What are the relationships between Celiac Disease, Non-Celiac Gluten Sensitivities and the Immune System and Neurodevelopmental and Psychiatric Disorders?

Immune-Mediated Gluten Disorders and the Brain: Key Relationships

Celiac disease (CD) and non-celiac gluten sensitivity (NCGS) are immune-mediated reactions to gluten that affect the gut, immune system, and—through several pathways—the nervous system and mental health.

Neurodevelopmental & Psychiatric Risks

- Large cohort and meta-analytic studies show CD is associated with higher odds of **depression, anxiety, headache, epilepsy, panic disorder, dysthymia, ADHD, ASD, eating disorders, and migraine** compared with controls (Sharma et al., 2021; Hansen et al., 2023; Clappison et al., 2020; Gaur, 2022; Nagarajappa et al., 2023; Butwicka et al., 2017; Alkhayyat et al., 2021).
- In children, CD increases risk of **mood, anxiety, eating, behavioral disorders, ADHD, ASD, and intellectual disability**; some psychiatric diagnoses also precede CD, suggesting bidirectional links (Butwicka et al., 2017).
- Reviews find consistent associations of CD with **depression and eating disorders**, with broader but less consistent links to other diagnoses (Slim et al., 2018).

Examples of Odds Ratios in CD

Outcome	Approx. risk vs controls	Citations
Depression	~1.6–2.0×	(Sharma et al., 2021; Clappison et al., 2020; Alkhayyat et al., 2021)
Anxiety	~1.4–6×	(Sharma et al., 2021; Hansen et al., 2023; Clappison et al., 2020)
Epilepsy	~12×	(Sharma et al., 2021; Hansen et al., 2023)
ADHD	~1.4–1.8×	(Clappison et al., 2020; Gaur, 2022; Alkhayyat et al., 2021)
ASD / childhood autism	~1.5–4.9×	(Clappison et al., 2020; Butwicka et al., 2017; Alkhayyat et al., 2021)
Eating disorders	~1.6–15.8×	(Sharma et al., 2021; Clappison et al., 2020; Alkhayyat et al., 2021)

FIGURE 1 Relative risks of key neuropsychiatric outcomes in celiac disease.

Immune System, Barrier, and Microbiota Mechanisms

- CD is driven by **innate and adaptive immune responses** to gluten, with Th1-type cytokines (e.g., IL-21, IL-2, IL-1β, TNF, IFN-γ) and chronic inflammation central to mucosal damage (Rossi et al., 2023; Casella et al., 2017; Sallese et al., 2023; Barone et al., 2022).
- Even before gluten exposure, at-risk individuals can show low-grade inflammation and cellular fragility, with gluten further amplifying this state (Barone et al., 2022).
- Both CD and NCGS/NCGWS involve **impaired intestinal barrier ("leaky gut")** and dysbiosis; gliadin peptides and other wheat components plus altered microbiota increase permeability and pro-inflammatory cytokines, shaping the **gut–brain axis** (Rossi et al., 2023; Casella et al., 2017; Freire et al., 2019; Popova & Kryvchykova, 2025; Caio et al., 2020; Cardoso-Silva et al., 2019).
- Organoid models show CD epithelium has **increased permeability and heightened cytokine release** to gliadin; microbiota-derived molecules (e.g., butyrate) can partially normalize these responses (Freire et al., 2019).

Non-Celiac Gluten Sensitivity / Wheat Sensitivity

- NCGS/NCGWS lacks villous atrophy and classic CD antibodies, and seems driven more by **innate immune activation, barrier dysfunction, and microbiota changes** than by adaptive autoimmunity (Cabanillas, 2019; Caio et al., 2020; Cardoso-Silva et al., 2019).
- Patients report extra-intestinal symptoms such as **"foggy mind," headache, tiredness, and anxiety**, suggesting immune–brain interactions even without CD pathology (Cardoso-Silva et al., 2019).
- Gene-expression studies show a **molecular overlap** between CD and NCGS, particularly in dysregulated immune-related non-coding RNAs, implying a shared immune "root" with different inflammatory severity (Sallese et al., 2023).

Clinical Implications and Diet

- Across pediatric and adult CD, multiple neurological and psychiatric manifestations (epilepsy, ADHD, neuropathy, RLS, developmental delay) often improve, at least partly, on a **gluten-free diet**, though evidence quality varies (Jackson et al., 2012; Nagarajappa et al., 2023).
- Reviews recommend **routine screening for psychiatric comorbidity** in gluten-related disorders and careful evaluation for CD/NCGS in unexplained neuropsychiatric presentations, especially in children (Jackson et al., 2012; Slim et al., 2018; Nagarajappa et al., 2023).

Conclusion

Immune activation against gluten in CD and NCGS—via chronic inflammation, gut barrier disruption, and microbiota-driven gut–brain signaling—is consistently linked to elevated rates of diverse neurodevelopmental and psychiatric disorders. Causality and exact mechanisms remain incompletely defined, but the evidence supports close integration of gastroenterologic, immunologic, and mental health care in these patients.

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