

Communication

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[Remigiusz Reclaw](#) * and [Anna Grzywacz](#)

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Communication

Divergent Myelination or Divergent Trajectories? Insights from MPF Mapping in Bipolar Disorder and Recurrent Depressive Disorder

Remigiusz Reclaw ^{1,2,*} and Anna Grzywacz ^{1,2}

¹ Independent Laboratory of Genetics and Behavioral Epigenetics, Pomeranian Medical University in Szczecin, Powstańców Wielkopolskich 72 St., 70-111 Szczecin, Poland

² Department of Medical Sciences and Public Health, Gdansk University of Physical Education and Sport, Kazimierza Górskiego 1 St., 80-336 Gdansk, Poland

* Correspondence: remigiusz.reclaw@pum.edu.pl

Abstract

Recent advances in quantitative MRI have renewed interest in white matter abnormalities as a potential neurobiological substrate of affective disorders, particularly as myelination is increasingly recognized as a dynamic and experience-dependent process. In this context, Gusakova et al. applied macromolecular proton fraction (MPF) mapping to compare global white matter myelination between bipolar disorder (BD) and recurrent depressive disorder (RDD), reporting reduced MPF in RDD alongside elevated MPF in BD. These findings challenge simplified deficit-based interpretations suggesting uniform hypomyelination across mood disorders. Here, we discuss the biological and clinical implications of divergent MPF profiles and propose a trajectory-based framework in which MPF differences may reflect altered timing, regulation, or rate of myelination across development rather than a single shared pathological endpoint. We emphasize that MPF should not be interpreted as a strictly unidirectional marker of white matter integrity, since elevated values may also represent compensatory or state-dependent processes. The observed divergence between BD and RDD highlights the potential of MPF mapping as a phenotype-differentiating biomarker and supports the need for longitudinal and multimodal neuroimaging studies integrating developmental factors, illness phase, and pharmacotherapy effects.

Keywords: macromolecular proton fraction; MPF mapping; white matter myelination; bipolar disorder; recurrent depressive disorder; quantitative MRI

Recent advances in quantitative MRI have renewed interest in white matter abnormalities as a potential neurobiological substrate of affective disorders, particularly in light of growing evidence that myelination is a dynamic and experience-dependent process rather than a static structural feature of the brain [1]. In this context, the study by Gusakova et al. [2] provides a valuable and methodologically robust contribution by applying macromolecular proton fraction (MPF) mapping to directly compare white matter myelination in bipolar disorder and recurrent depressive disorder. By demonstrating reduced MPF in recurrent depressive disorder alongside markedly elevated MPF in bipolar disorder, the authors challenge simplified models of uniform hypomyelination across affective conditions. These findings invite further discussion regarding the biological interpretation of MPF differences and their implications for understanding divergent pathophysiological processes underlying both affective conditions, particularly within a developmental framework [3].

The most striking finding is the opposite direction of MPF changes: hypomyelination in recurrent depressive disorder versus elevated MPF in bipolar disorder (both relative to controls and to each other). This pattern stands in contrast to the prevailing view that white matter pathology in affective disorders is predominantly characterized by global myelin loss, a perspective largely informed by diffusion-based imaging studies and meta-analytic evidence in major depressive

disorder [4]. Importantly, the elevation of MPF in bipolar disorder should not be regarded as a trivial or incidental finding [5], as it suggests that white matter alterations in mood disorders may follow qualitatively different biological trajectories rather than reflecting a shared deficit. Such divergence raises the question of whether MPF differences primarily index pathological damage or instead capture dynamic, state- or development-dependent processes within the myelination continuum.

One plausible framework for interpreting these findings is a neurodevelopmental and trajectory-based perspective on white matter myelination in affective disorders. Rather than reflecting a simple presence or absence of myelin pathology, MPF differences may capture alterations in the timing, rate, or regulation of myelination across the lifespan – processes known to be particularly sensitive during adolescence and early adulthood [3,6]. In this context, the elevated MPF in bipolar disorder (observed in a relatively young patient group, median age ≈ 24 years) could reflect accelerated or dysregulated white matter maturation rather than a protective or “hypermyelinated” state per se, consistent with reports of altered age-related white matter trajectories in bipolar disorder [5]. Conversely, the reduced MPF in recurrent depressive disorder may indicate a distinct trajectory characterized by impaired maintenance or progressive disruption of myelin integrity, in line with quantitative MRI evidence of reduced myelination in depressive disorders [7].

From a biomarker perspective, these findings underscore the need for caution in interpreting MPF as a unidirectional indicator of white matter pathology in affective disorders. While reduced MPF is often intuitively equated with demyelination or tissue damage, elevated MPF values – such as those observed in bipolar disorder – may reflect compensatory, state-dependent, or developmentally modulated processes rather than improved white matter integrity. This distinction is particularly relevant given the biophysical specificity of MPF as a myelin-sensitive metric and its fundamental differences from diffusion-based indices [8–10]; in this context, DTI and MPF probe different components of white matter microstructure, which may partly explain divergent directions of effects across imaging modalities. These non-unidirectional neuroimaging findings are consistent with broader evidence of atypical neurodevelopmental trajectories and microstructural organization in bipolar disorder, including meta-analytic reports of minor physical anomalies and increased cortical gray–white matter contrast across independent MRI studies [11,12]. Thus, MPF mapping holds greater promise as a phenotype-differentiating biomarker (bipolar disorder vs. recurrent depressive disorder) than as a nonspecific index of disease severity, with clear potential for aiding early diagnostic differentiation. It is worth noting that MPF differences may be partly modulated by the current illness phase and pharmacotherapy (especially mood stabilizers in BD), thereby reinforcing the need for longitudinal studies accounting for these factors [13–16].

In summary, the work by Gusakova et al. provides an important empirical foundation for rethinking white matter alterations in affective disorders beyond simplified deficit-based models. Their findings highlight the potential value of MPF mapping in capturing biologically meaningful heterogeneity between bipolar disorder and recurrent depressive disorder, while also emphasizing the need for longitudinal and multimodal approaches to fully elucidate the underlying mechanisms. Future studies integrating MPF with diffusion-based metrics, clinical staging, and developmental trajectories may help clarify whether observed differences reflect transient states, compensatory adaptations, or enduring neurobiological signatures across the lifespan [5,6]. Such efforts are crucial to advancing a truly trajectory-oriented, lifespan-informed understanding of white matter heterogeneity in mood disorders.

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