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ORIGINAL ARTICLE

Methylome and transcriptome analysis reveal the impact of psychological stress on the skin

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Abstract

Psychological stress is increasingly recognized as an important determinant of human skin health, but the molecular and epigenetic mechanisms by which it affects the epidermis are still not well understood. To investigate whether psychological stress is associated with molecular differences in the epidermis, and how these might relate to skin phenotypes, we performed a multi-omics study in 60 stressed and 60 relaxed young adults. From lower-back epidermal samples, we generated DNA methylation profiles and RNA-seq data, and additionally measured skin cytokines and skin phenotypes. We identified 289 differentially methylated probes and 10 differentially expressed genes associated with psychological stress. Integration of methylation and expression with a functional epigenetic module approach yielded seven network modules; enrichment analyses of DMP-annotated genes and module genes revealed significant enrichment of terms related to glutamatergic synapse and synaptic signaling, in line with the emerging concept of a cutaneous neuroendocrine system. None of the 36 tested skin cytokines differed significantly between groups after correction for multiple testing. Skin darkening scores were higher in the stressed group. A CpG site in the *SERPINA1* promoter and *SERPINA1* expression were associated with this phenotype, and mediation analysis suggested that *SERPINA1* expression partly mediated the association between cg01431455 methylation and skin darkening. Taken together, our study links psychological stress to coordinated differences in epidermal DNA methylation and gene expression, highlights glutamatergic and *SERPINA1*-related pathways as candidates for further mechanistic study, and establishes an epidermal multi-omics dataset for future work on stress–skin interactions.

Keywords Psychological stress · Methylation · Transcriptome · Skin · Multi-omics

Bingjie Li, Ying Zou, and Shenghua Tian contributed equally to this work. Yuling Shi and Sijia Wang contributed equally to this work as corresponding authors.

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Introduction

Skin health is affected by various environmental and lifestyle factors (Krutmann et al. 2017), including sun exposure (Krutmann et al. 2012), smoking (Knuutinen et al. 2002), and air pollution (Araviiskaia et al. 2019), all of which have been extensively investigated. Recent evidence also indicates that psychological stress significantly impacts skin physiology and pathology. Chronic stress has been shown to impair skin barrier recovery (Muizzuddin et al. 2003), delay wound healing (Cole-King and Harding 2001), disrupt skin homeostasis, and accelerate skin aging (Chen and Lyga 2014; Pujos et al. 2024). Moreover, psychological stress can trigger or exacerbate inflammatory dermatoses, such as atopic dermatitis (Arndt et al. 2008), psoriasis (Sarbu et al. 2018), contact dermatitis (Kaneko et al. 2003), and acne (Jović et al. 2017). Understanding how psychological stress becomes biologically embedded in the skin is therefore important for both cutaneous disease and the broader biology of stress responses.

Beyond serving as a physical barrier, the skin is increasingly recognized as a peripheral neuroendocrine organ that can sense, integrate, and respond to stress signals. Keratinocytes, melanocytes, immune cells, and cutaneous nerve endings communicate via locally produced neuropeptides, hormones, and classical neurotransmitters, forming a "cutaneous neuroendocrine system" (Slominski et al. 2022). Despite these well-documented observations, the molecular and epigenetic mechanisms through which psychological stress affects the skin remain poorly understood.

At the molecular level, emerging evidence suggests that DNA methylation, an epigenetic mechanism regulating gene expression, may play a key role. Cumulative lifetime stress has been shown to accelerate epigenetic aging, likely driven in part by glucocorticoid-induced epigenetic changes (Zannas et al. 2015). High-stress responses have also been linked to physical signs of skin aging and alterations in whole blood epigenetic profiles (Pattinson et al. 2016), further supporting the role of psychological stress in modifying the DNA methylation landscape. In the skin, aberrant DNA methylation patterns have been reported in ultraviolet-irradiated epidermis (Holzscheck et al. 2020), psoriasis (Zhou et al. 2016), and atopic dermatitis (Rodriguez et al. 2014), underscoring its relevance to skin biology.

Based on this evidence, we hypothesized that psychological stress may affect skin biology through epigenetic modifications and downstream changes in gene expression. To test this hypothesis, we conducted a multi-omics analysis of skin samples from 60 stressed and 60 relaxed individuals, integrating DNA methylation, transcriptomic, cytokine, and phenotypic data. Our findings reveal stress-associated alterations in both the methylome and transcriptome, providing new insights into the pathways linking psychological stress to skin health.

Materials and methods

Study participants

Between July 2017 and March 2018, we enrolled 300 healthy Han Chinese individuals from Shanghai for our study. Participants were selected based on their responses to a pre-screening psychological stress questionnaire (Fig. 1). Inclusion and exclusion criteria (Supplementary data S1) included a history of abnormal wound healing, any clinically diagnosed severe skin conditions and abnormal skin at the test areas, a history of HIV, infectious hepatitis, diabetes, cancer, rheumatic disease, cardiovascular disease, thyroid dysfunction, or asthma. We also excluded participants that taking medications for anti-phlogistic agents or analgetic, suppress immune defenses or antihistamines, or who

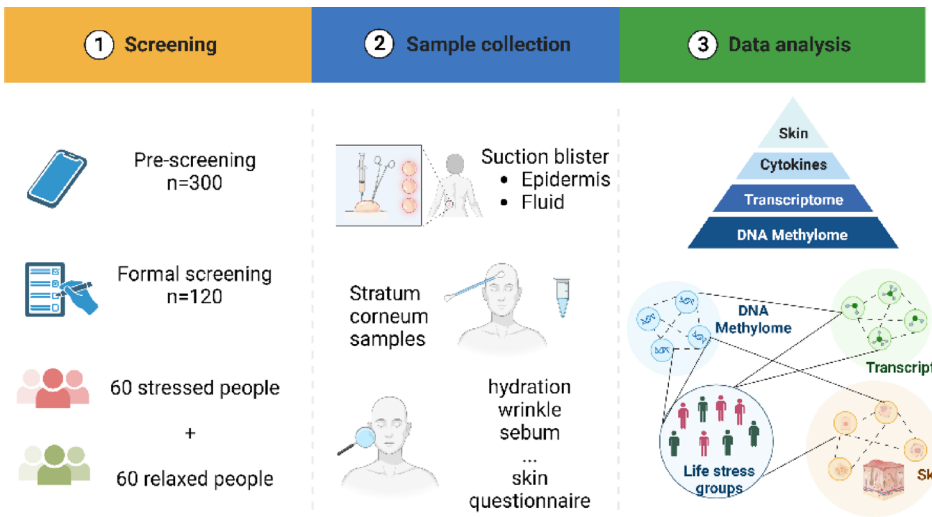

Fig. 1 Flow diagram illustrating the study design for participant recruitment

had used blood coagulation-related drugs within the last 2 weeks, or oral or topical retinoid within the last 2 months, as well as smokers and individuals who were pregnant or breastfeeding.

To select participants with the most extreme participants, all participants completed a detailed and comprehensive 31-item psychological stress questionnaire (Supplementary Data S2). The questionnaire was developed with reference to established stress theories (Lazarus 1984; McEwen 1998; Ingram and Luxton 2005) and previously validated stress measures (Levenstein et al. 1993; Schulz et al. 2004; Shimazu et al. 2012). Compared with commonly used scales such as the Perceived Stress Scale (PSS-10), this expanded questionnaire offers higher resolution for assessing individual stress levels. Stress score is derived from four modules (Eq. 1). Module A (stress load) indicates the stress index and includes 12 positive items (Q1, Q3, Q5, Q6, Q8, Q12, Q14, Q15, Q22, Q26, Q29, Q30) and 4 negative items (Q10, Q16, Q23, Q25). Module B (relaxation/recovery) represents the relaxation index and comprises 8 positive items (Q2, Q4, Q7, Q9, Q11, Q17, Q18, Q28). Module C (stress vulnerability) reflects enhanced stress and consists of 6 positive items (Q19, Q20, Q21, Q24, Q27, Q31) and a negative item (Q13). A constant of 16 is also included. Positive items are scored as 2 for "often", 1 for "sometimes", and 0 for "rarely", while negative items are scored as 0 for "often", 1 for "sometimes", and 2 for "rarely". The scores are calculated as follows: Score A is the total score from Module A, Score B is the total score from Module B, and Score C is the minimum of the sum of items scoring 2 in Module A and the sum of items scoring 2 in Module C.

$$\text{Stress score} = \text{Score A} - \text{Score B} + \text{Score C} + 16 \quad (1)$$

In this sample, the questionnaire demonstrated high internal consistency (Cronbach's $\alpha = 0.97$ for the total score; 0.96, 0.92 and 0.84 for Modules A, B and C, respectively). Corrected item–total correlations for the total scale ranged from 0.44 to 0.89. Exploratory factor analysis (maximum likelihood, oblimin rotation) indicated that a three-factor solution was appropriate (KMO = 0.96; Bartlett's test $\chi^2(465) = 3057.67$, $p < 0.001$), with factors broadly corresponding to Modules A–C and explaining 60.0% of the total variance. A confirmatory factor analysis specifying three correlated factors showed reasonably acceptable fit to the data ($\chi^2(431) = 660.95$, $p < 0.001$; CFI = 0.92; TLI = 0.92; RMSEA = 0.067, 90% CI 0.056–0.077; SRMR = 0.049). To validate the reliability, we collected both the PSS-10 questionnaire and our psychological stress questionnaire from 32 volunteers, calculating the stress scores for both instruments. The stress score obtained from the two questionnaires showed a strong correlation ($r = 0.75$). Additionally, individuals classified as stressed and relaxed groups exhibited significant differences in PSS-10 scores ($p = 9.6 \times 10^{-6}$). These findings support the reliability of psychological stress questionnaire in assessing psychological stress levels (Supplementary Figure S1).

We calculated the stress score for each participant based on the questionnaire data and selected the top 60 stressed individuals and top 60 relaxed individuals for the next stage of the study. The baseline characteristics of the study population are shown in Table 1 and Supplementary Table S1. At the time of sample collection and skin trait measurement (conducted 5 to 10 days later), participants completed a brief stress questionnaire to confirm the continued presence of between-group differences in perceived stress levels (Supplementary Table S2). The age range of these participants was 19 to 29 years, with 92 women [76.67%] and 28 men [23.33%]. This study was approved by the Ethical Committee of Fudan University, Shanghai, China, and all participants provided written informed consent.

Table 1 Baseline characteristics of the study population

	Relaxed group ($N = 60$)	Stressed group ($N = 60$)	P value[a]
Age (mean, sd)[min-max]	24.18 (1.99) [21–29]	24.15 (2.35) [19–29]	0.93
Sex (female, %)	47 (78.33)	45 (75.00)	0.83
BMI (mean, sd)	20.78 (2.63)	20.75 (4.56)	0.97
Stress score (mean, sd)	8.4 (3.32)	44.08 (6.39)	4.2×10^{-57}

[a] P values were calculated using t-test for continuous variables and chi-squared tests for categorical variables. *sd* standard deviation

Skin trait measurement

Prior to the measurements, participants were told to (i) not to use any kind of skincare products for the last 5 days, and (ii) not to wash face, not to perform sweat-inducing sports, and not to use a sauna or have a bath for the last 24 h. All volunteers reported that the sampling site (lower back) had not been exposed to intense sun exposure within the 28 days prior to the sample collection. We asked participants to wait for about 30 min to adapt to the room environment (25°C, 50%) before the measurement. Skin physiological traits were measured using skin code reader (Beiersdorf, Hamburg, Germany). We also collected self-reported skin questionnaire data. Participants rated 18 skin-related items on a 10-point scale, with higher scores indicating greater agreement with the described skin condition. To normalize differences in scale use across participants, ratings were rank-transformed within each individual: for each participant, the lowest rating was assigned rank 1 and the highest

rating rank 18, following the approach used in previous studies (Keller et al. 2007; Li et al. 2022).

Sample collection

Skin suction blisters were formed using a low-pressure device, by mounting one sterile 3-hole (3-mm diameter per hole) skin suction chamber onto the lower back of each participant. Negative pressure (180–240 mmHg) was applied over 1.5 to 2 h, until blister formation was complete. Standard surgical instruments were used to collect suction blister samples (roof and fluid). Rinse-off samples (skin surface protein) were collected by repeatedly scrubbing the forehead of volunteers with a sterile cotton tip that soaked in a buffer. All samples were taken and immediately stored at -80°C.

Cytokine

Skin cytokines levels were determined for both rinse-off and suction blister samples. For rinse-off samples, lactate level was measured by Lactate Reagent (Pointe Scientific, # 7596-50) and Lactate Standard Solution (Pointe Scientific, #7596-STD). IL-α, IL-1ra, IL-8, and BCA were measured by assay kit (R&D System, #DLA50; R&D System, # DRA00B; BD Biosciences, #550999; Thermo Scientific, #23227). For suction blister fluid, cytokine levels were measured by multiplexing with a Bio-Plex 200 System with a Bio-Plex Pro Human Cytokine 48-Plex Panel (#12007283), according to the manufacturer's instructions. BCA was determined by the BCA kit (Thermo Scientific, #23227). BCA protein level was used for normalization. Cytokines were compared between stressed and relaxed individuals using Mann-Whitney U-test, and p-values were adjusted for multiple testing using the Benjamini–Hochberg false discovery rate (FDR) procedure.

Transcriptome

Suction blister roofs (epidermis) were used to isolate total RNA through RNeasy Fibrous Tissue Mini Kit (Qiagen, Hilden, Germany). Single-end sequencing was performed at 75 base pairs (bps) on the Illumina NextSeq500 system, resulting in a final sequencing depth of approximately 100 million reads per sample. RNA reads with low quality and adaptors were removed. Clean reads were aligned to the GENCODE human genome assembly GRCh38 (hg38) using Bowtie2 (Langmead and Salzberg 2012). Read counts and FPKM values were calculated using RSEM(Li and Dewey 2011). Differential gene expression analysis was calculated using DESeq2 (Love et al. 2014), adjusting for age, gender, and top 2 hidden batch effect calculated by RUVseq (Risso et al. 2014). Differentially expressed genes (DEGs) were defined as genes with |log2 fold change| > 1 and adjusted $p<0.05$ after multiple testing adjustments by the Benjamini-Hochberg method. For gene set enrichment analysis (GSEA), we first filtered out lowly expressed genes and retained those with baseMean > 1,000 (Hergenreder et al. 2024), which were then ranked by log 2 fold change and analyzed using the fgsea R package (Korotkevich et al. 2016).

DNA methylome

Suction blister roofs (epidermis) were used to isolate DNA through DNeasy Blood & Tissue Kit (Qiagen, Hilden, Germany). Methylation profiling was performed using Infinium MethylationEPIC arrays (Illumina). Methylation data were processed using the R package ChAMP (Tian et al. 2017) pipeline. Probes were filtered out if the detection P value of > 0.01 or if 5% of probes failed. Non-CpG probes, SNP-related probes, multi-hit probes, and probes located in chromosome X and Y were also removed. Finally, 736,460 probes and 112 samples (56 stressed individuals and 56 relaxed individuals) remained after quality control. Intra-array and probe design variation were corrected for using beta-mixture quantile dilatation (BMIQ). Inter-array batch effects were corrected for using ComBat. Differentially methylated probes analysis was performed using limma (Ritchie et al. 2015) together with age and sex as covariates. Multiple testing was controlled using the Benjamini–Hochberg procedure, and differentially methylated positions (DMPs) were defined as CpG sites with adjusted $p<0.05$ and $|\Delta\beta| > 1\%$. The additional 1% Δβ threshold was applied to minimize false positives driven by technical variation and is consistent with previous epigenome-wide association study (EWAS) that used similar criteria (Campagna et al. 2022, 2023).

Statistical analyses

Skin traits were compared between the stressed and relaxed group using T-tests for continuous variables and chi-squared tests for categorical variables. Genes annotated by DMPs were used to do the enrichment analysis using clusterProfiler package (Wu et al. 2021). Region-based functional enrichment was performed for DMPs using GREAT (v4.0.4). The integrative analysis of DNA methylation and gene expression data was performed by the Functional Epigenetic Module (FEM) algorithm (Jiao et al. 2014) to identify biological modules and pathways that are related to psychological stress. FEM integrates information from DNA methylation, gene expression, and protein-protein interaction (PPI) networks, rather than just filtering DEGs or DEPs using a

specific cutoff, which can provide a more comprehensive understanding of the underlying biological mechanisms. Mediation analysis was conducted using the mediation R package (Tingley et al. 2014). Estimates and confidence intervals were estimated using 5,000 nonparametric bootstrap simulations with bias-corrected and accelerated (BCa) confidence intervals.

Results

Participant and sample characteristics

From July 2017 to March 2018, a total of 120 healthy Chinese participants were recruited for this study, with 60 individuals in each of the stressed and relaxed groups. The psychological stress score, derived from a 31-item questionnaire, was used to screen participants and ensure that the stressed and related groups were appropriately classified (details of the development and psychometric evaluation of this questionnaire are provided in the Materials and Methods). Multi-omics data, including skin transcriptome (24,389 transcripts) and skin DNA methylome (736,460 CpG probes) from the lower back suction blister roofs, 36 skin cytokines (4 from the forehead rinse-off samples, 32 from the lower back suction blister fluid), and 38 skin traits (14 from skin testing, 24 from self-reported questionnaire), were collected from these participants (Fig. 1).

Stressed individuals have an altered methylation and transcriptome profile involved in the synapse-related pathways

We analyzed genome-wide DNA methylation profiles of suction blister epidermis from 112 volunteers, comprising 56 stressed and 56 relaxed individuals. Using a Benjamini-Hochberg corrected p-value of less than 0.05 and a minimum intergroup methylation difference of 1%, we identified 289 DMPs that corresponded to 170 annotated genes (Fig. 2a, Supplementary Table S3). Among these DMPs, 79.58% ($N=230$) were significantly hypermethylated, whereas 20.42% ($N=59$) were hypomethylated in the stressed individuals Fig. 2b. Both hyper- and hypo-methylated DMPs were enriched in gene body regions (38.75%) and intergenic regions (38.75%), followed by TSS1500 regions (10.07%) Fig. 2c. Unsupervised hierarchical clustering analysis showed that DMPs clearly separated stressed from relaxed individuals (Fig. 2d. The most significant DMP was located in the body of *SLC8A3* (cg01862897, $\Delta\beta=1.38\%$, adjusted $p=2.94\times10^{-3}$), a gene that is required for normal oligodendrocyte differentiation and myelination (Boscia et al. 2012). To identify the biological gene ontologies affected by DMPs in stressed individuals, we performed enrichment analysis using the clusterProfile package (Wu et al. 2021). We identified 18 significantly enriched Gene Ontology (GO) terms, many of which were related to lumen and synapse, such as glutamatergic synapse and neuron to neuron synapse (Fig. 2e, Supplementary Table S4). Consistently, region-based GO enrichment using GREAT also highlighted glutamatergic-related pathways (Supplementary Figure S2).

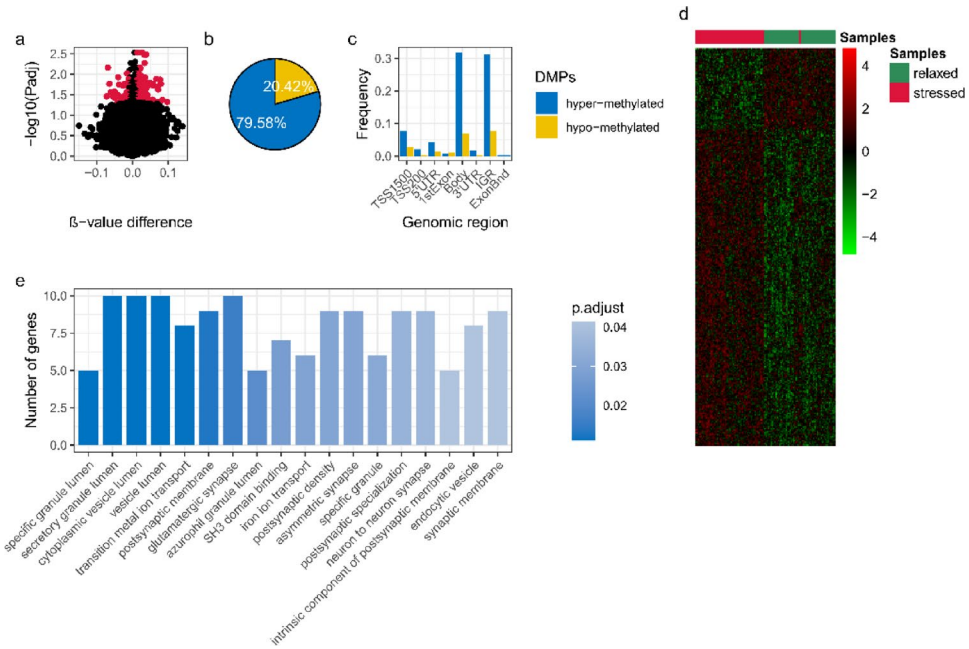

Fig. 2 Stressed individuals have an altered methylation profile compared to relaxed individuals. **a** Visualization of differential DNA methylation between the stressed ($n=56$) and relaxed ($n=56$) groups after control for age and sex. Probes with Benjamini-Hochberg adjusted $p<0.05$ and $|\Delta\beta|>1\%$ were highlighted. **b** Proportions of hyper-and hypo-methylated probes. **c** Distribution of DMPs across genomic regions. TSS1500 (200–1500 bases upstream from the transcriptional start site, TSS), TSS200 (0–200 bases upstream from the TSS), 5'UTR (5′ untranslated region), 3'UTR (3′ untranslated region), IGR (intergenic region). **d** Unsupervised hierarchical clustering of samples based on 289 DMPs. **e** Significantly enriched gene ontologies based on DMPs (adjusted $p<0.05$)

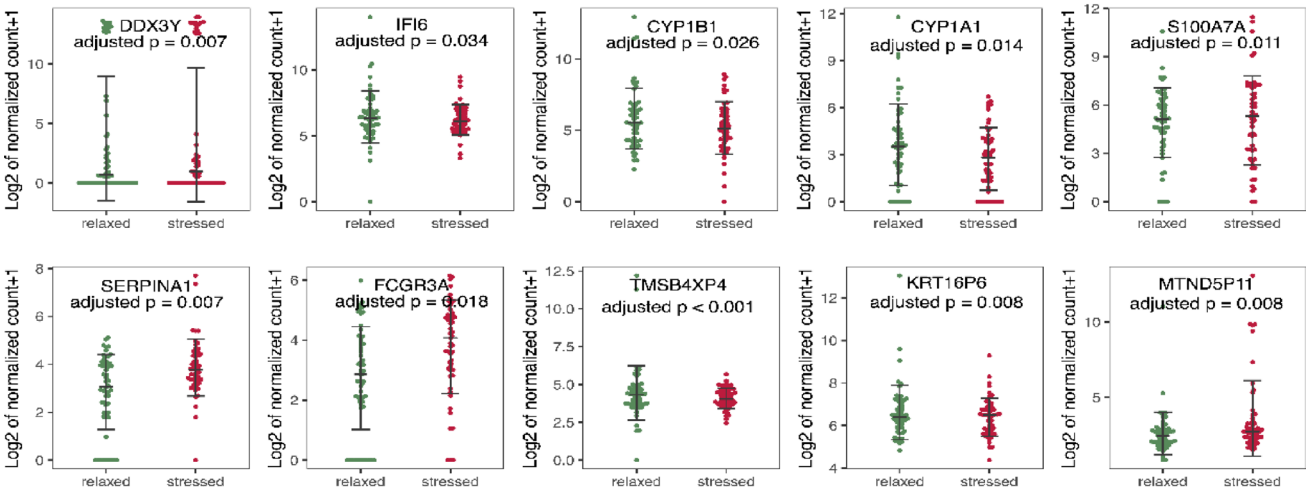

Fig. 3 Differential expression genes between stressed and relaxed individuals. Differential expression genes (adjusted $p<0.05$ and |log2 fold change| > 1) between stressed ($n=53$) and relaxed ($n=56$) groups were calculated based on the normalized read counts using DESeq2. The normalized counts were calculated by DESeq2's median of ratios method. Vertical bars correspond to the standard deviation of the mean

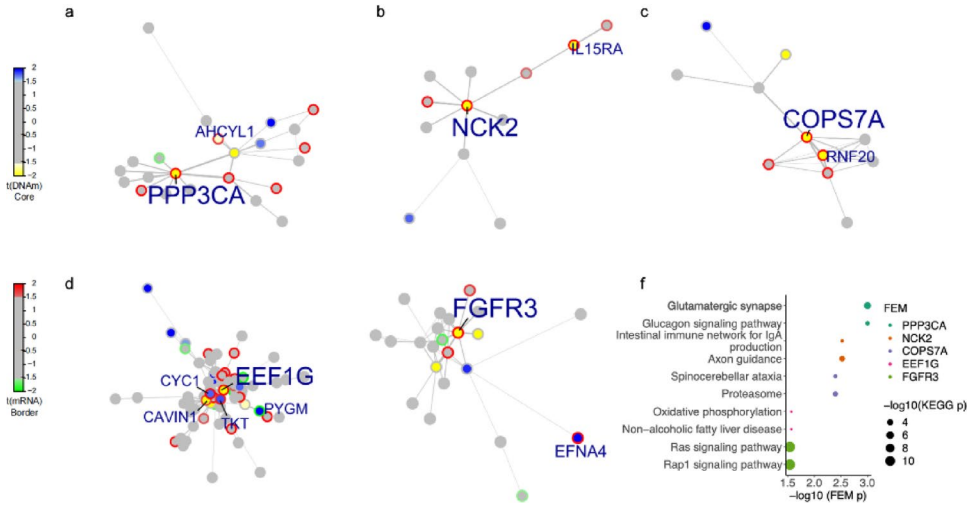

Fig. 4 The FEM modules associated with psychological stress. a-e, Five FEMs centered around seed genes *PPP3CA*, *EEF1G*, *NCK2*, *COPS7A*, and *FGFR3*. Edge widths are proportional to the average statistic of the genes making up the edge. Node shades denote the differential DNA methylation statistics as indicated. Border shades denote the differential expression statistics; The labeled genes show concurrent changes in DNA methylation and gene expression levels between the stress groups. Additional genes (nodes) can be found in the Supplementary Table S7; f, significantly enriched KEGG pathway based on genes in FEM modules

To compare the gene expression patterns between stressed and relaxed individuals, we conducted RNA sequencing (RNA-seq) analysis on the epidermis of 109 volunteers, comprising 53 stressed and 56 relaxed individuals. DEGs were identified using Benjamini-Hochberg corrected $p<0.05$ and |log2 fold change| > 1. A total of 10 genes were differentially regulated in the stressed individuals compared to the relaxed individuals (Fig. 3, Supplementary Table S5-6). Among these DEGs, 4 genes were up-regulated, and 6 genes were down-regulated in the stressed individuals.

We applied a FEM analysis (Jiao et al. 2014) to identify interactome hotspots of simultaneous differential methylation and gene expression associated with psychological stress. We identified seven FEM modules ($p<0.05$), comprising 190 unique genes (Supplementary Table S7). Among these genes, 56 exhibited significant differential methylated and expressed patterns, with eight genes in the *PPP3CA/EEF1G/NCK2/COPS7A/FGFR3* FEM modules showing an anti-correlation between DNA methylation and gene expression. To determine the biological significance of the FEM modules, we conducted a Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis, which revealed the top two significant pathways also involved in glutamatergic synapse and axon guidance (Fig. 4, Supplementary Table S8). Consistently, GSEA demonstrated significant positive enrichment of glutamatergic synapse (NES = 1.48, $p=0.04$) and axon guidance pathways (NES = 1.66, $p=0.001$) in the stressed group (Supplementary Figure S3). Sensitivity analyses of GSEA enrichment showed that axon guidance enrichment remained significant across baseMean thresholds and ranking metrics, whereas glutamatergic synapse enrichment was sensitive to the gene-universe definition and was most evident under conservative

Table 2 Altered skin cytokines between the stressed and relaxed groups

Cytokines [pg/mg][a]		Relaxed group Median (quartile) ($N=60$)	Stressed group Median (quartile) ($N=60$)	*P* value[b]
Rinse off samples	Lactate [ug/mg]	274.47 (167.12-367.08)	335.63 (175.61-396.58)	0.43
	IL-1a	1113.92 (826.88-1385.56)	1200.15 (921.13-1536.92)	0.46
	IL-1ra	229.71 (153.85-300.29)	256.98 (178.25-300.71)	0.76
	IL-1ra/IL-1a	217.95 (126.45-276.82)	207.75 (105.14-261.79)	0.45
	IL-8	157.55 (88.53-181.02)	151.06 (93.64-172.14)	0.88
Suction blister fluid samples	CTACK	304.44 (210.74-412.63)	351.38 (231.89-435.82)	0.27
	Eotaxin	1.23 (0.96–1.23)	1.16 (0.97–1.23)	0.76
	FGF.basic	1.92 (1.63–1.86)	1.83 (1.51–1.84)	0.48
	G-CSF	10.02 (8.06–11.02)	10.62 (7.47–12.32)	0.46
	GRO-a	10.73 (8.27–14.38)	10.29 (7.97–16.51)	0.76
	HGF	21.11 (16.57–21.94)	19.54 (16.42–21.14)	0.56
	IFN-a2	0.63 (0.51–0.63)	0.62 (0.52–0.73)	0.63
	IFN-g	6.79 (5.39–6.81)	6.18 (5.48–6.71)	0.35
	IL-1a	6.73 (4.14–10.37)	6.81 (3.87–10.77)	0.92
	IL-1b	0.16 (0.13–0.17)	0.16 (0.12–0.18)	0.83
	IL-1ra	1155.85 (978.87-1200.07)	1224 (1073.36-1258.12)	0.31
	IL-2	0.68 (0.56–0.74)	0.64 (0.47–0.73)	0.48
	IL-2Ra	1.67 (1.34–1.64)	1.52 (1.31–1.66)	0.88
	IL-6	0.78 (0.27–1.37)	0.84 (0.25–1.7)	0.88
	IL-8	13.46 (6.91–15.37)	14.56 (7.72–17.28)	0.75
	IL-9	1.36 (1.14–1.83)	1.39 (1.04–1.62)	0.67
	IL-10	1.05 (0.81–1.22)	1.17 (0.83–1.28)	0.55
	IL-16	2.69 (2.12–2.72)	2.63 (2.04–2.62)	0.59
	IL-18	2.82 (2.2–2.94)	2.49 (2.05–2.63)	0.14
	IP-10	30.36 (23.42–37.25)	29.94 (22.17–32.44)	0.6
	MCP-1	41.21 (26.68–52.35)	38.14 (27.02–64.94)	0.93
	MIF	495.41 (396.85-480.67)	457.74 (390.88-494.11)	0.91
	MIG	12.69 (8.91–15.28)	10.5 (8.33–13.62)	0.25
	MIP-1a	0.73 (0.47-1)	0.65 (0.33–1.03)	0.98
	MIP-1b	5.47 (3.13–8.84)	5.33 (3.04–10.25)	0.77
	RANTES	4.21 (2.67–10.93)	4.19 (2.66–9.22)	0.92
	SCF	4.17 (3.32–4.54)	3.85 (3.31–4.24)	0.32
	SCGF-b	2550.59 (2106.65-2754.88)	2786.13 (2417.06-2902.86)	0.13
	SDF-1a	45.94 (37.93–44.58)	45.5 (38.3-45.08)	0.86
	TNF-a	11.82 (8.36–14.51)	11.85 (6.7-14.47)	0.64
	VEGF	10.69 (8.45–10.63)	10.32 (8.22–10.3)	0.5
	Cortisol	345.73 (245.58-406.32)	426.02 (340.11-464.18)	0.12
	IL-1ra/IL-1a	165.02 (92.86-260.73)	188.77 (93.65-267.14)	0.53

[a] Cytokines were normalized by the level of BCA protein (pg/mg)

[b] P values were calculated by the Mann-Whitney U test. No cytokine reached FDR < 0.05

expression filtering (baseMean > 500 or > 1000, Supplementary Table S9).

No significant differences in the tested cytokines between stressed and relaxed groups

We compared 36 well-known pro-and anti-inflammatory cytokines between stressed and relaxed individuals. All cytokines were first normalized by the level of BCA protein, and most cytokines exhibited a skewed distribution (Supplementary Figure S4). Cytokines were compared between groups using the Mann-Whitney U test, and p-values were adjusted for FDR procedure. None of the unadjusted p-values were below 0.05, and no tested skin cytokine reached statistical significance after correction for multiple testing (Table 2, Supplementary Figure S5), which remained consistent across both females and males (Supplementary Table S10). Although no cytokine reached significance, the stressed group demonstrated a modest decrease in T helper 1 (Th1) cytokines, specifically interleukin-2 (IL-2), which showed a 1.4% decrease in the average level, and interferon-gamma (IFN-γ), with a 1.5% decrease in the average level. In contrast, there was a modest increase in pro-inflammatory cytokines, such as interleukin-6 (IL-6), which exhibited a 24% increase in the average level, as well as T helper 2 (Th2) cytokines, like IL-10, which showed a

4.9% increase in the average level. These quantitative differences are consistent with a shift from Th1 to Th2 mediated immune responses. Additionally, skin cortisol levels measured from suction blister fluids were on average 23% higher in the stressed group compared to the relaxed group, although this difference did not reach the significant threshold ($p=0.12$), and this difference remained similar after controlling for sample collection time.

Stressed individuals have more severe self-reported skin darkening than relaxed individuals

Skin traits were compared using Student's t-test and chi-squared test, with significance levels adjusted using Bonferroni correction for multiple comparisons. Individuals in the stressed group had higher self-reported skin darkening scores than those in the relaxed group (mean rank score 12.85 ± 4.41 vs. 9.40 ± 4.49, $p=4.32\times10^{-5}$), and this difference remained after controlling for skincare time (Supplementary Table S11). To explore how psychological stress affects skin darkening, we analyzed 10 stress-related DEGs and their correlation with skin darkening. Among these, *SERPINA1* expression showed a significant positive correlation with skin darkening ($r=0.21$, $p=0.04$). We also identified a stress-related CpG site, cg01431455, located in the promoter region of *SERPINA1*, which was also significantly correlated with skin darkening (r = -0.37, $p=0.0001$, Supplementary Figure S6) and may functioned as an expression quantitative trait methylation (eQTM) site for *SERPINA1* (beta = -2.69, $p=0.008$, Supplementary Table S12). Mediation analysis showed a significant indirect effect of cg01431455 on skin darkening via *SERPINA1* expression (ACME = −38.27, 95% CI −96.31 to −4.70, $p=0.045$), accounting for 15% of the total effect, while the direct effect remained significant (Supplementary Figure S6). These findings suggest that hypomethylation of cg01431455 in stressed individuals may lead to increased *SERPINA1* expression, thereby exacerbating skin darkening. Additionally, we found that *KLK5* and *KLK7*, which encode epidermal exfoliation enzymes previously implicated in skin dullness (Ishida et al. 2020), were significantly negatively correlated with *SERPINA1* expression (*KLK5*: r = -0.25, $p=0.01$; *KLK7*: r = -0.27, $p=0.005$) and skin darkening (*KLK5*: r = -0.21, $p=0.03$; *KLK7*: r = -0.14, $p=0.15$, Supplementary Figure S7).

Discussion

In this study, we used a multi-omics design to investigate how psychological stress is reflected in the human epidermis. Comparing 60 stressed and 60 relaxed young adults, we identified 289 differentially methylated CpG sites and 10 differentially expressed genes, with enrichment of pathways related to glutamatergic synapses. Stressed individuals reported more pronounced skin darkening; *SERPINA1* promoter hypomethylation and increased *SERPINA1* expression were associated with this phenotype, and mediation analysis suggested that *SERPINA1* expression partly mediates the association between cg01431455 methylation and skin darkening. Together, our findings highlight glutamatergic synapse pathways and *SERPINA1* as promising candidates for future mechanistic studies of stress–skin interactions.

Epigenetic regulation of gene expression has emerged as a crucial factor in the long-lasting impact of stress on the brain (Parade et al. 2021; Sanacora et al. 2022). Our findings revealed that psychological stress can significantly alter the skin methylome profile as well. Specifically, we identified 289 DMPs associated with psychological stress, which were significantly enriched for the lumen and synaptic related pathways, including specific granule lumen, glutamatergic synapse, neuron to neuron synapse. Further analysis revealed a FEM module centered around *PPP3CA* that was also strongly enriched in the glutamatergic synapse pathway. These findings are in accordance with previous investigations, which have demonstrated that stress-related mediators can induce structural remodeling of dendrites and synapses within the hippocampus and prefrontal cortex (McEwen 2012). Notably, an experimental study involving rats exposed to chronic stress for two weeks revealed significant DNA methylation changes in the prefrontal cortex, particularly within neural pathways associated with glutamatergic synapses (Wei et al. 2021). The glutamatergic system, as the vesicular neurotransmitter releaser, is known to play a crucial role in mediating the effects of psychological stress on cognition and psychopathology (Popoli et al. 2012). A recent study found that chronic stress dynamically regulates glutamatergic gene expression in the hippocampus by opening a window of epigenetic plasticity (Nasca et al. 2015). In addition, chronic stress may contribute to the pathophysiology of several psychiatric disorders through effects on the glutamatergic synapse in the prefrontal cortex (Popoli et al. 2012). Our study provides further support for the hypothesis that DNA epigenetic modifications may serve as a crucial mechanism underlying the disruption of synaptic functions in response to stress-induced perturbations. This effect is not limited to the central nervous system but extends to the peripheral nervous system (skin) as well. Psychological stress is not only confined to the central nervous system but also acts on the skin through broader neuro-cutaneous pathways. Activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system leads to the release of catecholamines and neuropeptides

from cutaneous nerve terminals, while keratinocytes can release glutamate and other mediators; keratinocytes and melanocytes express receptors for these signals, enabling direct neural regulation of epidermal proliferation, cytokine production and melanogenesis (Fuziwara et al. 2003; Denda 2015; Slominski et al. 2022). The skin has been proposed to function as a "cutaneous neuroendocrine system", in which keratinocytes, melanocytes, immune cells and cutaneous nerve endings communicate via locally produced neuropeptides, hormones and classical neurotransmitters to coordinate barrier and immune responses (Slominski et al. 2022). Within this framework, our glutamatergic findings can be viewed as part of a local stress-response circuit in the epidermis. Our results thus support a testable model in which stress-induced epigenetic changes in glutamatergic pathway genes reshape glutamate signaling in skin cells, activating downstream pathways that control epidermal renewal and barrier function.

Additionally, examination of the transcriptome data revealed 10 genes that were differentially expressed between stressed and relaxed individuals (Supplementary Table S5). Increased expression of *S100A7A* in hyperproliferative skin conditions such as atopic dermatitis and psoriasis has been linked to inhibited epidermal differentiation (Son et al. 2016). Upregulated expression of *S100A7A* in stressed individuals (log2 fold change = 1.599, adjusted $P = 0.01$) may supports previous evidence that psychological stress can trigger or exacerbate psoriasis (Xhaja et al. 2014).

In previous studies, exposure to chronic stress during academic examinations has been associated with elevated levels of plasma IL-1β, IL-6, and IL-10, along with reduced production of plasma IL-2 and IFN-γ (Paik et al. 2000; Kang et al. 2001). Alzheimer's caregivers reported significantly higher levels of distress and increased IL-6 concentrations (Lutgendorf et al. 1999; Kiecolt-Glaser et al. 2003). Additionally, burnout, characterized as a stress-induced work-related syndrome, has been found to correlate with an increase in the production of the anti-inflammatory cytokine IL-10 by monocytes (Mommersteeg et al. 2006). However, in our study, we did not observe any significant changes for cytokines in the skin. There are several possible explanations for this finding. First, it is possible that unstimulated chronic psychological stress experienced by healthy individuals may have less effect on skin cytokines in this observational study; Second, although we collected a large number of samples, detecting minor effects may require a larger sample size to provide sufficient statistical power; Third, mast cells are known to regulate neurogenic inflammation and are a source of skin cytokines during stress responses (Arck et al. 2006). The cytokines we measured in the epidermal tissue fluid may not fully represent the whole picture of the mast cells. In future studies, we recommend using whole skin samples for cytokine detection to obtain a more comprehensive understanding of the effects of stress on skin cytokines. Although suction blister fluid samples do not typically contain mast cells, mast cell–derived cytokines, enzymes, and other secretions can be partly detected in these samples (Brockow et al. 2002; Rojahn et al. 2020). The observed trends in their levels were consistent with previous research, suggesting that chronic psychological stress may promote a shift from Th1 to Th2 mediated immune responses. Additionally, we observed hypermethylation of *NFKB1*, a central regulator of inflammation, in stressed individuals, also suggesting that stress may have the potential to modulate inflammatory responses.

Our analyses showed that stressed individuals tend to have more pronounced skin darkening compared to relaxed individuals, which is in line with a previous study concluding that fatigue induces tired-looking and dull skin in Chinese women (Flament et al. 2019). Skin darkening was assessed using a self-reported questionnaire, which is inherently subjective; further studies should use more objective detection methods for validation. We found that *SERPINA1* expression may act as a candidate mediator linking stress-associated cg01431455 methylation to skin darkening. Because this mediation analysis is observational and cross-sectional, it should be interpreted as statistical consistency with partial mediation rather than causal confirmation. Interpretation of mediation effects requires strong causal assumptions, including no unmeasured confounding of the exposure-mediator, mediator-outcome, and exposure-outcome relationships; no exposure-induced mediator–outcome confounding; appropriate temporal ordering; and correct model specification. These assumptions are not fully testable here. Further longitudinal or interventional studies will be required to evaluate causality more directly. Previous studies have reported that *SERPINA1* influences morning plasma and salivary cortisol levels—key biomarkers of psychological stress—likely through modulation of total cortisol binding via corticosteroid-binding globulin (Bolton et al. 2014; Utge et al. 2018). Beyond its role in stress hormone regulation, *SERPINA1* also functions as an inhibitor of serine proteases. Kallikreins, a subgroup of serine proteases encoded by *KLK5*, play an essential role in the epidermal desquamation process (Meyer-Hoffert 2012), and their activity can be inhibited by serine protease inhibitors encoded by *SERPINA1* (Yousef et al. 2003). A previous study demonstrated that reduced expression of *KLK5* and *KLK7* leads to the accumulation of aged corneocytes on the skin surface, contributing to skin dullness (Ishida et al. 2020). Psychological stress may upregulate *SERPINA1* expression through hypomethylation of the CpG site cg01431455, thereby exacerbating skin dullness by downregulating the expression of epidermal exfoliation enzymes.

The multifunctional role of *SERPINA1* positions it as a key mediator in the relationship between psychological stress and skin condition and highlights its potential as a novel target for the treatment or prevention of stress-induced skin darkening.

We have generated a valuable multi-omics dataset. To minimize the confounding effects of cell heterogeneity, we analyzed the DNA methylome and transcriptome specifically in the epidermal samples. Similar to previous expression quantitative trait methylation (eQTM) studies in other tissues or cell lines (Gutierrez-Arcelus et al. 2015; Kim et al. 2020; Sharma et al. 2020), this dataset provides a valuable resource for performing eQTM analysis in the healthy epidermis.

Our study has some limitations. Firstly, while we confirmed the consistency between stress questionnaire and the PSS-10, incorporating more tools or objective measurement could further refine stress evaluation. Secondly, the cross-sectional and observational design limits causal inference and makes it difficult to fully separate stress effects from potential confounders such as sleep, pregnancy history, or diet. These issues could be addressed in future longitudinal and controlled studies. Thirdly, all participants were healthy young Han Chinese adults recruited in Shanghai; therefore, our findings may not be generalizable to other age groups or individuals of different ethnic backgrounds. Future studies in larger, multi-ethnic cohorts are needed to validate and extend these results. In addition, further validation of the findings using other methodological approaches (qRT-PCR) would be necessary to confirm the robustness of the results. Finally, because we assessed only epidermal methylation, gene expression and cytokines—without directly measuring neuro-cutaneous components such as intra-epidermal nerve fibres or local catecholamines and neuropeptides—future studies are needed to characterize more comprehensively.

Despite these caveats, our work reveals distinct DNA methylation and expression signatures that mark the epidermal response to psychological stress, particularly in glutamatergic pathways, and identifies a candidate *SERPINA1*-centred axis potentially linking stress to changes in skin darkening. The findings not only enhance our understanding of the impact of stress on the epidermis but also provide a valuable dataset resource for future mechanistic investigations.

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Declarations

Conflict of interest LG, AM, and LK is employee of Beiersdorf. The remaining authors state no other conflict of interest.

Ethical aprroval This study was approved by the Ethical Committee of Fudan University, Shanghai, China, and all participants provided written informed consent.

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