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Towards Low Risk Approaches to Prevent Bipolar Disorder in At-Risk Youth

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McNamara et al.,[1] in their recent *Bipolar Disorders* manuscript, present novel evidence for a role for fish oil (FO) supplementation in beneficially altering brain functional connectivity in youth at high risk for developing Bipolar I Disorder (BDI). They highlight research that suggests that lower brain levels of omega-3 polyunsaturated fatty acids (*n*-3 PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), putatively reflected in lower blood levels, can contribute to the etiology of mood disorders. As these may precede onset of mood episodes, they may therefore be modifiable targets for prevention in youths at highest risk. Considering that BDI is highly heritable, children with at least one parent with diagnosed BDI are at risk and are of prominent need for attention for prevention. The authors set forth results from their 12-week clinical trial supplementing FO in youth with a current depressive disorder who have at least one biological parent with BDI. Over the course of the trial, they observed increased orbitofrontal cortex (OFC)-superior temporal gyrus (STG) and decreased amygdala-inferior temporal gyrus (ITG) functional connectivity in the experimental group, opposite of the pattern observed in the control group, suggesting evidence of FO's role in influencing corticolimbic connectivity.

Neuroimaging studies of BD have converged supporting disruptions in the functional connectivity of frontotemporal corticolimbic systems that subserve emotion regulation, which aligns with emotion dysregulation symptoms of persons suffering from the disorder. This has been well supported in adults with BDI, more recent work has extended this to adolescents with BD, and the latest developments include suggestions that corticolimbic differences are evident as early as adolescence in youth at risk for developing BD. Functional and structural studies (e.g., of functional activation and connectivity, gray matter morphology, and white matter integrity) have begun to implicate abnormalities in corticolimbic regions and their connectivity, including the OFC and amygdala, in at-risk

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youth.[2] During adolescence, these corticolimbic system connections are still developing, including major white matter tracts such as the superior longitudinal fasciculus and uncinate fasciculus (UF). These tracts have been implicated to have differing neurodevelopmental trajectories in youth with BD in both cross-sectional and longitudinal studies.[3] McNamara and colleagues additionally discuss developmental changes in the white matter integrity of the superior longitudinal fasciculus and UF in non-human primate studies that support adolescence as a critical period in their development. Thus, the findings of this study are important in demonstrating that a low-risk intervention can have beneficial brain effects during the critical neurodevelopmental period of adolescence, specifically in brain tracts important in emotional regulation that could help in prevention of BD and potentially other related disorders.

This research is timely as many existing pharmacotherapies and prevention strategies lack widespread effectiveness, and can have substantial risks including exacerbation of mood symptoms and side effects. The latter is particularly of concern for at-risk youth for whom the benefit is not clear, as there is currently no method to identify which at-risk youth will develop BD. Further, in youths, BD is often misdiagnosed as major depressive disorder (MDD), as the presenting episode is often depression and there is no marker currently to distinguish the disorders.[4] This can lead to incorrect treatments with the possibility for detrimental outcomes. Thus, there is need for rational approaches to target brain-based dysfunction underlying risk for BD without worsening prognosis. Especially as a period of development during which brain connectivity is still plastic, adolescence is a critical period for generating interventions that can minimize harm while promoting healthy lifestyle changes that can reduce and prevent mood symptoms.[5] This highlights the importance of McNamara et al.'s findings with FO supplementation. Evidence from animal models suggests that PUFAs are critical for nervous system development, particularly relating to white matter integrity in stimulating expression of myelin proteins, and by supplementing FO during this adolescent critical period, this can serve as a low-risk way to improve white matter integrity. This strategy could be used in addition to psychotherapies which encourage low-risk lifestyle modifications such as regularizing 24 hour patterns of behavior. For example, social rhythm therapy is an evidence-based psychotherapy that has been well-studied in randomized clinical trials, including in youth, to decrease mood symptoms and telehealth versions are emerging increasing feasibility for wide dissemination.[5] Initial evidence suggests that addressing circadian rhythm instabilities can have beneficial effects on similar brain circuitry to that with observed effects in McNamara et al and that has been implicated in risk for suicide thoughts and behaviors.[5] Together, these lines of evidence support the very hopeful promise that the field is ripe for the introduction of complementary low risk interventions to reduce risk for the development of bipolar and related disorders and suicide.

Thus, McNamara et al. provides novel insights into a low-risk, mechanism-based and brain circuitry-targeted strategy that could have lifelong benefits in promoting brain health and improving prognosis in individuals at risk for BD.

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