Faster pace of hippocampal growth mediates the association between perinatal adversity and childhood depression

Jonas G. Miller a,*, Peter D. Gluckman b, Marielle V. Fortier c, Yap Seng Chong d,e,f, Michael J. Meaney d,c,e,f, Ai Peng Tan d,e,h,i, Ian H. Gotlib j

a Department of Psychological Sciences, University of Connecticut, CT, USA
b Liggins Institute, University of Auckland, Auckland, New Zealand
c Translational Neuroscience Program, Singapore Institute for Clinical Sciences, A*STAR Research Entities, Singapore
d Department of Diagnostic Radiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
e Department of Obstetrics & Gynecology, National University Health System, Singapore
f Douglas Mental Health University Institute, Department of Psychiatry, Faculty of Medicine, McGill University, Montreal, Canada
g Brain – Body Initiative, A*STAR Research Entities, Singapore
h Department of Diagnostic Imaging, National University Health System, Singapore
i Department of Psychology, Stanford University, CA, USA

A R T I C L E   I N F O

Keywords:
Adversity
Hippocampus
Development
Depression

A B S T R A C T

Early life adversity has been posited to influence the pace of structural neurodevelopment. Most research, however, has relied on cross-sectional data, which do not reveal whether the pace of neurodevelopmental change is accelerated or slowed following early exposures. In a birth cohort study that included neuroimaging data obtained at 4.5, 6, and 7.5 years of age (N = 784), we examined associations among a cumulative measure of perinatal adversity relative to resources, nonlinear trajectories of hippocampal and amygdala volume, and children’s subsequent depressive symptoms at 8.5 years of age. Greater adversity was associated with reduced bilateral hippocampal body volume in early childhood, but also to faster growth in the right hippocampal body across childhood. Further, the association between adversity and childhood depressive symptoms was mediated by faster hippocampal body growth. These findings suggest that perinatal adversity is biologically embedded in hippocampal structure development, including an accelerated pace of change in the right hippocampal body that is implicated in children’s psychopathology risk. In addition, our findings suggest that reduced hippocampal volume is not inconsistent with accelerated hippocampal change; these aspects of structural development may typically co-occur, as smaller regional volumes in early childhood were associated with faster growth across childhood.

Early adversity is a risk factor for the development of health problems across the lifespan, including for psychopathology in childhood (Nelson et al., 2020; Shonkoff et al., 2012). Exposure to psychosocial and biological hazards may be particularly consequential during sensitive windows, such as the perinatal period (Nelson and Gabard-Durnam, 2020). There are a range of events and conditions that constitute adversity during the perinatal period, such as low gestational age at birth, maternal smoking during pregnancy, institutionalization, and maternal depression, that have been linked to increased risk for psychopathology in offspring (Duko et al., 2020; Gotlib et al., 2023; Lund et al., 2020; Rice et al., 2010; Wade et al., 2020). Conversely, early positive experiences and environmental conditions or resources may help to offset risk related to adversity (Han et al., 2023; Masten et al., 2021), even during the perinatal period (McLoyd, 1998). Examples of such resources may include positive delivery outcomes related to the prenatal environment, such as being born at term or having an average birth weight, and factors related to perinatal care such as family income, parental mental health, and breastfeeding (Boyle et al., 2012; Hines et al., 2020; Huang et al., 2014; Roncallo et al., 2018). Adversity and resources both can be present and accumulate across multiple levels; indeed, researchers have emphasized the importance of considering their joint contributions to development (Evans et al., 2013; Han et al., 2023; Masten et al., 2021).
2023). From a perspective of cumulative risk and resources, evaluating the degree of adversity exposure relative to advantage may yield an index of the overall quality of early life experiences and conditions.

Researchers have recently proposed that an altered pace of maturation may underlie associations of early experience with health (Callaghan and Tottenham, 2016; Roubinov et al., 2021; Tooley et al., 2021). There is accumulating evidence that some developmental phenomena occur earlier in response to adversity. For example, exposures such as neglect and violence have been linked to earlier physical development (Colich et al., 2020; McDermott et al., 2021), to cellular indicators of accelerated biological aging (Colich et al., 2020; Jovanovic et al., 2017), and to brain features that more commonly characterize older individuals (Drobinin et al., 2022; Gee et al., 2013; Miller et al., 2020). From an evolutionary perspective, adversity may calibrate the pace of development in ways that enhance fitness in harsh environments, such as earlier sexual maturation, adult-like fear learning, and processes that support earlier independence from caregivers (Ellis et al., 2022). Thus, accelerated development may be an evolutionary adaptation that helps individuals meet the demands of adversity, despite associated costs for health and well-being (Belsky, 2019). Indeed, many adversity-related alterations in brain function and structure have been associated with symptoms of psychopathology (Drobinin et al., 2022; Miller et al., 2022) and with psychological processes implicated in psychopathology (Peterson et al., 2009). In contrast, nurturing and enriched environments may slow brain maturation and enhance plasticity (Tooley et al., 2021).

The rate of development of corticolimbic brain regions such as the hippocampus and amygdala may be particularly sensitive to early adversity. These regions are rich in glucocorticoid receptors and play key roles in memory, vigilance, and regulation of emotional and behavioral responses to salient stimuli (LeDoux, 2007; Murty et al., 2016). Previous research, however, has not provided clear evidence regarding whether adversity is associated with accelerated or delayed structural development of these brain regions. For example, whereas animal studies have demonstrated adversity-related acceleration of the structural development of the basolateral amygdala (Manzano Nieves et al., 2020; Ono et al., 2008) and some human neuroimaging studies have found larger amygdala volumes in youth who experienced institutionalization (Tottenham et al., 2010) or childhood maltreatment (Whittle et al., 2013), other studies have found institutionalization, physical abuse, or neglect to be associated with smaller amygdala volumes (Hanson et al., 2015; Luby et al., 2013) or have not found statistically significant relations (Hodell et al., 2015; Sheridan et al., 2012). In addition, a recent meta-analysis of studies with community samples did not find overall evidence for a relation between childhood adversity and amygdala volume (Calem et al., 2017). There is more consistent evidence that early adversity is associated with reduced hippocampal volume (Hanson et al., 2015; Hodell et al., 2015; Luby et al., 2013; VanTieghem et al., 2021). In this context, given that hippocampal volume is larger in older than in younger children (Coupé et al., 2017), some researchers have raised the possibility that adversity is associated with delayed rather than accelerated structural development of this region (Callaghan and Tottenham, 2016). Despite growing interest in this area of research and the development of generative theoretical models, there are significant gaps in our current understanding of the relation between adversity and the pace of neurodevelopment. Importantly, few studies of early life adversity have directly assessed the tempo or speed of change as a central feature of neurodevelopmental pace. In fact, most previous studies have used cross-sectional designs, focusing on outcomes at a single timepoint to infer developmental pace. Adversity-related findings of relatively larger corticolimbic volumes, reduced cortical thickness, and larger brain age gap estimates (BrainAGE) at a single assessment have often been interpreted as evidence of accelerated aging or maturation (Colich et al., 2020; Drobinin et al., 2022; Gotlib et al., 2022; Rifkin-Graboi et al., 2015). It is important to recognize, however, that the defining characteristics of growth processes, including their rates of change and potentially nonlinear developmental patterns, are not accurately modeled using data from only one or even two time points (Parsons and McCormick, 2022); repeated observations of putative brain-based measures of maturation are essential for modeling trajectories and for testing directly whether the pace of neurodevelopment is faster or slower in the context of adversity.

Another common approach for testing pace of development is to model interaction effects of age by adversity on brain outcomes (Tooley et al., 2021). Stronger cross-sectional associations between age and brain metrics at high or low levels of adversity are often interpreted as evidence of accelerated maturation. However, developmental trends inferred from cross-sectional age-associations do not always match longitudinal data (Pfefferbaum and Sullivan, 2015). For example, recent research suggests that cross-sectional associations of hippocampal volume with age are inconsistent with longitudinal changes in volume (Keresztes et al., 2022). Thus, cross-sectional associations of brain metrics with age may not yield accurate information about adversity-related differences in neurodevelopmental trends, including pace.

Given these issues, multiple neuroimaging assessments are needed to determine the nature of the relation between early life adversity and pace of neurodevelopment. In this context, some studies examining socioeconomic status (SES) have used longitudinal methods to consider rates of neurodevelopmental change. A recent review of this literature highlighted eight studies that included three or more waves of neuroimaging data and concluded that lower SES is associated with slower growth rates, which may indicate delayed or simply different neurodevelopment (Rakesh et al., 2023). Only a small number of these SES-focused studies, however, examined the pace of structural neurodevelopment during childhood (Barch et al., 2022; Hair et al., 2015); further, although low SES and adversity are related, it is important to recognize that they are not the same construct.

The goal of the present study was to expand on and extend this literature by using three waves of neuroimaging data to characterize trajectories and pace of hippocampal and amygdala structural development during childhood. We examined whether levels of perinatal adversity relative to resources, including but not limited to SES, are associated with a faster or slower pace of structural development, and examined the effects of pace of structural brain development on depression in late childhood. We hypothesized that greater cumulative perinatal adversity relative to resources will be associated with smaller hippocampal volume in early childhood and more severe depressive symptoms in late childhood. In accord with stress acceleration perspectives (Callaghan and Tottenham, 2016; Tooley et al., 2021), we expected greater cumulative perinatal adversity relative to resources will be associated with a faster pace of hippocampal growth over the course of childhood. We did not have specific hypotheses about the association between perinatal adversity and amygdala volume or amygdala growth given inconsistent findings in the literature.

1. Methods

1.1. Participants and study design

Participants were drawn from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) study. The GUSTO study was approved by the National Healthcare Group Domain Specific Review Board and the SingHealth Centralized Institutional Review Board in Singapore. Parents provided written informed consent for participation and received compensation. Exclusion criteria for GUSTO included mothers undergoing chemotherapy, taking psychotropic drugs, or having a diagnosis of type 1 diabetes mellitus. Data were collected at the hospital where each mother delivered her child (e.g., birthweight percentile) and at a clinic site (e.g., questionnaire measures). The GUSTO cohort and original study design is described in Soh et al. (2012). Participants were included...
in the current analyses if they provided data on at least one of the following measures: perinatal adversity, usable T1-weighted neuro-imaging scans at the age 4.5, 6, or 7.5 years, or child-reported depressive symptoms at the age 8.5 assessment (N = 784; 48 % female; 51 % Chinese, 26 % Malaysian, 16 % Indian, 7 % missing ethnicity).

2. Measures

2.1. Perinatal adversity relative to resources

Similar to prior analyses of GUSTO data, we used a cumulative score approach to assess perinatal adversity versus resources (Chan et al., 2024; de Lima et al., 2022; Silveira et al., 2017). The presence of each of the following components yielded one point on an adversity index: birthweight percentiles below 10th percentile or above 90th percentile; gestational age less than or equal to 37 weeks; smoking during pregnancy; household income less than $2000 per month; poor maternal mental health at 3 months of age defined as the presence of symptom severity scores greater than 13 on the Beck Depression Inventory (BDI) (Beck et al., 1996), scores greater than or equal to 12 on the Edinburgh Postnatal Depresion Scale (EDPS) (Cox et al., 1987), or scores greater than or equal to 92 on the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983); and offspring hospitalization within the first 6 months after birth. Broadly, these components serve as potential markers of exposure to adverse events or environmental conditions during the perinatal period (Staines et al., 2024; Zammit et al., 2009), and are akin to approaches that consider psychosocial and biological hazards, such as experiences of illness/injury, socioeconomic disadvantage, parental psychopathology, and toxin exposure, as forms of adversity in childhood and adolescence (Chahal et al., 2022; LeMoult et al., 2020; Nelson and Gabard-Durnam, 2020). In addition, these components and cutoffs have been used in prior analyses of GUSTO (Chan et al., 2024; de Lima et al., 2022; Silveira et al., 2017). The presence of each of the following components yielded one point on a perinatal resources index: birthweight percentiles between 40 and 70; gestational age less than or equal to 39 weeks; household income greater than $6000 per month; positive maternal mental health at 3 months of age defined as the presence of symptom severity scores greater than or equal to 10 on the Edinburgh Postnatal Depression Scale (EDPS) (Cox et al., 1987), or scores greater than or equal to 92 on the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983); and the absence of hospitalization within the first 6 months after birth. Broadly, these components serve as potential markers of exposure to favorable events or environmental conditions during the perinatal period (Staines et al., 2024; Zammit et al., 2009), and are akin to approaches that consider psychosocial and biological advantages, such as experiences of well-being, socioeconomic advantage, parental psychopathology, and toxin exposure, as forms of adversity in childhood and adolescence (Chahal et al., 2022; LeMoult et al., 2020; Nelson and Gabard-Durnam, 2020).

In the current analyses if they provided data on at least one of the following measures: perinatal adversity, usable T1-weighted neuro-imaging scans at the age 4.5, 6, or 7.5 years, or child-reported depressive symptoms at the age 8.5 assessment (N = 784; 48 % female; 51 % Chinese, 26 % Malaysian, 16 % Indian, 7 % missing ethnicity).

2.2. Magnetic resonance imaging at 4.5, 6, and 7.5 years of age

Participants completed magnetic resonance imaging (MRI) using a 3 T Siemens Skyra scanner at ages 4.5 and 6 years. MRI scans at age 7.5 years were collected using a 3 T Siemens Magnetom Prisma scanner. High-resolution T1-weighted structural scans were collected using a Magnetization-Prepared Rapid Gradient-Echo (MP-RAGE) sequence with the following parameters: 192 slices, repetition time = 2000 ms, echo time = 2.08 ms, 1 mm isotropic voxels, matrix size = 192 × 192. Data harmonization using longitudinal ComBat v.0.0.0.90 (Beer et al., 2020) was done with two batches – (1) ages 4.5 and 6 years and (2) age 7.5 years.

2.3. Segmentation

T1 MP-RAGE images underwent the standard FreeSurfer recon-all stream (v.7.0, http://surfer.nmr.mgh.harvard.edu). The output was manually inspected for registration between the structural images and atlas. Images with poor registration were manually edited and re-processed to ensure good correspondence between the structural image and the atlas. Auto-segmentation of hippocampal and amygdala subregions was performed using a probabilistic atlas built with ultra-high resolution ex vivo MRI data, permitting delineation of these subregions at a high degree of accuracy (Iglesias et al., 2015; Saygin et al., 2017). These segmented hippocampal and amygdala subregion masks were then used to estimate the volume measurements used in our analysis. Quality control of our scan data was performed at the raw T1 MP-RAGE data and the FreeSurfer recon-all output stages. For the raw data, individual scans were assigned a score of pass (no or minimal visible motion lines, clear WM/GM distinction), good (visible motion lines that may be persistent with clear WM/GM distinction), questionable (visible motion lines that may be persistent with poor WM/GM distinction), or fail (ripples of motion lines that are prominent and persistent – integrity of WM/GM distinction are almost lost; n = 98, 67, and 16 at ages 4.5, 6, and 7.5 years, respectively). We then performed a visual quality control check on the FreeSurfer outputs.

2.4. Child depressive symptoms at 8.5 years of age

At the 8.5-year assessment, children reported on their depressive symptoms using the Children’s Depression Inventory, 2nd edition (CDI-2) (Kovacs, 2011). Children responded to 28 items on a 3-point Likert scale ranging from 0 to 2 indicating graded severity of symptoms. We summed responses to yield scores reflecting the severity of depressive symptoms.

3. Data analysis

We first conducted latent growth curve analyses to model hippocampal and amygdala trajectories across childhood. We created separate models for the left and right hippocampal head, body, and tail, and the left and right basal and lateral nuclei of the amygdala. These models estimated latent factors for the initial volume of each region at 4.5 years of age (intercept) and the rate of change in volume over the course of childhood (slope). For each region, we tested and compared a linear growth model with a latent basis model in which the weight for the latent slope factor predicting regional volume at the second neuro-imaging assessment (i.e., 6 years of age) was estimated from the data. The linear and latent basis models are similar in that they both describe rate of change with a single latent factor. The latent basis, however, can represent nonlinear patterns of change because the differences between slope factor loadings are not equal across time (Grimm et al., 2011). For each model, we used several indices to assess model fit, including χ², the Comparative Fit Index (CFI), the Tucker-Lewis Index (TLI), and the root mean square error of approximation (RMSEA) with a 90 % confidence interval (CI). Good fit is indicated by higher CFI and TLI values and lower RMSEA values (Hu and Bentler, 1999). Chi-square difference tests were used to compare linear and latent basis models for each region. In all models, latent intercepts and slopes were allowed to covary with each other. Residual variances were constrained to be equal unless models did not converge or if model parameters were not identified (see Supplementary Methods B). If models did not provide statistically significant variability in intercept or slope factors for a particular region, we did not conduct analyses of individual differences using those trajectory data. It is important to note that the models of trajectories were based on absolute volumes at each age, not on volumes relative to ICV at each age. Conversely, in subsequent analyses testing covariate-adjusted relations between perinatal adversity and subcortical regional trajectories we controlled for intracranial volume trajectories (see below).

One of our primary research interests was in individual differences in neurodevelopmental pace. Thus, for each region and ICV, we set a prerequisite for conducting further analyses – the latent slope factor had to show statistically significant variance (p<.05). If regions did not show
significant slope variance, we interpreted this as a lack of evidence for meaningful individual differences in the pace of change of that region. For each regional model that showed superior fit, did not produce error messages, and included slope factors with significant variance, we report the model estimates and fit in the Supplement in Tables S1-S8. Further details regarding our analytic strategy for latent growth curve modeling are presented in Supplemental Methods B.

After model selection for each region, we extracted latent intercept and latent slope factor scores to test relations of volumetric size and growth with perinatal adversity and later childhood depressive symptoms. All factor scores were winsorized such that values lower and higher than the 5 %- and 95 %-quantile, respectively, were replaced with those values. We conducted Pearson correlations among variables of interest (i.e., zero-order correlations). For each region, we include false-discovery rate-adjusted (FDR) p-values that correct for testing multiple correlations tested of region-specific intercept and slope factors with perinatal adversity and child depressive symptoms. Subsequently, for regions showing associations with perinatal adversity, we conducted further testing to evaluate whether these associations persisted after controlling for trajectories of intracranial volume. To define intracranial volume trajectories, we conducted growth curve models and extracted latent intercept and latent slope factor scores for total intracranial volume. We used these factor scores as covariates. Thus, this approach allowed us to consider whether perinatal adversity is associated with the

![Graphs showing hippocampal, amygdala, and intracranial volume trajectories.](image-url)

Fig. 1. Estimated hippocampal, amygdala, and intracranial volume trajectories. Note. Black lines indicate individual trajectories based on the latent growth curve models. Blue lines indicate the average trajectory. Intracranial volume (ICV) was scaled by dividing values by 1000. The hippocampal and amygdala trajectories are based on volume values at each assessment that are not adjusted for ICV. R = right; L = left; mm³ = cubic millimeters.
pace of subcortical volume growth over and above the effect of pace of intracranial volume growth. For regions that continued to show associations with other variables of interest, we conducted a path analysis to test whether specific aspects of volumetric trajectories, either the intercept or slope, served as a mediating path from perinatal adversity to depressive symptoms at age 8.5 after controlling for covariates. We used the joint significance test to evaluate indirect effects in these mediation models (Kline, 2011); this test finds evidence for an indirect effect if each path comprising the indirect effect is statistically significant. Compared to other tests of mediation, the joint significance test has been shown to provide the best balance of statistical power and lower Type I error rates (MacKinnon et al., 2002; Taylor et al., 2008).

We used the lavaan package (Rosseel, 2012) in R to conduct all analyses, including using full-information maximum likelihood (FIML) to handle missing data and estimate models. FIML is recommended when moderate to large amounts of data are missing (Widaman, 2006).

4. Results

4.1. Hippocampal and amygdala trajectories and pace of change

The estimated trajectories for hippocampal and amygdala regions that were modeled successfully, and that showed significant slope variability, are presented in Fig. 1. Hippocampal and amygdala regions showed developmental trends that were better characterized by nonlinear than by linear growth. Over the course of the three neuroimaging assessments, hippocampal regions showed approximately 2.5 times more volumetric growth from 4.5 to 6 years of age than from 6 to 7.5 years of age (for nonlinear growth models, average of 71% of total growth across hippocampal regions; range from 68% to 73% for different hippocampal regions). The right hippocampal tail, however, required fitting a linear growth model. For the amygdala, the right basal and lateral nuclei and left lateral nuclei were also characterized by nonlinear growth. These regions showed approximately 2 times more volumetric growth from 4.5 to 6 years of age than from 6 to 7.5 years of age (average of 67% of total growth across amygdala regions; range from 63% to 71% for different amygdala regions). The left basal nuclei, however, required fitting a linear growth model. Further, all hippocampal and amygdala regions showed statistically significant variability in initial volume size at 4.5 years of age, and most regions showed meaningful variability in rates of change, except for the right hippocampal tail and left hippocampal head. Across models for hippocampal regions, amygdala regions, and ICV, initial volume size at 4.5 years of age was negatively associated with rates of changes (rs from −.23 to −.59; see Supplement Tables S1-S8). For each region, model fit and parameter estimates are presented in the Supplemental Results and Tables S1-S8.

4.2. Associations among perinatal adversity, hippocampal development, and childhood depression

Greater perinatal adversity was associated with lower right and left hippocampal body volume intercept values at 4.5 years of age (r = −.12, p = .013, FDR p = .060 and r = −.12, p = .014, FDR p = .060, respectively). These associations remained statistically significant (β = −.10, p = .038 and β = −.09, p = .042, respectively) after adjusting for intracranial volume at 4.5 years of age (β = .51, p < .001 and β = .52, p < .001, respectively). Right and left hippocampal body volume at 4.5 years of age, however, were not significantly associated with child depressive symptoms at 8.5 years of age (both ps > .215).

Greater perinatal adversity was also associated with faster pace of right hippocampal body growth (r = −.12, p = .008, FDR p = .060), which also remained statistically significant (β = −.13, p = .005) after adjusting for pace of intracranial volume growth across childhood (β = −.11, p = .004). Both greater perinatal adversity and faster pace of right hippocampal body growth were associated with more severe depressive symptoms at 8.5 years of age (r = .12, p = .039, FDR p = .133 and r = .16, p = .002, FDR p = .034, respectively).

Other hippocampal region intercept factors and pace of change factors were not significantly associated with perinatal adversity or depressive symptoms (all ps > .076). Correlations of regional trajectories and intracranial volume trajectories with sex, perinatal adversity, and child depression are presented in Table S9 in the Supplement.

4.3. Pace of right hippocampal body growth mediates the association between perinatal adversity exposure and childhood depression

Fig. 2 presents the model testing pace of right hippocampal body growth as a mediating pathway between perinatal adversity and children’s depressive symptoms at 8.5 years of age. The predictive paths from covariates were included in the model (see Table 1), but these estimates are omitted from Fig. 2 to focus on the mediation pathway of primary interest. As shown in Table 1 and Fig. 2, the direct effect of perinatal adversity on childhood depressive symptoms was no longer statistically significant with pace of right hippocampal body growth included in the model. According to the joint significance test (Kline, 2011; MacKinnon et al., 2002), because each path comprising the mediation was statistically significant, there is evidence for an indirect effect of perinatal adversity on depressive symptoms through faster pace of right hippocampal body growth. This effect was present controlling for sex assigned at birth and intracranial volume trajectories (intercept and pace of change factors) as predictors of pace of right hippocampal body growth, and sex as a predictor of depressive symptoms. The estimated right hippocampal body trajectories at high and low levels of perinatal adversity are presented in Fig. 3.

4.4. Associations of perinatal adversity and depression with amygdala and intracranial volume trajectories

Greater perinatal adversity was associated with lower right amygdala lateral nucleus volume intercept values at 4.5 years of age (r = −.10, p = .035, FDR p = .332), but this association was no longer statistically significant (β = −.06, p = .173) after adjusting for intracranial volume at 4.5 years of age (β = .53, p < .001). Greater perinatal adversity was associated with lower ICV intercept values at 4.5 years of age (r = −.12, p = .018). ICV intercept values at 4.5 years of age were not associated with child depressive symptoms at 8.5 years of age (r = −.05, p = .429). Further, neither perinatal adversity nor child depressive symptoms were associated with other basal and lateral nuclei volume intercept and pace of change factor scores, or with ICV pace of change (all ps > .078; see Supplement Table S9).

4.5. Separating adversity and resources scores and testing their interaction

Although not part of our original analysis plan, we conducted supplementary analyses predicting right hippocampal body intercept and pace and child depressive symptoms using separate perinatal adversity and resource scores and their interaction. Consistent with the perspective that resilience factors can buffer the association between adversity and developmental outcomes (Masten et al., 2021), adversity was associated with faster pace of right hippocampal body growth in the context of low, but not high, perinatal resources. In addition, at average levels of perinatal adversity, resources were associated with slower right hippocampal body growth. Further details are presented in the Supplementary Results, Table S10, and Figure S3.

5. Discussion

Researchers have posited that early life adversity alters the pace of structural development in stress-sensitive brain regions. Drawing on a longitudinal birth cohort with multiple waves of neuroimaging data, we
have raised the possibility that early adversity delays, or perhaps diminishes, the hippocampal volume in the right and left body in early childhood. In the context of research showing that hippocampal volume increases with age in childhood, findings of reduced hippocampal volume related to adversity and conceptual models positing that adversity accelerates neurodevelopment (Callaghan and Tottenham, 2016; Tooley et al., 2021). Specifically, reduced hippocampal volume across development does not appear to be inconsistent with a faster pace of hippocampal change; in fact, these aspects of neurostructural development may typically co-occur, as we found that smaller regional volumes in early childhood were associated with faster pace of growth. The possibility remains that faster pace of hippocampal growth in childhood is related to the severity of hippocampal underdevelopment in the first few years of life, which is rooted, in part, in exposure to perinatal adversity.

The majority of the literature has focused on cross-sectional research and the timing of milestones to infer altered developmental pace (Gee et al., 2013; Gotlib et al., 2022; McDermott et al., 2021). Our findings provide a different perspective, underscoring the importance of considering developmental pace as a rate of change, and noting that this is a defining feature of developmental trajectories. Our findings could be interpreted differently at the level of pace of change versus the level of the overall trajectory. When focusing on pace as a rate of change, our findings provide clear evidence that perinatal adversity is associated with faster regional hippocampal growth; however, when focusing on the overall trajectory, it is unclear whether perinatal adversity is associated with hippocampal development that is, overall, temporally shifted. Without established benchmarks for normative hippocampal development in childhood, it is impossible to say conclusively whether children exposed to perinatal adversity have trajectories that lead them to meet developmental milestones earlier or later in development (i.e., accelerated or delayed patterns of developmental trajectories, respectively). Thus, from a perspective that focuses on trajectories, the possibility remains that adversity is implicated in a pattern of hippocampal development that is altered but not strictly characterized by an overall acceleration or delay (Rakesh et al., 2023). That is, perinatal adversity could be associated both with accelerated pace of hippocampal growth in childhood and with delayed hippocampal development in terms of later emergence of milestones beyond childhood, such as achieving a volumetric plateau or starting volumetric decline at a later age.

Our findings serve as a call for more longitudinal neuroimaging data given that these study designs are necessary for making strong conclusions about neurodevelopmental pace and about the degree to which nonlinear trajectories are temporally shifted. Indeed, we found that regional and whole brain growth was more rapid between 4.5 and 6 years of age than between 6 and 7.5 years of age. On the one hand, more neuroimaging assessments during a shorter developmental window, perhaps one that is characterized by more rapid change, may uncover stronger associations between adversity and neurodevelopmental pace than what we observed. Conversely, neuroimaging assessments spanning infancy through adolescence will lead to a more comprehensive understanding of neurodevelopmental pace and trajectories. For

demonstrated that exposure to perinatal adversity is associated with volumetric reductions in bilateral hippocampal body in early childhood, but also with faster structural growth across childhood in the right hippocampal body. Children exposed to higher levels of perinatal adversity also reported more severe depressive symptoms 8.5 years later, an association that was mediated by the pace of volumetric change in the right hippocampal body. Specifically, faster volumetric growth in this hippocampal region across childhood served as a developmental pathway that linked perinatal adversity with depressive symptoms later in childhood. Together, these findings suggest that perinatal adversity is biologically embedded in hippocampal structure development, including an accelerated pace of change in the right body that is implicated in children’s risk for future psychopathology. After adjusting for ICV, basolateral amygdala development was not related to perinatal adversity or depressive symptoms in this study, which fits with inconsistencies already reported in the literature regarding the link between adversity and amygdala volume (Calem et al., 2017).

Consistent with prior work that has largely focused on adversity and hippocampal volume in adolescents (Hanson et al., 2015; Hodel et al., 2015), we found that greater perinatal adversity was associated with smaller hippocampal volume in the right and left body in early childhood. In the context of research showing that hippocampal volume increases with age in childhood, findings of reduced hippocampal volume have raised the possibility that early adversity delays, or perhaps damages, structural development of the hippocampus (Callaghan and Tottenham, 2016). Our findings, however, consider pace of neurodevelopment as a rate of change that can only be obtained with longitudinal neuroimaging data. From this perspective, we found that hippocampal growth in the right body is accelerated rather than slowed across childhood following exposure to perinatal adversity. This finding may indicate a pattern of developmental catch-up, as children exposed to greater adversity demonstrated a modest reduction in the observed gap with their low-adversity-exposed peers in terms of future hippocampal volume. Together, our findings may explain apparent inconsistencies between prior cross-sectional findings of reduced hippocampal volume related to adversity and conceptual models positing that adversity accelerates neurodevelopment (Callaghan and Tottenham, 2016; Tooley et al., 2021). Specifically, reduced hippocampal volume across development does not appear to be inconsistent with a faster pace of hippocampal change; in fact, these aspects of neurostructural development may typically co-occur, as we found that smaller regional volumes in early childhood were associated with faster pace of growth. The possibility remains that faster pace of hippocampal growth in childhood is related to the severity of hippocampal underdevelopment in the first few years of life, which is rooted, in part, in exposure to perinatal adversity.

The majority of the literature has focused on cross-sectional research and the timing of milestones to infer altered developmental pace (Gee et al., 2013; Gotlib et al., 2022; McDermott et al., 2021). Our findings provide a different perspective, underscoring the importance of considering developmental pace as a rate of change, and noting that this is a defining feature of developmental trajectories. Our findings could be interpreted differently at the level of pace of change versus the level of the overall trajectory. When focusing on pace as a rate of change, our findings provide clear evidence that perinatal adversity is associated with faster regional hippocampal growth; however, when focusing on the overall trajectory, it is unclear whether perinatal adversity is associated with hippocampal development that is, overall, temporally shifted. Without established benchmarks for normative hippocampal development in childhood, it is impossible to say conclusively whether children exposed to perinatal adversity have trajectories that lead them to meet developmental milestones earlier or later in development (i.e., accelerated or delayed patterns of developmental trajectories, respectively). Thus, from a perspective that focuses on trajectories, the possibility remains that adversity is implicated in a pattern of hippocampal development that is altered but not strictly characterized by an overall acceleration or delay (Rakesh et al., 2023). That is, perinatal adversity could be associated both with accelerated pace of hippocampal growth in childhood and with delayed hippocampal development in terms of later emergence of milestones beyond childhood, such as achieving a volumetric plateau or starting volumetric decline at a later age.

Our findings serve as a call for more longitudinal neuroimaging data given that these study designs are necessary for making strong conclusions about neurodevelopmental pace and about the degree to which nonlinear trajectories are temporally shifted. Indeed, we found that regional and whole brain growth was more rapid between 4.5 and 6 years of age than between 6 and 7.5 years of age. On the one hand, more neuroimaging assessments during a shorter developmental window, perhaps one that is characterized by more rapid change, may uncover stronger associations between adversity and neurodevelopmental pace than what we observed. Conversely, neuroimaging assessments spanning infancy through adolescence will lead to a more comprehensive understanding of neurodevelopmental pace and trajectories. For

### Table 1

<table>
<thead>
<tr>
<th>Paths</th>
<th>β (SE)</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome: Pace of Right Hippocampal Body Growth (Slope Factor)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>-0.55</td>
<td>-.09 (.04)</td>
<td>-.01,</td>
</tr>
<tr>
<td>ICV at Age 4.5</td>
<td>-0.49</td>
<td>-.17 (.04)</td>
<td>-.09,</td>
</tr>
<tr>
<td>Pace of ICV Growth</td>
<td>4.08</td>
<td>.10 (.04)</td>
<td>.03,18</td>
</tr>
<tr>
<td>Perinatal Adversity</td>
<td>0.22</td>
<td>.12 (.05)</td>
<td>.03,21</td>
</tr>
<tr>
<td>Outcome: Child Depressive Symptoms at Age 8.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.73</td>
<td>.05 (.05)</td>
<td>.06,15</td>
</tr>
<tr>
<td>Perinatal Adversity</td>
<td>0.44</td>
<td>.10 (.06)</td>
<td>.02,22</td>
</tr>
<tr>
<td>Pace of Right Hippocampal Body Growth</td>
<td>0.37</td>
<td>.15 (.05)</td>
<td>.05,26</td>
</tr>
</tbody>
</table>

Note: ***p<.001, **p<.01, *p<.05. B = unstandardized beta; β = standardized beta; SE = standard error; CI = confidence interval; ICV = intracranial volume (scaled by dividing ICV values by 1000); Sex coded as 0 = male and 1 = female.
example, this research could clarify when in development children start to demonstrate variation in hippocampal size as a function of the early environment. Our findings raise the possibility that perinatal adversity is implicated in hippocampal structural development characterized by slower initial growth that leads to reduced regional volume in early childhood, followed by accelerated growth that persists at least through childhood. That is, the pace of hippocampal change may speed up and slow down at different points in development.

Consistent with research suggesting that perinatal adversity has an enduring influence on risk for depression (Gotlib et al., 2023; Lund et al., 2020), we found that children exposed to higher levels of perinatal adversity reported more severe depressive symptoms at age 8.5. Further, we found that this association was mediated by faster pace of right hippocampal body growth, a pathway that was independent of effects related to the development of total intracranial volume and sex. These results provide support for the perspective that early life adversity is biologically embedded in a manner that increases risk for negative developmental sequelae (Nelson and Gabard-Durnam, 2020). Accelerated pace of growth in a specific hippocampal region may serve as a neurodevelopmental pathway that connects perinatal adversity with children’s depressive symptoms. While hippocampal volume development may reflect, in part, episodic memory and emotion regulation function (Barch et al., 2019), further research is necessary to identify the specific psychological processes related to faster right hippocampal body growth involved in linking perinatal adversity with children’s depression.

Although not part of our original aims, the results of supplemental analyses suggested that perinatal adversity and resource scores interact to predict pace of right hippocampal body growth in a manner consistent with resilience theory (Masten et al., 2021). Specifically, perinatal resources may buffer children from the association between exposure to high perinatal adversity and accelerated pace of right hippocampal body growth. We believe that these findings should be interpreted with caution given the lack of independence between the adversity and resource scores which, arguably, could preclude considering adversity and resources as independent sets of experiences and distinct predictors. Nonetheless, future studies of neurodevelopment should systematically test different resilience processes during the perinatal period and whether specific resources compensate for, versus buffer against, adversity effects.

We note several limitations of this study. First, we used a cumulative score approach to evaluate perinatal adversity relative to resources, considering both psychosocial and biological factors. This approach is based on the perspective that adversity and resources accumulate across multiple levels, and that resources can offset the effects of adversity (Evans et al., 2013; Han et al., 2023; Masten et al., 2021). It is important to acknowledge, however, that our cumulative scores of adversity and resources include some overlapping components (although these components were used to assess different aspects of perinatal experiences and conditions in the cumulative adversity and the resource scores). Thus, it is unclear whether contrasting cumulative adversity and resources is the most suitable approach for our data and analyses. As a
related point, there is a debate in the field regarding how to best conceptualize and measure adversity (McLaughlin et al., 2021; Smith and Pollak, 2021); further, recent theoretical models propose that faster or slower developmental pace may be expected in the context of different types of adversity (Roubinov et al., 2021). Future studies of perinatal adversity and pace of neurodevelopment should consider different types and dimensions of exposure, but also incorporate measures of resources. Second, our findings do not provide causal evidence for the effects of perinatal adversity on hippocampal development and on depressive symptoms. Other studies, such as those focused on the long-term effects of early life institutionalization (VanTieghem et al., 2021; Wade et al., 2022), could permit causal conclusions to be drawn, although it is not clear whether the experience and effects of institutionalization are comparable to those of perinatal adversity as assessed in our study and community sample. Third, we do not know whether our findings are specific to perinatal adversity or are due to broader exposure during a different developmental window. Given that children may experience similar environmental conditions across childhood, individual differences in adversity may be stable across time. Future research should include repeated assessments of adversity to examine the chronicity and timing of exposure. Lastly, our results are specific to child-reported depressive symptoms as measured by the CDI-2. Research focusing on parent-reported child depressive symptoms, or that capture other depressive symptoms that are not assessed by the CDI-2, would extend our findings.

Despite these limitations, these data show that perinatal adversity is associated with altered trajectories of regional hippocampal volume in childhood. In particular, perinatal adversity is implicated in reduced volume in the hippocampal body in early childhood, but also in a faster pace of growth across childhood. Faster growth of the right hippocampal body may serve as a neurodevelopmental pathway by which perinatal adversity is associated with depressive symptoms in late childhood. These findings highlight the importance of using longitudinal neuroimaging data to define neurodevelopmental pace as a rate of change versus a temporal shifting of developmental milestones or trajectories.

Funding

Funding was provided by the Singapore National Research Foundation (NMRC) under the Open Fund Large Collaborative Grant administered by the Singapore Ministry of Health’s National Medical Research Council. Additional funding was provided by the Agency for Science, Technology and Research (A*STAR) Strategic Research Program Brain-Body Initiative, the Hope for Depression Research Foundation (M.J.M.), the NMRC Transition Award (MOH-001273-00; A.P.T.), and the National Institute of Mental Health (grant R37MH101495; I.H.G.).

CRediT authorship contribution statement

Ian H. Gotlib: Writing – review & editing, Methodology, Funding acquisition. Yap-Seng Chong: Investigation, Funding acquisition, Conceptualization. Marielle V. Fortier: Resources, Investigation, Funding acquisition, Conceptualization. Ai Peng Tan: Writing – review & editing, Supervision, Investigation, Conceptualization. Michael J. Meaney: Writing – review & editing, Supervision, Funding acquisition, Conceptualization. Peter D. Gluckman: Funding acquisition, Conceptualization. Jonas Miller: Writing – original draft, Visualization, Methodology, Formal analysis.

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.

Acknowledgments

We thank the GUSTO team and all the families who participated in this study.

Data statement

The data for this paper are derived from the GUSTO longitudinal birth cohort study. Restrictions apply to data availability. However, the data can be requested at (https://gustodatavault.sg/), which will require a project description and scientific reasoning. Alternatively, the data used for the specific analyses in this paper can be requested from the corresponding author.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2024.101392.

References


