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Microbiome Signature of Posttraumatic Stress Disorder and Resilience in Youth

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Objective: Identifying biomarkers that can distinguish trauma-exposed youth at risk for developing posttraumatic pathology from resilient individuals is essential for targeted interventions. As trauma can alter the microbiome with lasting effects on the host, our longitudinal, multimeasure, cross-species study aimed to identify the microbial signature of posttraumatic stress disorder (PTSD). ***Method:*** We followed children exposed to war-related trauma and matched controls from early childhood (M_{age} = 2.76 years, N = 232) to adolescence (M_{age} = 16.13 years, N = 84), repeatedly assessing posttraumatic symptomatology and maternal caregiving. In late adolescence, we collected fecal samples from mothers and youth and assessed microbiome composition, diversity, and mother–child microbial synchrony. We then transplanted adolescents' fecal samples into germ-free mice to determine if behavioral changes are observed. ***Results:*** Youth with PTSD exhibited a distinct gut microbiome profile and lower diversity compared to resilient individuals, and microbiome diversity mediated the continuity of posttraumatic symptomatology throughout development. Low microbiome diversity correlated with more posttraumatic symptoms in early childhood, more emotional and behavioral problems in adolescence, and poor maternal caregiving. Youth with PTSD demonstrated less mother–child microbial synchrony, suggesting that low microbial concordance between mother and child may indicate susceptibility to posttraumatic illness. Germ-free mice transplanted with microbiomes from individuals with PTSD displayed increased anxious behavior. ***Conclusions:*** Our findings provide evidence that the trauma-associated microbiome profile is at least partially responsible for the anxiety component of the PTSD phenotype and highlight microbial underpinnings of resilience. Further, our results suggest that the microbiome may serve as additional biological memory of early life stress and underscore the potential for microbiome-related diagnosis and treatment following trauma.

Clinical Impact Statement

As trauma exerts lasting effects on the brain, health, and behavior, it is important to pinpoint biomarkers that can distinguish youth prone to posttraumatic stress disorder (PTSD) from resilient individuals. We followed children exposed to war-related trauma and examined their gut microbiome. Our results, including some derived from humanized mouse models, reveal that microbiome composition and diversity differentiate youth with and without PTSD, that mother–child microbiome synchrony is lower in cases of PTSD compared to resilient adolescents, and that sensitive parenting buffers the development of posttraumatic pathology. Results may contribute to the early identification of high-risk individuals and the development of novel psychobiotic interventions.

Keywords: posttraumatic stress disorder, trauma exposure, gut microbiome, mother–child relationship, germ-free mice

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The human study was approved by Reichman University's Institutional Review Board, and all parents signed informed consent. All animal procedures were approved by Bar-Ilan University's Azrieli Faculty of Medicine's Institutional Animal Care and Use Committee (permit 47-07-2020).

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to them containing information that could compromise research participants' consent.

continued

Since the first diagnosis of posttraumatic stress disorder (PTSD), the early identification of individuals at risk for developing posttraumatic pathology from those exposed to the same trauma who are more resilient has been a pressing challenge in psychiatry, public health, education, governance, and the military (Friedman et al., 2007). It has been suggested that the broad posttraumatic pathology is underpinned by susceptibility of specific neural and biological systems and typically involves exposure to heightened levels of stress in early life, when such systems undergo rapid maturation (Karl et al., 2006). Still, the correlative nature of human neurobiological research and the challenge of recruiting large cohorts of individuals exposed to the same trauma over time render research on the pathophysiology of PTSD a difficult endeavor. Studies are only beginning to chart links between specific biological indices and the posttrauma phenotype, which comprises the characteristics, symptoms, and behaviors that may develop after exposure to traumatic events. Particularly lacking are studies that can pinpoint biomarkers that distinguish posttraumatic individuals from resilient ones following war-related trauma exposure (Hemmings et al., 2017; Laudani et al., 2023; Levert-Levitt et al., 2022).

Our conceptual model on resilience, resulting from 2 decades of research on children growing up in contexts of war-related trauma and other adversities, contends that resilience goes beyond the mere absence of PTSD. Resilience involves a developmental perspective that integrates biobehavioral indicators of adaptation, stress management, and endurance (Feldman, 2020). Resilience stems from the provisions embedded within the parent–infant bond, relies on neurobiological systems that enable humans to collaborate and jointly face hardships, and comprises three tenets: plasticity, sociality, and meaning (Feldman, 2020, 2021, 2023). Behavioral, neural, hormonal, and immune biomarkers of resilience become particularly salient during periods of key developmental transitions, such as infancy and the transition to adolescence (Feldman, 2020; Feldman & Vengrober, 2011; Halevi et al., 2016; Yirmiya et al., 2020, 2023). Across development, resilience is also sustained by neurohormonal systems, such as the hypothalamic–pituitary–adrenal axis, which regulates the stress response, the oxytocin system, and markers of immunity (Halevi et al., 2017; Ulmer-Yaniv et al., 2018; Yirmiya et al., 2018). Resilience can shape the brain's fundamental architecture (Zeev-Wolf et al., 2019) and social functioning (Levy et al., 2019), and was found to be mediated by the mother's sensitive and synchronous caregiving (Halevi et al., 2017; Yirmiya et al., 2018).

A core mechanism of resilience is biobehavioral synchrony, the synchronized functioning of physiological and behavioral processes between affiliative partners (Feldman, 2017). Biobehavioral synchrony develops within the mother–infant bond and involves the coordination of nonverbal behavior, synchronized release of hormones, matching of heart rhythms, and coupling of activity between the two brains (Endevelt-Shapira & Feldman, 2023; Feldman, 2007; Feldman, Gordon, & Zagoory-Sharon, 2011; Feldman, Magori-Cohen, et al., 2011). These synchronized behaviors foster emotional regulation, stress management, and mental health across development and into adulthood, including in contexts of trauma and adversity (Feldman, 2012, 2020; Ulmer-Yaniv et al., 2023). The mother's sensitive style, including her ability to perceive, interpret, and appropriately respond to the child's cues in ways that nurture security and emotional connection, is critical for the establishment of biobehavioral synchrony. Maternal sensitivity functions as a buffer against the development of stress-related pathologies, particularly in contexts of early life stress, enhances biobehavioral synchrony, and boosts resilience and positive psychological outcomes (Birk et al., 2022; Feldman, 2012, 2015). Although synchrony has been explored across multiple developmental stages, high-risk conditions, and physiological systems (Bell, 2020; Birk et al., 2022), there are currently no studies that tested the associations between maternal caregiving, biobehavioral synchrony, and the gut microbiome. Apart from a single study that investigated gut microbiome composition similarity between mother–child dyads in children with or without autism spectrum disorder (Li et al., 2019), the role of mother–child microbial synchrony in psychopathology susceptibility versus resilience in general and PTSD in particular remains unexplored.

In contrast to the lack of research on mother–offspring microbial synchrony, there is a growing body of research connecting other parameters of the gut microbiome to stress- and trauma-related psychopathologies. Animal studies identified differences in the gut microbiome between stress-susceptible and stress-resilient rats (Tanelian et al., 2022). During both the pre- and posttrauma periods, gut microbiome abnormalities characterized susceptible mice who exhibited persistent PTSD-related phenotypes in comparison with resilient mice (Laudani et al., 2023). Several rodent studies employed

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transplantation techniques of fecal samples from stressed animals to nonstressed recipients and showed alterations in recipient behavior (for review, see Ke et al., 2023). However, to date, no study has examined the potential causal role of the gut microbiome in the development of PTSD phenotypes through the transplantation of microbiome from humans with and without PTSD into rodents. Therefore, there is a clear need for studies that investigate the causation between stress-related psychopathologies and the gut.

Despite the lack of cross-species research on the involvement of the microbiome in PTSD, correlative human studies described the associations between early-life stress and the developing microbiome (Hantsoo & Zemel, 2021). These studies postulated that the microbiome may mediate the long-term effects of early-life stress on the emergence of stress-related pathologies in later life (O'Mahony et al., 2017). Existing research suggests that lower microbial diversity as well as specific bacterial alterations are associated with stress-related pathologies (Bajaj et al., 2019; Foster et al., 2017; Levert-Levitt et al., 2022; Madan et al., 2020). Studies have also addressed the gut–brain axis and described how an organism's stress response can influence it (Agusti et al., 2023; Gao et al., 2022). Research has similarly pointed to the involvement of the gut microbiome in the onset and chronicity of stress-related pathologies and highlighted the microbial underpinnings of stress and mental health as an area in need of further research (Ke et al., 2023; Malan-Muller et al., 2018).

The main theory guiding our longitudinal, cross-generational, multimeasure study is that the microbiome plays a key role in the posttrauma pathology and mediates the development of at least part of the PTSD phenotype from early childhood to adolescence (Foster et al., 2017; Leclercq et al., 2016). Our investigation centered on three critical aspects of the microbiome: composition, diversity, and mother–child microbial synchrony. Consistent with our biobehavioral synchrony model (Feldman, 2012, 2017), we explored whether mother–child microbial synchrony is associated with fewer child PTSD symptoms and may thus serve as a mechanism of resilience.

To our knowledge, this is the first study that followed children exposed to chronic trauma throughout their development and examined the microbial underpinnings of posttrauma and resilience in youth exposed to the same traumatic events. Also of note is the gap in human microbiome research, which does not consider the key role of maternal caregiving on the developing microbiome in the context of trauma or general psychopathology. Studies have repeatedly shown that the mother's sensitive style is individually stable across development and noted the contribution of such stability to the child's well-being and resilience (Deans, 2020; Rodrigues et al., 2021). The mother's sensitive style and the child's stress-related pathologies also exert bidirectional influences on each other over time and jointly shape susceptibility versus resilience (Yirmiya et al., 2021). Maternal sensitive caregiving has been repeatedly identified as a protective factor against the development of psychopathology following trauma and other adversities (Ma et al., 2022), and findings from the current cohort at previous stages yielded similar results (Feldman et al., 2013; Ulmer-Yaniv et al., 2018; Yirmiya et al., 2018).

We propose four overall hypotheses, the first two relating to the period of adolescence and the last two adopting longitudinal and mechanistic approaches, respectively. First, we expected differences in microbiome composition between (a) adolescents and mothers exposed to chronic trauma versus nonexposed controls and (b) between adolescents and mothers exposed to chronic trauma who did or did not develop posttrauma symptoms. Second, consistent with our biobehavioral synchrony model, we hypothesized that higher mother–adolescent microbial synchrony would be associated with fewer adolescent PTSD symptoms. Third, we hypothesized that children's posttraumatic stress symptoms in early childhood and adolescence, as well as maternal sensitivity throughout development, would be associated with microbiome characteristics. We further expected that these microbiome features would mediate the consolidation of PTSD over time, from early childhood to adolescence. Finally, utilizing germ-free mice transplanted with feces from adolescents who exhibited posttraumatic symptoms and from resilient adolescents, we hypothesized that mice implanted with feces of participants with posttrauma symptomatology would exhibit features of anxious behavior as compared to those implanted with feces from more resilient adolescents (see Supplemental Methods for more details on fecal microbiome transplantation in health and disease research).

Method

Human Study Cohort: Participants

We recruited 232 mother–child dyads, comprising 148 trauma-exposed and 84 control (47.6% males and 47.1% firstborns). Trauma-exposed children lived in frontline neighborhoods in Sderot, Israel, a town located 10 km from the Gaza border. These children have been exposed to repeated rocket and missile attacks every few months since birth and to extended military operations requiring extensive periods in shelters that erupt every 2–3 years. The rocket attacks, often indiscriminate and unpredictable, have subjected the residents of Sderot to a relentless cycle of fear, stress, and insecurity (Halevi et al., 2016). The abrupt sound of air raid sirens serves as a distressing reminder of the imminent danger and prompts residents to seek shelter within seconds. As a result, daily life in Sderot is marked by constant vigilance and the necessity of staying close to safe spaces to protect against rocket fire. In addition to the persistent rocket attacks, the residents of Sderot have also faced the threat of tunnel infiltrations originating from the Gaza Strip. These tunnels are dug by militants and are intended for various purposes, such as smuggling weapons and explosives as well as launching sudden attacks within Israeli territory.

Control dyads consisted of families residing in towns in central Israel with comparable sociodemographic characteristics who were not exposed to these chronic war-related events (Feldman & Vengrober, 2011). Children in both groups were screened for records of other trauma (e.g., car accidents, burns) and physical abuse or neglect, as well as for adoption status, all of which were study exclusion factors, but very few such cases were found (in total, three children, 1.27% of all screened participants). We matched control dyads to the exposed group based on age, sex, birth order, maternal and paternal age and education, maternal employment, and marital status (Feldman & Vengrober, 2011; see more information in Supplemental Data). Participants were recruited using paper flyers displayed in kindergartens and community centers in the target areas. We also utilized a snowball sampling method that encouraged participants to refer their neighbors and acquaintances to the study, and this broadened our recruitment reach within the community. All stages of the study were approved by the university's

institutional review board, and at each stage, parents provided their informed consent after we fully described the study to them.

Procedure

Following recruitment, mothers received a phone call from research assistants, who provided a concise overview of the study's goals and the procedures to be conducted during the home visit. We followed up with these mothers and their children five times, from early childhood to late adolescence: early childhood: $n = 232$, $M_{age} = 2.76$ years, $SD = 0.91$; middle childhood: $n = 210$, $M_{age} = 7.68$ years, $SD = 0.7$; late childhood: $n = 177$, $M_{age} = 9.3$ years, $SD = 1.41$; early adolescence: $n = 111$, $M_{age} = 11.66$ years, $SD = 1.23$; late adolescence: $n = 84$, $M_{age} = 16.13$ years, $SD = 1.22$. Attrition was mainly related to the inability to locate families or families moving out of Sderot. No sociodemographic differences were found between continuing or noncontinuing families (Yirmiya et al., 2023), and the final sample included 54 exposed and 30 control dyads with data for all timepoints. Trained clinical psychologists conducted home visits in early childhood, late childhood, and late adolescence. In middle childhood, we interviewed participants over the phone, and in early adolescence, participants visited the laboratory. In early childhood and late adolescence, both full PTSD diagnosis and PTSD-related symptoms were evaluated. We coded mother–child behavioral interactions from early childhood, late childhood, and late adolescence using the well-validated coding interactive behavior system (CIB; Feldman, 1998; see Supplemental Methods). In late adolescence, trained clinicians conducted psychiatric interviews and left a stool collection kit for mothers and children to self-collect their stool samples (FloraPrep, Admera Health, South Plainfield, New Jersey; see Supplemental Methods and Figure 1a for timeline).

Measures

PTSD in Early Childhood

Mothers were interviewed by trained clinicians about their children's posttraumatic symptoms based on the diagnostic criteria for young children proposed by the Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood (DC:0-3R; Zero to Three, 2005). Mothers rated their child's symptoms from a list of 58 posttraumatic signs, which was built after a year-long pilot study in Israeli and Palestinian war-affected areas. This study involved in-depth interviews with parents, caregivers, and therapists about children's common reactions to repeated war-related violence (Feldman et al., 2007; see more details in Supplemental Methods). We utilized a continuous variable to measure the number of symptoms ("early childhood symptoms") and a dichotomous variable for PTSD diagnosis ("early childhood diagnosis"), based on criteria including exposure to trauma, hyperarousal, reexperience, avoidance, and the presence of symptoms from the "new fears and aggression" category.

Psychiatric Diagnosis in Adolescence

We used the Developmental and Well-Being Assessment (DAWBA) to diagnose adolescents' Axis-I PTSD and internalizing disorder in early adolescence (Goodman et al., 2000). The DAWBA is a well-validated measurement, including cultural relevant validation by a large epidemiological study in Israel (Mansbach-Kleinfeld et al., 2010). We also included severe PTSD symptoms without a full-blown PTSD diagnosis if they were accompanied by anxiety and/or depression diagnoses. The DAWBA was administered to mothers by clinical psychologists and supervised by a child psychiatrist, blind to all other information. Cases were conferred with reliability exceeding 85%.

Behavioral and Emotional Problems

In late adolescence, mothers completed the Child Behavior Checklist 6–18 years (CBCL; Achenbach & Edelbrock, 1983), a well-validated questionnaire of a child's psychological symptoms yielding externalizing, internalizing, and total behavior symptom scores, which is the most widely used instrument for assessing behavioral and emotional problems in children with established reliability and validity (Dutra et al., 2004). The CBCL has been translated into Hebrew and has been used in a number of Israeli studies of child development (Apter et al., 1988; Dollberg & Hanetz-Gamliel, 2022). The internal consistency and reliability of the CBCL total score scale were assessed using Cronbach's α, yielding a coefficient of $\alpha = .955$, indicating excellent internal consistency. The checklist consists of 113 items related to eight syndrome scales, including anxious/depressed, depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior.

Maternal Psychiatric Diagnosis at Early Adolescence

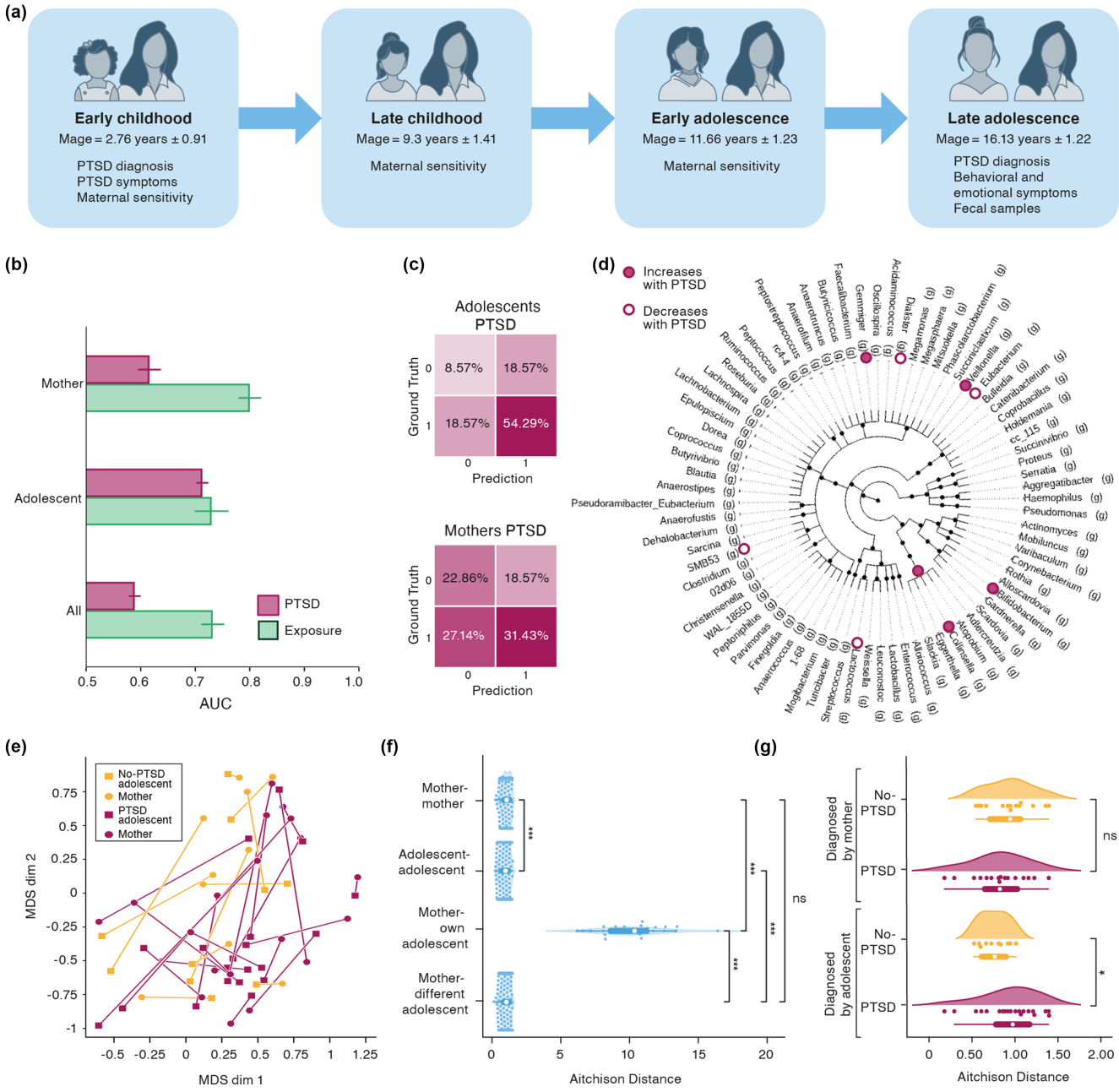
Mothers were diagnosed using the Structured Clinical Interview for *Diagnostic Manual of Mental Disorder and Disease*, *fourth edition* (*DSM-IV*) Axis-I Disorders (SCID-I; First et al., 1997). This is a semistructured, clinician-administered diagnostic interview that includes modules corresponding to major *DSM* psychiatric classifications with high reliability and validity (Zanarini et al., 2000). The SCID has been used in numerous studies, and its Hebrew version has also been validated (Shalev et al., 1996). Similar to the DAWBA, interviews were conducted by clinical psychologists with reliability scores of >0.85 between the interviewer and the supervising psychiatrist.

Maternal Sensitivity

In early childhood, late childhood, and early adolescence, mothers and children were videotaped in age-appropriate tasks that were later coded offline using the CIB manual (Feldman, 1998). In early childhood, we videotaped 10 min of mother–child free play interactions. The experimenter placed a box of preselected toys in front of the mother, and instructions were "Play with your child as you normally do" (Feldman et al., 2013). In late childhood, we used the well-validated positive interaction paradigm in which mother and child are given 7 min to plan the "best day ever" to spend together (Halevi et al., 2017). In early adolescence, dyads visited the laboratory and were asked to play an "Etch a Sketch" game together for 7 min. Each partner controlled one knob, and the two collaborated in drawing a joint picture (Yirmiya et al., 2018). The CIB is a well-validated global (macro) rating tool employed in numerous studies across various cultures, ages, and psychopathologies with

Figure 1

War-Related Trauma Exposure and PTSD Are Linked With Microbial Composition, Diversity, and Synchrony



Note. (a) Timeline and study parameters. (b) Trauma exposure and PTSD predicted from gut microbial composition for all participants, only adolescents, and only mothers ($n = 65$; 31 mothers, 34 adolescents). (c) Confusion matrix of predictions of the adolescents' PTSD model (upper) and the mothers' PTSD model. The *x*-axis represents the predictions (0 = no PTSD and 1 = PTSD). (d) Taxa tree representing the input microbiome of the adolescents' PTSD XGBOOST model. Big circles represent taxa with significant feature importance, according to the XGBOOST model. Empty circles indicate lower and filled circles indicate higher bacterial abundance among PTSD youth. (e) Illustrative representation of the Aitchison distance of the log normalized amplicon sequence variants at the genus level of the mother and her own adolescent. High microbial synchrony is defined by smaller distances between dyads. (f) Comparison of Aitchison distances between all mothers, all adolescents, mothers and their adolescents, and mothers and other adolescents. Squares denote children, and circles denote mothers (*n* of mother–adolescent dyads = 30). (g) Comparing microbial synchrony between dyads with and without adolescent PTSD and between dyads with and without maternal PTSD. PTSD = posttraumatic stress disorder; AUC = area under the curve; ns = nonsignificance; MDS dim = Multidimensional Scaling dimension. See the online article for the color version of this figure.

$^{*}p < .05$. $^{***}p < .001$.

good psychometric properties (Feldman, 2021). The construct of maternal sensitivity was used to assess maternal caregiving behavior and included the following constructs: maternal acknowledgment of her child's social communication, consistent caregiving style, appropriate range of affect, recognition of distress or changing state, expansion of child's nonverbal or verbal signals, creativity, maternal supportive presence, and affectionate touch. The maternal sensitivity construct was calculated as the average from the interactions in early childhood, late childhood, and early adolescence. Coding was conducted by two trained coders, blind to any other information, and exceeded 90% reliability on 20% of interactions for all coded behaviors (k = 0.82, range = 0.74–0.95). To assess the internal consistency of the different facets of maternal sensitivity, Cronbach's α values were calculated for each time point, resulting in values of .91, .87, .89, for early childhood, late childhood, and early adolescence, respectively.

Health and Diet

Prior to scheduling the home visits in late adolescence, mothers were asked whether they or their child had taken antibiotics in the past 6 months and about digestive problems, bowel diseases, COVID-19, and other medication use. Additionally, mothers reported on delivery type, breastfeeding (>1 month), antibiotic use during their children's first 6 months of life, children's vegetarian or picky eaters, and the presence of a pet at home. Home visits and subsequent fecal sample collection were scheduled only if mother and child did not take antibiotics in the preceding 3 weeks, had no infection, felt healthy, and were at least 1 week after their last menstrual period.

Microbiome Sequencing and Sequence Processing

We performed DNA extraction and 16S rRNA gene amplification and sequencing of the V4 region (Caporaso et al., 2012) for both human and mouse samples as previously reported (Pinto et al., 2023; see Supplemental Methods for workflow). Following sequencing, we analyzed microbial communities using QIIME2 (Bolyen et al., 2019). We demultiplexed reads by per-sample barcodes, and we corrected errors using the Divisive Amplicon Denoising Algorithm (Callahan et al., 2016). We then generated a phylogenetic tree. Next, for the machine learning and statistical analyses, we analyzed the human microbiome samples using the Microbiome Preprocessing Machine Learning Pipeline (Jasner et al., 2021). In the human analyses, we merged taxa data at the genus level using the mean procedure and applied log normalization. All analyses for mouse fecal samples were rarefied to 8,000 sequences. Further information and a list of terms related to the microbiome can be found in the Supplemental Material accompanying this article.

Data Analysis

We compared behavioral and psychiatric variables between exposed individuals and controls using chi-square tests and t tests and tested association among variables using Pearson and Spearman correlations. To predict exposure and PTSD from the gut microbiome (16S rRNA gene sequences) among adolescents, mothers, and all subjects together, we employed XGBOOST gb linear classification with the default genera (Brownlee, 2016) for mothers and adolescents together and separately. We split the data 50 times into training (80%) and test (20%) sets. We chose area under the curve (AUC) as our test metric. To assess the significance of our learning results, we employed a one-sample t test between the test AUC values obtained from 50 runs and the AUC of 0.5, representing a random model. Moreover, we then predicted the continuous CBCL from the microbiome using XGBOOST gb linear regression, reporting results as an average of 50 runs, similar to the above classification. Our metrics were R^2 as well as Spearman's correlation coefficient (SCC). We employed PICRUSt2 to predict functional changes in the gut microbiome (Douglas et al., 2020).

We calculated mother–adolescent microbial synchrony by Aitchison distance (Euclidean distance over centered log-ratio -transformed values) of amplicon sequence variants of the mother and her adolescent. High synchrony was defined as a lower Aitchison distance, while low synchrony was defined as a high mother–adolescent distance. To account for multiple measurements, we applied Bonferroni correction to all significance analyses. As a result, all reported p values have been adjusted to address multiple comparisons. We examined differences in Shannon's α diversity scores (i.e., variety of microbes in a single sample; see Supplemental Table S3 for more details) between groups in early childhood using a Kruskal–Wallis H test, specifically comparing exposed with PTSD versus exposed without symptoms versus controls, and used Mann–Whitney post hoc tests. Gender, body mass index, and all other health and diet variables were added as covariates.

Finally, to test the direct and indirect paths from children's PTSD in early childhood to emotional problems in late adolescence (CBCL) via the late adolescent microbiome, we formulated two models. In the first, we conducted a path analysis using IBM SPSS Amos 25.0 (IBM Corporation, Armonk, New York). Child age and gender were controlled, and missing data were handled using the maximum likelihood method, a state-of-the-art method for obtaining estimates of the parameters. Indicators of model fit were nonsignificant chi-square values; root-mean-square error of approximation equal to or less than .06; and comparative fit index, with Tucker–Lewis index values > 0.95 considered good fit (Hu & Bentler, 1999). To assess the significance of the mediation effects, we used a procedure recommended by A. F. Hayes (2017) and calculated the 95% confidence intervals (CIs) of the indirect effects based on 5,000 bias-corrected and accelerated bootstrapped samples. Indirect effects in which zero is not included in the 95% CI indicate a significant effect at $\alpha < .05$. To confirm that our findings were not affected by missing data imputation, we ran the same linear mediation model using the PROCESS macro for SPSS (v. 3.4.1; A. Hayes, 2013). PROCESS employs bootstrapping calculations, a nonparametric resampling procedure, which provides a powerful method of obtaining confidence limits for specific indirect effects. For this analysis, bias-corrected standard errors and confidence intervals were generated using 5,000 bootstrapped samples (Preacher & Hayes, 2008). Mediation was considered present when the 95% CI for the estimation of the indirect effect did not contain zero. In the second model, we predicted CBCL scores at adolescence from PTSD diagnosis in early childhood and the microbiome composition utilizing two alternative Ridge regression models (see Supplemental Methods). Analyses were conducted using QIIME2, SPSS, and Python.

Mouse Phenotypic Transfer Experiment

To confirm the microbiome's role in the PTSD-resilience phenotype, we performed fecal microbiome transplants (FMTs)

using fecal samples from trauma-exposed adolescents divided into two groups: (a) PTSD: adolescents with a full clinical PTSD diagnosis, and (b) no diagnosis: adolescents without any clinical diagnosis (Figure 2a and Supplemental Table S2). These samples were transplanted into 6-week-old germ-free mice (see Supplemental Methods). Three weeks after the transplant, we collected fecal samples from the mice and examined anxiety-related behavior using the elevated plus maze (Kraeuter et al., 2019). We recorded the number of times mice entered each of the open/closed arms, which is a well-validated measure of anxious behavior (Walf & Frye, 2007). All animal procedures were approved by the Medicine Institutional Animal Care and Use Committee Committee (permit 47-07-2020).

Statistical Analyses of Mouse Fecal Microbiome

We characterized the fecal microbiome of mice following the FMT experiment as described above and calculated Faith's phylogenetic diversity (Faith, 1992), Jaccard similarity, and Bray–Curtis dissimilarity. We tested between-group differences using Permutational Multivariate Analysis of Variance. We also examined phylogenetically based β-diversity metrics, which consider the phylogenetic relationship of identified bacteria in calculations of similarity, and did not find any differences between groups, so we do not present them here. Last, we performed differential abundance testing Analysis of Composition of Microbiomes with default parameters; Mandal et al., 2015).

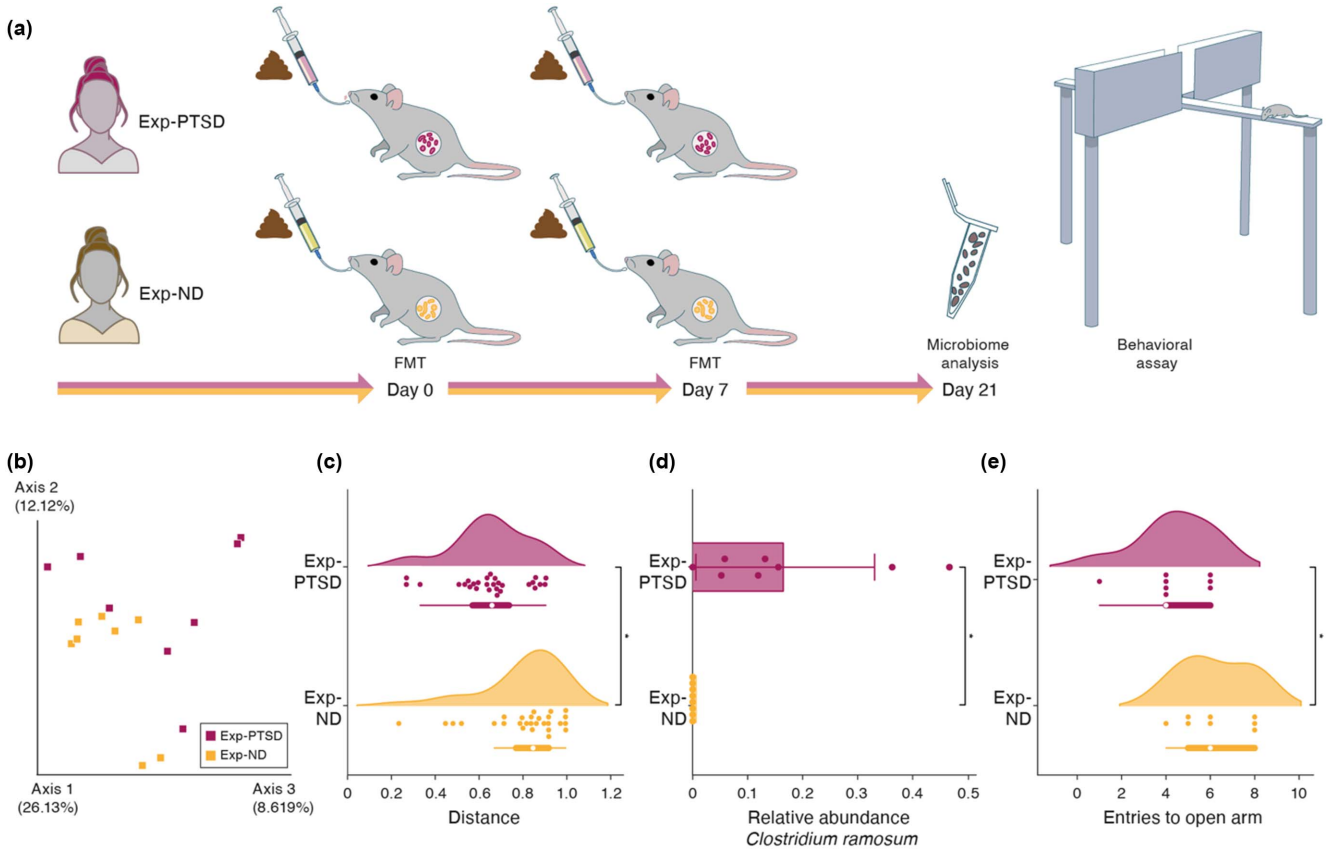
Results

Differences Between War-Exposed and Control Dyads in Child Symptoms, PTSD Diagnosis, and Maternal Caregiving in Early Childhood and Adolescence

In early childhood, war-exposed children had significantly more PTSD symptoms, $t(82) = -6.03$, $p < .001$, and a greater likelihood of

Figure 2

Germ-Free Mice Implanted With Feces of Youth With PTSD Exhibit a Distinct Microbial Profile and Anxious Behavior



Note. (a) The germ-free mouse model was used to determine the role of the microbiome in PTSD. Germ-free mice received two fecal microbiome transplants (FMTs) from war-exposed adolescents with (pink) and without (yellow) PTSD, and 3 weeks later, anxious behavior was tested with an elevated plus maze behavioral assay. (b) Principal coordinates analysis based on Jaccard distances showing a significant difference in β diversity of the post-FMT mouse microbiome. (c) Microbiome distance comparisons calculated using Bray–Curtis dissimilarities also showed a significant difference in post-FMT mouse microbiome. (d) Differential abundance analysis at the species level revealed differences in *Clostridium ramosum* in post-FMT mice ($W = 82$). (e) *t* test between post-FMT mice with ($n = 8$) and without ($n = 8$) PTSD in the number of entries to the open arms of the EPM. EPM = elevated plus maze; PTSD = posttraumatic stress disorder; Exp-PTSD = exposed with PTSD; Exp-ND = exposed with no PTSD. See the online article for the color version of this figure.
* $p < .05$.

clinically diagnosed PTSD, $\chi^2(1) = 84.00$, $p < .001$, than controls. In late adolescence, exposed adolescents had more emotional and behavioral problems according to the CBCL, $t(82) = -3.03$, $p = .001$, and a greater likelihood of clinically diagnosed PTSD, $\chi^2(1) = 12.85$, $p < .001$, as compared with control adolescents. Trauma-exposed mothers exhibited significantly less sensitive caregiving across development compared with control mothers, $t(82) = 2.04$, $p = .044$. A further breakdown of the exposed group into exposed with PTSD (Exp-PTSD) and exposed with no diagnoses (Exp-ND) in comparison with the control group in main study variables is presented in Table 1.

Hypothesis 1: PTSD and Emotional and Behavioral Problems Are Reliably Identified Using the Microbiome Composition in Adolescence

To validate the association between war exposure, its psychiatric sequelae, and the composition of the gut microbiome in late adolescence, we first tested whether the microbiome can be used to characterize PTSD versus resilient adolescents. We were able to classify both war exposure (vs. controls) and PTSD (vs. resilient children) in late adolescence based solely on microbial community composition for the entire sample (mothers and adolescents together), as well as for adolescents and mothers separately (Figure 1b). AUC (significant according to one-sample *t* test) values for exposed children and mothers were 0.72 and 0.8, respectively, and 0.75 for mother and children together. AUC (significant according to one-sample *t* test) values for children and mothers' diagnoses were 0.71 and 0.63, respectively, and 0.58 for the entire sample together. Adolescents' war exposure status and PTSD diagnosis were both strongly linked with their microbial profile, whereas among mothers, the microbial profile was more closely associated with exposure status than with maternal PTSD (Figure 1c, Supplemental Figure S1a–S1d, and Supplemental Table S1).

Classifier models identified eight important genera (four positively and four negatively correlated with PTSD) that differed in abundance in the adolescent PTSD group compared to those without PTSD (Figure 1d), and nine important genera characterized youth exposed to war compared to controls (Supplemental Figure S1e). PICRUSt2 predicted increased nitrate reductase-associated metabolites (KEGG IDS: K00370, K00371, K00373, and K00374) in the PTSD group (Supplemental Figure S1f). These metabolites are associated with several KEGG pathways (map00910—nitrogen metabolism, map01100—metabolic pathways, map01120—microbial metabolism in diverse environments, and map02020—two-component system), and nitrite reductase activity can increase nitrite. We were also able to characterize adolescents' CBCL scores based on their microbial community using an XGBOOST regression model ($r = 0.59$, $R^2 = 0.28$, $p = .004$).

Hypothesis 2: PTSD Is Associated With Less Mother–Adolescent Microbial Synchrony

To test microbial synchrony, we examined the distances between mothers' and adolescents' microbiome composition using the Aitchison distance of the microbiome (Figure 1e, referred to as "synchrony"). Overall, adolescents were more similar to their own mothers than to other mothers, and mothers were more similar to their own adolescents than to other mothers in our cohort (Figure 1f). Comparing microbial synchrony in dyads of adolescents with and without PTSD revealed that adolescents with PTSD had microbial composition less similar to that of their mothers as compared with dyads without PTSD diagnosis, $t(32) = 1.71$, $p = .049$. This difference also remained significant when gender, body mass index, and all other health and diet variables were added as covariates. Comparing microbial synchrony between dyads with and without maternal PTSD diagnosis did not reveal a significant effect (Figure 1g). Similarly, there was no difference in microbial synchrony between exposed and control dyads, suggesting that the lower microbial synchrony in cases of adolescent PTSD is diagnosis-specific. To verify that microbial synchrony is not just associated with overall microbiome dysbiosis, we used sensitivity analyses, dividing the data into four groups based on child/maternal diagnosis, and found no significant differences between the PTSD and no-PTSD distances from the average in both mothers and adolescents (Supplemental Figure S1g). To ensure that synchrony is not

Table 1
Group Differences in Sociodemographic and Main Study Variables

Late adolescence diagnosis	Exp-PTSD ($n = 32$)	Exp-ND ($n = 22$)	No-TR ($n = 30$)	F/χ^2
Age (late adolescence)	15.95 (1.28)	16.53 (1.14)	16.01 (1.20)	$F(2) = 4.97$, $p = .194$
Gender (male)	16 (50%)[a,b]	16 (72.7%)[a]	9 (30%)[b]	$\chi^2 = 9.30$, $p = .010$
Delivery type	7 (25%)	3 (14%)	4 (14.8%)	$\chi^2 = 1.28$, $p = .528$
Breastfeeding more than a month (yes)	23 (82.1%)	20 (95.25%)	21 (77.8%)	$\chi^2 = 2.85$, $p = .240$
BMI	23.25 (5.17)	22.50 (3.40)	22.27 (2.99)	$F(2) = .43$, $p = .647$
Pet	8 (28%)	5 (23%)	8 (29.6%)	$\chi^2 = .22$, $p = .896$
Antibiotics at the six first months of life (yes)	4 (14.8%)	3 (14.3%)	4 (14.8%)	$\chi^2 = .003$, $p = .998$
Microbiome diversity	4.76 (.64)	5.26 (5.2)	5.30 (.55)	$F(2) = 3.17$, $p = .056$
Microbial synchrony	10.86 (2.36)	9.51 (2.26)	9.50 (1.50)	$F(2) = 1.45$, $p = .251$
Maternal sensitivity	3.65 (.43)[a]	4.15 (.57)[b]	4.10 (.50)[b]	$F(2) = 8.96$, $p < .001$
PTSD symptoms in early childhood	61.19 (11.46)[a]	49.68 (6.02)[b]	45.93 (4.83)[b]	$F(2) = 28.50$, $p < .001$
PTSD full diagnosis in early childhood	17 (68.0%)	15 (51.7%)		$\chi^2 = 1.47$, $p = .225$
CBCL in late adolescence	30 (19.77)[a]	11.19 (8.29)[b]	10.83 (10.33)[b]	$F(2) = 16.18$, $p < .001$

Note. PTSD was assessed using the Developmental and Well-Being Assessment. PTSD = posttraumatic stress disorder; Exp-PTSD = exposed with PTSD; Exp-ND = exposed with no PTSD; No-TR = no trauma exposure (control); BMI = body mass index; CBCL = Child Behavior Checklist (6–18 years). Groups with different superscripts are significantly different from each other ($p < .05$). Groups with the same superscript are not significantly different from each other.

induced by any other confounding factors, we computed the correlation between synchrony and all possible confounders in the study. Our results showed that none of these confounders were significantly correlated with the microbial synchrony score ($p > .05$).

Hypothesis 3: Longitudinal Associations Between Maternal Sensitivity, Microbial Components, and PTSD

We found that mothers' sensitive caregiving across development was linked with youth α diversity (SCC = 0.38, $p = .026$, Figure 3a), and a negative correlation was found between the number of PTSD symptoms in early childhood and α diversity 15 years later (SCC = −0.49, $p = .003$, Figure 3a), suggesting that early-childhood PTSD may play a role in the consolidation of the microbiome. Furthermore, we found a significant negative correlation between adolescents' microbial diversity and their emotional problems, as reflected in their CBCL scores (SCC = −0.52, $p = .005$, Figure 3a. See further sensitivity analyses in Supplemental Methods and Supplemental Figure S2). We also found differences in late adolescents' α diversity when based on early-life PTSD diagnosis, $\chi^2(2) = 6.72$, $p = .035$, and post hoc comparisons revealed that the Exp-PTSD group had significantly lower microbial diversity compared with the Exp-ND and no trauma exposure groups ($U = 42.00$, $Z = -2.10$, $p = .036$ and $U = 27.00$, $Z = -2.13$, $p = .034$, respectively; Figure 3b).

The continuity of trauma-related symptoms from early childhood to late adolescence was utilized in two structural models. In the first model, we investigated the association between early-childhood PTSD and CBCL scores in late adolescence as mediated by microbial α diversity and microbial synchrony. Our findings revealed a significant direct effect of early-childhood PTSD on adolescents' CBCL, indicating the continuity in emotional problems throughout development. Moving beyond this direct relationship, our results unveiled evidence of mediation through adolescent α diversity but not via microbial synchrony. Specifically, we found that microbial diversity partially mediated this association, with a significant indirect effect observed (estimate = .556, 95% CI [0.038, 1.074]). However, the mediation through microbial synchrony was not significant (estimate = −.008, 95% CI [−.047, .458]). The model had an excellent fit to the data, confirming our key hypothesis that the gut microbiome mediates the pathway between PTSD in early life and emotional problems (CBCL scores) in adolescence in contexts of chronic trauma (Figure 3c). Similar results were found without missing data imputation (Supplemental Figure S1h). The second model predicted adolescents' CBCL scores from early childhood PTSD status and adolescent microbiome composition. The model predicting adolescents' CBCL from both PTSD diagnosis and the microbiome was better (F-score = 0.239) than the model including only PTSD. In both models, the genus *Dialister* was negatively correlated with PTSD, and the genus *Veillonella* was positively correlated with PTSD (Figures 1d and 3d).

Hypothesis 4: Microbiome Differences in PTSD Donors in a Mouse Model

While mouse models of PTSD differ in substantial ways from their human counterparts, we still managed to observe differences between FMT results from donors with and without PTSD. FMT was successful with mice and donors, sharing 46.7% of genera among the Exp-PTSD groups and 47.4% of genera among the Exp-ND groups. We did not find significant differences in α diversity between the two mouse groups; however, there were significant differences in β-diversity (Permutational Multivariate Analysis of Variance: Jaccard, $p = .038$; Bray–Curtis, $p = .039$; Figures 2b and 2c) such that mice receiving transplants from Exp-PTSD adolescents had significantly different microbiome communities than those receiving Exp-ND transplants. Analysis of Composition of Microbiomes analysis revealed that *Clostridium ramosum* was the only significantly more abundant taxon in mice receiving FMT from adolescents with PTSD compared with Exp-ND recipient mice (Figure 2d). Mice receiving transplants from adolescents with PTSD entered the open arms of the elevated plus maze less frequently compared to those receiving transplants from no-diagnosis-exposed adolescents, $t(14) = 2.29$, $p = .04$, Figure 2e.

Discussion

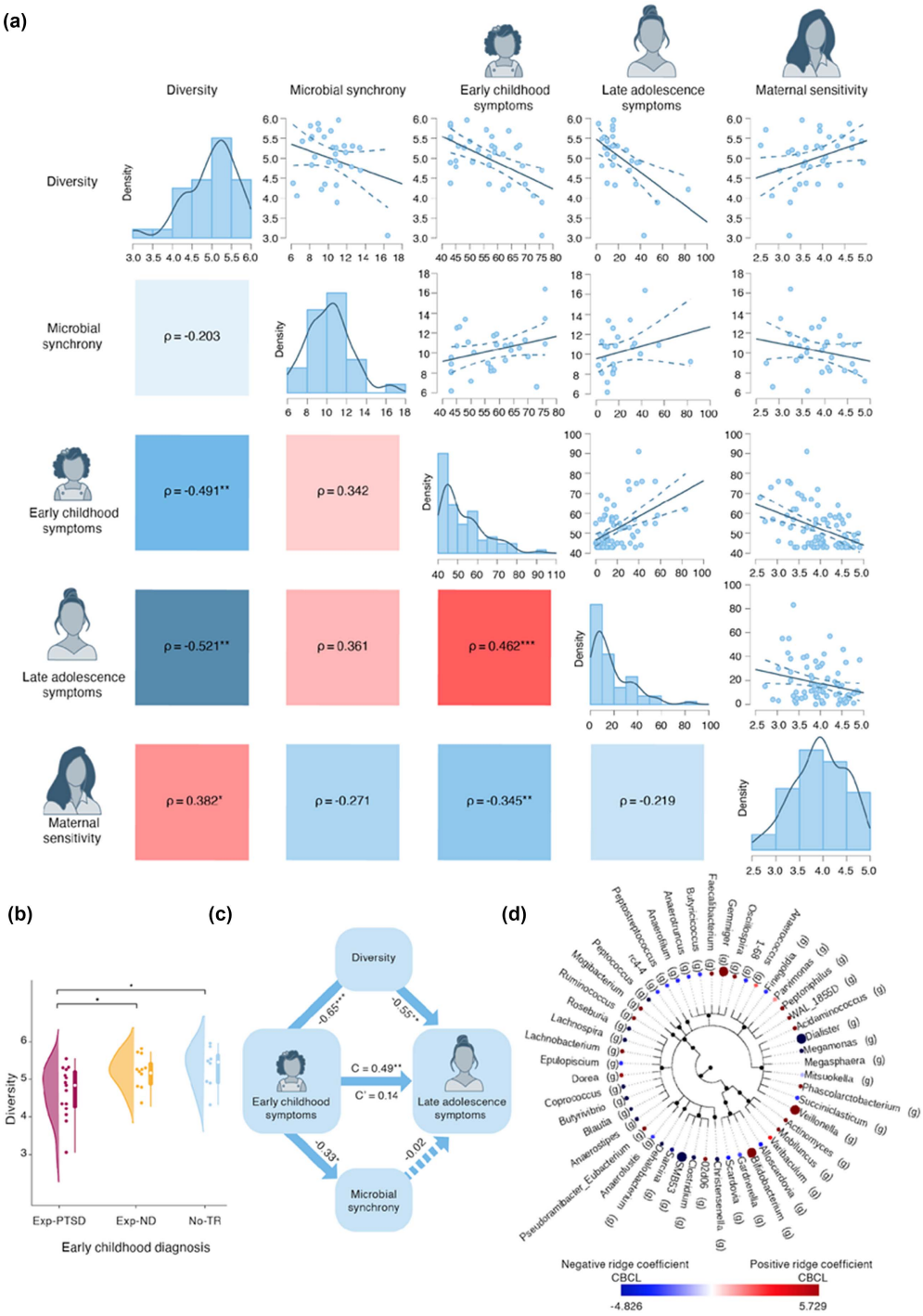
Our cross-generational, longitudinal, multimeasure, cross-species study is among the first attempts to assess the role of the gut microbiome in the consolidation of the posttrauma symptomatology across development. We followed mother–offspring dyads from a zone of chronic war-related trauma and a matched nonexposed region for over 15 years to determine the involvement of the trauma-exposed microbiome in posttraumatic illness. Using machine learning, we identified a trauma-specific microbial profile that distinguished youth exposed to chronic trauma from their nonexposed counterparts and, moreover, to specify youth who were at greater risk of developing posttraumatic pathology from those exposed to the same trauma but who were more resilient. Furthermore, we conducted sensitivity analyses to assess the robustness of our findings, which consistently demonstrated significance when compared to the results of a random model. We further examined whether microbial synchrony among cohabitating, genetically related individuals may be associated with posttrauma symptomatology. Our findings on lower microbial synchrony among mother–child pairs in cases of youth PTSD can be of assistance in the classification of the disorder.

Overall, the early identification of youth at greater risk in the face of trauma has been a key issue in medicine, public health, and allocation of government resources to trauma-stricken regions. It has also been a major concern in the recruitment of young adults into positions that involve hazards, such as police, military, firefighting, or emergency medicine. Our findings may assist in the formation of microbiome-specific tools that can distinguish the posttraumatic from the resilient profiles in contexts of chronic trauma and may help inform the construction of microbiome-related interventions.

Results indicate that adolescents' war-related trauma exposure, PTSD diagnosis, and the number of posttrauma symptoms were classifiable using the microbiome profile in adolescence. We identified several important genera that differentiated adolescents with and without PTSD, and our findings are consistent with the literature regarding the associations between these microbiome features and mental health. For instance, the genera *Dialister* and *Eubacterium*, which were found to be less abundant in cases of PTSD, stress, and depression (Gao et al., 2022; Malan-Muller et al., 2022; Valles-Colomer et al., 2019), were also less abundant in our PTSD participants. Similarly, *Collinsella,* previously linked with the number of deployments among veterans (Stanislawski

Figure 3

Gut Microbiome Is Associated With Posttraumatic Symptomatology and Sensitive Caregiving



Note. (a) Bottom left corner: Spearman's correlation coefficient (ρ) between the study's main variables; colors represent negative (blue) and positive (red) correlations. Upper right corner: scatterplots of main variables; the diagonal line presents the linear trend, and the dashed lines represent the 95% confidence interval around it; variable distributions are presented on the diagonal. (b) Differences in adolescent α diversity across groups based on early childhood PTSD (n = 15 exposed with PTSD [Exp-PTSD], n = 11 exposed with no PTSD or other diagnosis [Exp-ND], n = 8 not exposed with no PTSD or other diagnosis [no trauma exposure]). Kruskal–Wallis H test and Mann–Whitney post hoc tests. (c) Direct–indirect paths from children's PTSD in early childhood to emotional problems in late adolescence (CBCL) via the adolescent microbiome with child age and gender controlled (n = 84). Model parameters were

(figure continues)

et al., 2021), and *Veillonella*, which is overrepresented in individuals with depression (Amirkhanzadeh Barandouzi et al., 2020), were also associated here with PTSD diagnosis. Accordingly, predicted microbially associated metabolites found here to characterize the PTSD group have been associated with several pathways related to increased nitrite, and this is consistent with prior research. Specifically, following exposure to predator threat, as a well-established model of PTSD, levels of nitrite/nitrate in the medial prefrontal cortex of rats were elevated in concordance with the anxiety exhibited during the predator exposure (Campos et al., 2013). In zebrafish, nitrate and nitrite treatments were found to facilitate anxiogenic-like behaviors and may possibly reduce the inhibitory neurotransmitter γ-aminobutyric acid and its precursor glutamine (García-Jaramillo et al., 2020). Our findings are the first to show increases in these same metabolic components in adolescents with PTSD and may point to their role in the consolidation of PTSD following chronic early stress.

The presence of PTSD in adolescence was associated with lower mother–child microbial synchrony, in comparison with dyads in which adolescents were free of PTSD diagnosis. These results are consistent with studies that indicate associations between lower levels of biobehavioral synchrony and poor outcome in contexts of adversity and psychopathology. For instance, lower mother–child hormonal synchrony was found in cases of childhood adversities among children who exhibited poor developmental outcomes (Atkinson et al., 2013). Similarly, lower synchrony of mother–child electrodermal activity was associated with symptoms of autism spectrum disorder (Baker et al., 2015), and lower mother–child respiratory sinus arrhythmia synchrony was related to maternal depression (McKillop & Connell, 2018). This suggests that greater concordance between mother and child on multiple biomarkers and across a variety of physiological systems may indicate better mental health. Our results are also consistent with studies that identified a general positive correlation between interindividual microbial volatility and perceived stress, cortisol awakening response, and social avoidance behaviors following chronic social defeat (Bastiaanssen et al., 2021). While this represents a separate line of research, its results support the idea that stress is associated with less microbial stability within individuals, mirroring the lower similarity between mother and child in our PTSD participants. Although microbial synchrony may be considered an indicator of attachment or parental attunement, consistent with the well-documented buffering effect of sensitive caregiving, our findings do not support this interpretation. The correlation between microbial synchrony and maternal sensitivity was relatively weak and statistically insignificant. An alternative explanation may be that microbial synchrony is related to the shared lifestyle habits between mother and child, including shared meals or time in close proximity. These lifestyle factors present an intriguing avenue for future studies in the context of trauma and the microbiome. To date, microbiome studies on trauma that tested the associations between child outcomes, maternal microbiome, mental health, and stress symptomatology have used only self-reported questionnaires, and our study is the first to incorporate real-life, mother–child observed interactions within microbiome assessment or test mother–child microbial synchrony. Therefore, our findings require further research and validation in other contexts of trauma and adversity.

In addition to mother–child microbial synchrony, our findings also show lower microbial diversity among adolescents with PTSD as compared to adolescents without PTSD. Such findings are consistent with studies that report lower α diversity in individuals with PTSD, anxiety, and depressive disorders (Bajaj et al., 2019; Levert-Levitt et al., 2022; Madan et al., 2020). The findings are also in line with studies that show association between low α diversity and stressful life events (Gao et al., 2022), psychiatric symptom severity (Madan et al., 2020), childhood adversity, and disrupted caregiving (Callaghan et al., 2020), highlighting the association of stress and psychopathology with lower diversity of microbiota.

Trauma-exposed children suffered not only from higher rates of PTSD and related psychiatric symptoms but also received less optimal caregiving, which further exacerbated the degree of toxic stress exposure. These findings are consistent with research on the lower quality of caregiving experienced by children exposed to harsh and unpredictable environments worldwide (Eltanamly et al., 2021; Yirmiya et al., 2018). It is important to note that parents under extreme stress have fewer resources to care for their children in a sensitive and synchronous manner as they struggle with their own stress. Such difficulties can hinder the parent's emotional availability and responsiveness to their child's needs in what is called "a compound effect" (Christie et al., 2019; Scheering & Zeanah, 2001). The longitudinal associations found between maternal sensitive caregiving across development, early-childhood PTSD, and later microbiome diversity are unique and resemble the findings reported in animal studies (Cryan & Mazmanian, 2022; Jašarević et al., 2015). The link between early maternal caregiving and adolescents' microbial diversity underscores the long-term impact of maternal sensitive attunement, empathy, and affect matching on the maturation of diverse microbiome. In addition, children who were exposed to trauma and suffered from PTSD as young children had lower diversity many years later, and these findings highlight the long-term effects of early posttrauma and resilience on the maturation of the microbiome in the context of chronic trauma.

Results from the mouse experiment further support the role of the microbiome and associated metabolites in the pathophysiology

examined with maximum likelihood estimation using the AMOS 21.0 program. Model fit: $\chi^2(1) = 0.08$, $p = .78$, CFI = 1.00, TLI = 1.60, NFI = 0.99, RMSEA < 0.001. (d) Taxa tree represents the input microbiome of both the XGBOOST of the adolescents' prediction of PTSD and the input of the combined Ridge model of the PTSD diagnosis from early childhood and the microbiome from adolescence predicting emotional problems (CBCL) at adolescence. The big circles represent the bacteria that significantly contribute to the XGBOOST prediction. The color represents the coefficient of the taxa in the Ridge model, such that high positive coefficients are marked in blue and low negative coefficients are marked in red. The enlarged and bolded taxa are consistent between the two models. PTSD = posttraumatic stress disorder; CBCL = Child Behavior Checklist; CFI = comparative fit index; TLI = Tucker–Lewis index; RMSEA = root-mean-square error of approximation. See the online article for the color version of this figure. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

of PTSD. The elevated plus maze test revealed that FMT from trauma-exposed youth with PTSD to germ-free mice increased anxious behavior. Consistently, Bercik and colleagues found that microbiome transplant from a high-anxiety mouse strain (adult germ-free BALB/c) into a low-anxiety mouse strain (adult germ-free National Institutes of Health Swiss Webster mice) caused an evident behavioral profile of the donor in the recipient animal (Bercik et al., 2011). Here, we were able to replicate these results using humanized mice, and our findings lend support to the role of the microbiome in anxiety and PTSD (Kraeuter et al., 2019). Importantly, trauma exposure was not the driver of the anxiety-like behavior, as the resilient trauma-exposed FMT recipient mice exhibited more open-arm entries than their nonresilient recipient counterparts.

The present study has many strengths as well as a few notable limitations. Our findings indicate that PTSD is underpinned by distinct microbial composition, diversity, and synchrony profiles, and microbial diversity significantly mediated the pathway from posttraumatic symptomatology in early childhood to PTSD pathology 15 years later, demonstrating, for the first time, microbial mediation in the trajectory of a distinct psychiatric disorder. It is important to note that while our findings do not imply causality of initial PTSD onset, they suggest that the microbiome may be involved in the posttrauma phenotype, yet further research is needed to validate our findings further. This is due to the fact that we did not have access to fecal samples from the early childhood of the adolescents who did and did not develop PTSD. Still, we were able to provide some evidence for the role of the gut microbiome in posttrauma and resilience using a germ-free mouse model and specify directions for further research. One limitation is the absence of a mechanism explaining our FMT results. Future studies can examine the effect of monocolonization or supplementation with *C. ramosum*, the differentially expressed taxa between the mouse groups, to further pinpoint gut–brain dynamics. Another significant limitation lies in the reliance on mothers' reports of childhood and adolescent psychopathologies, which may be subject to biases influenced by the mothers' own mental health and may be limited by what adolescents disclose to their parents. Additionally, while controlling for several variables known to affect microbial composition, other relevant factors, such as diet, could not be meaningfully included. Another limitation is the attrition and the difficulty in collecting stool samples from all study participants, which resulted in reduced small sample size. Furthermore, including only one paradigm that reflects anxious mice behavior is another limitation, and future animal studies with microbial transplantation could utilize multiple tests that reflect other aspects of the PTSD phenotype. Despite these limitations, we believe our findings open a line for future research that adopts a developmental approach, follows families exposed to early adversity over time, and integrates physiological, observational, and psychological factors for a better understanding of the microbiome's involvement in mental health. Importantly, the uniqueness of our cohort provides a novel perspective in exploring these complex interactions, not only contributing to its originality but also to the depth and applicability of our findings in understanding the intricate relationship between the microbiome and war-related trauma pathology.

Conclusions

Our results expand current knowledge on the mechanisms underlying the effects of early exposure to war-related trauma and parental caregiving on the gut microbiome. A possible conclusion from our study is that beyond its direct impact on the development of PTSD, the gut microbiome may form an additional layer of biological memory that retains the impression of previous events, particularly those occurring in early life. Such memory may define one pathway by which stress experienced in early life induces posttraumatic pathology many years later, when stressful events reoccur, by shaping the child's lifetime stress response, thereby charting a microbiome-specific pathway for the lifelong impact of early-life stress. While research on psychobiotics is still in early stages and evidence supporting their efficacy in psychiatric disorders remains mixed (Vasiliu, 2023), recent findings suggest that interventions that involve a psychobiotic diet can effectively reduce perceived stress. This underscores the potential of dietary approaches in alleviating stress in humans (Berding et al., 2023). Further research is required to pinpoint the involvement of the gut microbiome in the consolidation of psychiatric illness, test microbial alterations in illness-susceptibility following early life stress, and address the trajectory of resilience in contexts of trauma toward the construction of novel and disease-specific microbiome-based interventions.

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