

# T-cell abnormalities in bipolar disorder

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Why the immune system?



# The immune privileged brain-not what we thought

## T-cell surveillance of the human brain in health and multiple sclerosis

Joost Smolders<sup>1,2</sup>  · Marvin M. van Luijn<sup>3</sup>  · Cheng-Chih Hsiao<sup>1,4</sup>  · Jörg Hamann<sup>1,4</sup> 

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> Nat Immunol. 2020 Aug;21(8):938-949. doi: 10.1038/s41590-020-0711-8. Epub 2020 Jun 22.

## Peripherally induced brain tissue-resident memory CD8<sup>+</sup> T cells mediate protection against CNS infection

Stina L Urban<sup>1</sup>, Isaac J Jensen<sup>1,2</sup>, Qiang Shan<sup>3</sup>, Lecia L Pewe<sup>1</sup>, Hai-Hui Xue<sup>3,4</sup>, Vladimir P Badovinac<sup>1,2,5</sup>, John T Harty<sup>6,7</sup>

Affiliations + expand

PMID: 32572242 PMCID: PMC7381383 DOI: 10.1038/s41590-020-0711-8

Review | [Open access](#) | Published: 02 December 2014

## T-cell-mediated regulation of neuroinflammation involved in neurodegenerative diseases

[Hugo González](#) & [Rodrigo Pacheco](#) 

*Journal of Neuroinflammation* **11**, Article number: 201 (2014) | [Cite this article](#)

9565 Accesses | 178 Citations | 6 Altmetric | [Metrics](#)

Review | > Br J Pharmacol. 2024 Mar;181(6):799-815. doi: 10.1111/bph.16214. Epub 2023 Sep 2.

## Update on the role of T cells in cognitive impairment

Ignacio Ruiz-Fernández<sup>1</sup>, Raquel Sánchez-Díaz<sup>1,2</sup>, Enrique Ortega-Sollero<sup>1</sup>, Pilar Martín<sup>1,2</sup>

Affiliations + expand

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Review Article | Published: 01 December 2023

## Brain regulatory T cells

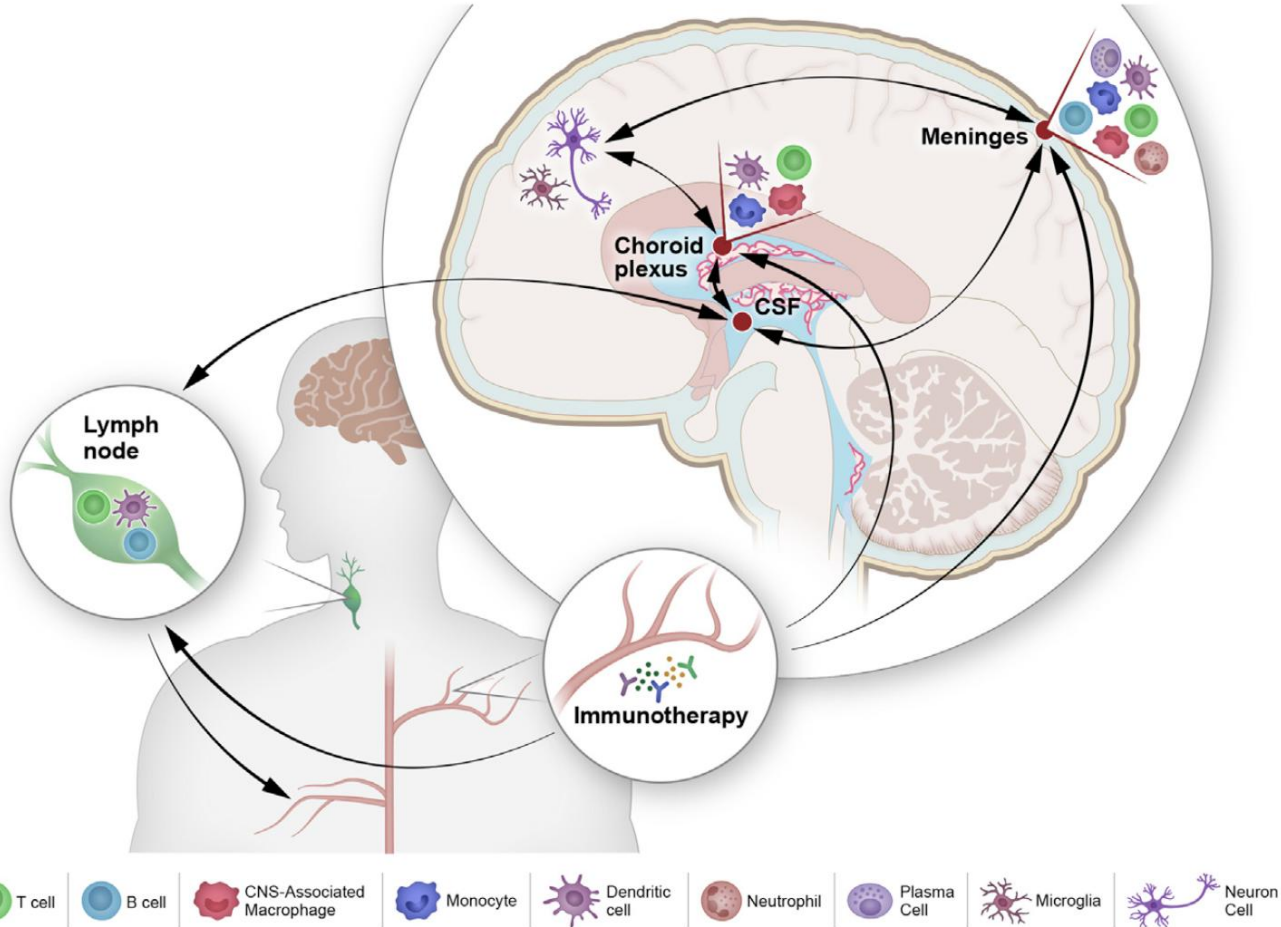
[Adrian Liston](#) , [Emanuela Pasciuto](#) , [Denise C. Fitzgerald](#)  & [Lidia Yshij](#) 

*Nature Reviews Immunology* **24**, 326–337 (2024) | [Cite this article](#)

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- Peripheral immune cells play a role in brain repair
- Peripheral immune cells play a role in higher brain function
- Dysregulation of the immune system plays a role in neuroinflammation

# The immune privileged brain-not what we thought



*Croese et al, 2021-* Innate and adaptive **immune cells** reside in **choroid plexus, meninges, and perivascular spaces**, where they regulate leukocyte entry as needed.

*Herisson et al, 2018-* The **brain connects to skull bone marrow** for rapid immune cell delivery during injury or inflammation.

*Louveau et al, 2018-* The brain's **meningeal lymphatics** link to **neck lymph nodes** for immune surveillance and communication.

*Schwartz et al. 2022, Neuron*

# Immune abnormalities in psychiatric disorders: Current state of understanding





- Abnormal levels of peripheral proinflammatory cytokines
  - T cell abnormalities
  - Abnormal pro-inflammatory gene expression in circulating monocytes
  - Microglial activation
- 
- Immune abnormalities linked to greater symptom severity and
  - Resistance to currently available treatments



## Studying the immune abnormalities in BD

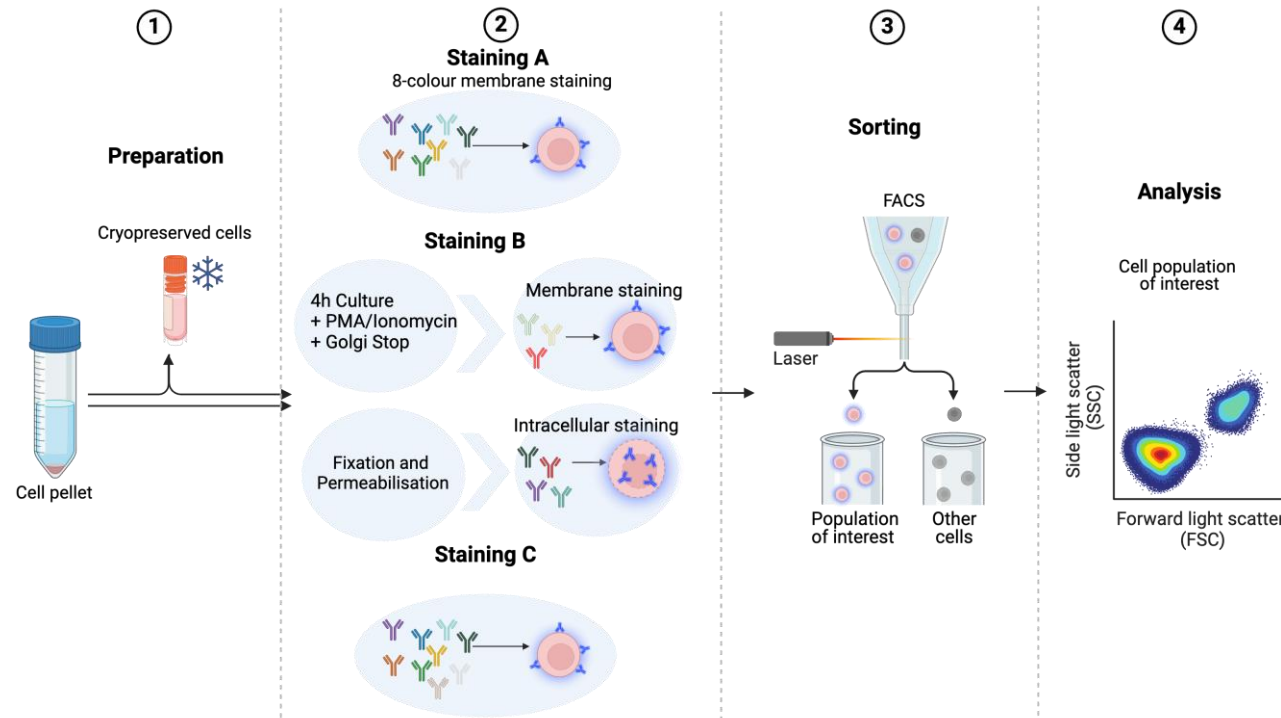
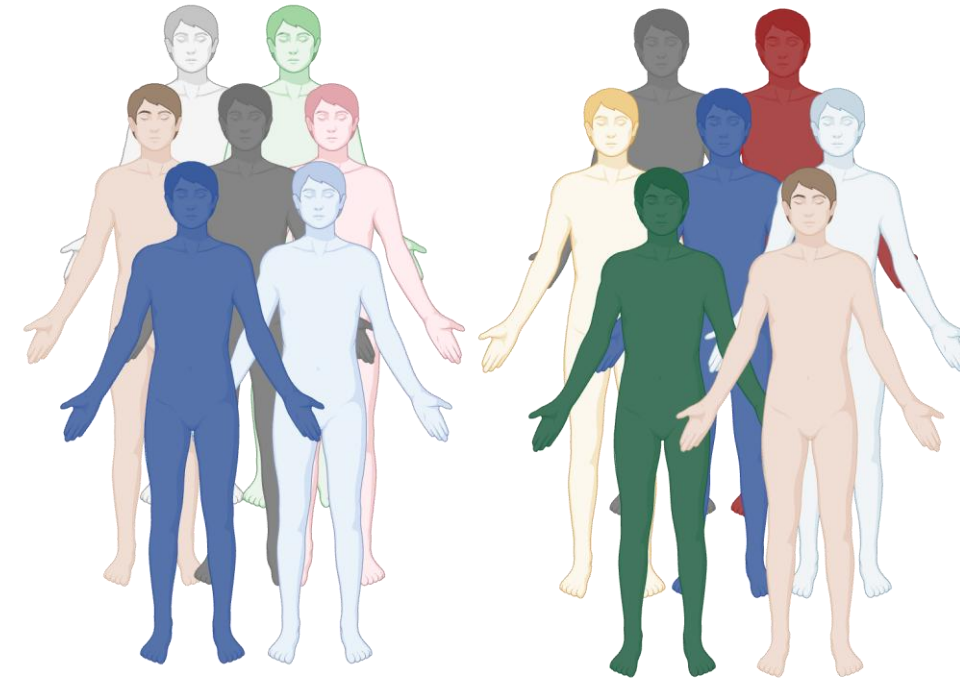
- Opportunities to better understand the disease and
- Potentially treat

# Higher T central and lower effector memory cells in bipolar disorder: A differentiation abnormality?

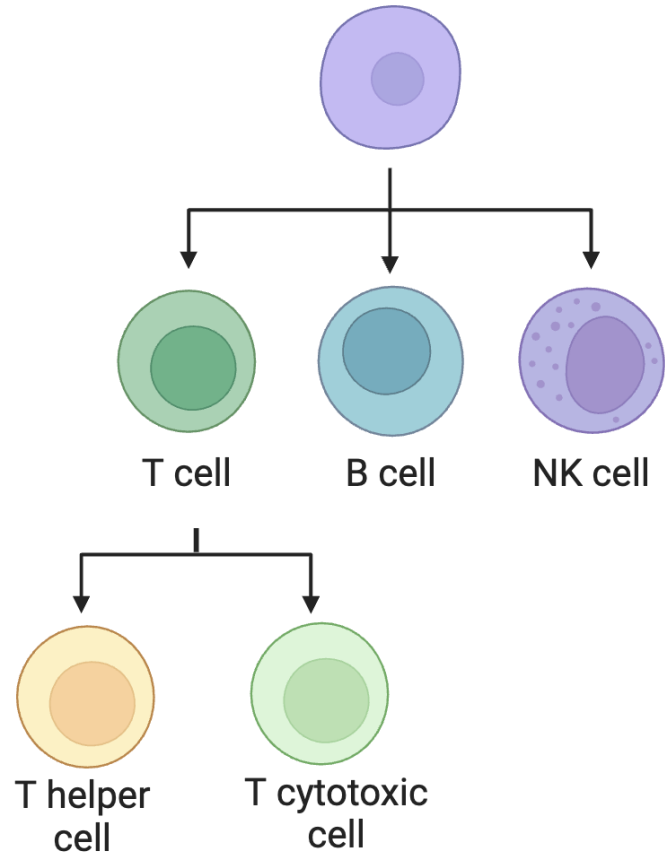
Magdalini Ioannou <sup>a</sup>  , Maria S. Simon <sup>b</sup>, Jenny Borkent <sup>a</sup>, Annemarie Wijkhuijs <sup>c</sup>, Raf Berghmans <sup>d</sup>, Bartholomeus C.M. Haarman <sup>a,1</sup>, Hemmo A. Drexhage <sup>c,1</sup>

Bipolar Disorder (n=58)

Healthy controls (n=113)



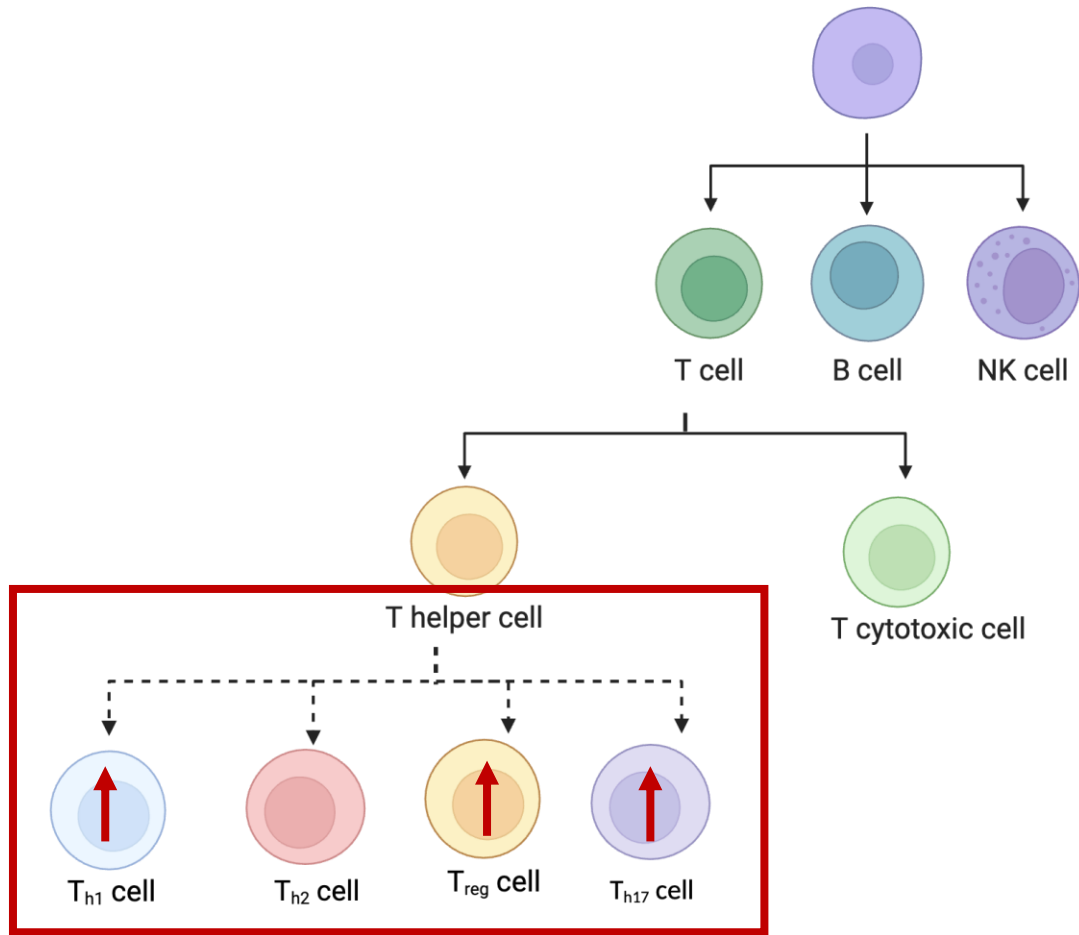
# Staining A



	Healthy Controls	Bipolar Disorder	p-value	p-value age, sex, BMI adjusted
T cell%	59.6 (54.4, 65.1)	56.7 (49.4, 62.2)	0.03	0.4
B cell%	7.3 (5.8, 8.9)	7.0 (5.5, 9.3)	0.98	0.4
Natural killer cell%	8.3 (6.1, 11.6)	8.6 (6.8, 11.2)	0.5	0.5
T helper cell%	50.1 ( $\pm$ 8.1)	48.0 ( $\pm$ 9.1)	0.1	0.07
T cytotoxic cell%	17.0 (13.3, 20.8)	16.5 (12.0, 20.4)	0.3	1



# Staining B



	Healthy Controls	Bipolar Disorder	p-value	p-value after age, sex, BMI adjustment
$T_{h1}$ cell%	4.6 (3.0, 6.3)	5.2 (3.6, 7.1)	0.09	<b>0.03</b>
$T_{h2}$ cell%	0.44 (0.35, 0.62)	0.42 (0.35, 0.64)	0.7	0.8
$T_{h17}$ cell%	0.27 (0.19, 0.36)	0.33 (0.22, 0.45)	0.02	<b>0.04</b>
$T_{REGS}$ cell%	1.9 (1.5, 2.4)	2.4 (1.9, 3.1)	<0.001	<b>0.003</b>

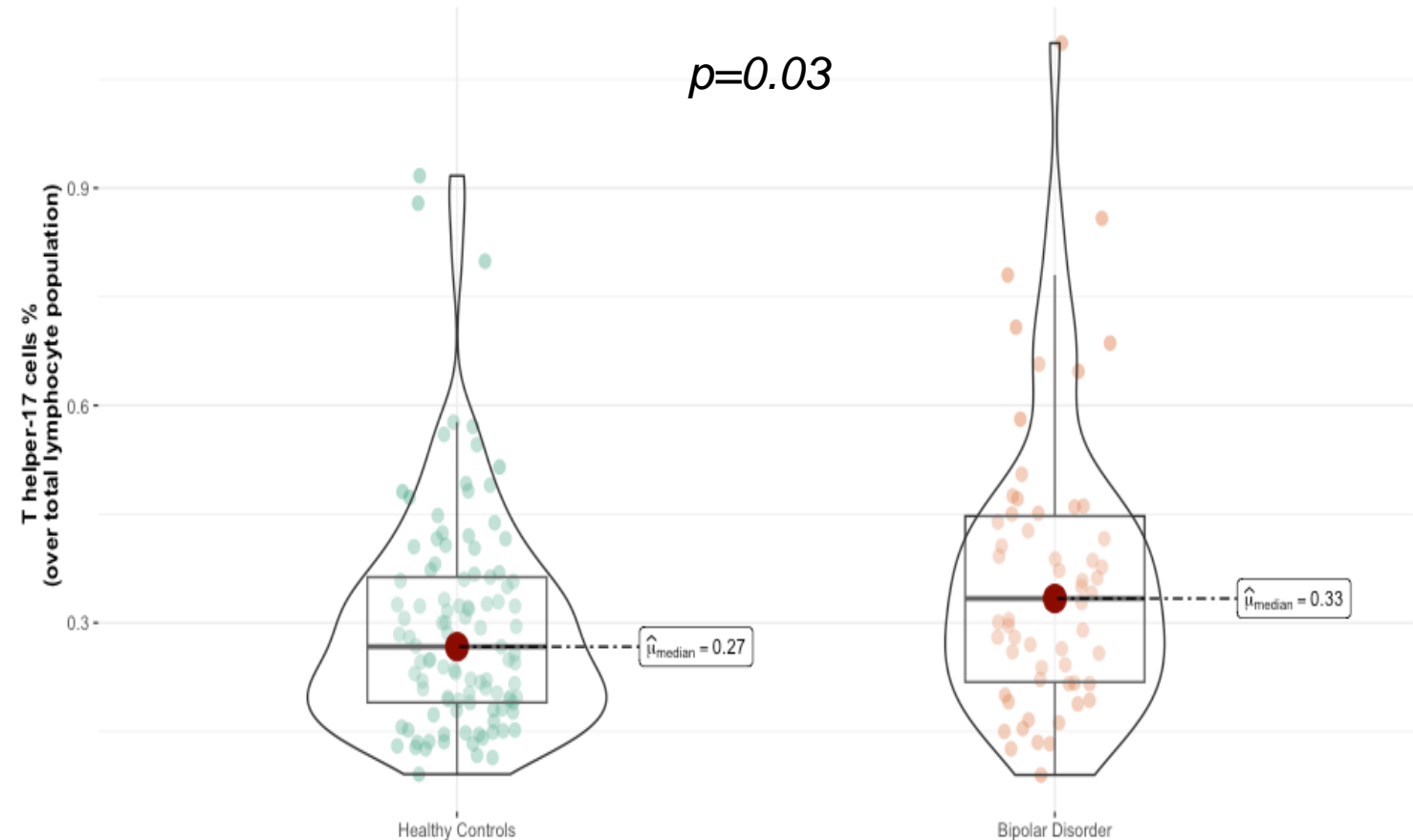
# T helper 17 cells

## What are they?

- Strongly pro-inflammatory.
- Defence against bacteria, viruses, and fungi.
- Maintain mucosal barrier integrity with IL-17 .
- Overactivation linked to chronic inflammatory and autoimmune diseases.

## Findings in Bipolar Disorder

- Patients in a euthymic state show elevated Th17 levels compared to healthy controls.
- Consistent with previous findings in a cohort of 97 BD patients but not replicated in a smaller cohort (n=38).
- Elevated Th17 levels align with reported higher circulating IL-17 in BD patients in remission.

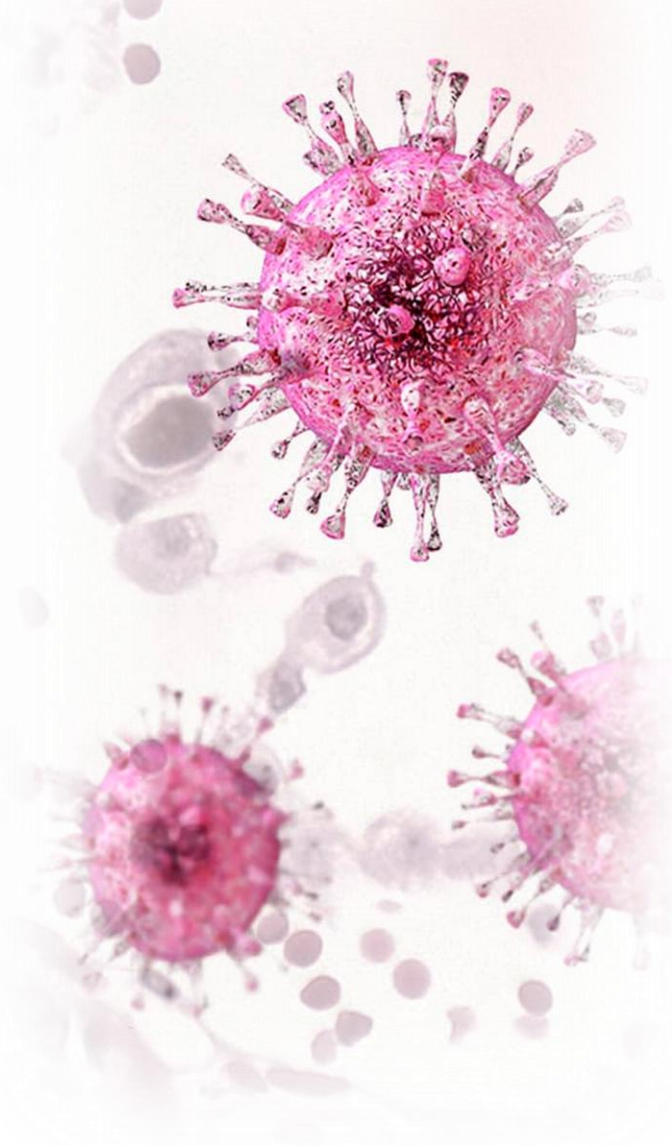


# Maybe patients have higher prevalence of chronic infections?

## Cytomegalovirus (CMV)

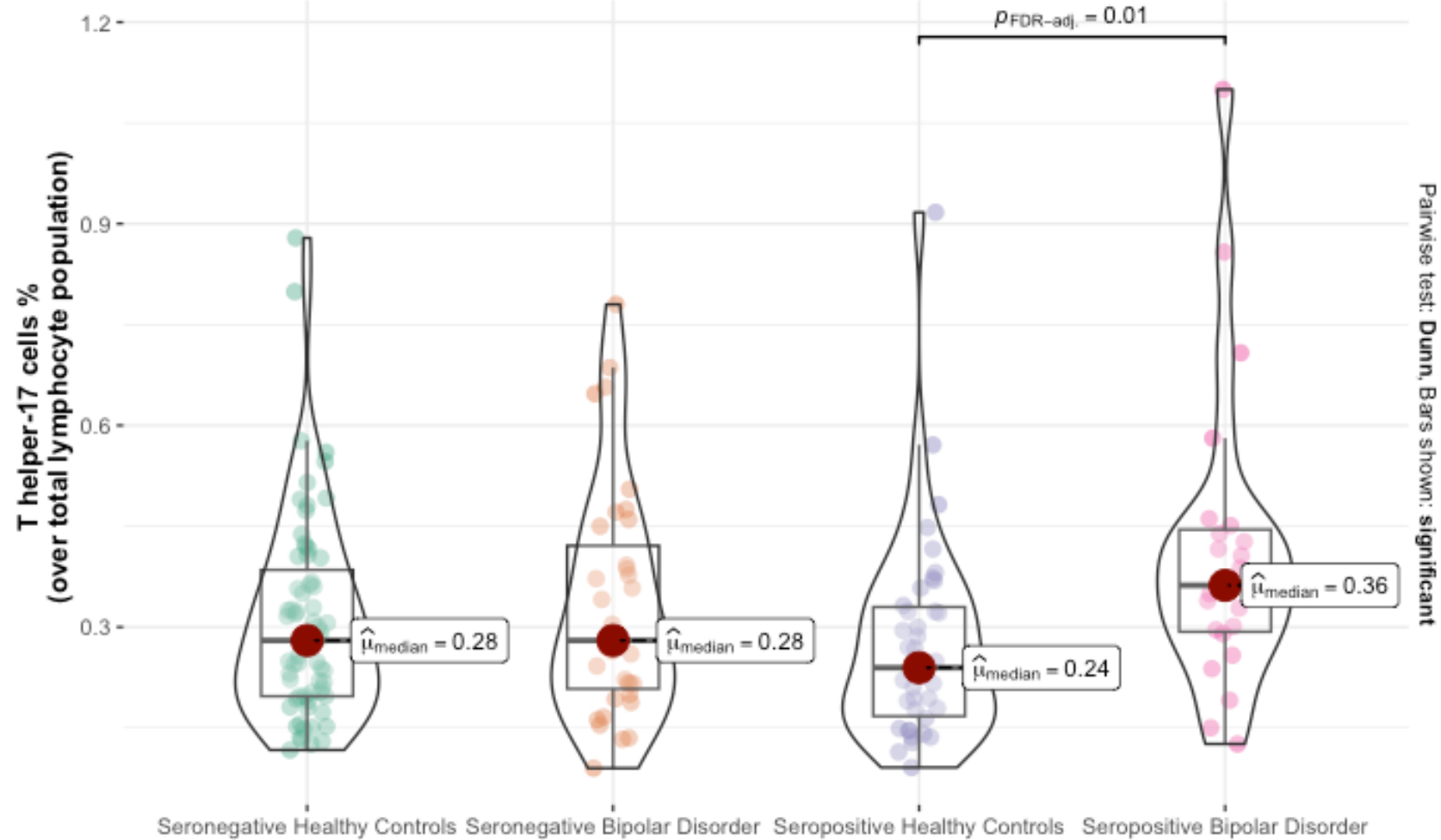
- Common virus
- Once infected, the body retains the virus for life
- It gets re-activated by inflammation, immunosuppression, and stress

	Healthy Controls (n=113)	Bipolar Disorder (n=58)	<i>p</i> -value
CMV seropositive (%)	35.4%	39.7%	0.6
Anti-CMV titers (U/ml)	5.2 (3.7, 32.4)	5.0 (3.1, 45.7)	0.9



What if patients react differently to chronic infections?

- Interaction between CMV and BD linked to a trend of increased  $T_{h17}$  levels.
- Stratified analysis shows CMV-seropositive BD patients have significantly higher  $T_{h17}$  levels compared to CMV-seropositive HCs.
- Suggests BD patients may exhibit heightened  $T_{h17}$  responses to CMV infection.



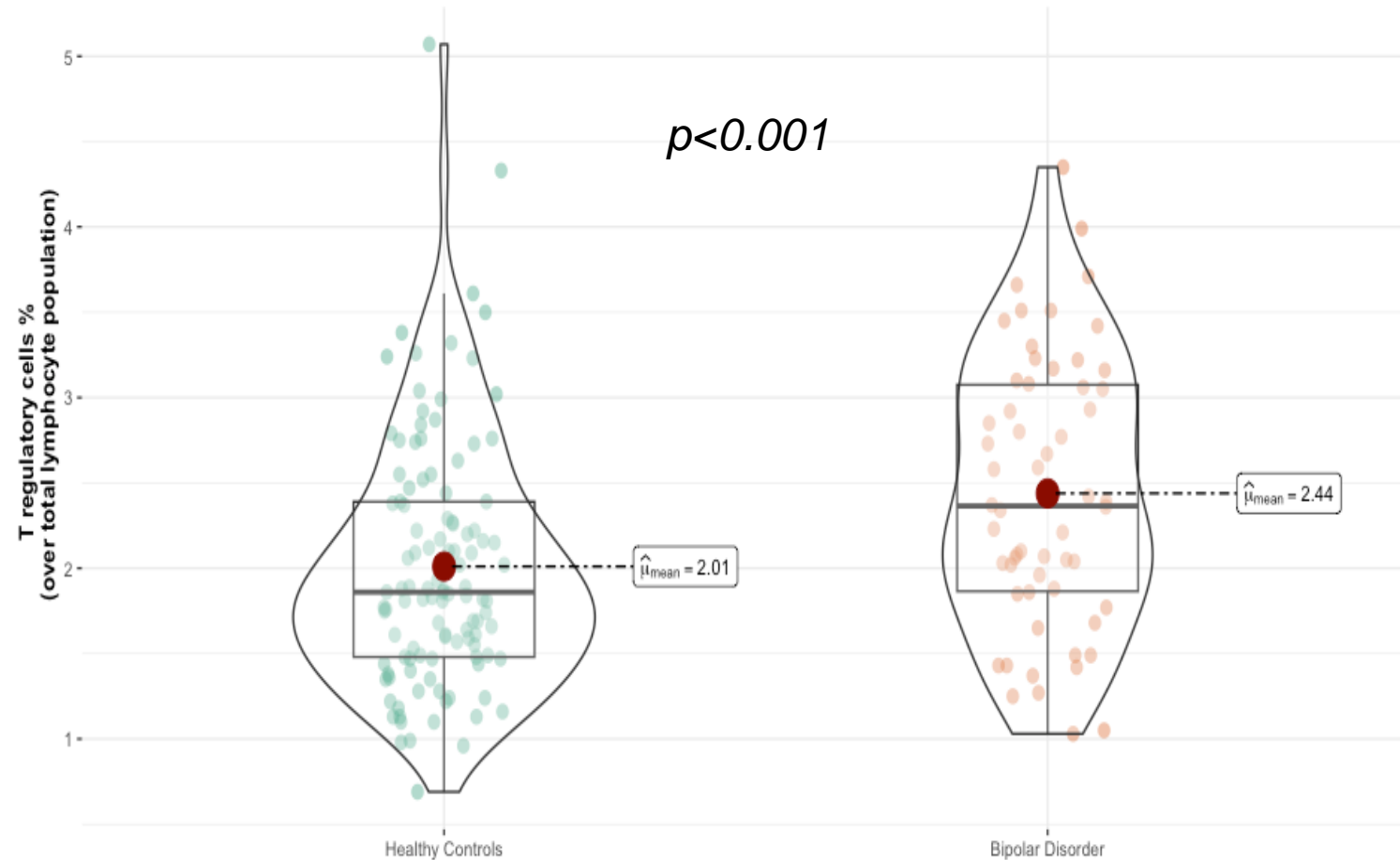
# T Regulatory Cells

## What are they?

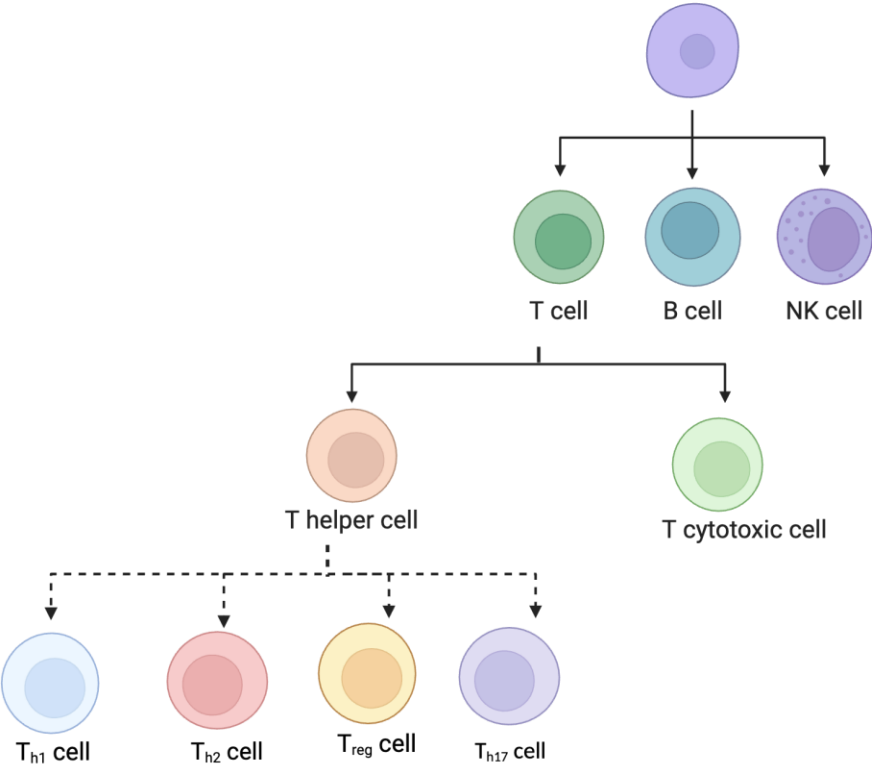
- Essential for maintaining immune homeostasis and preventing autoimmunity.

## Findings in Bipolar Disorder

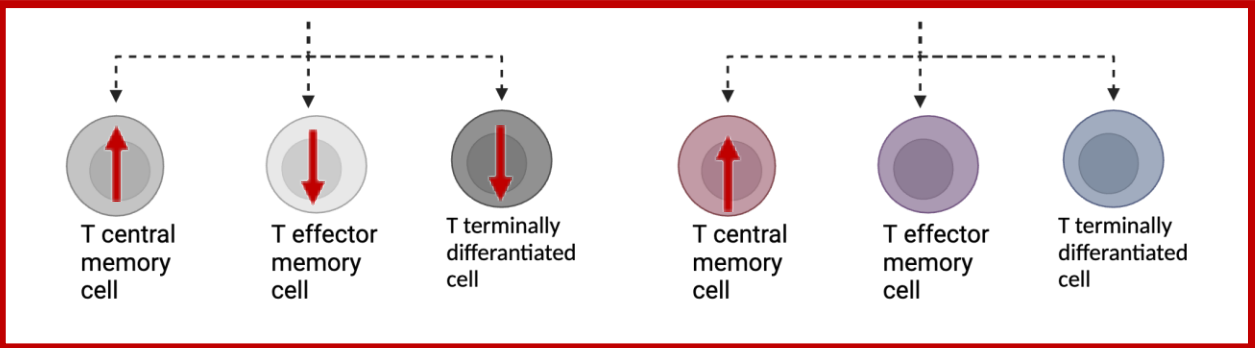
- Euthymic patients have elevated levels compared to healthy controls.
- This may reflect a compensatory mechanism to counteract heightened pro-inflammatory activity.
- Previous studies suggest the immune-regulatory reflex system could play a role in recovery from acute episodes.



# Staining C



	Healthy Controls	Bipolar Disorder	p-value	p-value after age, sex, BMI adjustment
CD4 <sup>+</sup> T <sub>CM</sub> cell%	12.6 (10.5, 16.6)	19.2 (13.7, 23.6)	0.001	<b>0.05</b>
CD4 <sup>+</sup> T <sub>EM</sub> cell%	6.0 (4.1, 7.8)	3.5 (2.7, 5.2)	<0.001	<b>0.002</b>
CD4 <sup>+</sup> T <sub>EMRA</sub> cell%	1.5 (0.8, 2.5)	0.8 (0.5, 1.6)	0.004	<b>0.04</b>
CD8 <sup>+</sup> T <sub>CM</sub> cell%	0.7 (0.4, 0.9)	1.2 (0.7, 2.0)	<0.001	<b>0.01</b>
CD8 <sup>+</sup> T <sub>EM</sub> cell%	2.5 (1.6, 3.7)	2.4 (1.2, 3.9)	0.8	0.9
CD8 <sup>+</sup> T <sub>EMRA</sub> cell%	8.4 (7.4, 12.2)	9.2 (6.1, 14.2)	0.8	0.7



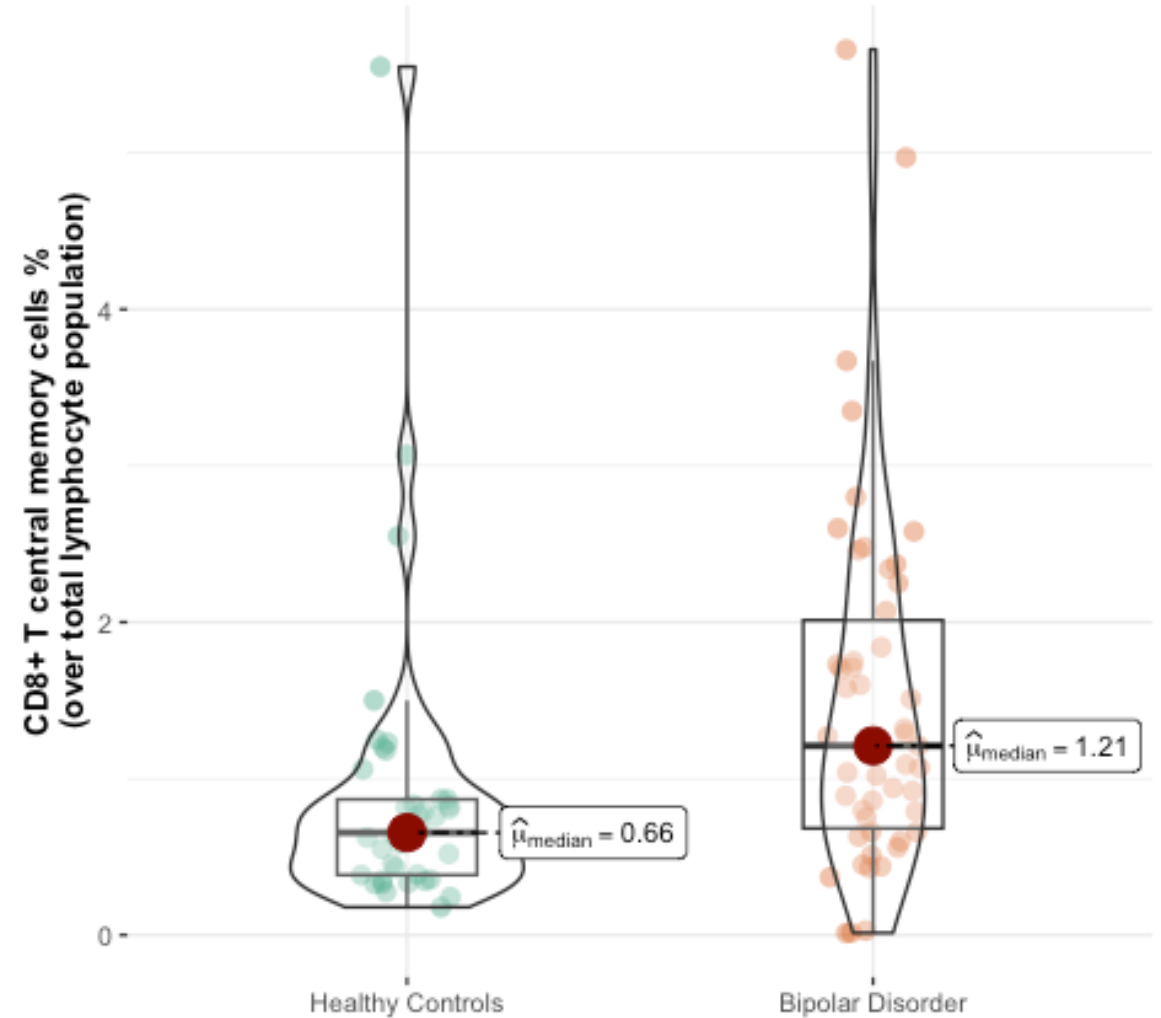
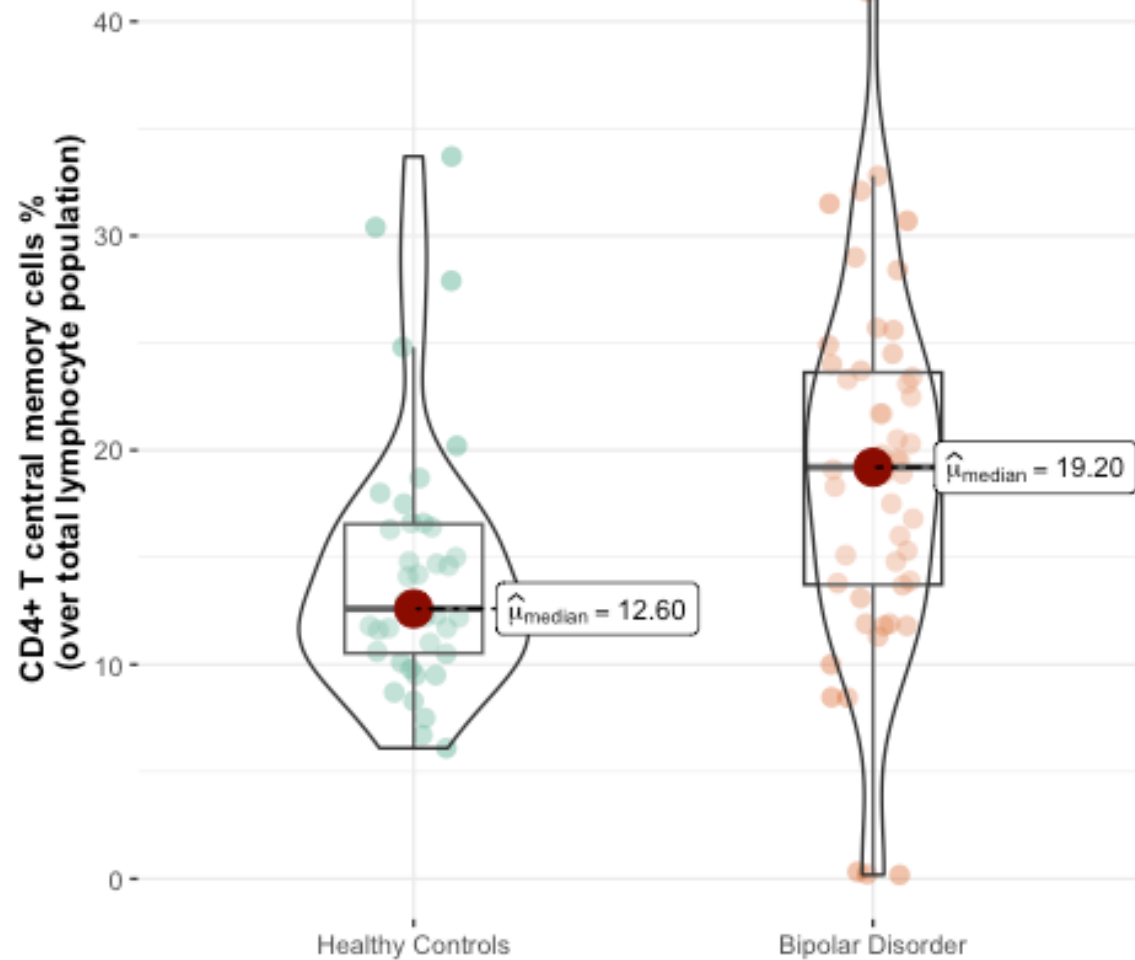
# T central memory cells

## What are they?

Long-lived cells in lymphoid organs that support T cell proliferation and activation upon antigen re-exposure.

## Findings in Bipolar Disorder

Elevated in BD, suggesting prolonged immune activation.



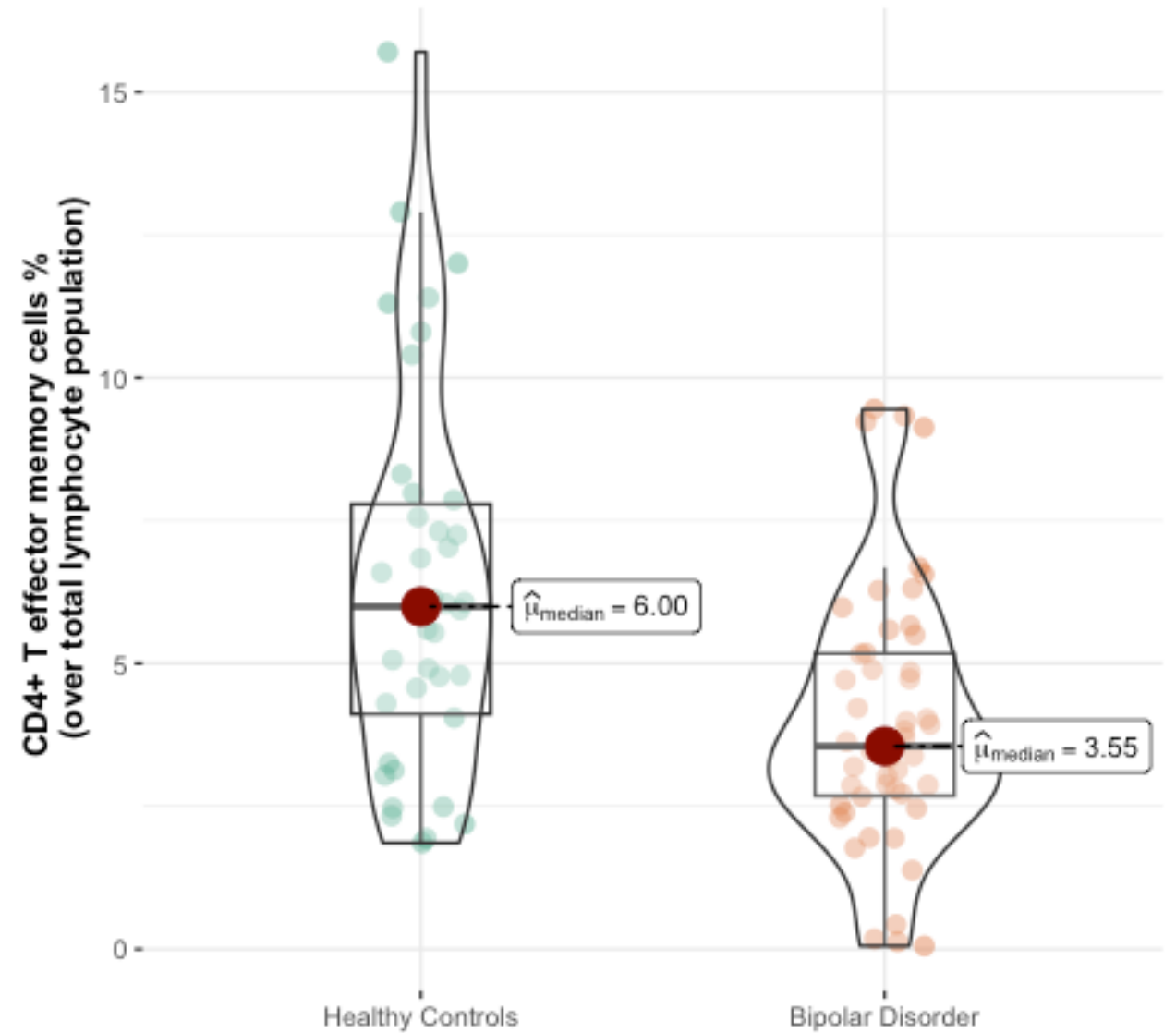
# T effector memory cells

What are they?

Circulate in peripheral tissues and respond quickly to infection.

Findings in Bipolar Disorder

Reduced in BD. A differentiation abnormality?





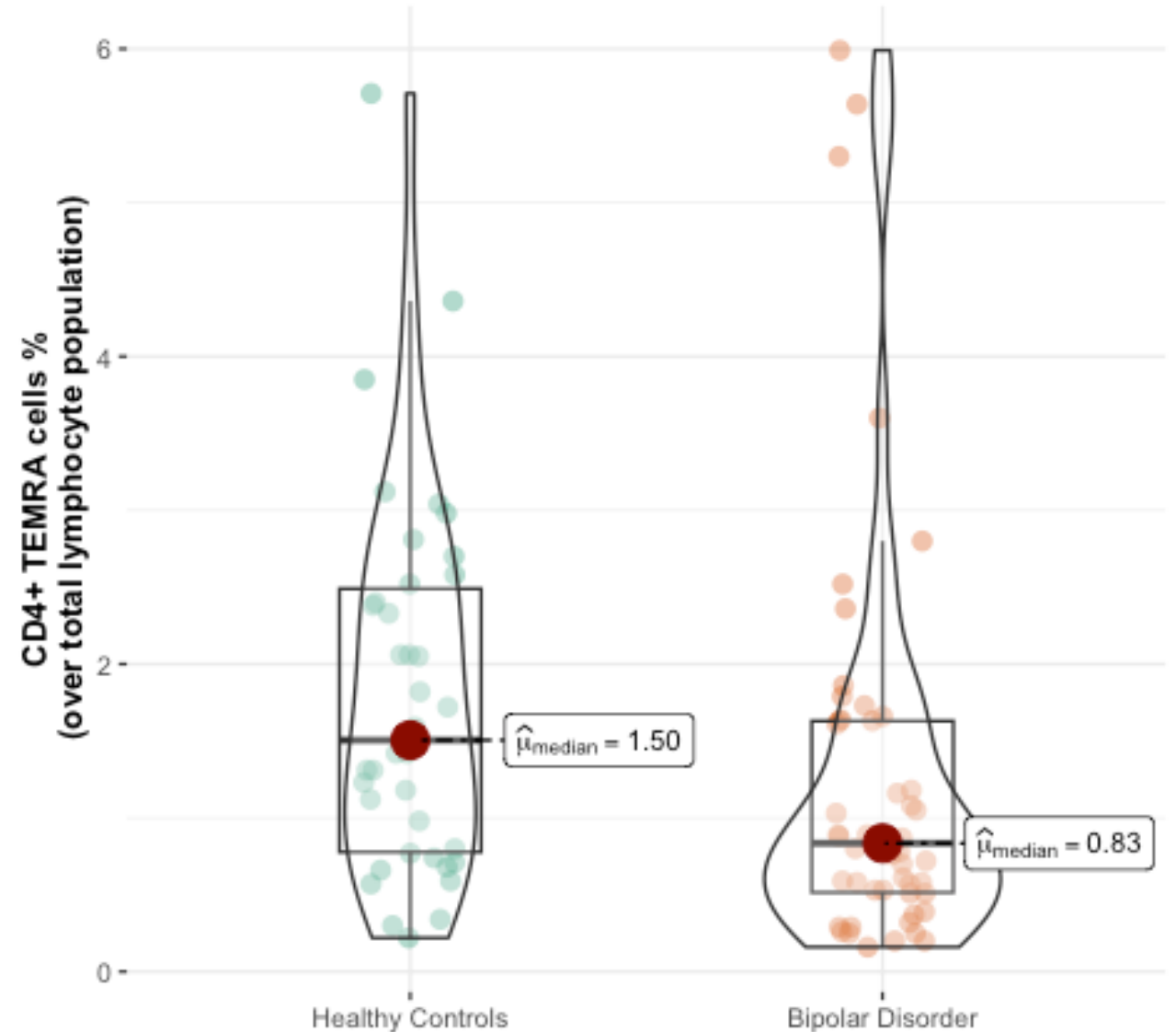
# TEMRA (Effector Memory RA+ T Cells)

What are they?

Terminally differentiated cells, critical for strong immune responses.

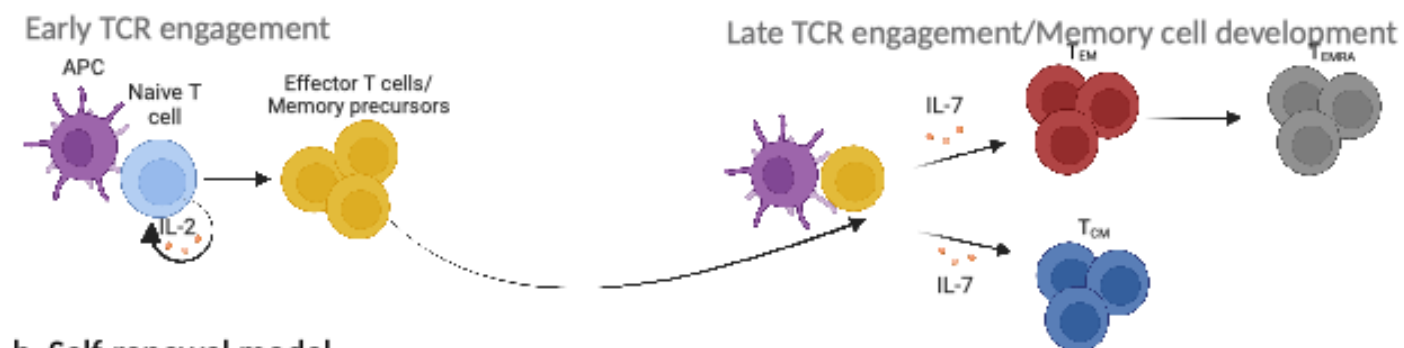
Findings in Bipolar Disorder

Reduced in BD. A differentiation abnormality?

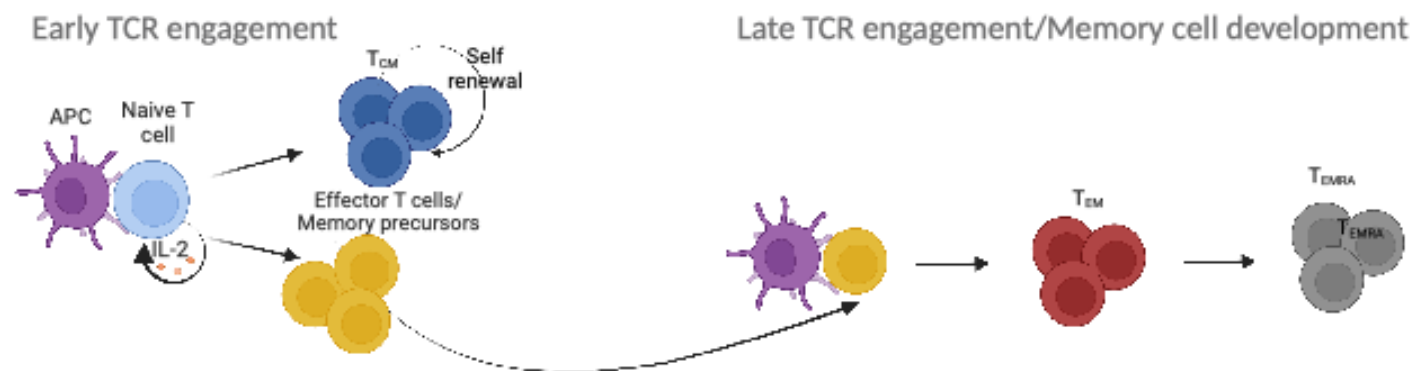


## A. Hypothesis on models of T cell differentiation

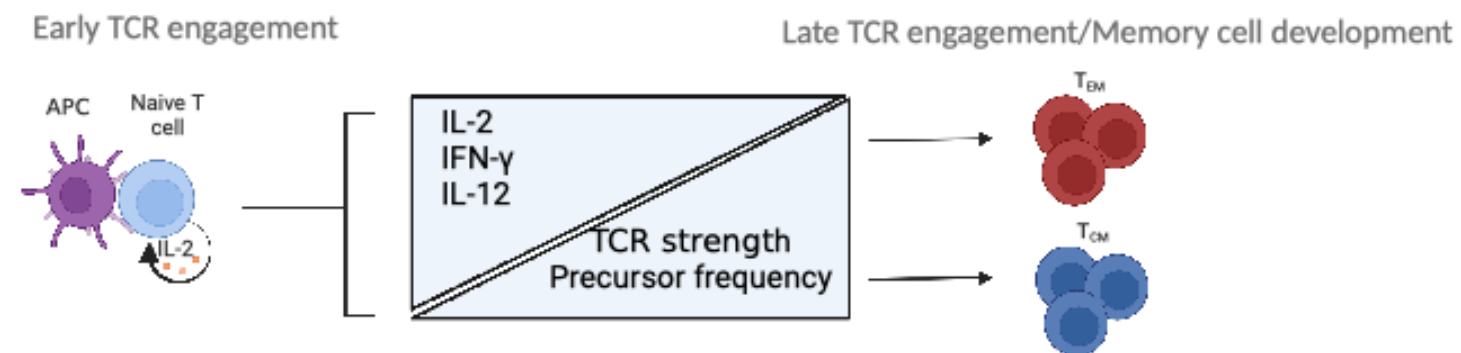
### a. Linear model



### b. Self-renewal model



## B. Hypothesis on influencing factors of T memory cell apportioning



# Interleukin 7

## Role?

Essential cytokine for T-cell development.

## Study Findings

IL-7 levels are significantly lower in BD patients compared to healthy controls.

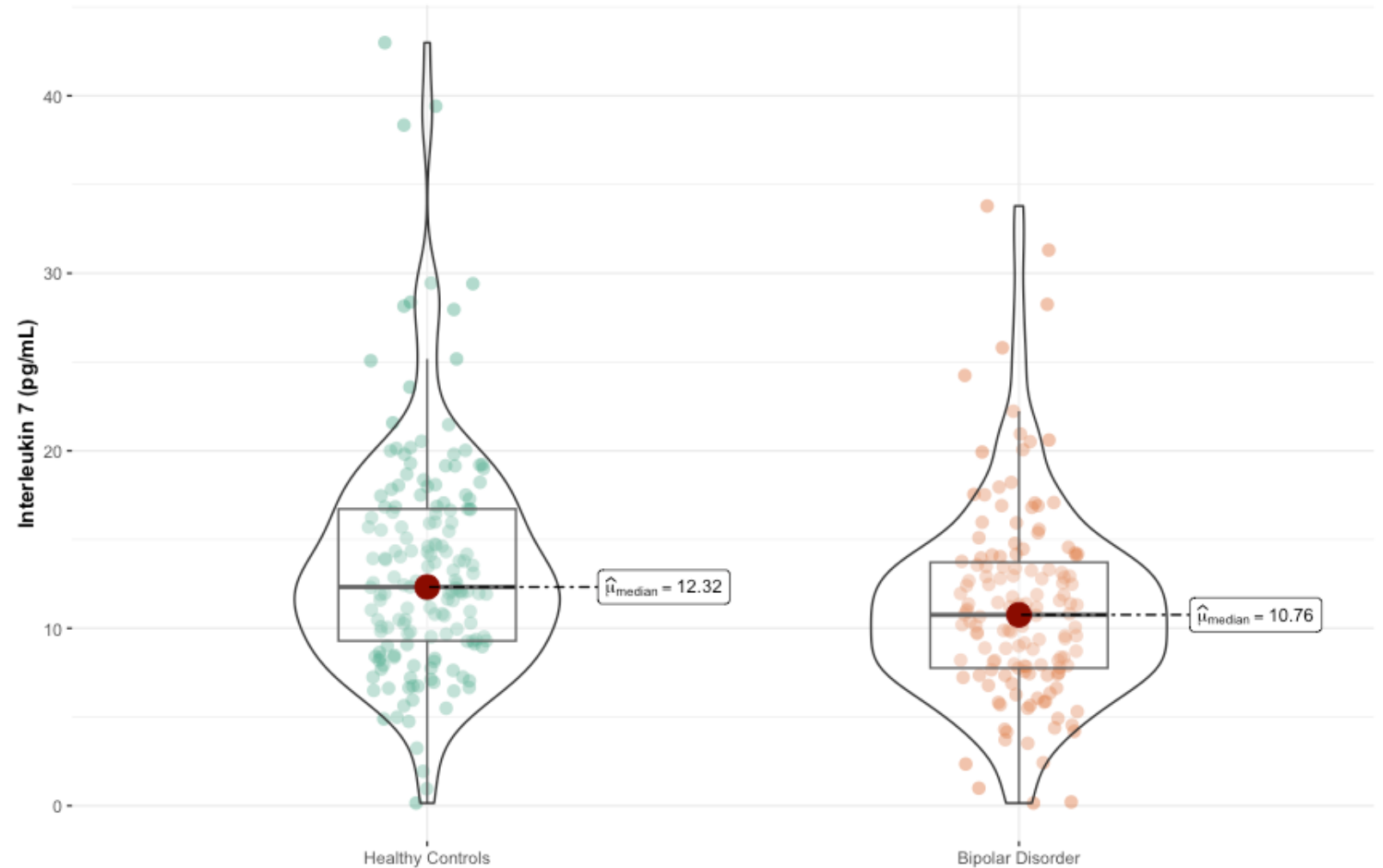
Suggests impaired T-cell maturation in BD.

## Therapeutic Potential

Experimental IL-7 therapies (e.g., rhIL7, Efineptakin- $\alpha$ ) show promise in boosting T-cell counts in immune-deficient conditions.

## Implications

Lower IL-7 may underlie T-cell dysregulation in BD, warranting further research into IL-7-based treatments.



# Discussion

## Key Findings

- Elevated  $T_{h17}$  and  $T_{REGS}$ .
- Interaction between BD diagnosis and CMV viral infection linked to  $T_{h17}$  skewing.
- Skewing towards central memory and away from effector memory populations. Differentiation abnormality?
- Lower IL-7 levels, suggesting impaired T-cell maturation.

# Discussion

## Future Directions

- T cell abnormalities. Do they precede the onset of BD?
- T cell abnormalities and their relationship with specific symptoms domains?
- T cell abnormalities and their relationship to physical comorbidities in BD?



Thank you for your  
attention

