

Long-term transcriptomic changes in patients with suicidal ideation

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BACKGROUND AND AIMS

- Suicide is a complex multifactorial event resulting from an interaction between biological and psychosocial factors.
- Identifying the molecular basis of **suicidal ideation (SI)** and its improvement may provide targets for the development of novel treatment strategies and help better identify individuals at risk of suicide.

AIMS: To longitudinally characterize the transcriptomic and methylomic dynamics of peripheral blood mononuclear cells (PBMCs) from hospitalized individuals with mood disorders admitted due to acute SI.

HYPOTHESIS: Improvement of SI is associated with significant changes in blood gene expression, DNA methylation levels, and cell composition that can inform the development of biomarkers and novel treatments for SI.

METHODS

Sample



N = 42 hospitalized individuals with mood disorders (BD or MDD) Beck Scale for Suicide Ideation (BSS) \geq 4

Harris County Psychiatric Center (HCPC), Houston, TX

Clinical assessments

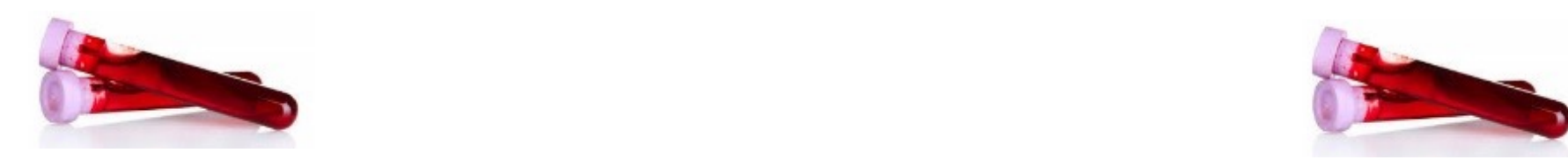
Admission (T1)

- Demographic data
- BSS
- Columbia-Suicide Severity Rating Scale (C-SSRS), Recent version
- NIDA Quick Screen V1.0 and NIDA-Modified ASSIST V2.0
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Young Mania Rating Scale (YMRS)
- Barratt Impulsiveness Scale (BIS)

Discharge (T2)*

- BSS
- MADRS
- YMRS
- C-SSRS, Recent version
- Hollingshead Socioeconomic Rating Scale
- Childhood Trauma Questionnaire (CTQ)

*SI improvement \rightarrow \geq 50% reduction in BSS scores from T1



RNA-sequencing (bulk), n=15 with improved SI (T1 and T2): Illumina, 2x 150bp, single index, ~20M raw paired-end reads/sample, covariates: age, sex; FDR < 0.10.

Single-cell (sc) RNA sequencing, n=3 with improved SI (T1 and T2): 10X Genomics® Chromium™ 3' gene expression; target # cells/sample: 3,000; # reads/cell: 50,000.

Genome-wide DNA methylation, n=16 with improved SI (T1 and T2): Infinium EPICMethylation BeadChip v1 (Illumina).

Table 1. Sample Demographics and Suicidal Ideation Improvement

	Improved SI (n = 26)	Unimproved SI (n = 16)	Test Statistic (degrees of freedom)	p-value
Age, median (IQR)	40.5 (20)	47 (19.75)	W = 254.5	0.2331 ^a
Sex				
Female (%)	26.9%	12.5%		
Male (%)	73.1%	87.5%	n/a	0.4424 ^b
Race (%)				
Black or African American	42.3%	31.3%	$\chi^2 (1) = 0.1517$	0.6969 ^c
White or Caucasian	57.7%	68.8%		
Ethnicity (%)				
Hispanic	26.9%	31.3%	$\chi^2 (1) = 0.00$	1.0000 ^c
Non-Hispanic	73.1%	68.8%		
Sexual Orientation (%)				
Heterosexual	73.1%	93.75%	n/a	0.1231 ^b
Non-Heterosexual	26.9%	6.25%		
Currently Employed (%)	23.1%	18.8%	n/a	1.0000 ^b
Years of Education, Mean (SD)	12.8 (2.91)	11.2 (2.68)	t (33.9) = -1.84	0.0746 ^d

BSS - Beck Scale for Suicidal Ideation; IQR - Interquartile Range; SD - Standard Deviation; SI - suicidal ideation. ^aWilcoxon Ranked Sum; ^bFisher's Exact test; ^cChi-square test; ^dIndependent Student's t-test. SI improvement was defined as \geq 50% reduction in BSS scores between admission and discharge.

Table 2. Clinical Variables and Suicide History

	Improved SI (n = 26)	Unimproved SI (n = 16)	Test Statistic (degrees of freedom)	p-value
BSS Baseline, mean (SD)	17.8 (8.31)	21.3 (6.36)	t = 1.52 (37.94)	0.1364 ^a
BSS Discharge, median (IQR)	1 (4.75)	16 (7.75)	W = 404	< 0.0001 ^a
Duration of Hospitalization (Days), median (IQR)	5 (2.00)	5 (3.25)	W = 209.5	0.8061 ^a
Diagnoses (%)				
Bipolar Disorder	25%	20.8%	n/a	0.8431 ^b
Major Depressive Disorder	31.3%	41.7%		
Unspecified Mood Disorder	43.7%	37.5%		
Inpatient medications (%)				
Antidepressants	76.0%	93.3%	n/a	0.2237 ^b
Antipsychotics	80.0%	86.7%	n/a	0.6913 ^b
Anxiolytics	60.0%	86.7%	n/a	0.1523 ^b
Mood Stabilizers	32.0%	20.0%	n/a	0.4861 ^c
MADRS Baseline, mean (SD)	32.3 (7.09)	34.7 (8.68)	t = 0.923 (27.12)	0.3643 ^a
MADRS Discharge, median (IQR)	8 (10.75)	25 (12.00)	W = 382.0	< 0.0001 ^a
YMRS Baseline, median (IQR)	2 (3.75)	2 (6.00)	W = 201.0	0.8647 ^a
YMRS Discharge, median (IQR)	1 (4.5)	3.5 (6)	W = 266.5	0.1217 ^a
Previous Suicide Attempt (%)	87.5%	80.8%	n/a	0.6829 ^b
Number of Previous Suicide Attempts, median (IQR)	2 (2.75)	2 (3.25)	W = 241	0.3860 ^a
Lethality of Most Recent Attempt (%)				
No Physical Damage	56.3%	34.6%	n/a	0.4551 ^b
Minor Physical Damage	19.2%	30.8%		
Moderate Physical Damage	6.3%	19.2%		
Moderately Severe Physical Damage	18.8%	15.4%		
Severe Physical Damage	0.0%	0.0%		
Lethality of Highest Attempt (%)				
No Physical Damage	23.1%	25.0%	n/a	0.5342 ^b
Minor Physical Damage	19.2%	6.3%		
Moderate Physical Damage	30.1%	18.8%		
Moderately Severe Physical Damage	19.2%	31.3%		
Severe Physical Damage	7.7%	18.8%		
Number of Previous Inpatient Admissions, median (IQR)	1.5 (7.75)	2.5 (3.50)	W = 210	0.9684 ^a
Readmission 30 days after Discharge (%)				
Yes	11.5%	25.0%	n/a	0.3971 ^b
No	88.5%	75.0%		

BSS - Beck Scale for Suicidal Ideation; IQR - Interquartile Range; MADRS - Montgomery-Asberg Depression Rating Scale; SD - Standard Deviation; SI - suicidal ideation; YMRS - Young Mania Rating Scale. ^aWilcoxon Ranked Sum; ^bFisher's Exact test; ^cIndependent Student's t-test.

CONCLUSIONS

- SI improvement was associated with significant blood transcriptomic and methylomic changes;
- SI improvement was associated with major blood cell changes, including monocyte subpopulations;
- **Next steps:** assessments in unimproved SI individuals, full sample size (n=200), replication.

RESULTS

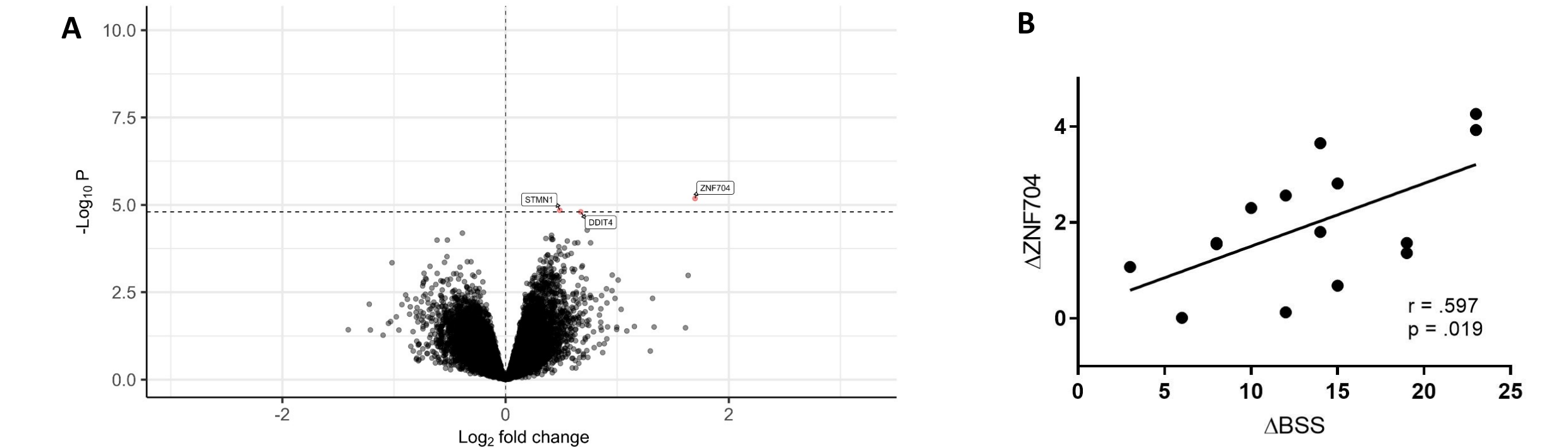


Figure 1. Bulk RNA-sequencing results comparing T1 and T2 among n=15 individuals that showed SI improvement (\geq 50% reduction in BSS scores). A) Volcano plot depicting the three significant genes at FDR=0.10: *ZNF704* (logFC=1.70), *STMN1* (logFC=0.49), and *DDIT4* (logFC=0.67). B) Correlation between change in SI symptoms (BSS) and change in the expression levels of the top-ranked gene *ZNF704*.

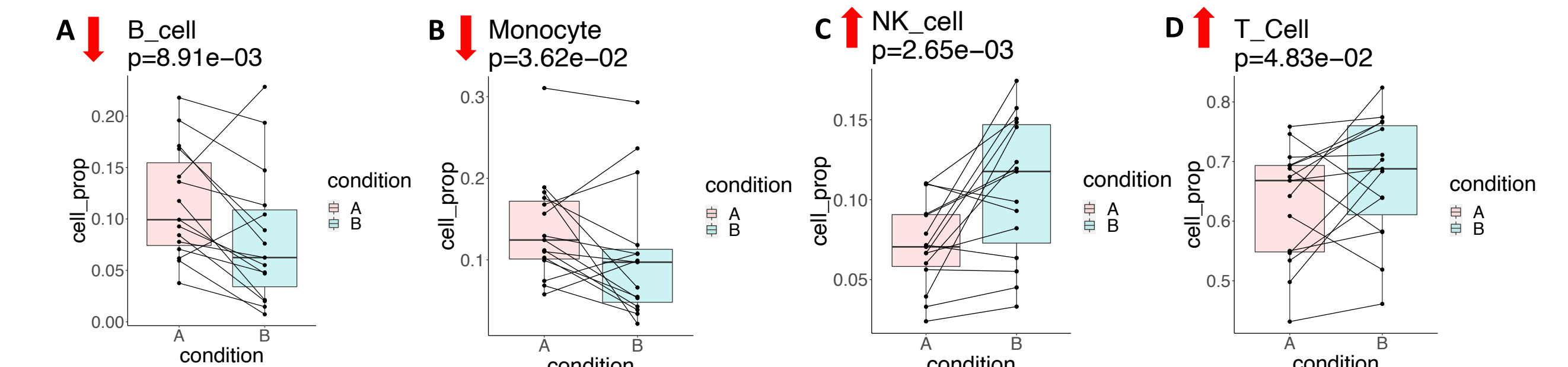


Figure 2. Cell deconvolution analysis of PBMCs between T1 (condition A) and T2 (condition B) in n=15 individuals that showed SI improvement (\geq 50% reduction in BSS) from bulk RNA-sequencing data. A) B-lymphocytes; B) monocytes; C) Natural Killer (NK) cells; D) T-lymphocytes.

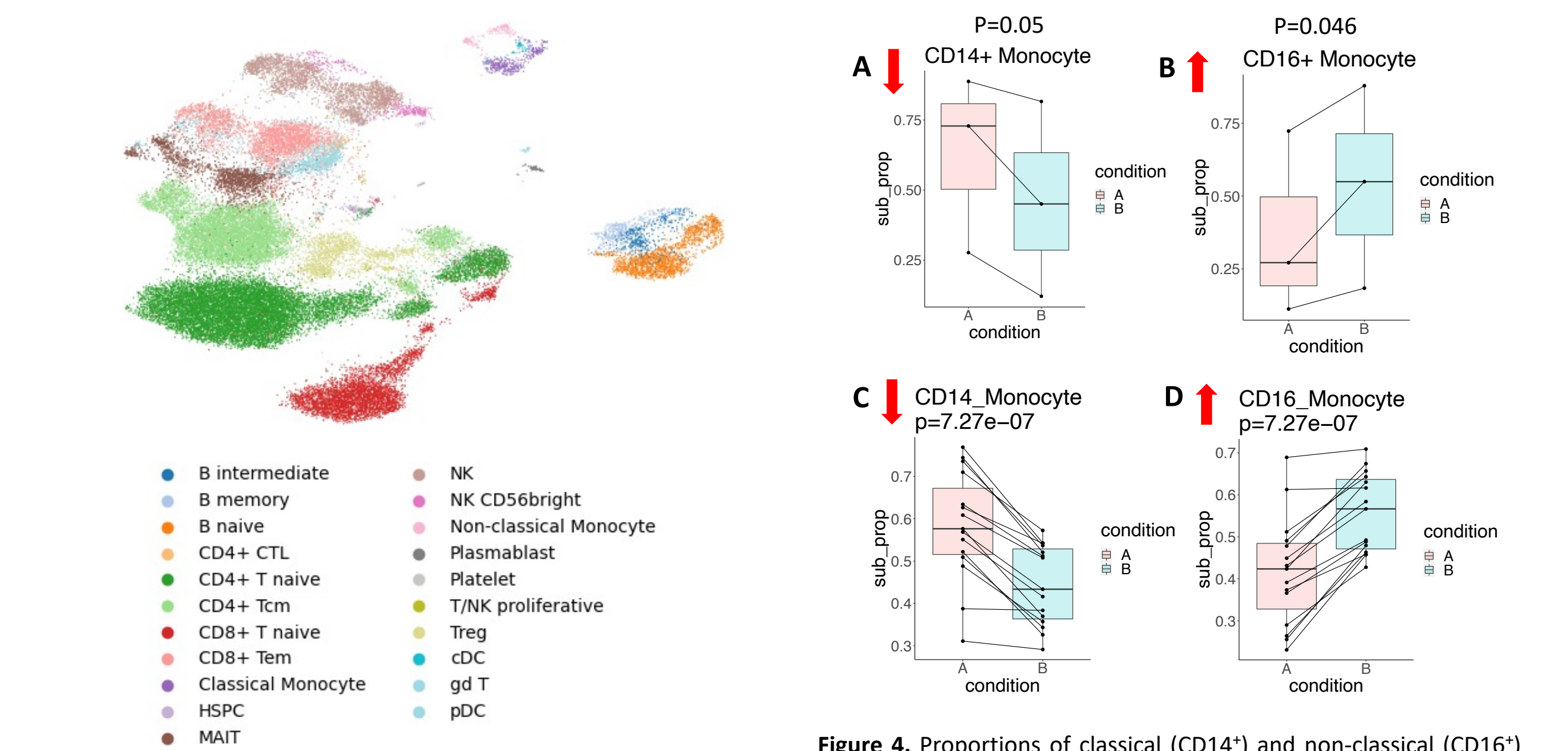


Figure 3. UMAP plot of identified cell populations in the scRNA-seq analyses of PBMCs (n=3 individuals with SI improvement). A) CD14+ Monocyte; B) CD16+ Monocyte; C) CD14- Monocyte; D) CD16- Monocyte.

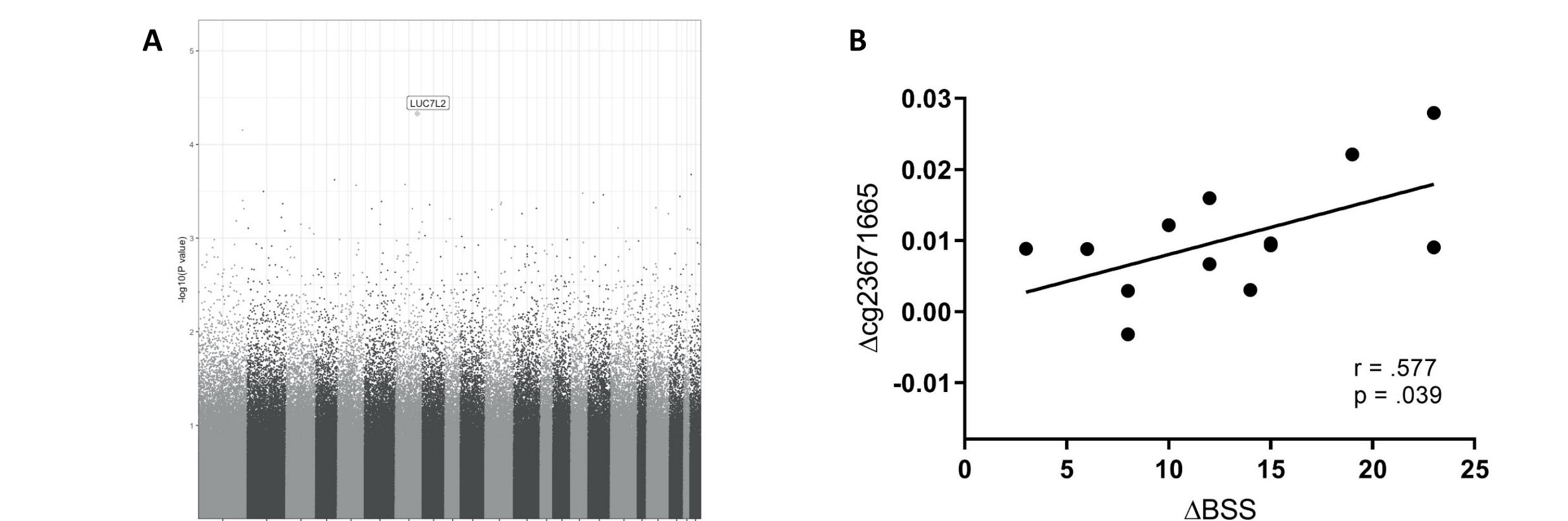


Figure 5. A) Manhattan plot showing epigenome-wide differences in DNA methylation between T1 and T2 in n=16 individuals who significantly improved SI symptoms (no FDR corrected probes identified). B) Correlation between change in SI symptoms (BSS) and change in methylation (beta levels) of the top-ranked probe cg23671665 (annotated to *LUC7L2* gene, log2FC=-0.69, p=4.69x10⁻⁵).

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