How can Invisible Fatigue lead to catastrophic consequences in Neurodevelopmental and Psychiatric Disorders?

Invisible fatigue drives disability, relapse, and psychopathology through underrecognized neurobiological and inflammatory pathways

Invisible fatigue—pathological exhaustion that is underrecognized, poorly measured, and frequently dismissed by clinicians—produces cascading functional, cognitive, and psychiatric consequences across neurodevelopmental and psychiatric conditions (Penner & Paul, 2017; Quadt et al., 2024; Mozūraitytė et al., 2022). Its "invisibility" stems from inconsistent definitions, lack of validated assessment tools, and overlap with symptoms such as apathy, depression, and anhedonia, which together delay diagnosis and intervention (Penner & Paul, 2017; Mozūraitytė et al., 2022; Bojtos et al., 2025).

Mechanisms Linking Fatigue to Catastrophic Outcomes

A transdiagnostic meta-analysis identified a widespread **frontal-striatal-limbic-parietal network** underlying mental fatigue, with key nodes in the lateral frontal cortex, cingulate, insula, thalamus, precuneus, and caudate (Schumann et al., 2025). Abnormal activation in these regions impairs compensatory mechanisms and contributes to cognitive, emotional, and attentional deficits (Schumann et al., 2025). State mental fatigue additionally disrupts the **cognitive control network** while increasing default-mode network activity, degrading executive performance (Salihu et al., 2022).

Neuroinflammation and GABAergic dysfunction represent a shared pathological pathway. Proinflammatory cytokines, particularly **IL-6**, drive sickness behaviors including fatigue, anhedonia, and social withdrawal (Quadt et al., 2024). In post-COVID patients, IL-6–mediated hyperinflammation reduces GABA receptor density, shifting inhibitory-excitatory balance and producing concurrent neuromotor fatigue, executive deficits, and apathy (Ortelli et al., 2020). Mitochondrial dysfunction compounds these effects by limiting energy availability for synaptic transmission, with impaired astrocyte glutamate signaling and glucose uptake further degrading cognitive endurance (Johansson & Rönnbäck, 2025).

Disorder Context	Fatigue Mechanism	Catastrophic Consequence
Autism (ASD)	Sensory over-processing, camouflaging, mitochondrial allostatic load	Autistic burnout, meltdowns, psychopathology (Keville et al., 2021; Mahony & O'Ryan, 2022; Keville et al., 2021)
Psychosis / Schizophrenia	Rumination, catastrophizing, antipsychotic-induced fatigue	55% prevalence; daily functional interference (Poole-Wright et al., 2025)
Parkinson's disease	Dopaminergic, serotonergic, glutamatergic disruption	Underrecognized disability; early retirement (Bojtos et al., 2025)
Childhood neurodivergence	IL-6–mediated inflammation linking traits to fatigue	2× risk of chronic disabling fatigue by age 18 (Quadt et al., 2024)

Disorder Context	Fatigue Mechanism	Catastrophic Consequence
Long COVID	Persistent mental fatigue, GABAergic impairment	Cognitive impairment, depression, anxiety, PTSD (Bao et al., 2025; Ortelli et al., 2020)

FIGURE 1 Catastrophic consequences of invisible fatigue across five neurodevelopmental and psychiatric disorder contexts

Diagnostic Invisibility and Clinical Dismissal

Fatigue remains one of the **least-studied and least-understood** conditions in neurology and psychiatry, with scarce evidence-based pharmacological treatments (Penner & Paul, 2017). In psychiatric populations, mental fatigue is frequently indistinguishable from anhedonia, depression, and apathy, leading to misattribution and inadequate treatment (Mozūraitytė et al., 2022; Bojtos et al., 2025). Patients regularly report being dismissed about their fatigue experience, particularly when no underlying medical condition is identified (Quadt et al., 2024).

In autism specifically, social camouflaging and chronic suppression of autistic traits generate a **mitochondrial allostatic overload** that culminates in autistic burnout—a pathophysiological state contributing to depression and suicidality (Mahony & O'Ryan, 2022). Undiagnosed autistic individuals internalize their exhaustion as personal failing, compounding shame and low self-worth that elevate psychopathology risk (Mahony & O'Ryan, 2022). Children with ASD face meltdowns when fatigue and demands co-occur, and managing this exhaustion is perceived as essential to preventing burnout (Keville et al., 2021).

Cascading Functional and Psychiatric Consequences

- **Mental fatigue dominates the chronic phase** of post-COVID recovery, showing the strongest impact on anxiety, depression, PTSD, and cognitive impairment at 3 months (Bao et al., 2025).
- In psychosis, fatigue reaches **55% prevalence** and is rated as severe, comparable to chronic fatigue syndrome and fibromyalgia (Poole-Wright et al., 2025).
- Fatigue catastrophizing—characterized by rumination and helplessness—intensifies both physical and psychological fatigue in schizophrenia, creating a self-reinforcing cycle (Poole-Wright et al., 2025).
- Residual mental fatigue **persists in up to 91%** of partially remitted psychiatric patients, diminishing work productivity and increasing relapse risk (Mozūraitytė et al., 2022).
- In Parkinson's disease, fatigue affects **50% of patients**, manifests from prodromal stages, and is recognized as one of the most disabling symptoms despite remaining underrecognized clinically (Bojtos et al., 2025).

Invisible fatigue thus leads to catastrophic consequences not through a single mechanism but through converging neurobiological, inflammatory, and psychosocial pathways that are systematically underdiagnosed, dismissed, and undertreated across neurodevelopmental and psychiatric populations (Penner et al., 2025; Quadt et al., 2024). Early transdiagnostic screening and targeted intervention addressing both the biological substrates and the clinical dismissal of fatigue are essential to interrupt these cascades before they produce irreversible functional and psychiatric deterioration (Quadt et al., 2024; Bojtos et al., 2025; Bao et al., 2025).

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