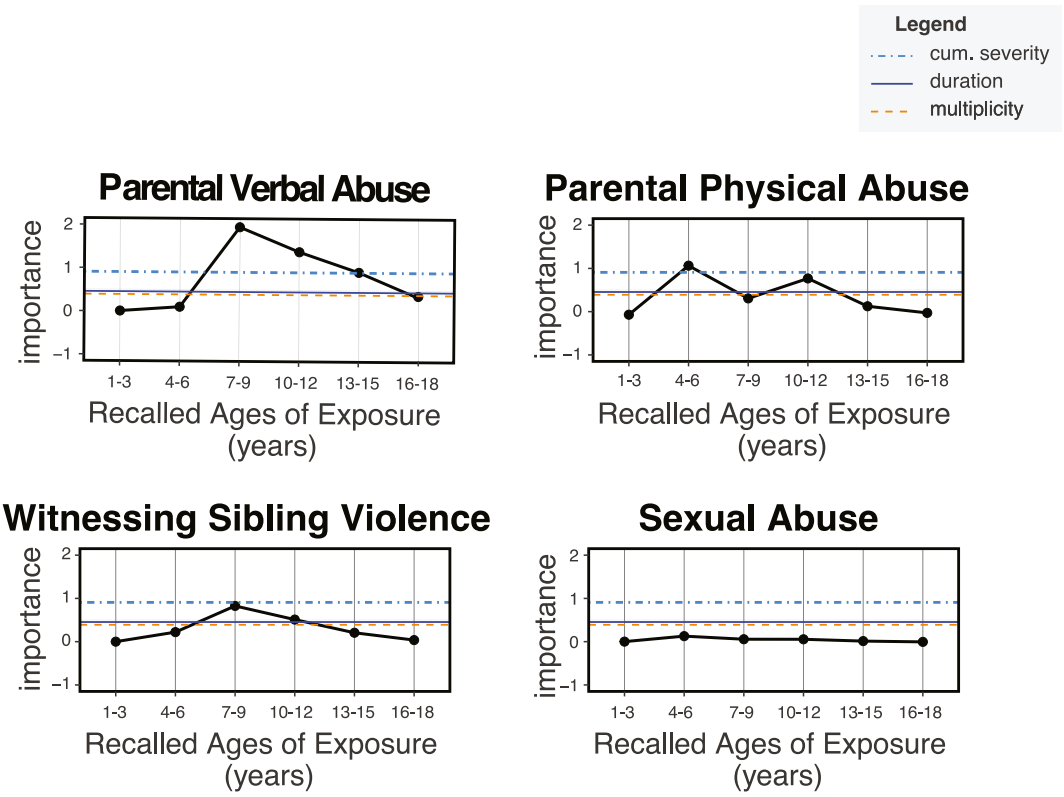

Fig. 2. Sensitive periods by maltreatment subtypes. A random forest regression with conditional inference trees was conducted to gain a more detailed view into how exposure to specific subtypes of maltreatment influences brain aging (brain age gap) during adulthood. Variable importance is shown for the four types of maltreatment that were significantly associated with BAG. The horizontal axis for each plot shows the recalled age window of exposure to each maltreatment in years. Vertical axes show mean variable importance, defined as the average rise in the mean square error of the model's fit after permutation of each individual variable. Importance levels are shown for the 3 global maltreatment characteristics (cumulative severisty, duration, and multiplicity). Parental verbal abuse between ages 7–15 and parental physical abuse between ages 4–6 years were more significant predictors of BAG than any of the global maltreatment metrics. Although significant predictors, witnessing sibling violence and sexual abuse were not more significant predictors of BAG than the three global metrics.

4.1. Sensitive periods for the effects of parental verbal abuse

We observed significant associations between BAG and parental verbal abuse at 7–15 years of age. These sensitive periods for brain aging align well with those relating emotional/verbal abuse to various psychiatric outcomes. For example, earlier work showed that emotional abuse experienced between 7 and 12 years of age was a strong predictor of psychological and somatoform dissociation symptoms in PTSD (Mueller;Pfeiffer et al., 2013). Similar effects have also been observed specifically in women during the postpartum period, where parental verbal abuse at age 12 significantly predicted lifetime major depressive disorder (Gerke et al., 2018). Work from our own group has also observed significant effects of emotional abuse experienced near this period on depressive symptoms in young adulthood (Khan et al., 2015). Here, we extend these findings by demonstrating a link between emotional/verbal abuse experienced during a similar window and adult brain aging.

An important question is why, neurobiologically speaking, parental verbal abuse within the observed time periods would result in accelerated brain aging later in life. One possible explanation may be that parental verbal abuse negatively impacts brain regions involved in verbal language processing. This is supported by earlier reports that language-associated regions, such as the superior temporal gyrus, show increased volume following exposure to parental verbal abuse (Tomoda et al., 2011). Given that these regions are undergoing rapid synaptic pruning during our observed ages (Gogtay et al., 2004), exposure to chronic verbal abuse during this sensitive developmental window may dysregulate pruning, leading to premature maturation or atrophy specifically in language regions. Parental verbal abuse has also been linked to decreased white matter integrity in language regions like the superior temporal gyrus, which in turn was associated with both verbal IQ and verbal comprehension (Choi et al., 2009). Such alterations may represent disruptions to language-related processing of emotionally charged speech and contribute to long-term alterations to processes like emotional communication in adulthood. However, this interpretation remains speculative, as the present study did not directly assess the contribution of changes in language-related regions to the observed alterations in global brain aging trajectories. Other regions, like the hippocampus, may also potentially be involved, given work showing a link between hippocampal volume in women and verbal abuse experienced at ages 10, 11, 15, and 16 years (Teicher et al., 2018). Together, these findings suggest that exposure to emotional/verbal abuse may produce effects that impact multiple, parallel processes related to mental well-being, including both psychiatric symptoms and accelerated brain aging.

4.2. Sensitive periods for the effects of parental physical abuse

We found that exposure to parental physical abuse between ages 4–6 years was inversely associated with BAG in adulthood. This period is generally parallel to that observed in other work relating physical abuse to psychiatric outcomes. Dunn and colleagues (2013) found that individuals exposed to physical abuse around age 5 years had a 77 % higher risk for depression (Dunn et al., 2013). Manly and colleagues (2001) also found significant effects for the impact of physical abuse experienced during the preschool age window (3–5 years) on externalizing behaviors during later childhood (Manly et al., 2001). There is also evidence linking exposure to physical abuse before age 12 years to

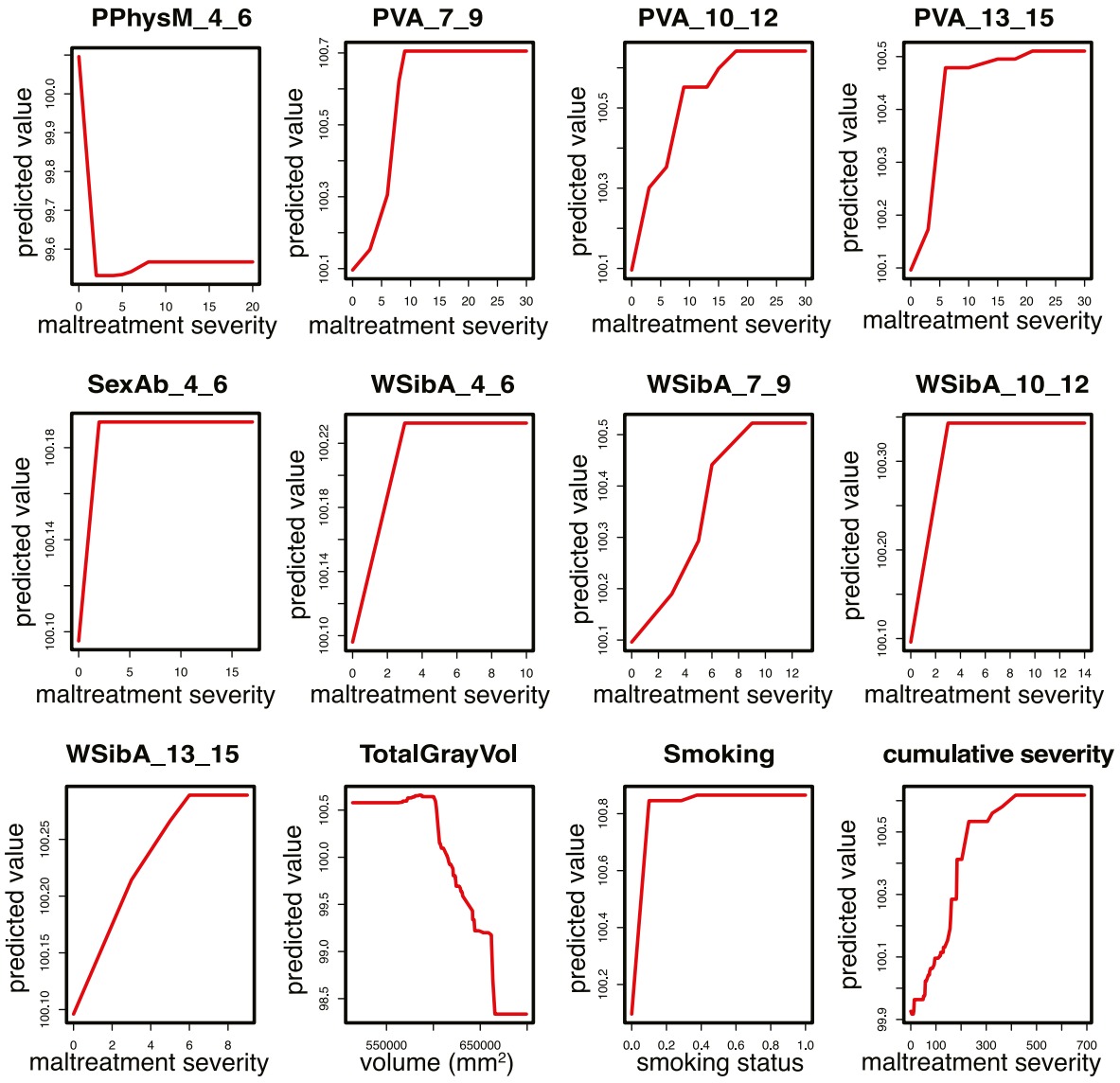

Fig. 3. Dose-response effects. Dose-response plots are shown to depict the directionality of effects for the significant predictors from the random forest regression. Horizontal axes represent severity scores while vertical axes represent scaled, predicted model values. Overall, greater severity was primarily associated with faster brain age acceleration during adulthood. Physical abuse (4–6 yrs), however, showed an inverse effect in which greater severity was associated with decelerated brain age. Abbreviations are as follows: PVA, parental verbal abuse; PPhys, parental physical abuse; WSibA, witnessing violence toward siblings; SexAb-sexual abuse.

increased risk for adult psychotic disorder (Fisher et al., 2010). These findings across studies demonstrate the significance of experiences during early developmental periods on adult brain development and psychopathological outcomes.

Our finding of a negative association between BAG and physical abuse between ages 4 and 6 years may have multiple explanations. While maltreatment has generally been linked to accelerated pubertal development, the impact on brain maturation appears more complex and non-uniform across the brain (Fleming and McDermott, 2024; Hill et al., 2010; Liuzzi et al., 2023). Developmentally, age 4–6 years is a time when brain regions, like the prefrontal cortex, are in transition from a period of rapid synaptogenesis characteristic of early life to synaptic pruning (Teffer and Semendeferi, 2012). Experiencing parental physical abuse during this time may cause disruptions to this crucial transitional period during development, with delays that are still apparent during adulthood. Other work has also shown developmental delays of individual brain regions related to physical abuse. For example, our finding aligns with earlier work showing delayed maturation of emotional circuitry regions in girls aged 8–18 years with histories of physical abuse (Keding et al., 2021; Stenson and Jovanovic, 2021). However, work focusing specifically on the maturation of emotional circuity in relation to early life adversity is mixed, with some reports indicating accelerated development (Callaghan and Tottenham, 2016; Colich and McLaughlin, 2022), while others report delayed development (Keding et al., 2021; Luby et al., 2013; Stenson and Jovanovic, 2021). Further, exposure to physical abuse in this age range was associated in early adulthood with a blunted amygdala response to threat, whereas postpubertal exposure to maltreatment was associated with an enhanced response (Zhu et al., 2019, 2023). Blunted response to threats may exert a beneficial anti-aging effect by reducing threat-associated surges in stress hormones and allostatic load. This suggests a need to disentangle the sources of variability that may contribute to more global associations between maltreatment and brain age, including the contribution of individual regions, timing, and phenotypic variation such as internalizing vs. externalizing psychopathology (Keding et al., 2021).

4.3. BAG and witnessing violence toward siblings

Witnessing sibling violence showed significant associations with BAG at ages 4–15 years. However, exposure during this age range did not meet the criteria for sensitive periods under the competing hypotheses definition, as it was not a greater predictor than cumulative maltreatment severity, duration, and multiplicity. Still, its overall significant association with BAG is notable. Historically, the study of this form of maltreatment has received limited attention, despite being an important dimension of early life adversity. Limited prior work has demonstrated that witnessing violence towards siblings is associated with ratings of depression, anger-hostility, dissociation, anxiety, somatization, and 'limbic irritability' (Teicher and Vitaliano, 2011). The same study found that witnessing violence towards siblings was a stronger predictor of such symptoms than witnessing interparental violence (Teicher and Vitaliano, 2011). Other work has also shown patterns of both brain structure and function linked to childhood maltreatment history. For example, witnessing violence towards siblings at age 5 has been previously associated with lower fiber stream number in the mid-anterior corpus callosum (Ohashi et al., 2022). Other work has shown that witnessing sibling violence at ages 6 and 12 results in reduced threat responses in the fusiform cortex and dorsal cingulate cortex, respectively (Zhu et al., 2023). However, further work is needed to determine how alterations in these specific brain regions contribute to the observed association between witnessing sibling violence and accelerated brain aging. Together, these findings highlight witnessing sibling violence as an understudied yet consequential dimension of childhood adversity with potential long-term implications for brain health.

4.4. BAG and sexual abuse

In this analysis, sexual abuse showed significant positive associations with BAG between the ages of 4 and 6 years. However, in the current dataset, we did not find evidence for sensitive periods under the competing hypotheses definition. Previous work has shown evidence of associations between childhood sexual abuse and regional brain volumes later in life. For example, sexual abuse between ages 3–5 years was associated with reduced hippocampal volume in adult women ages 18–22 (Andersen et al., 2008). This matches other findings that have also shown lower hippocampal volume in individuals with more cumulative measures of childhood sexual abuse history (Bremner et al., 2003; Stein et al., 1997). Given the well-documented evidence of reduced hippocampal volume as a hallmark of aging (Bettio et al., 2017; Jack et al., 1999; O'Shea et al., 2016; Salthouse, 2010; Shi et al., 2009), these findings suggest that the hippocampus, in particular, may be one brain region that contributes to the overall observed pattern of accelerated global brain aging in relation to sexual abuse.

4.5. Relevance to the postnatal period

In this study, we characterized the effects of childhood maltreatment on the biological aging of the brain in postnatal women. These findings are important, given that the perinatal period is a unique time period of rapid changes in age-associated physiological phenotypes for both mothers (Giller et al., 2020; Ryan et al., 2024) and their infants (Dye et al., 2024). Also, given the design of the original study from which this sample was drawn, this dataset is a well-controlled sample with regard to proximity in time to pregnancy, a potentially large driving factor of variability when not accounted for in a normative population.

Characterizing the effects of childhood maltreatment on maternal biology during the perinatal period is also important for understanding how early life adversity contributes to long-term health trajectories. For example, previous work demonstrates a significant association between maternal adverse childhood experiences and biological aging measures, as assessed using epigenetic markers in pregnant mothers and their offspring (Dye et al., 2024). However, whereas most existing work has emphasized epigenetic aging, the current study is the first to our knowledge to focus on maternal adverse childhood experiences and biological aging of the brain during adulthood.

4.6. Limitations and future directions

While interpreting the findings described above, it is important to consider the specific context of the study, as well as opportunities for future directions. First, the current study provided valuable results in a population of postnatal women. This is an important population given the unique set of physiological changes associated with pregnancy and the postnatal period (Giller et al., 2020). Additionally, the uniformity of sex here facilitates the detection of a clearer signal than would be expected in a mixed-sex cohort of similar size. Building upon the current results, future work can extend these findings by investigating whether similar sensitive periods also exist outside of the postnatal period (i.e. – prenatal women, non-pregnant women, males, children, etc.).

Another consideration in interpreting the results of the current study is its retrospective design, relying on participants to recall maltreatment experiences at specific ages. Such recollections may be susceptible to recall bias, as memories of childhood events, especially those associated with trauma, can be fragmented, reinterpreted, or suppressed over time, although reported events have been remarkably consistent on test-retest. Additionally, while we did not find any significant results for earlier timepoints (i.e., ages 1–3), a more comprehensive assessment of maltreatment during these years would benefit from corroborative reports, such as those from siblings, other caregivers, or child welfare records. Future longitudinal studies that incorporate these sources would strengthen the evaluation of early childhood maltreatment and better capture how early experiences influence biological aging. However, it should be noted that previous work demonstrates that psychopathology is better predicted by retrospective, self-report measures of maltreatment compared to prospective measures. Prospective measures, which typically rely on information from a third party like a parent or official records, do not necessarily capture the first-person, subjective appraisal of childhood events reflected in memory as measured by retrospective, self-report assessments. A meta-analysis of over 15,000 study participants demonstrated that, relative to prospective measures, these subjective interpretations of such experiences are more strongly related to maltreatment-related psychopathology (Baldwin et al., 2024). Indeed, the importance of subjective appraisal and the need for accurate accounts during a time in which memory is limited poses a challenge that requires innovative ways of assessing maltreatment early in life.

A potential limitation in the application of pretrained brain age models is that the original training datasets may have included individuals with a history of childhood maltreatment. Because such experiences are not routinely used as exclusion criteria in large, publicly available "healthy control" cohorts, variance associated with maltreatment could have been incorporated into the normative model. If so, this may reduce the sensitivity of the model to detect maltreatment-related effects in subsequent samples. However, the advantage of using a large and heterogeneous training set is that it was explicitly designed to encompass a wide spectrum of normative brain aging, thereby minimizing the disproportionate influence of any single risk factor.

One challenge in the study of sensitive periods is balancing dimensionality reduction with examining meaningful developmental windows (Schaefer et al., 2022). While using broader definitions of development windows increases statistical power, these windows may mask information related to meaningful development windows. Moreover, much like different brain regions develop along different trajectories (Fleming and McDermott, 2024; Hill et al., 2010; Liuzzi et al., 2023), different traits and abilities also develop along different trajectories (Adolph et al., 2011; Bernstein, 2014; Gooch et al., 2016; Keen, 2011). As a result, future investigations will need to use larger samples to identify sensitive periods that reflect meaningful development windows for

different aspects of development that may be impacted by childhood maltreatment.

Gene-environment interactions also play a crucial role in shaping brain development and aging (Argentieri et al., 2025). While genetic predispositions can influence how the brain responds to environmental factors, the interaction between these two domains remains complex and not fully understood. Unfortunately, our study did not include genotyping data, preventing us from directly examining the genetic influences on brain aging or how they might interact with environmental factors. Future research that incorporates genetic data alongside environmental exposure information will be crucial for unraveling how gene-environment interactions contribute to individual differences in brain aging following maltreatment exposure.

While the current study was designed to examine brain aging and childhood maltreatment in a general population, further work is needed to investigate the association between maltreatment and brain aging in other subpopulations. For example, previous work demonstrates that the prevalence of adverse childhood experiences is higher among ethnic minorities and individuals from low socioeconomic backgrounds (Merrick et al., 2018). As a result, it is important to consider how additional potential stressors faced by these unique subpopulations may moderate the link between childhood maltreatment and brain aging.

Lastly, in the current sample, ten types of maltreatment were investigated using the Maltreatment and Abuse Chronology of Exposure scale. Given that we did not pre-screen for the prevalence of each maltreatment subtype in recruitment, some maltreatment subtypes had relatively lower frequency in the current sample (e.g. – sexual abuse, witnessing sibling violence). Future work may require more targeted recruitment to include greater representation of specific forms of maltreatment.

5. Conclusion

The current study contributes to our understanding of the enduring effects of early life adversity and augments our knowledge of how the human brain is shaped by experience. Importantly, our findings identified age-related periods of particular sensitivity to the effects of childhood maltreatment on brain aging. These results also suggest a set of time periods during which screening or clinical attention may help mitigate the long-term risks of childhood maltreatment. Together, our findings point to the complexity of maltreatment effects on brain aging and highlight the need for nuanced approaches to the study of brain development and early life adversity.

CRediT authorship contribution statement

Leland L. Fleming: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Kyoko Ohashi:** Data curation, Writing – review & editing. **Michelle Bosquet Enlow:** Writing – review & editing. **Jennifer Khoury:** Data curation, Writing – review & editing. **Torsten Klengel:** Conceptualization, Methodology, Writing – review & editing. **Karlen Lyons-Ruth:** Data curation, Funding acquisition, Investigation, Project administration, Supervision, Writing – review & editing. **Martin Teicher:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Kerry J. Ressler:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Leland Fleming reports financial support was provided by National Institute of Child Health and Human Development. Kerry Ressler reports financial support was provided by National Institute of Mental Health. Karlen Lyons-Ruth reports financial support was provided by National Institute of Child Health and Human Development. Martin Teicher reports financial support was provided by National Institute of Child Health and Human Development. Michelle Bosquet Enlow reports financial support was provided by National Institute of Child Health and Human Development. Kerry Ressler reports a relationship with Acer that includes: consulting or advisory. Kerry Ressler reports a relationship with Bionomics that includes: consulting or advisory. Kerry Ressler reports a relationship with Jazz Pharma that includes: consulting or advisory. Kerry Ressler reports a relationship with Sage that includes: board membership. Kerry Ressler reports a relationship with Boehringer Ingelheim that includes: board membership. Kerry Ressler reports a relationship with Senseye that includes: board membership. Kerry Ressler reports a relationship with Brain and Behavior Research Foundation that includes: board membership. Kerry Ressler reports a relationship with Alto Neuroscience that includes: funding grants. Martin Teicher reports a relationship with the Law Office of Marci A. Kratter that includes: paid expert testimony. Martin Teicher reports a relationship with Sgro & Roger, Attorneys at Law that includes: paid expert testimony. Martin Teicher reports a relationship with Deratany & Kosner that includes: paid expert testimony. Martin Teicher reports a relationship with The Reardon Law Firm that includes: paid expert testimony. Martin Teicher reports a relationship with Romanucci & Blandin, LLC that includes: paid expert testimony. Martin Teicher reports a relationship with Trauma Research Foundation that includes: board membership. Martin Teicher reports a relationship with Juvenile Bipolar Research Foundation that includes: board membership. Martin Teicher reports a relationship with Words Matter Foundation that includes: board membership. Martin Teicher reports a relationship with ANS Foundation that includes: funding grants. If there are other authors, they 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. Supplementary data

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Data availability

Data will be made available on request.

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