scientific reports

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The long-term associations of childhood parental loss with attachment, creativity, and epigenetic regulation

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The loss of a parent during childhood is a profound event with enduring impacts on psychological and emotional development. This study investigates the long-term effects of childhood parental loss on attachment patterns and openness to experience, with a focus on the epigenetic modulation of the oxytocin and dopamine systems. The sample included 371 participants (51.2% women, ages 26–43), of whom 33 experienced parental loss during childhood. In those individuals who lost a parent, findings revealed comparably lower attachment avoidance and a DNA methylation profile associated with a potential for increased oxytocin activity. Additionally, a DNA methylation profile associated with a potential for heightened dopamine activity was identified in this group, aligning with greater creativity. These findings highlight the intricate interplay of genetic and environmental factors in fostering resilience and personal growth, shedding light on the roles of oxytocin and dopamine in social bonding and the potential for long-term adaptation following early-life trauma.

The loss of a parent during childhood casts a long and often dark shadow over a young person's psychological landscape[1,2], embedding itself deeply within their developmental trajectory. This profound disruption is consistently linked to a heightened risk of mental health issues[3], including depression, anxiety disorders, post-traumatic stress disorder (PTSD), and even prolonged grief disorder. Children enduring such a loss frequently grapple with fear, anger, and dysphoria, experiencing intrusive thoughts, insomnia, and a pervasive sense of life's meaninglessness[1,3]. The social ramifications are equally severe, with bereaved children facing altered family dynamics, increased insecurity, and a propensity toward high-risk behaviors, including a heightened long-term risk of suicide[1]. Yet, amidst these harrowing consequences, a counter-narrative emerges: the potential for long-term growth and resilience[4]. This investigation examines this paradox, exploring both the psychological aftermath of childhood parental loss and its association with epigenetic modulation of the oxytocin and dopamine systems, focusing on their potential implications for attachment and openness to experience. By examining these intertwined dimensions, we aim to illuminate the pathways through which external experiences might intersect with our genetic blueprint, fostering both vulnerability and resilience.

Several systematic reviews and meta-analyses have explored the impact of losing a parent during childhood, consistently highlighting the profound effects on social and emotional development[1–5]. Specifically, studies on early adolescence reveal that parental loss is associated with inappropriate social reactions, leading to feelings of isolation and withdrawal from others. A review on parental death during adolescence underscores that adolescence, a period marked by intense psychological and neurobiological development, is particularly vulnerable to disruptions caused by parental death[6]. Adolescents, in particular, may feel misunderstood by their peers and adults, contributing to their social detachment and further complicating the grieving process[7]. Without sufficient social support, these adolescents may experience prolonged isolation, which exacerbates mental health challenges such as anxiety and depression, and further strains their social relationships[8].

These processes can affect individuals' social-emotional ties and, through allostatic mechanisms[9,10], foster attachment avoidance—a chronic, trait-like tendency to be self-reliant in times of need and to trust oneself over others[11–13]. Adaptive allostatic mechanisms relate to the body's ability to achieve stability through change and respond dynamically to environmental demands and stressors. These mechanisms encompass anticipatory regulation, where the brain predicts and adjusts physiological responses to meet expected environmental

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challenges, moving beyond mere reactions to changes. This predictive capacity ensures efficient energy use, prioritizing bodily needs and redirecting resources to critical systems. Flexibility within these systems facilitates adaptive changes across multiple physiological domains, including neural, neuroendocrine, and immune mechanisms[9,10].

Additionally, changes can occur in one of the key neurobiological systems sustaining our social tendencies—the oxytocin system[14–16]. Several studies have linked adverse childhood experiences, particularly emotional maltreatment, to lower oxytocin concentrations in the cerebrospinal fluid (CSF)[17]. Moreover, single-nucleotide variants in the oxytocin receptor gene have been associated with depression, anxiety, and stress, but only in individuals with one or more early-life stressors[18]. Other research connects DNA methylation patterns, which indicate reduced oxytocin receptor gene expression, with attachment avoidance[19] and social avoidance tendencies[20]. DNA methylation refers to an epigenetic mechanism where methyl groups are added to the DNA molecule, often modifying the function of genes and affecting gene expression without altering the DNA sequence itself[21,22].

People who have lost a parent also report feelings of devastation and depression[23], which may be linked to cognitive processes that reflect a withdrawal from openness to experience and a shift in motivation to engage with the world[24]. For instance, studies show that growing up with one or no parents, or experiencing parental separation or divorce, is associated with reduced openness to experience[24]. This motivation, partly sustained by the neurobiological dopamine system, is crucial for the sensation of "wanting"[25] —a state that drives the desire to obtain a reward—distinct from "liking," which pertains to the sensory pleasure experienced after actually obtaining the reward. For example, studies demonstrate that dopamine is integral to "wanting" by enhancing incentive salience without necessarily increasing "liking" for rewards. Moreover, the absence of dopamine can impair the ability to seek rewards without altering their perceived enjoyment[25,26]. Studies in rodents show that maternal deprivation is associated with blunted dopamine release in the prefrontal cortex (PFC)[27,28], a region critical for executive functions such as decision-making, social behavior, and impulse control. Additionally, there is a decreased density of dopamine cell bodies in the ventral striatum (VS)[29], which plays a key role in reward processing and motivation, and in the ventral tegmental area (VTA)[29], a central hub for the production of dopamine that projects to various brain regions involved in reward and emotional regulation.

As time passed, individuals who lost a parent reported that the trauma from their loss had contributed to their personal growth. Studies on adults indicate that experiencing the loss of a parent often disrupts one's assumptive world and leads to rumination. Rumination, while often distressing, can also serve as a mechanism for processing grief and making sense of the loss. Through this intense reflection, individuals may begin to re-evaluate their priorities, values, and life goals. This cognitive and emotional processing can lead to posttraumatic growth, a positive psychological change experienced as a result of struggling with highly challenging life circumstances[30,31]. Furthermore, research shows that the early loss of attachment figures may play a crucial role in shaping a 'secure base' in future interpersonal relationships[32]. However, alongside this personal growth, many individuals acknowledge that their relationship with the remaining parent often becomes more distant[23]. Thus, while personal growth may positively influence one's future relationships and life motivations, it appears to have a more limited impact on strengthening ties with the surviving parent.

We, therefore, predict that a dual process might be at play. On the one hand, parental loss may impact one's remaining attachment ties, particularly the tendency to distance oneself from others, especially during the first years after the loss and specifically toward the remaining parent. These years are marked by processes aimed at minimizing painful experiences. Accordingly, we predict that attachment ties with the remaining parent and the symbolic image of the deceased parent would exhibit higher attachment avoidance. On the other hand, there are indications of long-term personal growth. We, therefore, also predict that ties with current attachment figures, such as one's romantic partner and best friend, would show lower attachment avoidance. Given that the brain's plasticity is considerably greater in the first years of life than later, we also predict that changes in the oxytocin system would reflect the first years after the loss rather than the growth in later years, resulting in a less expressed oxytocin system among those who lost a parent. Studies on the epigenetic layer that governs gene expression and acts as the intermediate layer between the genetic code and the environment corroborate these plasticity phases[21]. It is important to note that we are not implying a direct mediation effect of DNA methylation changes on psychological processes. Rather, we suggest that these DNA methylation changes reflect parallel alterations at different layers of the phenotype, such as neurobiological and psychological responses to early parental loss. While our study examines the epigenetic changes in conjunction with attachment outcomes, it does not propose that these epigenetic modifications mediate the psychological impacts of loss. Instead, the DNA methylation patterns observed may provide insight into how both biological and psychological processes respond to the shared environmental stressor of parental loss. Therefore, the suggestion is not speculative but rather aims to present a broader picture of how epigenetic, psychological, and behavioral layers may evolve in response to early-life trauma without making a causal mediation claim.

Likewise, we predict that long-term post-traumatic growth would include greater openness to new experiences[33–35]. When reflecting on their experiences, many individuals report a notable increase in openness to new ideas and possibilities following highly stressful events[36]. In the face of such profound challenges, people often find themselves compelled to scrutinize their most deeply held beliefs. This introspective process fosters a readiness to entertain previously disregarded ideas, perspectives, and opportunities. It is as if the stress acts as a catalyst, breaking down the barriers of entrenched thought and allowing a more broadening and flexible mindset to emerge. This transformation underscores the intricate interplay between adversity and cognitive growth, revealing the human capacity for resilience and adaptability in the aftermath of stress[36]. The Personal Growth Process (PGP) model also highlights openness to experience and change as crucial mental shifts that drive personal growth[37] and post-traumatic growth[38]. Building on Rogers' organismic valuing process[39], the PGP model emphasizes that embracing new experiences is vital for growth. Openness to experience, one of the "Big

Five"[40,41] and "HEXACO"[34,35] personality traits, is consistently linked to post-traumatic growth among people of the general community[42] and military veterans[43]. Finally, research shows that personal growth involves a self-directed journey of realizing one's potential[44], and a sense of experiencing continued development while being open to new experiences that potentially challenge one's views and continuing to seek self-improvement[44–46].

In addition to an overall openness to experience, we predict that post-traumatic growth can manifest in specific facets of openness: aesthetic appreciation, inquisitiveness, creativity, and unconventionality[35]. Enhanced aesthetic appreciation may emerge, with individuals developing a deeper sensitivity to art and beauty, finding solace and meaning in creative expressions. Inquisitiveness might flourish, driving a pursuit of knowledge and a profound interest in understanding the world's complexities. Creativity could significantly heighten, leading to the generation of novel and valuable ideas. Unconventionality might manifest as a greater willingness to challenge traditional norms and embrace alternative viewpoints, fostering innovation and adaptability.

Aside from the predicted differences in the psychological construct of openness to experience, differences could arise in the epigenetic makeup of the biological system that might be at the heart of this construct—the dopamine system. In line with our predictions regarding oxytocin, we propose that changes in the biological system underlying the motivation for new experiences—specifically dopamine—would be more sensitive during early years rather than later periods of personal growth[21]. Hence, we expected a DNA methylation profile associated with a potential for lower dopamine activity, which would align with early experiences of closing in.

Results

Attachment and oxytocin

In keeping with research indicating that losing a parent during childhood is associated with an elevated sense of insecurity and worry[5,47], we found that those who lost a parent reported considerably higher attachment avoidance to their actual or symbolic memory of their fathers (*Median* = 7 compared to 3.67 among participants who did not lose a parent) and mothers (*Median* = 3.33 compared to 2.83). Conversely, in accordance with studies showing long-term positive adjustments among individuals who lost a parent[4], we also found that their current, general attachment avoidance was lower than participants who did not lose a parent (*Median* = 3.00 compared to 3.50). The detailed statistical values and patterns of these results are presented in Supplementary Table 1 and Fig. 1.

To dive deeper into this pattern of results, we calculated a series of Bayesian Pearson correlations between attachment avoidance in different relationships among participants who lost a parent compared to those who did not (see Fig. 2). Among participants who did not lose a parent, higher attachment avoidance in one relationship was linked to higher attachment avoidance in all other relationships. However, the pattern was different for participants who lost a parent during childhood. Specifically, we found that whereas avoidance towards current relationships with a best friend and a romantic partner was positively linked to general attachment avoidance, attachment avoidance towards fathers was negatively associated with these constructs. This means that higher attachment avoidance towards fathers corresponded to lower attachment avoidance (and hence more security with respect to the avoidance domain) in relationships with best friends, romantic partners, and general attachment tendencies. Most of our participants lost their father (84.85%), and thus, this result mainly reflects the association with the symbolic image of the late parent and, to a lesser extent, the remaining parent.

In contrast to our prediction, in addition to the allostatic change in attachment avoidance, we also found a DNA methylation pattern associated with greater expression of oxytocin among participants who lost a parent during childhood (see Supplementary Table 2). Specifically, we identified three Bayesian credible DNA methylation sites on the oxytocin gene and one on each of the RyR1 and RyR2 genes, which are essential to oxytocin's positive feedback loop. The role of the RyR genes in the oxytocin system is less familiar but crucial[48]. When oxytocin binds to its receptor, it activates a pathway that releases calcium from the endoplasmic reticulum. This initial calcium release triggers ryanodine receptors (RyRs) to release even more calcium, amplifying the calcium signal. This amplified signal stimulates the release of additional oxytocin from neurons, creating a positive feedback loop[48]. This loop enhances oxytocin secretion, which is vital for social behaviors like lactation and maintaining attachment-related memories.

Participants who lost a parent during childhood had significantly less DNA methylation on all three oxytocin DNA methylation sites—cg19592472 BC11, cg13725599 BC11, and cg19776589 TC11 (see Supplementary Fig. 1 for the locations of these sites on the oxytocin gene). Cg19592472 BC11 and cg13725599 BC11 are located within and adjacent to (respectively) a zinc finger and BTB domain-containing protein (ZBTB24) binding site. ZBTB24 functions as a transcriptional regulator, affecting gene activation[49]. Its binding site has been identified as the consensus sequence CT(G/T)CCAGGACCT, which occupies multiple loci, including the promoter region of different genes. Cg19776589 TC11 is located within ZKSCAN5, a Zinc Finger protein with KRAB and SCAN domains. ZKSCAN5 plays a significant role in gene activation, directly influencing the transcriptional landscape of the genes it binds to, often leading to higher activation of these genes[50]. Reduced DNA methylation at these sites is likely associated with increased expression of the oxytocin gene. This DNA methylation-expression relationship is further supported by data from the EWAS Open Platform[51], which demonstrates a significant association between DNA methylation levels at these CpG sites and oxytocin gene expression.

Additionally, participants who lost a parent during childhood had less DNA methylation on RyR1's cg02226644 BC21 site and more DNA methylation on RyR2's cg02172884 TC21 site (see Supplementary Figs. 2 and 3 for the locations of these sites on the ryanodine receptor 1 and 2 genes, respectively). RyR1's cg02226644 BC21 is located within the interferon-stimulated response element (ISRE) where Interferon Regulatory Factor 5 (IRF5) binds. IRF5 binding significantly contributes to higher gene activation[52]. In contrast, RyR2's cg02172884 TC21 is adjacent to the binding site of the FOS::JUN heterodimeric complex, which contains inhibitory regions that can repress transcription. The inhibitory regions in FOS are major contributors to transcriptional repression in vitro[53]. Therefore, the DNA methylation pattern on the RyR genes potentially reflects a higher expression of

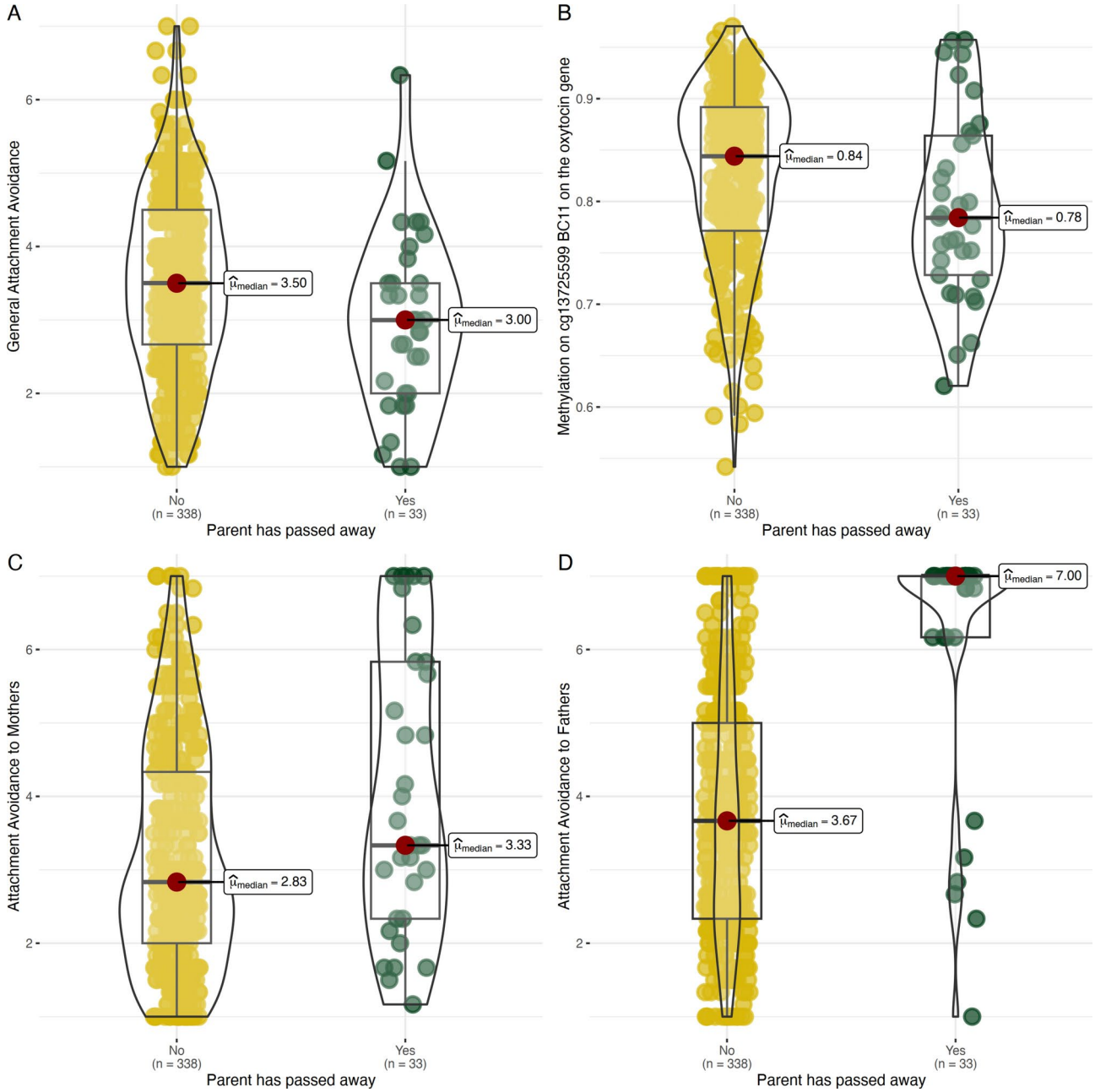

Fig. 1. Significant differences between participants who lost a parent during childhood and those who did not in general attachment avoidance (**A**), attachment avoidance to mothers (**C**), and attachment avoidance to fathers (**D**), as well as an exemplar difference in oxytocin-related DNA methylation levels (**B**). Although participants who lost a parent showed higher attachment avoidance to their parents (symbolic and/or actual figure), they exhibited lower general attachment avoidance and a DNA methylation pattern associated with higher oxytocin expression.

these genes in participants who lost a parent during childhood, leading to a more pronounced positive feedback loop of oxytocin and lengthier expression of the oxytocin system. While our DNA methylation data derives from saliva, we note that the ImageCpG database[54] demonstrates a moderate positive correlation (mean $r = 0.30$) between significant oxytocin-related CpG sites in saliva and brain tissue under baseline conditions. However, it does not account for whether environmentally induced changes in DNA methylation are similarly represented in both tissues. Therefore, the extent to which our findings in saliva reflect epigenetic activity in the brain remains uncertain and warrants further investigation.

Openness to experience and dopamine

We found a single Bayesian credible result concerning openness to experience and its facets. Participants who lost a parent reported significantly higher creativity (Median = 4.33) compared to those who did not lose a parent

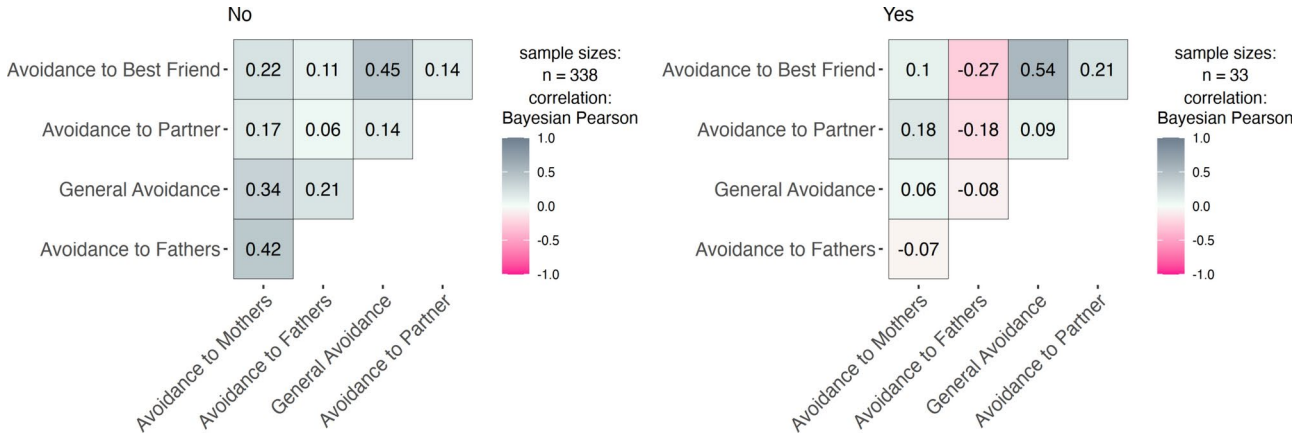

Fig. 2. The pattern of associations between attachment avoidance in different relationships among participants who lost a parent (yes) compared to those who did not (no). In participants who did not lose a parent, higher attachment avoidance in one relationship was linked to higher attachment avoidance in all other relationships. However, the pattern was different for participants who lost a parent during childhood. Specifically, we found that while avoidance towards a best friend and a romantic partner was positively linked to general attachment avoidance, attachment avoidance towards fathers was negatively associated with these constructs. This means that higher attachment avoidance towards fathers corresponded to lower attachment avoidance (and hence more security with respect to the avoidance domain) in relationships with best friends, romantic partners, and general attachment tendencies.

(Median = 4.00). Unconventionality showed a similar trend with a high probability of direction (0.97), although its credible interval included 0. The detailed statistical values and patterns of these results are presented in Supplementary Tables 1 and 3 and Fig. 3.

A credible difference was also observed in SLC6A3's cg16614020 TC21 DNA methylation site (i.e., on the dopamine transporter gene; see Supplementary Fig. 4 for the locations of these sites on the gene). Participants who lost a parent had lower DNA methylation levels compared to those who did not. The cg16614020 TC21 site is located within the binding site of Zinc Finger Protein 324 (ZNF324), which belongs to the Krueppel C2H2-type zinc-finger protein family known for functioning as transcriptional repressors[55]. Higher DNA methylation at this site would decrease the repression capability of ZNF324, resulting in increased expression of SLC6A3. This DNA methylation-expression relationship is further supported by data from the EWAS Open Platform[51], which demonstrates a significant positive association between DNA methylation levels at these CpG sites and dopamine transporter gene expression. Consequently, fewer dopamine transporters would be present, leading to higher dopamine levels in the synaptic cleft and presumably a greater sense of "wanting." Although this result contrasts our prediction, it aligns with the findings regarding a DNA methylation pattern associated with higher expression of oxytocin and an allostatic response. According to ImageCpG database[54], the correlation between DNA methylation levels at the significant dopamine-related CpG site in saliva and brain tissue is strong ($r = 0.70$), suggesting that higher levels observed in saliva likely correspond to higher levels in the brain. However, it is important to note that the database does not assess whether environmentally induced changes in DNA methylation are equivalently represented in both tissues. As such, while our saliva-based findings may partially reflect brain-specific epigenetic activity, further investigation is needed to confirm the extent of this correspondence.

Background measures

To ensure that the groups did not differ on constructs that might influence the outcome measures, we conducted comparisons on a series of background variables, as presented in Supplementary Table 3. The analyses showed no significant differences between participants who lost a parent in childhood and those who did not in terms of years of education, economic status, self-rated health, smoking prevalence, family history of mental health issues, general severity index, somatization, depressive or anxiety symptoms, number of major negative life events in adulthood, or the number of self-defined addictive behaviors.

Discussion

The loss of a parent, a major event in a child's development, leaves lasting marks on their psychological and emotional well-being. Unlike most research that highlights the short-term effects of parental loss, such as increased depression, anxiety, and PTSD[1–3,23,27,56], this study aimed to uncover the long-term effects and potential traces of personal growth. Based on qualitative investigations of parental loss, we hypothesized that on an epigenetic level, individuals who lost a parent during childhood would show lower expression of oxytocin due to DNA methylation on oxytocin-related genes and lower expression of dopamine because of DNA methylation on dopamine-related genes. On a psychological level, we anticipated higher attachment avoidance towards the deceased parent and the remaining parent but lower attachment avoidance in current relationships, reflecting a

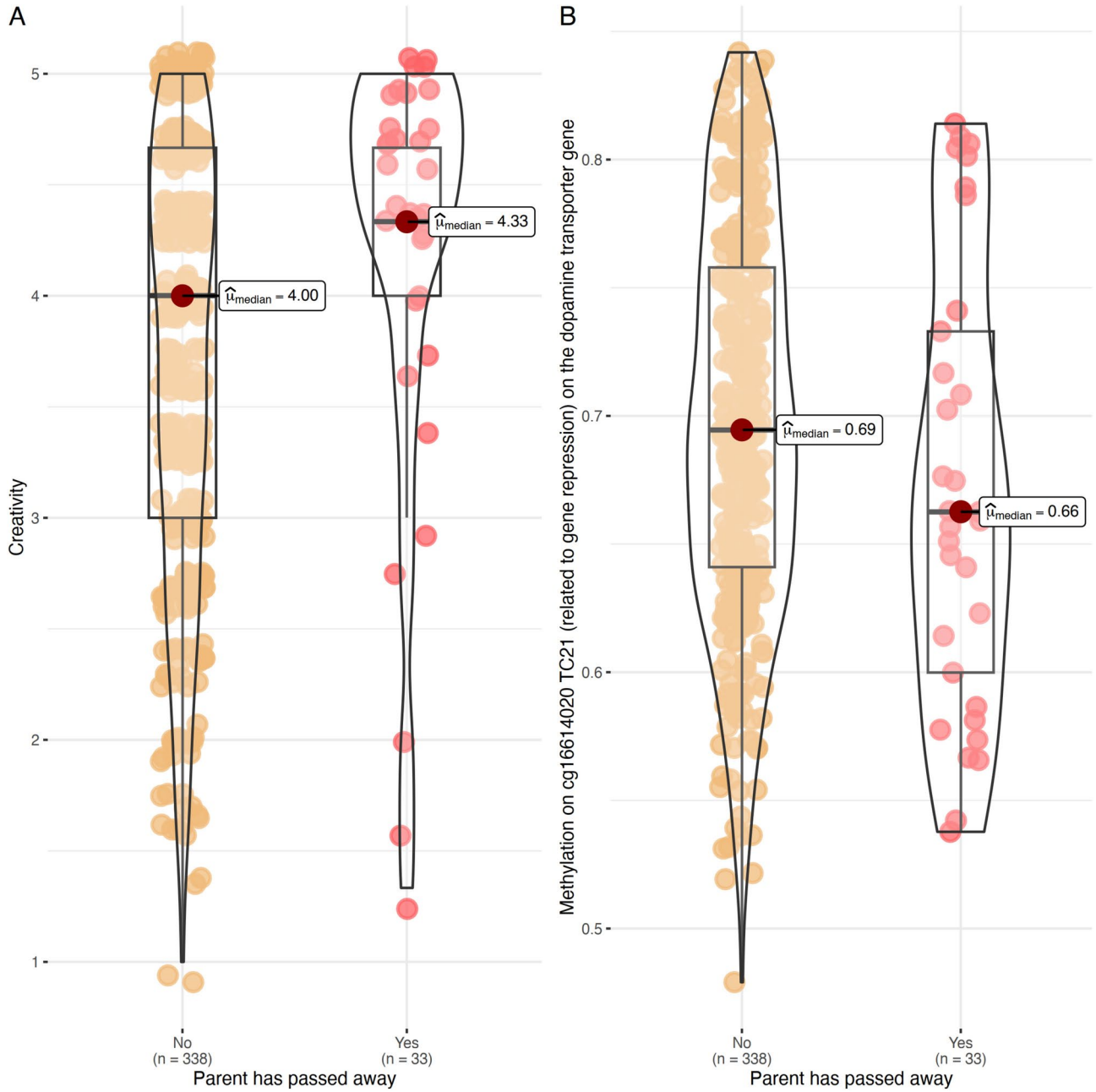

Fig. 3. Significant differences between participants who lost a parent during childhood and those who did not in creativity (**A**) and DNA methylation levels of the dopamine transporter gene (**B**). Participants who lost a parent showed higher creativity and exhibited a DNA methylation pattern associated with lower expression of the dopamine transporter gene, resulting in arguably higher availability of dopamine in the synaptic cleft.

shift towards greater security in adulthood. Additionally, we predicted increased openness to experience and/or its facets, such as creativity and unconventionality, as a long-term manifestation of personal growth.

We observed an allostatic change at both the psychological and epigenetic levels. In the social-emotional domain, individuals who experienced parental loss during childhood exhibited higher attachment avoidance towards the deceased and remaining parent but lower general attachment avoidance in adulthood, reflecting a shift towards greater security. This lower attachment avoidance in adulthood was also accompanied by a DNA methylation profile associated with a potential for higher oxytocin activity. Specifically, we observed a DNA methylation profile linked to a potential for increased activity of the oxytocin gene (OXT), which codes for the production of oxytocin, and the RyR genes that code for the production of proteins that regulate oxytocin's positive feedback loop.

The allostatic response observed at both psychological and epigenetic levels highlights the multifaceted role of oxytocin in mediating attachment behaviors and personal growth. Oxytocin could foster lower attachment avoidance in several ways. First, higher oxytocin expression can reduce the reactivity of the hypothalamic–

pituitary–adrenal (HPA) stress axis[57] by potentiating gamma-aminobutyric acid ($GABA_A$) receptors[58] and subsequent suppression of corticotropin-releasing hormone (CRH) and the adrenocorticotropic hormone (ACTH) secretion. This reduction would allow the attachment system and fight-or-flight responses to subside[12,59] and, as Bowlby noted, to facilitate the activation of other systems, such as the affiliation and exploration systems[60,61].

In addition, higher expression of oxytocin influences dopamine activity in a region-specific manner[62,63]. In the substantia nigra pars compacta (SNc), oxytocin reduces dopamine activity[63], decreasing locomotion and the motivation to move, thereby reinforcing proximity-seeking behaviors essential for attachment and social bonding. Conversely, in the ventral tegmental area (VTA), oxytocin enhances dopamine neuronal firing[62,63], promoting behaviors associated with reward, positive social interactions, and a sense of "wanting" attachment ties[25,64]. Oxytocin neurons originating from the hypothalamus also extend to the nucleus accumbens (NAc), influencing opioid signaling related to pleasurable rewards and a sense of "liking." In a rat study, activating the oxytocin receptor (OXTR) resulted in higher expression of the preproenkephalin gene, which produces enkephalin, a natural compound that binds to the mu-opioid receptor (MOR), known for inducing feelings of euphoria and pain relief. According to the Brain Opioid Theory of Social Attachment (BOTSA[65]), this heightened sense of "liking" of attachment ties would also aid in increasing security and reducing avoidance.

Finally, oxytocin allows for long-term neural plasticity and memory consolidation by acting on the CA1 and CA2 subregions of the hippocampus[15]. Consequently, oxytocin enhances the brain's ability to detect and recognize social signals, amplifying neural responses to these cues. This increased sensitivity is then solidified through long-term plasticity mechanisms, ensuring that areas of the brain, such as the auditory and visual cortex, remain attuned to these important social stimuli potentially throughout the individual's life, thereby sustaining less attachment avoidance. This process also adheres to the learning theory of attachment[66] and a recent narrative on the neurobiological roots of attachment-system functioning[67].

We also observed an allostatic response in one facet of openness to experience—creativity—that was accompanied by a DNA methylation pattern associated with a greater availability of dopamine in the synaptic cleft. Several studies have demonstrated that dopamine is more closely related to "wanting" or desire for rewards rather than the pleasure or "liking" of rewards[68]. Research showed that dopamine depletion in rats did not reduce their expressions of pleasure when consuming sweet foods but did reduce their motivation to seek out those rewards, indicating that dopamine is primarily involved in "wanting" rather than "liking"[69]. Similarly, in experiments where dopamine levels were artificially increased, rats displayed more motivation to eat without showing increased enjoyment of the food[70]. In humans, neuroimaging studies have confirmed that dopamine release correlates more strongly with "wanting" a reward than with the pleasure derived from it[71]. This aligns with findings in Parkinson's disease patients, who can still enjoy pleasures but often struggle with motivation[72]. The incentive-sensitization theory of addiction also posits that addiction involves an excessive amplification of "wanting" due to dopamine system sensitization without necessarily increasing "liking"[68]. Furthermore, pharmacological studies have found that suppressing dopamine reduces "wanting" for rewards without affecting "liking" reactions, while increasing dopamine can heighten "wanting" without enhancing "liking"[73]. In light of these findings, the DNA methylation profile observed in our study, which is suggestive of a potential for increased dopamine activity, likely supports the heightened creativity in individuals who experienced parental loss during childhood. This potential for enhanced dopaminergic activity may drive a stronger motivation to explore and engage in creative pursuits, reflecting an allostatic change that leverages the "wanting" system to foster personal growth and resilience.

While our study offers valuable insights, several limitations must be acknowledged. First, as a correlational study, we cannot assign causality to the observed relationships between parental loss, attachment, openness to experience, dopamine, and oxytocin. Second, our use of peripheral tissue from saliva samples, despite controlling for cell type composition, may not directly reflect epigenetic changes in specific brain areas. Third, although Project Alpha's longitudinal design provides a naturalistic setting, the specific inclusion criteria for our sample—couples of reproductive age, without children, and interested in starting a family—may limit the generalizability of our findings. While this homogeneity was necessary to ensure equality between groups (i.e., those who lost a parent versus those who did not), it narrows the applicability of the results to other populations. Additionally, we aimed to better understand the biological function of each CpG site by utilizing the JASPAR 2024 database and assessing the correlation between saliva-based and brain DNA levels through the ImageCpG database. However, the attempt to link single CpG DNA methylation sites to complex psychodynamic outcomes may be seen as reductionist. While these findings provide a valuable starting point, further exploration is required to capture the complexity of these psychodynamic processes fully. Lastly, the sample size for participants who lost a parent was relatively small, potentially further limiting the generalizability of our findings. Despite these limitations, our study highlights the profound long-term effects of early parental loss and the potential for personal growth, emphasizing the intricate interplay between genetic and environmental factors in shaping psychological resilience. By demonstrating the link between early adversities, DNA methylation profiles associated with a potential for increased oxytocin and dopamine activity, and improved social connections, our study contributes to a deeper understanding of how early trauma can influence the capacity for resilience and social bonding, aligning with the broader theme of oxytocin and social bonding explored in this special issue.

Methods

Ethics information

The study was embedded within a large-scale longitudinal study named "Project Alpha," pre-registered at https://osf.io/kcns7/. It was approved by Reichman University's Institutional Review Board and by the Helsinki Committee of the Israel Ministry of Health (approval number 5-2020). The current examination was pre-registered at https://osf.io/5ge4t/. All participants signed an informed consent form prior to participation.

Participants

The study comprised 384 participants ($n = 192$ couples). The biological sample of 11 participants was of low quality (either 5% of low-quality DNA methylation data points across probes for each participant or bisulfite intensity score lower than 3 standard deviations below the mean), and an additional 2 participants refused to complete the psychological measures. These participants were excluded from the analyses, so the analyses are based on data from 371 participants. Out of those, a total of 33 participants lost a parent during childhood (51.5% women, current age $M_{age} = 31.06$, $SD_{age} = 3.67$), and 338 participants did not (51.2% women, current age $M_{age} = 29.35$, $SD_{age} = 3.28$). Of those who lost a parent, 1 lost both parents, 27 lost their father, and 5 lost their mother. Given that Bayesian hypothesis testing was employed, no power analysis is reported. Instead, a minimum cut-off of bulk and tail effective sample sizes (ESS) > 400 was used to ensure reliable and stable estimates of central tendencies, variability, and credible intervals of parameters.

Inclusion criteria for participation in the study

Inclusion criteria for participation in the study required couples in a romantic relationship who met the following conditions: they had to be of reproductive age with a minimum age of 18, heterosexual, before their first pregnancy and without adopted children, and interested in having a child during the first year of the study. Additionally, they needed to reside in Israel, with a preference for couples not planning to immigrate outside the country in the coming years, and both partners had to hold Israeli citizenship or a permanent residency permit in Israel. Participants had to be capable of having children, and the participation of couples not in a relationship but planning to have a child through co-parenting (provided the child is biologically related to both the mother and father) was allowed. If a couple divorced during the study after having a shared child, this did not prevent them and the child from continuing to participate in the study.

Exclusion criteria for participation in the study

Couples in a romantic relationship were excluded from participating in the study if they met any of the following criteria: known or diagnosed fertility problems, diagnosed chronic illness, personal acquaintance with the study initiator and/or researcher, or if they were students of the study initiator and/or researcher. This exclusion aimed to ensure the integrity of the study by avoiding potential biases, conflicts of interest, and the perception of academic benefits as compensation for participation.

Measures

DNA methylation

DNA was sampled using an Oragene-DNA OG-600 saliva kit (2 ml of saliva and approximately 110 µg of DNA), which allows high specimen stability at room temperature for up to 5 years, a standardized format for high-throughput processing, and low bacterial content[74]. Samples were shipped at room temperature to the Genomics Core Facility of Erasmus Medical Center, Rotterdam, the Netherlands. Upon delivery, DNA was extracted, isolated, and normalized using the internal procedures of the Human Genomics Facility (HuGe-F). An epigenome-wide DNA-methylation scan was then performed using Illumina's Infinium® MethylationEPIC v2 BeadChip kit, which includes data on 935,000 DNA methylation sites. Raw data was saved in iDAT (Illumina Data) files.

Normalization and correction of DNA methylation values In the comprehensive preprocessing of DNA methylation data derived from the Illumina MethylationEPIC v2 kit, a sequence of advanced normalization and correction techniques were employed to ensure the highest quality and comparability of DNA methylation measurements across samples. Initially, the *preprocessENmix* method from the *ENmix* R package was utilized for background correction, leveraging a sophisticated exponential-normal mixture model to differentiate between signal and noise, thus enhancing the clarity and reliability of the DNA methylation signal. This was followed by *norm.quantile*, also from the *ENmix* package, to apply quantile normalization across samples. This is a crucial step in adjusting for batch effects and technical variability by aligning the distribution of probe intensities for all participants, thereby standardizing the data. The third method applied was the Regression on Correlated Probes (RCP) technique using *rcp* of *ENmix*, aimed at correcting probe design type biases by adjusting the DNA methylation data based on expected correlations between proximal probes targeting the same genomic features. Subsequently, the data underwent Beta-Mixture Quantile normalization (BMIQ) using the *wateRmelon* package, specifically tailored to adjust type-2 probe values, ensuring that they match the distribution of type-1 probes and accurately reflect true biological DNA methylation levels. We applied the *ComBat* method to adjust for batch effects using an empirical Bayes framework as a final step in this meticulous combination of normalization and correction procedures (using the *sva* R package). ComBat, renowned for its effectiveness in minimizing batch-related variability, further refines the data by correcting for any remaining batch effects that could confound the analysis. This step ensures sample variations reflect genuine biological differences rather than technical artifacts. This comprehensive suite of preprocessing methods — each addressing different aspects of technical variability and bias inherent in DNA methylation data — significantly improves downstream analyses' accuracy and biological relevance, facilitating a deeper understanding of epigenetic patterns and their implications.

Selection of CpGs for analysis Following the preprocessing phase of normalization and correction procedures, we filtered out CpG sites deemed unsuitable for further analysis. Initially, we utilized the *nmode* function from the *ENmix* package to identify such probes (referred to as "gap probes"), which exhibit an apparent multimodal distribution. These gap probes often indicate the presence of SNPs within the CpG probe region or other unknown factors leading to DNA methylation beta values with a multimodal distribution. Probes displaying multimodal distributions (ranging from 2 to 4 modes) were excluded from all subsequent analyses. Next, we

eliminated CpG sites exhibiting less than a 7% interquartile range in their beta values, ensuring the selected CpGs possessed sufficient variance for follow-up analyses and that this variance surpassed the level of technical variability (see Supplementary Fig. 5). Furthermore, research has demonstrated that selecting CpGs with adequate variance is also associated with improved reliability indices[75]. After this phase, 157,909 DNA methylation sites were eligible for further analyses. For the current study, specific CpGs were selected from oxytocin and dopamine system genes. For oxytocin, we selected sites on OXT—the OXT gene encodes for the hormone oxytocin, which plays a central role in social bonding, sexual reproduction, childbirth, and the period after childbirth; OXTR—the OXTR gene encodes the oxytocin receptor, which is crucial for the oxytocin signaling pathway, affecting social behavior and stress responses; CD38—CD38 is involved in the regulation of oxytocin release and has been linked to social behavior, suggesting a significant role in the oxytocin system for social cognition and interaction; and RYR1 to RYR3—these genes encode the ryanodine receptors 1 to 3, which are involved in calcium signaling pathways that contribute to the positive feedback mechanism of oxytocin release, influencing various physiological processes including muscle contraction and neuronal activity. Sixty-three DNA methylation sites on these genes were used in the analysis.

For dopamine, we selected the sites on DDC—the DDC gene encodes for the enzyme aromatic L-amino acid decarboxylase, which is essential in dopamine biosynthesis. This enzyme catalyzes the decarboxylation of L-DOPA to dopamine, playing a crucial role in neurotransmitter production and overall dopamine regulation in the brain, impacting mood, motor function, and cognitive processes; DRD1 and DRD5—the DRD1 and DRD5 genes encode the dopamine receptor D1 and D5, respectively. These receptors are part of the D1-like receptor family, which stimulates adenylyl cyclase and activates cyclic AMP-dependent signaling pathways. They are involved in modulating neuronal excitability, synaptic plasticity, and overall brain function, influencing behaviors such as learning, memory, and reward processing; DRD2, DRD3, and DRD4—the DRD2, DRD3, and DRD4 genes encode the dopamine receptors D2, D3, and D4, respectively. These receptors belong to the D2-like receptor family, which inhibits adenylyl cyclase activity, reducing cyclic AMP levels. They are critical in regulating dopamine's inhibitory effects, playing roles in motor control, motivation, reward, and emotional responses; and SLC6A3—The SLC6A3 gene encodes the dopamine transporter (DAT; Solute Carrier Family 6 Member 3), which is responsible for the reuptake of dopamine from the synaptic cleft back into presynaptic neurons. This transporter is pivotal in terminating dopamine signaling and maintaining dopamine homeostasis in the brain, affecting mood regulation, reward mechanisms, and attention processes. Thirty-two DNA methylation sites on these genes were used in the analysis.

Estimation of cell type composition Research has noted that different cell types have distinct DNA methylation profiles, suggesting that a portion of the variance in DNA methylation values stems from differences in cell type composition between participants[76,77]. These differences should be accounted for in analyses. To estimate the cell type composition of each sample, we employed the HEpiDish package[77]. The distribution of cell types is presented in Supplementary Fig. 6, and the correlation between the ratio of different cell types in Supplementary Fig. 7. The most common cell types were neutrophils and epithelial cells. In addition, whereas the correlations between epithelial cells and all immune cell types were exceptionally high (above 0.80), the correlation with fibroblasts was only moderate ($r = 0.26$). Hence, in the analyses, we controlled for the contribution of the percentage of the epithelial and fibroblast cells to account for the different ratio of cell types across samples.

Regulatory structure estimation The biological significance of our findings was examined by appraising the possible function of each CpG using the JASPAR 2024 database[78]. JASPAR is an open-access repository of transcription factor (TF) binding profiles derived from high-throughput experiments and curated datasets. Its 2024 update features expanded coverage of TF binding motifs across diverse species, offering a critical tool for investigating regulatory mechanisms linked to DNA methylation. JASPAR's inclusion in methylation-based analyses adds significant depth to the interpretation of CpG site functionality. By integrating TF binding profiles with CpG DNA methylation data, it becomes possible to hypothesize how DNA methylation at specific loci might influence TF binding, gene regulation, and downstream biological processes. For instance, DNA methylation at CpG sites within TF binding motifs can inhibit binding, thereby altering gene expression patterns and contributing to phenotypic variability or disease susceptibility.

Saliva-to-brain association in DNA methylation levels We utilized the ImageCpG[54] database to estimate the strength of the association between the DNA methylation levels observed in our saliva samples and those in the brain. ImageCpG is a resource designed to identify CpG sites with concordant DNA methylation patterns across peripheral tissues and the central nervous system. By leveraging genome-wide DNA methylation datasets, the database facilitates the identification of CpG sites that are representative of brain DNA methylation, even in non-invasive peripheral samples such as saliva. This is particularly valuable for studies focusing on neurodevelopmental or psychiatric conditions in humans, where direct brain tissue sampling is not feasible. Furthermore, ImageCpG highlights tissue-specific regulatory regions and enables the prioritization of brain-relevant CpG sites, providing a foundation for exploring the functional and regulatory significance of peripheral methylation patterns.

Methylation-expression association We utilized the EWAS open platform[51] to examine the association between DNA methylation levels observed in our samples and the expression (i.e., RNA levels) of the gene associated with each CpG site. The EWAS Open Platform integrates extensive DNA methylation and transcriptomic datasets, providing a comprehensive framework to explore the regulatory relationship between DNA methylation and gene expression. By focusing on CpG sites located within regulatory elements such as promoters, enhancers, and gene bodies, this platform enables the identification of patterns where DNA methylation status is correlated

with transcriptional activity. By integrating expression data, the EWAS Open Platform facilitates the generation of mechanistic insights, bridging the gap between epigenetic regulation and functional gene output.

Loss of a parent during childhood

Participants were asked to indicate whether their father and/or mother passed away before the age of 16 (yes or no).

Attachment patterns

To examine participants' attachment patterns, we employed the Relationship Structures (ECR-RS) questionnaire[79], a self-report measure designed to assess attachment patterns with respect to 4 targets (i.e., mother, father, romantic partner, and best friend) and a general tendency. The same 9 items are used to assess attachment styles, with 6 items appraising attachment avoidance (e.g., "I don't feel comfortable opening up to others"), and 3 assessing attachment anxiety ("I often worry that other people do not really care for me"). Participants are asked to indicate, on a scale from 1 ("strongly disagree") to 7 ("strongly agree"), the extent to which they agree with each item. The average rating score of attachment anxiety and avoidance regarding each target was calculated. The internal consistency values ranged between 0.70 and 0.89 for Cronbach's Alpha and 0.71 and 0.89 for McDonald's Omega, ensuring that the questionnaire demonstrated sufficient reliability in the current sample. Validity was verified by previous research[80,81].

Openness to experience

To examine participants' openness to experience, we used the HEXACO-60 (honesty-humility, emotionality, extraversion, agreeableness, conscientiousness, and openness to experience) questionnaire[34]. The openness to experience domain assesses individual differences in the trait-like tendency to be open to new experiences, measuring 4 aspects of the trait: aesthetic appreciation (e.g., "I would be quite bored by a visit to an art gallery" (reversed)), inquisitiveness (e.g., "I'm interested in learning about the history and politics of other countries"), creativity (e.g., "I would enjoy creating a work of art, such as a novel, a song, or a painting"), and unconventionality (e.g., "I like people who have unconventional views"). Participants were asked to indicate, on a scale from 1 ("strongly disagree") to 5 ("strongly agree"), the extent to which they agree with each item. The average rating score of items in each aspect and the total score were calculated to reflect participants' trait-like tendency to be open to experience. The internal consistency values (alpha and omega) range between 0.61 and 0.67 for the aspects of openness to experience, which is in keeping with previous research, and 0.76 for the total score. Validity was verified by previous research[35].

Data analysis plan

Individual differences in DNA methylation values do not solely reflect biological differences in DNA methylation levels, but also arise from measurement variability (known as the "batch effect", where samples measured in the same kit are more similar than samples measured in different kits), differences in the frequency of the various cell types composing the sample (as DNA methylation values depend on the cell type or tissue from which they are derived)[76,77], and variation due to the biological sex and age of the participants—the data analysis models need to account for and remove these sources of variance to isolate the variance arising from biological differences alone. Finally, the data analysis framework in the current study needs to consider that the participants are not independent, but instead represent couples. Accordingly, multilevel analyses that address both the individual and couple levels were employed. In addition, two common biases in epigenetic analyses need to be addressed by the chosen analysis approach: (1) outliers (participants with extreme values that skew the overall pattern of results) and (2) heteroscedasticity (unequal distribution of observations along the regression line). Robust priors were selected in the Bayesian analytical approach to address these concerns.

Accordingly, a series of Bayesian Mixed-Effects models were used to test the research hypotheses using the *brm* function of the *brms* R package. In each analysis, the loss of a parent (0 = no, 1 = yes) served as the predictor. The outcome variables were (i) the psychological constructs of attachment anxiety and avoidance in each relationship and in general and openness to experience (4 aspects and overall); and (ii) DNA methylation beta-values of CpGs in the oxytocin and dopamine systems. Additionally, to control for the frequency of cells found in each sample, as well as the participant's biological sex and age, these measures were added to the models as covariates. Controlling for the batch effect was done using the *ComBat* function from the *sva* package in R. Finally, controlling for couples' interdependence was achieved by including the couple's sequential number as a random effect. In the Bayesian models, we set two robust priors, one for the regression coefficients and one for the group-level standard deviations. The priors were based on Student's t distribution, which is more robust than a normal distribution; degrees of freedom for the priors were set to 8 to balance robustness with sensitivity, and the scale parameter was set to 0, resulting in a tighter distribution around the mean, assuming smaller effect sizes and less variation as is often the case in DNA methylation-based analysis.

The reported effects are those with Bayesian's 95% credible intervals excluding 0, indicating exceptionally high credibility for the direction of the effect (often accompanied by a "probability of direction" of 97% or higher).

Data availability

Data is publicly available at https://osf.io/5ge4t/.

Code availability

The R code comprising the analytical steps is publicly available at https://osf.io/5ge4t/.

Received: 12 August 2024; Accepted: 5 February 2025
Published online: 10 February 2025

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Author contributions

The study is part of A.S.D. and H.Z. honor's thesis, which was supervised by T.E.; A.S.D. and H.Z. wrote the first draft of the paper, which was edited by T.E., P.V., W.V. and A.S.; T.E. was in charge of the analytical plan and the analyses. N.N.S. provided genetic analysis guidelines and was responsible for the study's ethical approval.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-89467-2.

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