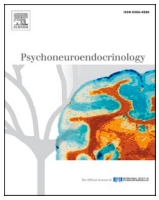
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The creative mind in the shadow of depressive symptoms: Epigenetic variation in HPA axis genes is associated with the link between depressive symptoms and creative personality

Daniel Feinmesser [a], Stav Shohat [a], Roi Gerda [a], Adi Nin Nun [a], Anat Shoshani [a], Nadra Nasser Samra [b,c], Willem Verbeke [d], Pascal Vrticka [e], Tsachi Ein-Dor [a,*]

[a] Reichman University, Israel
[b] Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel
[c] Ziv Hospital Center, Bar-Ilan University, Safed, Israel
[d] Erasmus University, the Netherlands
[e] University of Essex, United Kingdom

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ABSTRACT

This cross-sectional study investigated the relationship between depressive symptoms and creative personality through the lens of epigenetic modifications within Hypothalamic-Pituitary-Adrenal (HPA) axis genes. By analyzing DNA methylation patterns in key HPA axis genes—including corticotropin-releasing hormone (CRH), its receptor (CRHR1), CRH binding protein (CRHBP), melanocortin 2 receptor (MC2R), steroidogenic acute regulatory protein (STAR), FK506 binding protein 5 (FKBP5), and the glucocorticoid receptor (NR3C1), we examined how methylation variation was associated with the depressive symptoms-creativity link in 371 participants (190 women, 181 men). Our findings revealed that among individuals with methylation patterns putatively associated with reduced HPA axis activity, higher depressive symptoms were positively associated with creative personality, suggesting that in this biological context, introspective aspects of depressive symptoms may coincide with creative propensities. Conversely, among individuals with methylation patterns putatively associated with heightened HPA axis activity, higher depressive symptoms were negatively associated with creative personality. These results suggest that the association between depressive symptoms and creativity is not uniform but differs based on methylation variation in genes involved in stress response regulation. The findings highlight the potential role of HPA axis-related biological factors in understanding individual differences in the depression-creativity relationship, though the cross-sectional design precludes causal inference.

1. Introduction

What do Ernest Hemingway, Virginia Woolf, Leo Tolstoy, Vincent van Gogh, Edvard Munch, and Ludwig van Beethoven have in common? Their writings, art, and music have captivated the hearts and minds of millions due to their extraordinary talent and creativity. However, these figures also shared another trait: a profound struggle with depression. This apparent link between depression and creativity has long intrigued researchers (Chambers, 2022; Gino and Ariely, 2012; Nijstad et al., 2010), yet empirical findings remain inconsistent. Some studies report that individuals with depressive symptoms show elevated creative tendencies, particularly among highly artistic populations (Andreasen, 2008; Xu et al., 2021a; Zhao et al., 2021). For example, studies of award-winning writers found high rates of depression (Andreasen, 2008), and examinations of renowned artists revealed similar patterns (Jamison, 1989). In contrast, a meta-analysis of 89 studies examining ADHD, anxiety, and depression in relation to everyday creativity found no overall association, with effect sizes ranging from strongly negative to strongly positive (Paek et al., 2016). The directionality of the depression-creativity association also remains unclear; creative individuals may be predisposed to depression, depression may influence creative processes, or both may stem from shared vulnerability factors such as heightened associational thinking or reduced latent inhibition that, depending on executive function capacity, may either enhance

* Corresponding author.
E-mail address: teindor@runi.ac.il (T. Ein-Dor).

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creativity or predispose to psychopathology (Carson, 2011; Xu et al., 2021a; Zhao et al., 2021).

One potential explanation for these mixed findings lies in the heterogeneity of depressive presentations. Depression is characterized by diverse symptom profiles, ranging from cognitive and emotional heaviness that may constrain innovative thinking, to deep rumination and introspection that, while painful, can occasionally yield novel insights (Crowe et al., 2020; Verhaeghen et al., 2005). This symptomatic heterogeneity may be linked with biological differences in stress-regulatory systems, particularly the Hypothalamic-Pituitary-Adrenal (HPA) axis.

Chronic HPA-axis activation has been linked to cognitive rigidity and reduced exploratory behavior, both of which constrain flexible thinking and creative engagement (Arnsten, 2009; Herman and Cullinan, 1997; Lyons et al., 2009). Elevated cortisol narrows attentional focus and impairs prefrontal functioning, limiting openness to novel ideas (Arnsten, 2009; Guo et al., 2024; Mobbs et al., 2009). In contrast, individuals without chronic HPA hyperactivation may retain greater cognitive flexibility, allowing depressive rumination in some cases to facilitate rather than hinder creative thought (Baas et al., 2008; Gabrys et al., 2018).

To examine whether individual differences in HPA axis function are associated with the depression-creativity link, we investigated epigenetic modifications within key HPA axis genes. DNA methylation, a well-characterized epigenetic process involving the addition of methyl groups to CpG sites, can modulate gene expression in response to environmental factors (Greenberg and Bourc'his, 2019; Pérez et al., 2019). Importantly, methylation patterns are dynamic and reversible (Weaver et al., 2005), and variation in HPA-related genes has been linked to individual differences in stress reactivity (Huan et al., 2020). We focused on genes spanning the HPA axis cascade: corticotropin-releasing hormone (CRH) and its receptor (CRHR1) for stress response initiation; CRH binding protein (CRHBP) for CRH regulation; pro-opiomelanocortin (POMC) and the melanocortin 2 receptor (MC2R) for adrenocorticotropic hormone (ACTH) signaling; steroidogenic acute regulatory protein (STAR) for cortisol synthesis; and FK506 binding protein 5 (FKBP5) and the glucocorticoid receptor (NR3C1) for feedback regulation.

We predicted that the association between depressive symptoms and creative personality would differ based on HPA axis methylation patterns. Specifically, we hypothesized that depressive symptoms would be positively associated with creative personality among individuals whose methylation patterns are linked to reduced HPA axis activity, potentially reflecting a context where introspective aspects of depression can be channeled toward creative thinking without the cognitive constraints imposed by chronic stress responses. Conversely, we predicted that depressive symptoms would be negatively associated with creative personality among individuals whose methylation patterns are linked to heightened HPA axis activity, consistent with research showing that amplified stress responses impair cognitive flexibility and divergent thinking (Guo et al., 2024).

2. Methods

2.1. Participants

The study initially involved 384 participants. However, biological samples from 11 participants were deemed low quality due to either having 5 % low-quality methylation data points across probes or bisulfite intensity scores falling more than three standard deviations below the mean. Additionally, 2 participants opted out of completing the psychological assessments. As a result, the final analyses included data from 371 participants, of whom 190 were women (mean age = 28.80, SD = 3.16) and 181 were men (mean age = 30.24, SD = 3.39). Participants were recruited as couples planning their first pregnancy, and the current investigation draws on Wave 1 data collected prior to conception, when none of the participants had children. Given the use of Bayesian hypothesis testing, a power analysis was not conducted. Instead, a minimum threshold of bulk and tail effective sample sizes (ESS) greater than 400 was applied to ensure the reliability and stability of the central tendency estimates, variability, and credible intervals of the parameters. This study is part of the larger longitudinal "Project Alpha," pre-registered at https://osf.io/kcns7/. It received ethical approval from Reichman University's Institutional Review Board and the Helsinki Committee of the Israel Ministry of Health (approval number 5–2020). The specific hypotheses examined in the current study were pre-registered at https://osf.io/tq859/ prior to conducting the analyses. The project-level pre-registration establishes the overarching longitudinal design and data collection protocol, while the study-specific pre-registration documents the hypotheses and analytic plan for the current investigation, formalized before any analyses were performed on these data. Inclusion and exclusion criteria are depicted in the Supplementary Information file.

2.2. Measures

2.2.1. 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 (Nunes et al., 2012). 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 methylation sites. Raw data was saved in iDAT (Illumina Data) files.

Normalization and correction of methylation values. In the comprehensive preprocessing of methylation data derived from the Illumina MethylationEPIC v2 kit, a series of advanced normalization and correction techniques were employed to ensure the highest quality and comparability of 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 methylation signal. This was followed by norm.quantile, also from the ENmix package, to apply quantile normalization across samples. This crucial step adjusts 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 from ENmix, aimed at correcting probe design type biases by adjusting the 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 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 methylation data — significantly improves the accuracy and biological relevance of downstream analyses, facilitating a deeper understanding of epigenetic patterns and their implications.

Following the preprocessing phase, which included normalization

and correction procedures, we filtered out CpG sites deemed unsuitable for further analysis using a pipeline consistent with established practices for Illumina methylation arrays. Probes with multimodal methylation distributions ("gap probes") were identified using the nmode function from the ENmix package and excluded from all subsequent analyses. ENmix has been shown to outperform alternative normalization approaches (e.g., noob, funnorm), increasing the proportion of high-reliability CpG sites (ICC > 0.75) from approximately 10 % to 29–37 % across 450k and EPIC arrays, directly supporting its use for gap probe removal in HPA axis genes such as FKBP5 and NR3C1.

Next, we eliminated CpG sites exhibiting less than a 7 % interquartile range (IQR) in their beta values. This threshold was established a priori, consistent with our pre-registered analysis plan and with the same filtering criterion applied in our prior published epigenome-wide studies using the same analytical pipeline (Dvilansky et al., 2025; Oren et al., 2025). The 7 % IQR criterion corresponds to a standard deviation of approximately 0.05 on the beta scale (IQR ≈ 1.35 × SD for normally distributed data). Xu and Taylor (Xu et al., 2021b; Xu and Taylor, 2021), using 128 technical replicate pairs on the Illumina 450 K array, demonstrated that this SD value marks a reliability transition point: 87 % of CpGs with SD < 0.05 exhibited poor measurement reliability (intraclass correlation coefficient [ICC] < 0.5), whereas 95 % of CpGs with SD ≥ 0.05 achieved acceptable reliability (ICC > 0.5). Critically, after mutual adjustment for methylation level and variance, only variance remained correlated with ICC, establishing variance as the key determinant of probe reliability. We opted for IQR rather than SD because IQR is robust to extreme values: individuals with exceptionally high or low methylation can inflate SD substantially even when variance across most of the distribution is low, whereas IQR, by focusing on the middle 50 % of observations, provides a more stable measure of biological variability that is less influenced by outliers (see Supplementary Figure 1). This approach is consistent with broader evidence that variance-based CpG filtering effectively selects for measurement reliability: CpGs with adequate variability substantially overlap with those exhibiting high ICC, while low-variance sites tend to reflect technical noise rather than biological signal (Bose et al., 2014; Chen et al., 2016; Sugden et al., 2020). Among smoking-associated CpGs, 96 % fall within high-reliability probe clusters (ICC > 0.5; Bose et al., 2014), and 96.7 % of age-associated CpGs exceed the median ICC threshold (Chen et al., 2016). CpGs with higher variance also demonstrate greater responsiveness to environmental perturbations, as low-variance sites tend to remain stable while variable sites capture dynamic gene–environment interactions relevant to stress and related exposures. Thus, our variance-based filtering (IQR > 7 %) effectively selects for CpGs with both sufficient biological signal and high measurement reliability.

After this filtering phase, 157,909 methylation sites remained eligible for further analyses. This preprocessing and filtering pipeline was developed in our laboratory and has been applied successfully in previous epigenome-wide association studies (Dvilansky et al., 2025; Oren et al., 2025). For the current study, we selected all CpGs from this filtered set that mapped to HPA axis genes, an approach consistent with HPA-focused epigenome-wide studies that routinely apply similar filtering before selecting approximately 70–250 CpGs from stress-related genes for targeted analyses. Specifically, we selected CpG sites from genes spanning the HPA-axis cascade, including initiation (CRH, CRHR1, CRHBP), intermediate ACTH signaling (POMC, MC2R), and cortisol synthesis and feedback regulation (STAR, FKBP5, NR3C1). Seventy-two methylation sites on these genes passed the filtering criteria and were included in the analysis, falling within the typical range for HPA-targeted methylation studies. Detailed information for each CpG site, including probe identifiers, genomic coordinates, and genomic context (promoter, gene body, or enhancer region), and gene function is provided in Supplementary Table 3.

2.2.1.1. Regulatory structure estimation. The biological significance of our findings was examined by appraising the possible function of each CpG using the JASPAR 2024 database (Rauluseviciute et al., 2023). 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 DNA methylation. JASPAR's inclusion in DNA 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.

2.2.1.2. DNA methylation-expression association. We utilized the EWAS Open Platform (Xiong et al., 2022) to examine the relationship between the DNA methylation levels observed in our samples and the expression (i.e., RNA levels) of the genes 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 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 correlates 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. The current EWAS Open Platform DNA methylation data is based on Illumina's 450k DNA methylation kit, so it only partially covers the CpGs studied in this research derived from Illumina's DNA methylationEPIC v2 kit.

2.2.1.3. Estimation of cell type composition. Research has noted that different cell types have distinct methylation profiles, suggesting that a portion of the variance in methylation values stems from differences in cell type composition between participants (Zhang et al., 2013; Zheng et al., 2018). These differences should be accounted for in analyses. To estimate the cell type composition of each sample, we employed the HEpiDish package (Zheng et al., 2018). The distribution of cell types is presented in Supplementary Figure 2, while the correlation between the ratios of different cell types can be seen in Supplementary Figure 3. The most prevalent cell types were neutrophils and epithelial cells. Furthermore, while the correlations between epithelial cells and all immune cell types were exceptionally high (r > .80), the correlation with fibroblasts was only moderate (r = .26). Therefore, in our analyses, we controlled for the contributions of the percentages of epithelial and fibroblast cells to account for the varying ratios of cell types across samples.

2.2.2. Depressive symptoms

To assess participants' depressive symptoms, we utilized the Brief Symptom Inventory-18 (BSI-18) (Derogatis, 2001). This self-report questionnaire consists of 18 items rated on a 5-point scale (0 = not at all to 4 = extremely), reflecting distress experienced in the past week. Of these items, six specifically target depressive symptoms (e.g., "Feeling hopeless about the future"). The internal consistency of the depression subscale in our sample was adequate, with Cronbach's Alpha at.73 and McDonald's Omega at.76, ensuring reliability. Previous research has validated its use (Recklitis et al., 2017). The BSI-18 depression subscale is strongly correlated with other established measures, such as the Patient Health Questionnaire (r = .72) (Franke et al., 2017) and the Beck Depression Inventory (r = .77) (Prinz et al., 2013). Scores ranged from 0 to 18, and based on Heinrich et al., (1994), 14 % of the sample were

identified as high-risk for depression.

2.2.3. Creative personality

To assess participants' creative personality levels, we utilized the 60-item HEXACO Personality Inventory (HEXACO-PI) (Ashton and Lee, 2009). The creativity subscale comprises three self-report items rated on a 5-point scale (1 = strongly disagree to 5 = strongly agree; e.g., "I don't think of myself as the artistic or creative type" [reversed]). The internal consistency of the creativity subscale in our sample was adequate, with Cronbach's Alpha at.70 and McDonald's Omega at.73, ensuring reliability. Previous research has validated its use (Ashton and Lee, 2009). The HEXACO-PI creative personality subscale correlates with other established measures, such as Hocevar's creative behavior inventory (Hocevar, 1980) (comprised 77 activities that are deemed as creative, e.g., "Worked as an editor for a newspaper or similar organization."), Gough's creative personality scale (Gough, 1979) (comprised adjectives such as clever, inventive, insightful, and original), and creative cognitive style (Gino and Ariely, 2012) (e.g., "I have a lot of creative ideas").

2.3. Procedure

This study is part of Project Alpha, a pre-registered longitudinal study designed to investigate genetic and epigenetic correlates of various psychological phenomena across the family lifespan, comparable in scope to Generation R in the Netherlands. The project follows families from couple formation through child development, beginning with couples before their first pregnancy and tracking them and their future families over a 20-year period. The current investigation utilizes data from Wave 1 — the pre-pregnancy assessment when all participating couples did not yet have children — and represents a cross-sectional examination of this baseline data.

Recruiting a large cohort for a long-term longitudinal study presents challenges, particularly in minimizing attrition. Participants were recruited through a targeted social media campaign in collaboration with an advertising agency, targeting young Israeli couples planning to start families. To support retention, participants received a monetary incentive (100 ILS per assessment) and access to an online knowledge center with research-based information relevant to prospective parents. Study information and registration were managed through a dedicated project website.

Sampling took place at a location convenient for the participants, either at Reichman University or their residence, based on their preference. Prior to sampling, participants were reminded to fast for 30 min to ensure the accuracy of the saliva samples. Upon arrival, participants provided informed consent and were briefed on the study's objectives and procedures. Saliva samples were collected using the Oragene-DNA OG-600 kit, which collects 2 ml of saliva, yielding approximately 110 μg of DNA, and ensures high specimen stability at room temperature for up to 5 years. The samples were then shipped at room temperature to the Genomics Core Facility of Erasmus Medical Center in Rotterdam, where DNA was extracted, isolated, and normalized using the internal protocols of the Human Genomics Facility (HuGe-F). An epigenome-wide DNA methylation scan was conducted using Illumina's Infinium® MethylationEPIC v2 BeadChip, which provides methylation data across approximately 935,000 sites. Following the sampling, participants engaged in a series of documented interactions (not within the scope of the current study). Subsequently, participants completed a series of questionnaires via the Qualtrics platform, including the Brief Symptom Inventory-18 (BSI-18) to assess depressive symptoms, the HEXACO Personality Inventory (HEXACO-PI) to measure creative personality traits, and a socio-demographic questionnaire. The session lasted approximately an hour and a half, and participants received 100 ILS for their time and contribution.

Given the broad aims of Project Alpha across multiple psychological domains, Wave 1 included the BSI-18 as the sole measure of psychopathological symptoms and the HEXACO-PI creativity subscale as the sole measure of creative tendencies. No direct measures of stress (e.g., perceived stress questionnaires, cortisol assays, or life event inventories) were included in Wave 1, which limits our ability to directly assess stress exposure in relation to HPA axis methylation patterns.

2.4. Data analysis plan

Individual differences in methylation values are not purely indicative of biological differences but are also influenced by measurement variability, known as the "batch effect" (where samples processed with the same kit show more similarity than those processed with different kits). Additionally, differences in cell type composition (as methylation values vary based on the originating cell type or tissue) (Zhang et al., 2013; Zheng et al., 2018), as well as the participant's biological sex and age, contribute to these variations. Therefore, data analysis models must account for and eliminate these sources of variability to reflect biological differences accurately.

Furthermore, the current study's data analysis must acknowledge that participants are couples rather than independent individuals. Consequently, multilevel analyses were employed to address both individual and couple levels. Two common biases in epigenetic analyses were also considered: (1) outliers (extreme values that can skew results) and (2) heteroscedasticity (unequal distribution of observations along the regression line). To mitigate these issues, robust priors were utilized in a Bayesian analytical approach.

The research hypothesis was tested using Bayesian mixed-effects models with the *brm* function from the *brms* R package. In these models, the outcome variable was creative personality, with predictors being self-reported depressive symptoms, methylation beta-values of CpGs in the HPA axis, and their interaction. To prevent multicollinearity, these measures were centered around the sample mean. The frequency of epithelial and fibroblast cells, the participant's biological sex, and age were included as covariates to account for their contributions to the results. The batch effect was controlled using the *ComBat* function from the *sva* R package, and couples' interdependence was managed by incorporating the couple's identifier number as a random effect. Significant interactions were examined through simple slope tests using the *interactions and effects* R packages.

The analysis employed Monte Carlo Markov Chains (MCMC), a robust computational method that iteratively samples from probability distributions to approximate the posterior distributions of the parameters. MCMC offers several significant advantages over traditional regression models for this study's design and data structure. First, Bayesian mixed models yield full posterior distributions for fixed effects, random effects, and variance components, which is especially valuable when random effects are a primary substantive focus—in our case, couple-level effects. This approach avoids the small-sample and boundary problems that often affect maximum-likelihood estimates of random effects in frequentist mixed models. Second, partial pooling and shrinkage in hierarchical Bayesian models stabilize estimates when group sizes are small or unbalanced, reducing overfitting and extreme estimates that can arise with classical multilevel models. Third, posterior probabilities and information criteria (such as WAIC/LOO) allow direct probability statements about parameters and more coherent model comparison than null-hypothesis significance testing with p-values. Fourth, MCMC-based Bayesian models naturally accommodate missing data under missing-at-random (MAR) assumptions and latent constructs (e.g., random intercepts/slopes representing unobserved couple-level tendencies), integrating over uncertainty rather than relying on ad-hoc imputation. Fifth, it is straightforward to specify non-Gaussian likelihoods (e.g., skewed, heavy-tailed, or mixture distributions), which can better match methylation and symptom distributions than standard linear regression assumptions. These properties are particularly beneficial in high-dimensional dyadic data, where reliable estimation of random effects and variance components is crucial for understanding couple-level psychological and epigenetic processes.

Additionally, Bayesian approaches provide more accurate uncertainty quantifications through credible intervals, thus enhancing the interpretability and reliability of the findings.

In the Bayesian models, two robust priors were set: one for the regression coefficients and one for the group-level standard deviations. These priors were based on Student's t distribution, which is more robust than a normal distribution, with degrees of freedom set to 8 and the scale parameter set to 0, resulting in a tighter distribution around the mean. The biological significance of the findings was assessed using the JASPAR 2024 database (Rauluseviciute et al., 2023) to evaluate the potential function of each CpG, and by associating the level of methylation with that of RNA expression using the EWAS open platform (Xiong et al., 2022). The latter database derives methylation-expression associations based on Illumina's 450k methylation kit; consequently, data is not available for all CpG sites in the current analyses. The reported effects include Bayesian 95 % credible intervals that exclude 0, indicating a high likelihood of the effect's direction, often accompanied by a probability of direction of 97 % or higher.

3. Results

3.1. Results are presented in Supplementary Table 1

3.1.1. Direct effects of HPA axis methylation on creative personality

The analyses identified two credible direct effects of HPA axis methylation on creative personality: FKBP5's cg07696519 and CRHBP's cg26261055 sites. According to the JASPAR 2024 database (Rauluseviciute et al., 2023), both sites are located within binding sites associated with gene activation – FKBP5's cg07696519 within a heat shock factor 1 (HSF1) binding site (Gomez-Pastor et al., 2018), and CRHBP's cg26261055 within an ELK1::HOXA1 complex binding site (Besnard et al., 2011). Methylation-expression correlations from the EWAS Open Platform (Xiong et al., 2022) inform the functional interpretations described below and are reported in Supplementary Table 2.

The analyses indicated that higher methylation at FKBP5's cg07696519 was linked to greater creative personality. Based on the regulatory context identified through JASPAR and the methylation-expression associations from the EWAS Open Platform, this increased methylation likely reduces FKBP5 expression, leading to diminished suppression of the HPA axis's negative feedback loop, thereby potentially enhancing stress alleviation capability and creative potential. Lower methylation at CRHBP's cg26261055 was also associated with greater creative personality. Based on the same databases, lower methylation at this site likely increases CRHBP expression, heightening the suppression of CRH activation and resulting in more subdued HPA axis activation.

3.1.2. HPA axis methylation moderates the association between depressive symptoms and creative personality

Our analyses furthermore identified a widespread moderating effect of HPA axis methylation on the relationship between self-reported depressive symptoms and creative personality. Specifically, the results revealed twenty credible interactions between HPA axis methylation and depressive symptoms. These interactions span different phases of the HPA axis: the initiation phase (7 interactions involving the CRHR1

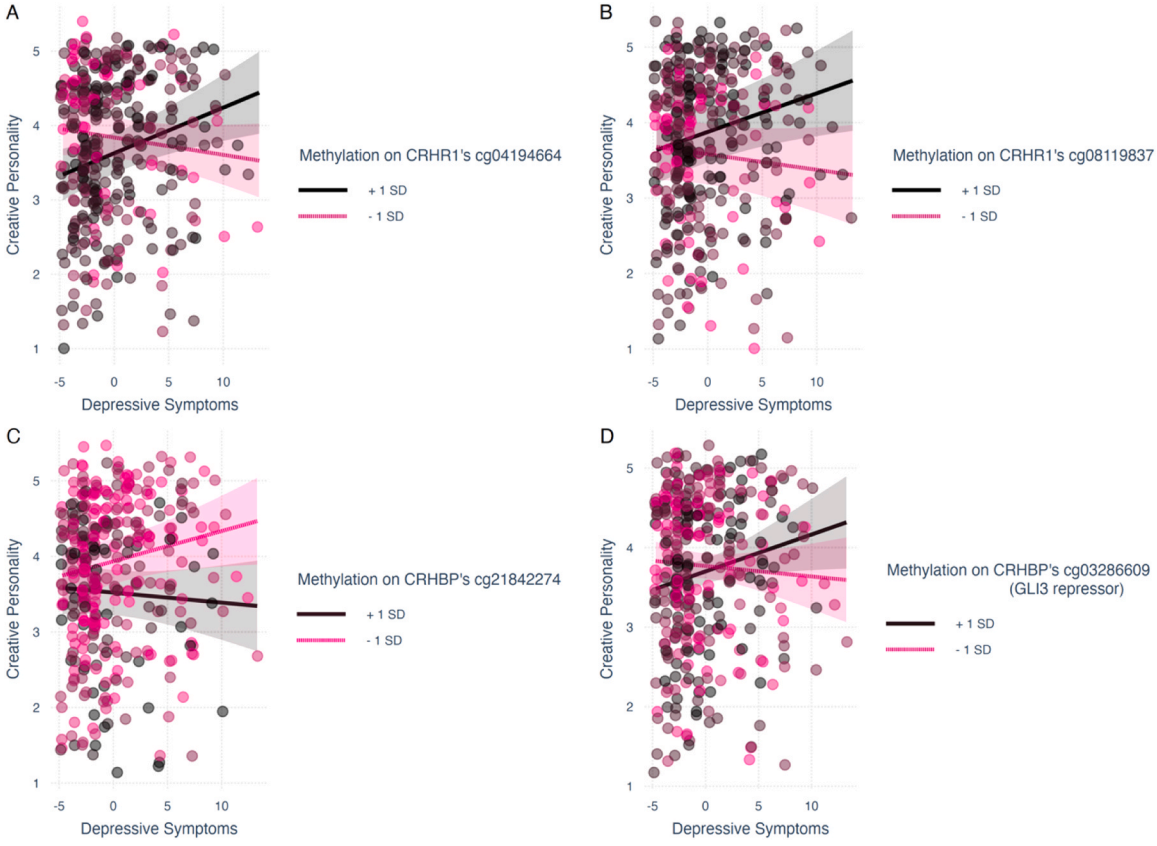


Fig. 1. Credible interactions between self-reported depressive symptoms (x-axis), creative personality (y-axis) and level of methylation (colored lines) on CRHR1's cg004194664 (A) and cg08119837 sites (B), and CRHBP's cg21842274 (C), and cg03286609 sites (D). As evidenced by simple slopes analyses (Supplementary Table 2), depression was positively correlated with creativity among participants with a methylation pattern associated with dampened CRH activity (i.e., increased methylation). Conversely, depression was negatively correlated with creativity among participants with a methylation pattern associated with increased CRH activity (i.e., decreased methylation). Please note that the CRHBP's cg03286609 site depicted in (D) is located within a GLI3 binding site, which acts as a repressor following embryogenesis. This means that high methylation presumably relates to higher activation because it suppresses the repressor construct.

and CRHBP genes), the intermediate phase of ACTH activation (2 interactions involving the MC2R gene, which encodes ACTH's receptor), and the termination phase of the axis (11 interactions involving the STAR, FKBP5, and NR3C1 genes). Exemplary effects are illustrated in Fig. 1 (CRH-related), 2 (ACTH-related), and 3 (cortisol activation and the negative feedback loop). The results of simple slope analyses for all interactions are presented in Supplementary Table 2 alongside the methylation-expression correlations that inform the functional interpretations. The entire set of findings portrays a cohesive and consistent pattern.

Regarding CRH-related genes and the initiation of the HPA stress axis, the analyses revealed that only among participants with a methylation pattern putatively associated with lower CRHR1 expression (indicating fewer CRH receptors) and higher CRHBP expression (indicating a greater ability to suppress CRH activation) were depressive symptoms positively correlated with creative personality. Similarly, only among participants with a methylation pattern putatively associated with lower MC2R expression (fewer ACTH receptors) and lower STAR expression (reduced cortisol synthesis) were depressive symptoms positively correlated with creative personality. Finally, only among participants with a methylation pattern putatively associated with higher NR3C1 expression (enhanced ability to alleviate stress via the negative feedback loop) and lower FKBP5 expression (reduced suppression of the negative feedback loop) were depressive symptoms positively correlated with creative personality.

As predicted, we also found the opposite pattern among participants with a methylation pattern putatively associated with higher HPA activity. Specifically, among participants with a methylation pattern putatively associated with higher CRHR1 expression (indicating more CRH receptors) and lower CRHBP expression (indicating a decreased ability to suppress CRH activation), depressive symptoms were negatively correlated with creative personality. Similarly, among participants with a methylation pattern putatively associated with higher MC2R expression (more ACTH receptors) and higher STAR expression (increased cortisol synthesis), depressive symptoms were also negatively correlated with creative personality. Finally, among participants with a methylation pattern putatively associated with lower NR3C1 expression (dampened ability to alleviate stress via the negative feedback loop) and higher FKBP5 expression (increased suppression of the negative feedback loop), depressive symptoms were once more negatively correlated with creative personality.

In summary, our findings suggest that depressive symptoms are linked to a creative personality primarily when methylation patterns are putatively associated with reduced HPA axis activity, from its initiation through to its cessation. In contrast, depressive symptoms are associated with lower creativity when methylation patterns are putatively associated with heightened HPA axis activity, from its commencement to termination.

3.1.3. *Bayesian multiplicity control*

To address the multiple-testing burden inherent in epigenome-wide analyses, we applied Bayesian multiplicity control methods alongside enrichment analyses to strengthen biological interpretation. Rather than relying on traditional frequentist false discovery rate (FDR) correction, which can be overly conservative for Bayesian analyses, we employed three complementary approaches: (1) Bayesian False Sign Rate (FSR)

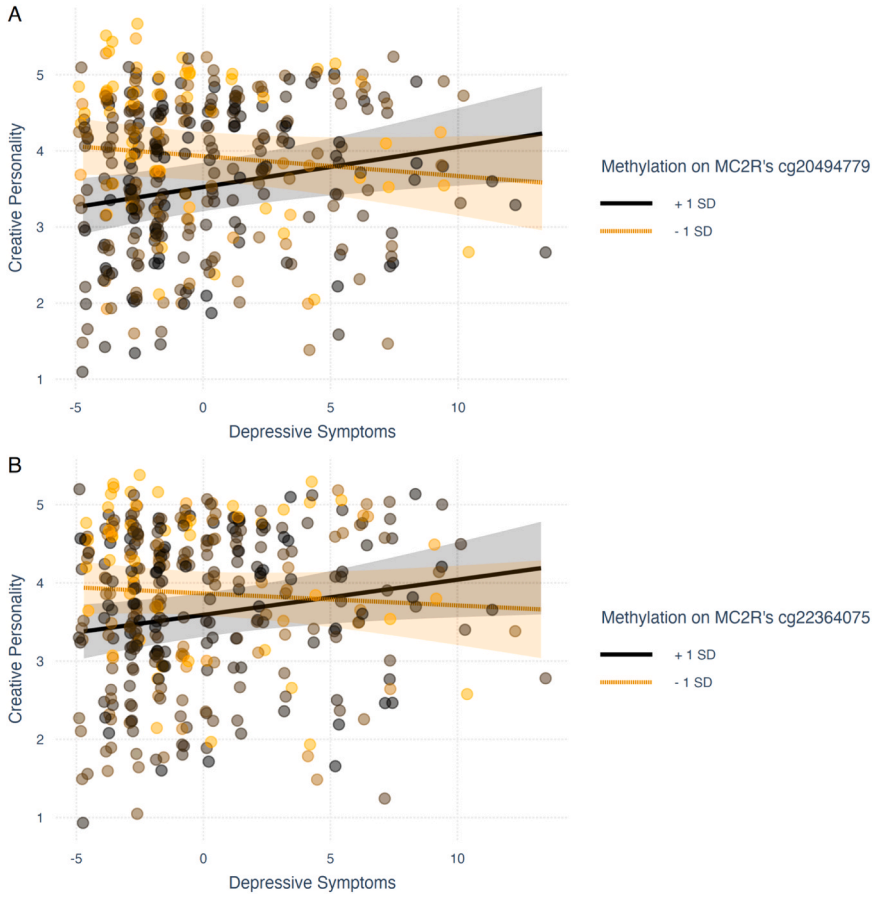


Fig. 2. Credible interactions between depressive symptoms (x-axis), creative personality (y-axis) and level of methylation (colored lines) on MC2R's cg20494779 (A) and cg22364075 sites (B). As evidenced by simple slopes analyses (Supplementary Table 2), depression was positively correlated with creativity among participants with a methylation pattern associated with dampened ACTH activity (i.e., increased methylation – black lines). Conversely, depression was negatively correlated with creativity among participants with a methylation pattern associated with increased ACTH activity (i.e., decreased methylation – orange lines).

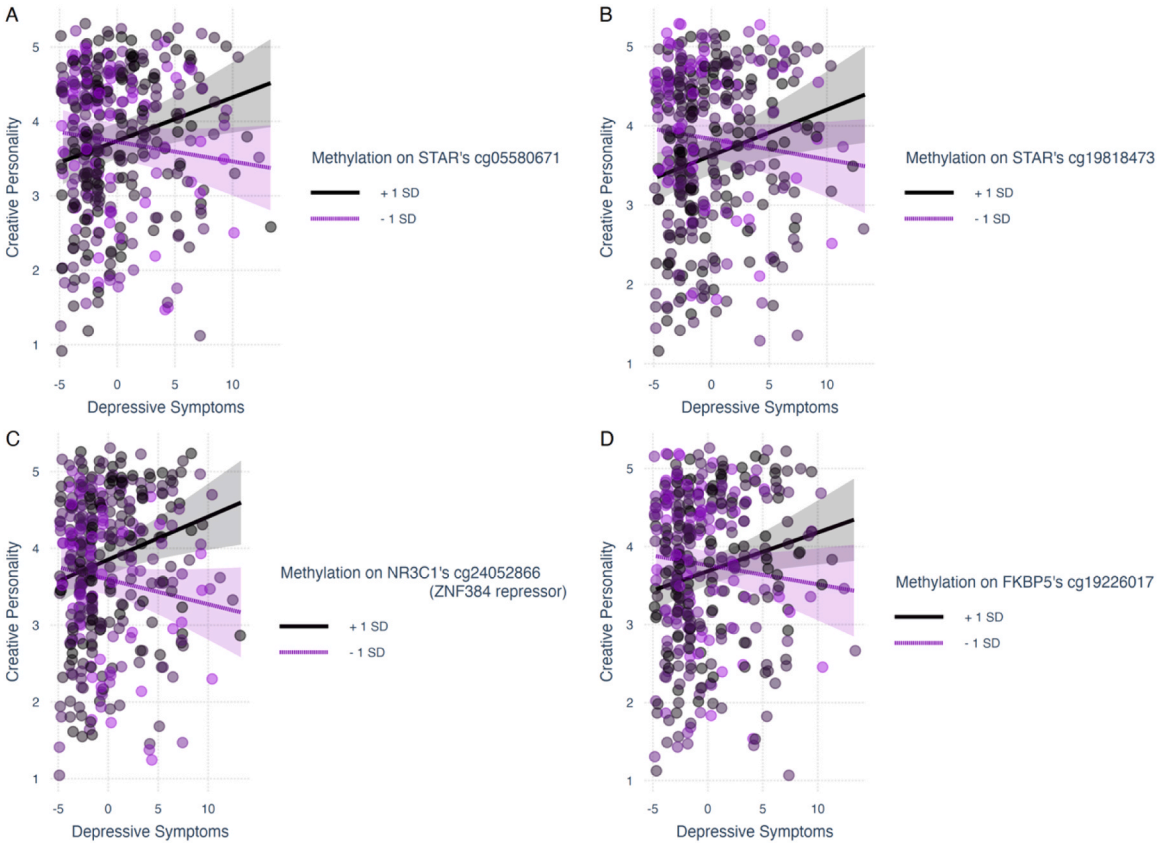


Fig. 3. Credible interactions between depressive symptoms (x-axis), creative personality (y-axis) and level of methylation (colored lines) on STAR's cg05580671 (A) and cg19818473 sites (B), NR3C1's cg24052866 (located within a ZNF384 binding site, which acts as a repressor by recruiting co-repressors or interacts with other transcription factors to repress gene expression) (C), and FKBP%'s cg19226017 sites. As evidenced by simple slopes analyses (Supplementary Table 2), depression was positively correlated with creativity among participants with a methylation pattern associated with dampened cortisol activity and higher affinity of HPA's negative feedback loop (i.e., higher methylation – black lines). Conversely, depression was negatively correlated with creativity among participants with a methylation pattern associated with increased cortisol activity and lower affinity of HPA's negative feedback loop (i.e., lower methylation – purple lines).

control using local false sign rate (lfsr = 1 - pd), (2) adaptive shrinkage methods via the ASH algorithm, and (3) hybrid approaches using the mcp.project package for comparative validation.

We considered $\alpha = 0.05$ as our primary discovery threshold, with $\alpha = 0.10$ and 0.15 reported as exploratory cut-offs for hypothesis generation. The FSR control method, which directly utilizes our posterior probability of direction values, identified 57 discoveries at $\alpha = 0.05$, 78 at $\alpha = 0.10$, and 85 at $\alpha = 0.15$. The latter should be interpreted as exploratory findings under a relaxed error tolerance. The adaptive shrinkage approach (ASH), known for its conservative yet powerful performance, confirmed 26 discoveries at lfsr ≤ 0.05 and 56 at lfsr ≤ 0.15. These findings demonstrate substantial evidence for methylation × depression interactions, with discovery rates far exceeding what would be expected by chance alone.

The convergence of evidence across methods was particularly notable for our strongest findings. The top-ranking interactions, including CRHR1's cg04194664, NR3C1's cg24052866, and STAR's cg05580671 and cg19818473, consistently emerged as discoveries across all approaches, with lfsr values as low as 0.0007, providing very strong evidence for effect direction. These interactions represent the most reliable evidence for HPA axis methylation moderating the depression-creativity relationship.

4. Discussion

The link between depressive symptoms and creativity has long fascinated researchers. While some argue that the emotional depths of depression may fuel creative insight, others suggest that the cognitive impairments associated with depressive states could hinder creative expression (Andreasen, 2008; Baas et al., 2008; Chambers, 2022; Gino and Ariely, 2012; Jamison, 1989). Our study sought to explore this complex relationship by examining how epigenetic modifications within HPA axis genes are associated with creative personality in individuals reporting varying levels of depressive symptoms.

In line with our predictions, we found that among individuals with methylation patterns putatively indicative of reduced HPA axis activity, such as patterns associated with lower expression of CRH receptors, decreased ACTH receptor activity, and enhanced stress regulation via the negative feedback loop, higher depressive symptoms were associated with higher levels of creative personality. We observed the opposite pattern among individuals with methylation patterns putatively associated with heightened HPA axis activity. These findings suggest that the relationship between depressive symptoms and creativity is not uniform but may instead be associated with biological factors involved in stress response regulation.

Our findings are consistent with previous research indicating that chronic stress, often linked to prolonged HPA axis activation, is associated with cognitive rigidity and a reduced capacity for open-ended problem-solving and innovation (Herman and Cullinan, 1997; Lyons et al., 2009; Mobbs et al., 2009). One interpretation of our results is that the link between depressive symptoms and creative personality in individuals with methylation patterns associated with reduced HPA axis activity may reflect decreased cognitive rigidity and increased cognitive flexibility. Additionally, depressive symptoms themselves, such as repetitive rumination and deep thinking (Lyubomirsky et al., 2015), may play a role. When individuals are not constrained by survival-oriented,

rigid thinking patterns that may accompany an overactive HPA axis, the deep rumination characteristic of depressive states (Xu et al., 2021a) might, under certain conditions, facilitate novel associations and creative insights. Thus, it may be the combination of methylation patterns associated with reduced HPA axis activity and the introspective processes accompanying depressive symptoms that relates to creative thinking in these individuals.

However, alternative explanations for our findings must be considered. First, the directionality of associations remains unclear. Creative individuals may be predisposed to experience depressive symptoms, or both creativity and depressive symptoms may stem from shared vulnerability factors, such as heightened associational thinking or reduced latent inhibition, that manifest differently depending on individual differences in stress regulation (Carson, 2011). Second, the observed methylation patterns may not reflect stress exposure per se but could instead represent stable individual differences in HPA axis regulation that independently influence both mood and cognitive style. Third, unmeasured confounders, such as personality traits, lifestyle factors, or concurrent psychiatric symptoms, may account for some of the observed associations.

The observed associations between methylation variation in genes such as CRHR1, MC2R, STAR, FKBP5, and NR3C1 and the depressive symptoms-creativity relationship are consistent with the notion that stress regulation mechanisms may be relevant to understanding when depressive symptoms co-occur with creative tendencies. For instance, higher methylation at FKBP5's cg07696519, which based on JASPAR and EWAS Open Platform data is putatively associated with reduced FKBP5 expression, was linked to higher creative personality scores, possibly reflecting more effective termination of stress responses. Similarly, lower methylation at CRHBP's cg26261055, putatively associated with enhanced CRH suppression, was also associated with higher creativity. These patterns suggest that methylation variation in HPA axis genes may be one biological factor, among potentially many, that relates to the depression-creativity association.

While our study provides valuable insights, it is not without limitations. First, the cross-sectional design of the current study prevents us from establishing temporal precedence or causal relationships among HPA axis methylation, depressive symptoms, and creativity. Longitudinal research is needed to determine whether methylation patterns precede and predict changes in depressive symptoms or creative output, or whether these associations reflect concurrent or reverse-causal processes.

Second, depressive symptoms and creative personality were assessed exclusively via self-report subscales (BSI-18 and HEXACO-PI, respectively) rather than clinical diagnoses or behavioral measures. Self-report measures are subject to response biases and may not fully capture the constructs of interest. Future research would benefit from incorporating clinical interviews, behavioral creativity tasks, and multi-informant assessments.

Third, no direct measures of stress exposure were included in the current study (e.g., cortisol assays). Consequently, we cannot determine whether participants' methylation patterns reflect antecedent stress exposure, consequences of depressive or other physiological states, or stable individual differences unrelated to environmental stress. The term "HPA axis activity" as used throughout this manuscript refers to inferred functional associations based on methylation patterns and external databases (JASPAR, EWAS Open Platform), not direct measurements of HPA axis function in our sample.

Fourth, the use of peripheral tissue (saliva samples) for methylation analysis may not fully capture epigenetic modifications occurring in brain regions directly involved in creativity and mood regulation. Although saliva-derived methylation has been used in psychiatric epigenetics research, tissue-specific effects may limit generalizability to central nervous system processes.

Fifth, our sample represents a convenience sample of young Israeli couples planning their first pregnancy, which may limit generalizability to other populations, age groups, or relationship configurations. The specific demographic and cultural context of our sample should be considered when interpreting findings.

Sixth, although our hypotheses were pre-registered prior to analysis, the measures available in Wave 1 of Project Alpha constrained the constructs we could examine. The BSI-18 depression subscale and HEXACO-PI creativity subscale were the only available measures of these constructs, and we utilized all post-filtered CpG sites from HPA axis genes rather than selecting specific sites. While this comprehensive approach reduces concerns about selective reporting, the exploratory nature of examining 72 CpG sites should be acknowledged. We addressed multiple testing through Bayesian multiplicity control methods, and the convergence of findings across HPA axis genes strengthens confidence in the overall pattern, but replication in independent samples remains essential.

Finally, as outlined in our recent perspective on the biology of depressive symptoms (Levin and Ein-Dor, 2023), multiple neurobiological pathways may link depressive symptoms with inflammatory processes. These may include immune-related shifts in tryptophan metabolism along the kynurenine pathway, whereby pro-inflammatory cytokines can alter the balance between serotonin and neuroactive kynurenine metabolites; stress-related modulation of glucocorticoid signaling and HPA-axis feedback, which can interact with immune activity; and neuroendocrine pathways involving reproductive hormones and oxytocin that may shape both inflammatory tone and stress regulation. These pathways likely operate in partially overlapping and heterogeneous ways across individuals rather than as a single unified mechanism. Future studies could therefore examine the association between depressive symptoms and creativity from an inflammatory perspective, including potential epigenetic variation in immune-, stress-, and neuroendocrine-related genes.

Despite these limitations, our findings contribute to the growing literature on the epigenetic correlates of complex psychological traits. The results suggest that methylation variation in HPA axis genes may be one factor associated with individual differences in how depressive symptoms relate to creative personality. Rather than a uniform relationship between depression and creativity, the association may differ based on biological factors involved in stress regulation. These findings underscore the potential value of incorporating epigenetic measures in psychological research, while highlighting the need for longitudinal designs, direct measures of stress and HPA axis function, and replication across diverse samples. As Norwegian painter Edvard Munch observed: "Without anxiety and illness, I should have been like a ship without a rudder… My sufferings are part of myself and my art. They are indistinguishable from me, and their destruction would destroy my art."

CRediT authorship contribution statement

Roi Gerda: Investigation, Data curation, Conceptualization. **Adi Nin Nun:** Investigation, Data curation, Conceptualization. **Daniel Feinmesser:** Methodology, Investigation, Conceptualization. **Stav Shohat:** Investigation, Data curation, Conceptualization. **Tsachi Ein-Dor:** Writing – original draft, Visualization, Validation, Supervision, Project administration, Formal analysis. **Pascal Vrticka:** Writing – review & editing. **Nadra Nasser Samra:** Methodology. **Verbeke Willem JMI:** Writing – review & editing. **Anat Shoshani:** Writing – review & editing.

Declaration of Competing Interest

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

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Code availability

The R code comprising the analytical steps is publicly available at https://osf.io/tq859/.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2026.107783.

Data availability statement

Data is publicly available at https://osf.io/tq859/.

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