

# Biological mechanisms of environmental stressors in psychiatry : the role of the immune system

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## **Valorization**



Mood disorders (bipolar disorder and major depressive disorder) are highly prevalent, and are associated with increased morbidity and mortality. Although treatment of depression has advanced, current medications do not meet expectations – only one-third of patients diagnosed with major depression respond to first level treatment. Likewise, polypharmacy is a rule rather than an exception for treatment of bipolar disorder – even lithium, closest to the definition of an ideal mood stabilizer aside from its side-effects, has limited success as a monotherapy. It appears that the monoamine theory, solely, cannot explain all features of mood disorders, and accordingly, current antidepressants targeting monoamine systems are efficient in only a subgroup of patients. Novel treatment options are urgently needed. To improve treatment, pathoetiology of mood disorders should be elucidated. Understanding pathoetiology –in contrast to serendipitous drug discoveries– would enable us to design disorder-specific drugs and optimize treatment by measuring target engagement.

## Relevance

Converging evidence has moved the scientific community to view inflammation as a key process that might improve understanding of the pathoetiology of mood disorders. Insight into the aberrant immune functioning as a complementary mechanism underlying mood disorders can deliver important prognostic information to personalize and optimize treatment. From a general perspective, this thesis seeks to deliver the next step in this translational aim.

The findings add important and potentially transformative data to explain the relationship between inflammation and mood disorders. To date, inflammation in the acute phase of mood disorders (e.g. mania, depression) has been widely acknowledged. However, few studies, usually not taking into account the effect of medication on immune markers, have examined whether the aberrant immune functioning in bipolar disorder resolves during euthymia. This thesis, examining the circulatory immune profile of medication-free euthymic bipolar patients and the role of immune modulation as a mechanism of action of lithium, has therefore filled an important gap in the scientific field. In combination with recent evidence, this suggest that inflammatory state likely resolves in euthymic period of bipolar disorder, and that the immune-balancing effects of lithium, along with several other postulated mechanisms, may be essential for its long-term mood stabilizing effects.

This thesis also provides important evidence towards the role of immune-related pathways (immune mediated tryptophan catabolism) in the mechanism of action of ECT, which has thus far received little attention. Current knowledge about antidepressant effects of infliximab (an anti-inflammatory drug) in Crohn's Disease

is extended, thereby facilitating the concept of anti-inflammatory treatment of mood disorders. Recent data suggest that prenatal and perinatal complications impact on the maternal immune activation and microglial activity, and this work was further extended with a study investigating whether hypoxia-related genes moderate the impact of obstetric complications on expression of psychopathology. The findings further support the idea of gene X environment interaction, whereby hypoxia-response genes operate in synergy with obstetric complications to influence the expression of mental ill health in general in adulthood.

The exploration of inflammation and the pathoetiology of mood disorders is an active area of investigation in the scientific community. This thesis offers some insight into indices of inflammation underlying mood disorders, and delivers translational information about the role of inflammation in treatment of mood disorders. Although further longitudinal studies are required, these findings, from a broad perspective, suggest that immune stratification of patients with mood disorders –such as, from the most basic perspective, categorizing patients into low and high inflammation groups– might be helpful in predicting treatment response and remission. In addition, identifying subtypes, such as “inflamed” depression, may open up new avenues leading to individually tailored treatment with better outcomes.

Social and economic burden of mood disorders include disability, decreased work productivity, and increased health services utilization. A more effective treatment would not only decrease mood symptoms, but also improve quality of life and restore functioning. Although treatment of mood disorders has improved substantially, the rate of complete remission is low –indicating a need for treatment with novel mechanisms of action. There is some evidence to suggest that anti-inflammatory drugs (i.e. aspirin, celecoxib, omega-3 fatty acids, and minocycline) are beneficial as an augmentation treatment for mood disorders. However, study results are inconsistent. This is likely due to collective analysis of immunologically heterogeneous samples. Therefore, immune profiling may be essential to define patients who may benefit more from adjuvant anti-inflammatory treatment.

Although reported findings can be considered as another brick in the wall, even the Great Wall of China was built laying one brick at a time. Studies investigating immune hypotheses have thus far provided substantial evidence suggesting that measurement of immune alterations may serve as biomarkers in mood disorders. However, we are still far from translating these findings to be applied in clinical practice because further prospective, controlled investigations are needed. Studies should aim to investigate large samples and carefully take into account various

confounders that can easily distort results, such as medication effect demonstrated in this thesis.

## Target groups

Considering that the impact of mood disorders spread across the society, with various effects, from patients to family members and from organizations to taxpayers, a wide range of people can benefit from optimization of diagnosis and treatment of mood disorders, either directly or indirectly. Therefore, the findings of this thesis extending the knowledge to pave the way to advanced diagnostic panels and better treatment options may be of use to a broader population. In psychiatric practice, healthcare professionals usually struggle to identify future treatment-resistant cases, and this results in inadequate treatment initially, followed by several drug trials until optimal treatment is achieved. Not to mention that extended duration of inadequate treatment is associated with disability, but it also poses a great risk to patients by increasing the likelihood of suicide. Unfortunately, there exists no biomarker that can help healthcare professionals to predict response or remission in patients with mood disorders. Given that, healthcare professionals can certainly benefit from tracking immune markers to develop personalized treatment strategies, which eventually reduce duration of inadequate treatment. This decrease of time lost by inadequate treatment, will subsequently decrease service utilization and costs. These are also important objectives that policy makers seek to achieve for improving cost-effectiveness. However, it would be an overstatement to claim that immune markers are ready for use in everyday clinical practice. Circulatory immune markers are prone to the impact of confounding factors, unreliable at times, and still expensive to measure with available methods. Rapidly advancing measurement technologies delivered assays that allow measurement of multiple immune markers using a single kit and, therefore, led to a dramatic reduction in costs. This downward trend in costs will accelerate even more in the forthcoming years.

Obviously, the present findings support the development of anti-inflammatory therapy for mood disorders. There is already some evidence that augmentation treatment with potent anti-inflammatory therapies might increase response rates and reduce time to response, particularly in treatment-refractory cases. However, side effects that include increased risk of serious infections limit their use. Hopefully, the next generation of anti-inflammatory drugs, targeting specific molecular pathways, with fewer side effects may add to clinicians' arsenal for treatment-resistant cases.

## **Innovation**

This thesis delivers actionable and reliable information for future studies, and it is innovative in several specific ways. First, it used several approaches in a variety of samples to delineate putative role of inflammation in pathoetiology of mood disorders. Second, it shed light on neglected areas in the literature on psychoneuroimmunology, such as the role of immune-related pathways in the mechanism of action of ECT. Third, it analyzed data derived from unique patient populations, such as unmedicated euthymic bipolar patients and euthymic bipolar patients with subthreshold symptoms.