What are T-cell immune abnormalities across Neurodevelopmental and Psychiatric Disorders?

T-Cell Abnormalities Span Neurodevelopmental and Psychiatric Disorders

T-cell immune abnormalities — including altered subset frequencies, skewed T-cell receptor repertoires, disrupted Treg/Th17 balance, and aberrant cytokine signaling — are consistently reported across autism spectrum disorder (ASD), schizophrenia, major depressive disorder (MDD), bipolar disorder, tic disorders, and psychosis (Moreno et al., 2024; Debnath et al., 2021; Pape et al., 2019; Wang et al., 2026). These defects span both neurodevelopmental conditions (ASD, ADHD, tic disorders, intellectual disability) and major psychiatric disorders (MDD, schizophrenia, bipolar disorder, PTSD), suggesting T-cell dysregulation as a **transdiagnostic vulnerability factor** whose clinical manifestation depends on genetic background, developmental timing, and environmental exposures (Wang et al., 2026; Lynall et al., 2022; Gibney & Drexhage, 2013).

Treg/Th17 Imbalance Across Disorders

A recurring finding across multiple disorders is a shift favoring pro-inflammatory Th17 cells over immunoregulatory Tregs. In ASD, a meta-analysis of 13 studies (388 patients, 326 controls) found significantly decreased CD4+ lymphocytes and Tregs alongside increased Th17 cells (Ellul et al., 2021). This Th17/Treg imbalance is positively correlated with **depression severity** in MDD (Wang et al., 2026), and elevated Th17 percentages are specifically associated with psychotic symptoms in 22q11.2 deletion syndrome, a genetic model for schizophrenia (Vergaelen et al., 2018). Treg dysfunction is also proposed as a mechanism in psychosis broadly, where a hypofunctional Treg state may fail to dampen excessive pro-inflammatory monocyte and macrophage responses (Corsi-Zuelli et al., 2021; Vergaelen et al., 2018).

Disorder	Treg Change	Th17 Change	Key Citation
ASD	Decreased	Increased	(Ellul et al., 2021)
MDD	Decreased (with childhood trauma)	Increased	(Susam et al., 2025)
Psychosis / 22q11.2DS	Hypofunctional	Increased (linked to positive symptoms)	(Vergaelen et al., 2018; Corsi-Zuelli et al., 2021)
Tic disorders	Decreased	Th17-mediated BBB disruption	(Gagliano et al., 2025; Sun & Bai, 2026)

FIGURE 1 Treg and Th17 abnormalities across four neurodevelopmental and psychiatric conditions.

Disorder-Specific T-Cell Findings

ASD and neurodevelopmental disorders. Beyond the Treg/Th17 shift, ASD shows dysregulated T-cell activation characterized by altered cellular function, increased cytokine release, and inflammatory phenotypes observed across multiple laboratories and geographic regions (Moreno et al., 2024). Comprehensive immunoprofiling of ASD, ADHD, and intellectual disability disorder (IDD) reveals shared immune abnormalities including Th1 polarization, increased IL-1 signaling, and depletion of the compensatory immune-regulatory system, with machine learning identifying three immunologically distinct NDD subgroups (Sreenivas et al., 2023). Mendelian randomization analyses further support a causal protective role for resting CD4+ Tregs and CD127− CD8+ T cells against ASD risk (Nie et al., 2025).

Major depressive disorder. Approximately 37% of MDD patients show dysregulated T-lymphocyte populations, including reduced CD4+ naïve T cells and elevated Th1 cells (Wang et al., 2026). Antidepressant-free MDD patients exhibit a skewed T-cell phenotype with lower surface expression of the chemokine receptors CXCR3 and CCR6, a shift toward CD4+CD25highCD127low cells with higher FOXP3 expression, and a **less diverse CD4+ TCR repertoire** (Patas et al., 2018). Childhood trauma, a major MDD risk factor, independently reduces total CD3+ T cells, Th2 cells, and Tregs, with specific T-cell subsets correlating with trauma subtypes such as physical abuse and emotional neglect (Susam et al., 2025).

Schizophrenia and psychosis. In 22q11.2 deletion syndrome — which carries a 25–40% risk for schizophrenia spectrum disorders and features congenital T-cell deficits from thymus hypoplasia — patients show reduced circulating T and T-helper cells alongside elevated inflammatory Th1, Th17, and memory T-helper cells (Vergaelen et al., 2018). Mendelian randomization in schizophrenia identifies naive CD4+ T cells and activated/resting Tregs as significantly associated with disease risk (Wang et al., 2023). GWAS variants for schizophrenia and depression are enriched at epigenetically active sites in stimulated CD4+ T cells but not in myeloid cells, suggesting environmental stimuli activate T cells to unmask psychiatric risk variants (Lynall et al., 2022).

Tic disorders and PANDAS/PANS. Pediatric Tourette syndrome shows disproportionate T-cell subpopulation changes, with a meta-analysis identifying significantly reduced CD4+ T-helper cells and elevated pro-inflammatory cytokines IL-6 and TNF-α (Li et al., 2022). Post-infectious autoimmunity models (PANDAS/PANS) involve Th17-mediated blood-brain barrier disruption and molecular mimicry producing autoantibodies targeting basal ganglia neurons, including dopamine D2 receptors (Sun & Bai, 2026; Gagliano et al., 2025).

Shared Mechanisms and Genetic Evidence

Several converging pathways explain how T-cell abnormalities impact brain function across diagnostic boundaries. T cells regulate key neurobiological processes including neurodevelopment, neurogenesis, cognition, learning, and memory, and deficits in T-cell homeostasis alter these processes to drive psychopathology (Debnath et al., 2021). Atypical T cells may disrupt brain function through at least two routes: stimulus-driven peripheral and CNS inflammation via soluble mediators and contact-dependent mechanisms, and developmental disruption of **microglial synaptic pruning** during childhood and adolescence (Lynall et al., 2022).

- Psychiatric risk variants are enriched at epigenetically active sites specifically in **stimulated CD4+ T cells**, linking genetic susceptibility to T-cell activation (Lynall et al., 2022).
- Single-cell transcriptomic Mendelian randomization identifies 73 and 156 putative causal genes during CD4+ T-cell activation for Alzheimer's disease and MDD respectively, with 21 genes prioritized as drug-repurposing targets (Zhang et al., 2026).
- T cells can infiltrate the CNS via the choroid plexus, meninges, and blood-brain barrier, directly modulating neuroinflammation and neural function in depression and other conditions (Wang et al., 2026; Zhang et al., 2026).
- The gut-microbiota-Th17/Treg axis links intestinal dysbiosis to altered T-cell differentiation, indirectly influencing CNS inflammation through the gut-brain axis (Wang et al., 2026; Sun & Bai, 2026).

Evidence for T-cell involvement is mixed in important ways: T-cell subset abnormalities show considerable overlap across MDD, schizophrenia, and bipolar disorder, making disorder-specific immune signatures difficult to establish (Patas et al., 2018; Hughes & Ashwood, 2020). In PTSD, immune dysregulation often reflects stress-induced HPA-axis disruption and glucocorticoid resistance rather than sustained Th17 predominance, distinguishing its T-cell profile from other conditions (Wang et al., 2026). Most studies are cross-sectional and confounded by medication effects, and longitudinal data in drug-naïve patients remain scarce (Corsi-Zuelli et al., 2021). Nonetheless, the convergence of genetic, clinical, and experimental evidence positions T-cell dysregulation as a shared immunopathogenic mechanism with therapeutic implications, including Treg-enhancing strategies and anti-CD3 immunotherapy currently entering clinical trials (Zhang et al., 2026; Corsi-Zuelli et al., 2021; Nie et al., 2025).

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References

Corsi-Zuelli, F., Deakin, B., De Lima, M. D., Qureshi, O., Barnes, N., Upthegrove, R., Louzada-Júnior, P., & Del-Ben, C. (2021). T regulatory cells as a potential therapeutic target in psychosis? Current challenges and future perspectives. *Brain, Behavior, & Immunity - Health, 17*. https://doi.org/10.1016/j.bbih.2021.100330

Debnath, M., Raison, C., Maes, M., & Berk, M. (2021). Role of the T-Cell Network in Psychiatric Disorders. *Immuno-Psychiatry*. https://doi.org/10.1007/978-3-030-71229-7_7

Ellul, P., Rosenzwajg, M., Peyre, H., Fourcade, G., Mariotti-Ferrandiz, E., Trebossen, V., Klatzmann, D., & Delorme, R. (2021). Regulatory T lymphocytes/Th17 lymphocytes imbalance in autism spectrum disorders: evidence from a meta-analysis. *Molecular Autism, 12*. https://doi.org/10.1186/s13229-021-00472-4

Gagliano, A., Cucinotta, F., Giunta, I., Di Modica, I., De Domenico, C., Costanza, C., Germanò, E., & Frankovich, J. (2025). The Immune/Inflammatory Underpinnings of Neurodevelopmental Disorders and Pediatric Acute-Onset Neuropsychiatric Syndrome: A Scoping Review. *International Journal of Molecular Sciences, 26*. https://doi.org/10.3390/ijms26167767

Gibney, S., & Drexhage, H. (2013). Evidence for a Dysregulated Immune System in the Etiology of Psychiatric Disorders. *Journal of Neuroimmune Pharmacology, 8*, 900 - 920. https://doi.org/10.1007/s11481-013-9462-8

Hughes, H., & Ashwood, P. (2020). Overlapping evidence of innate immune dysfunction in psychotic and affective disorders.. *Brain, behavior, & immunity - health, 2*, 100038. https://doi.org/10.1016/j.bbih.2020.100038

Li, Y., Wang, X., Yang, H.-X., Li, Y., Gui, J., & Cui, Y. (2022). Profiles of Proinflammatory Cytokines and T Cells in Patients With Tourette Syndrome: A Meta-Analysis. *Frontiers in Immunology, 13*. https://doi.org/10.3389/fimmu.2022.843247

Lynall, M., Soskic, B., Hayhurst, J., Schwartzentruber, J., Levey, D., Pathak, G., Polimanti, R., Gelernter, J., Stein, M. B., Trynka, G., Clatworthy, M., & Bullmore, E. (2022). Genetic variants associated with psychiatric disorders are enriched at epigenetically active sites in lymphoid cells. *Nature Communications, 13*. https://doi.org/10.1038/s41467-022-33885-7

Moreno, R. J., Amara, R., & Ashwood, P. (2024). Toward a better understanding of T cell dysregulation in autism: An integrative review.. *Brain, behavior, and immunity*. https://doi.org/10.1016/j.bbi.2024.10.009

Nie, Z., Xu, X., Chen, J., Chen, H., Li, M., Zhang, Y., Li, Z., Shen, C., Wen, J., & Cao, X. (2025). Treg Cells Modulate Neuroinflammation and Behavioral Deficits in Autism: Evidence From MR-Based Genetic Analyses and Experimental Models. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 201*, 127 - 143. https://doi.org/10.1002/ajmg.b.33061

Pape, K., Tamouza, R., Leboyer, M., & Zipp, F. (2019). Immunoneuropsychiatry — novel perspectives on brain disorders. *Nature Reviews Neurology, 15*, 317-328. https://doi.org/10.1038/s41582-019-0174-4

Patas, K., Willing, A., Demiralay, C., Engler, J., Lupu, A., Ramien, C., Schäfer, T., Gach, C., Stumm, L., Chan, K., Vignali, M., Arck, P., Friese, M., Pless, O., Wiedemann, K., Agorastos, A., & Gold, S. (2018). T Cell Phenotype and T Cell Receptor Repertoire in Patients with Major Depressive Disorder. *Frontiers in Immunology, 9*. https://doi.org/10.3389/fimmu.2018.00291

Sreenivas, N., Maes, M., Padmanabha, H., Dharmendra, A., Chakkera, P., Choudhury, S. P., Abdul, F., Mullapudi, T., Gowda, V., Berk, M., Kommu, J. V. S., & Debnath, M. (2023). Comprehensive immunoprofiling of neurodevelopmental disorders suggests three distinct classes based on increased neurogenesis, Th-1 polarization or IL-1 signaling.. *Brain, behavior, and immunity*. https://doi.org/10.1016/j.bbi.2023.11.013

Sun, X., & Bai, X. (2026). Immune dysregulation in pediatric tic disorders: mechanisms, biomarkers, and therapeutic frontiers. *Frontiers in Immunology, 17*. https://doi.org/10.3389/fimmu.2026.1708940

Susam, Z., Boller, A., Freff, J., Kircher, T., Dannlowski, U., Baune, B., & Alferink, J. (2025). Blood Circulating T Cell Subsets in Relation to Childhood Trauma and Major Depressive Disorder. *European Psychiatry, 68*, S1003 - S1004. https://doi.org/10.1192/j.eurpsy.2025.2036

Vergaelen, E., Schiweck, C., Van Steeland, K., Counotte, J., Veling, W., Swillen, A., Drexhage, H., & Claes, S. (2018). A pilot study on immuno-psychiatry in the 22q11.2 deletion syndrome: A role for Th17 cells in psychosis?. *Brain, behavior, and immunity, 70*, 88 - 95. https://doi.org/10.1016/j.bbi.2018.03.022

Wang, H., Tao, H., Yuan, M., & Zhang, W. (2026). The emerging role of T cells in depression. *Frontiers in Psychiatry, 17*. https://doi.org/10.3389/fpsyt.2026.1780383

Wang, C., Zhu, D., Zhang, D., Zuo, X., Yao, L., Liu, T., Ge, X., He, C., Zhou, Y., & Shen, Z. (2023). Causal role of immune cells in schizophrenia: Mendelian randomization (MR) study. *BMC Psychiatry, 23*. https://doi.org/10.1186/s12888-023-05081-4

Zhang, H., Lyu, H., Gong, Q., Wang, C., Wang, Q., Wang, W., Li, K., & Liu, Z. (2026). Single-cell transcriptome-wide Mendelian randomization during CD4+ T cell activation reveals immune-mediated mechanisms and drug targets for neuropsychiatric disorders. *Communications Biology, 9*. https://doi.org/10.1038/s42003-026-09941-z