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Commentary

Bridging Inflammation and Brain Microstructure: Diffusion Magnetic Resonance Imaging as a Window Into Psychiatric Neurobiology

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Despite decades of research and multidisciplinary efforts, psychiatry remains one of the few fields of medicine without definitive biological tests for diagnosis or prognosis. The complexity of mental illness, arising from the interplay of genetic, environmental, and neurobiological factors, has long limited our ability to identify objective biomarkers that can guide clinical decision making. However, recent advances in computational psychiatry, neuroimaging, and translational neuroscience are beginning to challenge this status quo. Emerging biomarkers, which range from microstructural changes in brain tissue to transcriptomic signatures and digital phenotyping, hold the potential to redefine how we conceptualize, diagnose, and treat mental illness. These developments mark a critical turning point for psychiatry: a move from qualitative, symptom-based classification to biologically informed, precision approaches.

Central to this paradigm is the recognition that inflammation is a shared biological mechanism across multiple psychiatric disorders. Recent large-scale peripheral biomarker studies have consistently reported that inflammatory markers, including interleukins, tumor necrosis factor α, and C-reactive protein, are elevated across a spectrum of psychiatric disorders, such as depression, schizophrenia, bipolar disorder, and posttraumatic stress disorder (1). Building on these findings, advanced neuroimaging techniques now enable noninvasive detection of subtle neuroinflammatory changes in vivo, which are often measurable before clinical symptoms emerge. For example, diffusion tensor imaging (DTI)–based free-water imaging has revealed increased extracellular water in individuals at clinical high risk for psychosis, with elevated interstitial free water in cortical gray matter predicting accelerated volume loss and conversion to psychosis (2). Likewise, neurite orientation dispersion and density imaging (NODDI) has demonstrated sensitivity to microstructural changes associated with neuroinflammation. Andica *et al.* (3) reported reduced neurite density and increased extracellular free water in key white matter tracts associated with social communication in individuals with autism, findings that mirror postmortem evidence of neuroinflammation and neuronal alterations in this disorder.

Importantly, these imaging methods have also been experimentally linked to neuroinflammation. In rodents, Di Biase *et al.* (4) demonstrated that maternal immune activation resulted in increased extracellular free water in white matter tracts such as the corpus callosum and striatum, findings consistent with neuroinflammatory changes observed in individuals with first-episode psychosis. Similarly, Kim *et al.* (5) used a lipopolysaccharide (LPS) challenge to induce acute systemic inflammation in rats and found widespread increases in interstitial free water within gray matter, consistent with histologically confirmed microglial activation. Rodent models using NODDI have revealed parallel microstructural disruptions. Following mild traumatic brain injury in mice, increased orientation dispersion index (ODI) and decreased neurite density index (NDI) were observed in white matter regions such as the corpus callosum and fimbria, indicating altered neurite organization and reduced neurite density (6). Similarly, in a rat model of early-life systemic inflammation induced by repeated LPS administration, ex vivo NODDI detected persistent decreases in NDI and increases in ODI across subcortical white matter and neocortex, aligned with histologically confirmed disruptions in oligodendrocyte maturation and dendritic arborization (7). In humans, Dowell *et al.* (8) demonstrated that interferon alpha administration, which elevates peripheral inflammatory cytokines, also induced changes in NDI, underscoring NODDI's potential to capture inflammation-related microstructural shifts in vivo.

Building on this growing body of translational work, in a timely study published in the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Plank *et al.* (9) demonstrate that advanced diffusion MRI techniques can detect subtle experimentally induced neuroinflammatory changes in healthy humans. In a randomized, placebo-controlled, crossover design study, participants received a typhoid vaccine to elicit transient inflammation, providing an important experimental model that minimizes confounding factors commonly encountered in clinical populations. By integrating DTI, diffusion kurtosis imaging (DKI), and NODDI, the study observed consistent inflammation-induced microstructural changes across both white and gray matter. Notably, a global reduction in mean diffusivity in white matter tracts, increased kurtosis in white matter tracts and gray matter regions, and a modest increase in the NODDI-derived metric fractional intracellular volume fraction (otherwise referred to as NDI) were reported. Figure 1 summarizes the regions involved and the corresponding diffusion changes. These findings suggest heightened tissue complexity and cellular activation in response to inflammation, likely reflecting glial cell activation and associated changes in the extracellular space.

Crucially, Plank *et al.* (9) correlated diffusion-based metrics with peripheral inflammatory markers and observed several associations between elevated interleukin 6 (IL-6)

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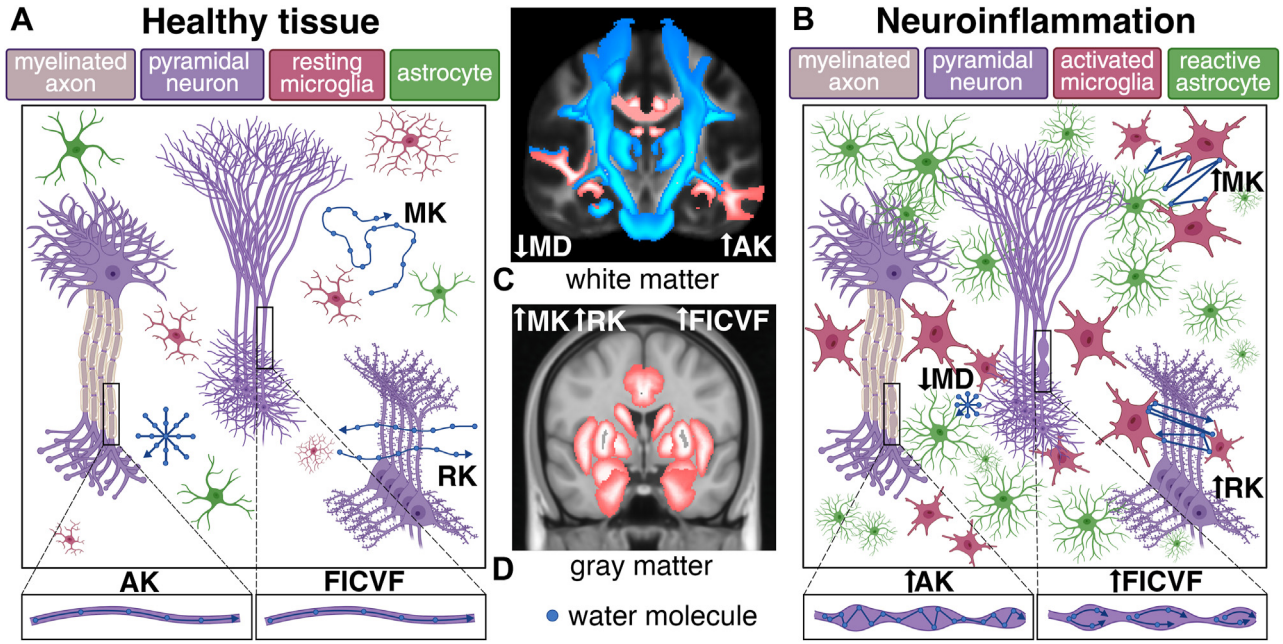

Figure 1. Schematic illustration of microstructural brain changes and associated diffusion magnetic resonance imaging metrics in response to inflammation. **(A)** In healthy brain tissue, neurons and glia are organized in a stable microenvironment. Water diffusion is directionally constrained along axons and dendrites, resulting in low mean diffusivity (MD), high axial kurtosis (AK), radial kurtosis (RK), mean kurtosis (MK), and fractional intracellular volume fraction (FICVF). **(B)** In neuroinflammatory states, activation of microglia and astrocytes leads to increased extracellular space, cell swelling, and structural disorganization. These changes increase FICVF, MK, RK, and AK while reducing MD. **(C)** Diffusion changes in white matter, as observed with diffusion magnetic resonance imaging, include decreased MD (blue) and increased AK (pink). **(D)** In gray matter, neuroinflammation is associated with elevated MK, RK, and FICVF (pink).

levels and diffusion alterations indicative of microstructural change, although these findings did not survive correction for multiple comparisons. By combining multimodal diffusion imaging with peripheral cytokine measures, the study bridges a long-standing gap between systemic inflammation and central neuroinflammatory responses. These findings underscore the promising clinical and translational potential of diffusion MRI, particularly for disorders in which neuroinflammation is implicated, and pave the way for noninvasive monitoring of neuroinflammation in psychiatric and neurodegenerative disorders.

Plank *et al.* (9) did not observe significant group-level changes in the amount of isotropically diffusing water molecules, as measured by the NODDI metric fraction of isotropic (free) water (FISO), despite prior research linking increased extracellular water with neuroinflammation (3). This finding mirrors Kim *et al.* (5), who reported a strong correlation between FISO and free water estimates from a bi-tensor model (ρ = 0.93), yet only free water, not FISO, showed significant increases after acute LPS administration. While both FISO and free water are designed to estimate the proportion of isotropically diffusing water within a voxel, typically interpreted as interstitial or extracellular fluid, their divergence likely stems from key differences in model assumptions. Free water imaging is derived from a relatively flexible bi-tensor model that separates tissue and isotropic water compartments with fewer geometric constraints, rendering it highly sensitive to acute and dynamic physiological changes, such as glial activation, vasogenic edema, or osmotic shifts associated with neuroinflammation. In contrast, FISO is derived from the more constrained 3-compartment NODDI model, which simultaneously estimates intraneurite, extraneurite, and isotropic volumes based on assumed neurite geometry and orientation dispersion. While these additional constraints enhance specificity, they may dampen the metric's responsiveness to subtle or transient inflammatory effects, particularly when signal-to-noise ratios are low or inflammation is spatially diffuse.

A plausible explanation for these discrepancies is that DTI metrics such as mean diffusivity and free water, kurtosis metrics, and NODDI-derived intraneurite measures may be particularly sensitive to acute neuroinflammatory processes. In contrast, FISO may preferentially capture more stable or chronic microstructural changes, such as those resulting from gliosis, extracellular matrix remodeling, or sustained immune activation. Although free water and FISO are highly correlated at the global level, their divergence in experimental and clinical findings underscores that they are not interchangeable. Instead, they may offer complementary insights into the temporal dynamics of neuroinflammation, with DTI and DKI capturing acute processes and NODDI-derived FISO indexing more established structural adaptations.

In this context, the use of the typhoid vaccine as an experimental inflammatory stimulus in the study by Plank *et al.* (9) is particularly noteworthy. This well-validated model induces transient, low-grade systemic inflammation in otherwise

healthy individuals, and crucially, it reliably elevates circulating IL-6 without causing undue adverse effects. IL-6 has emerged as a key cytokine in the pathophysiology of depression and other psychiatric conditions, with meta-analytic evidence consistently linking elevated peripheral IL-6 levels to mood disorders (1). By leveraging a well-tolerated, reproducible immune challenge that selectively increases IL-6, Plank *et al.* (9) ensure high translational relevance while maintaining experimental control, which is often lacking in clinical studies, where inflammation is confounded by comorbidities, medications, and variable illness duration.

Nonetheless, the very features that make the typhoid vaccine ideal for probing acute immune responses also constrain its utility for investigating the sustained inflammatory processes implicated in psychiatric disorders. The vaccine's relatively short inflammatory profile, which typically peaks within hours and resolves within 24 to 48 hours, poses limitations when attempting to investigate more enduring neurobiological consequences of inflammation. In contrast, psychiatric disorders are increasingly understood to involve chronic, low-grade inflammation and gradual alterations in brain structure and function (10). This temporal mismatch may underlie the weak correlations between peripheral IL-6 levels and diffusion MRI metrics reported by Plank *et al.* (9), despite IL-6's well-established relevance in psychiatric pathophysiology. As such, while DTI, DKI, and the intraneurite compartment of NODDI may be well suited to capture rapid fluid shifts associated with acute immune activation, more constrained NODDI-derived measures such as FISO may require prolonged or repeated inflammatory exposures to register detectable changes. Future studies should employ extended immune challenges or longitudinal imaging in clinical populations to directly test these biomarkers' temporal sensitivities and disentangle acute from chronic neuroinflammatory signatures.

Together, these findings illustrate how advanced diffusion MRI measures, particularly when paired with well-characterized immune challenges and peripheral biomarkers, can illuminate subtle yet meaningful neuroinflammatory processes in the living human brain. Plank *et al.* (9) provide a critical experimental bridge between peripheral immune signaling and central microstructural alterations, advancing the field toward biologically grounded, precision psychiatry. It will be essential for future work to refine these imaging biomarkers and test their relevance in chronic inflammation models that more closely mirror psychiatric pathophysiology.

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Article Information

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