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

Summary

In chapter 1, a brief summary about phenomenology, classification and epidemiology of mood disorders was provided. Furthermore, the pathoetiology of mood disorders, with a focus on immune-related mechanisms, was discussed. First, the close relationship between immune-related diseases and mood disorders was discussed. Second, evidence implicating the role of disturbed cytokine network in mood disorders was provided. Third, tryptophan metabolic pathway, linking immune system to central nervous system, was promoted. Fourth, the potential of anti-inflammatory medications for the treatment of mood disorders is discussed. Fifth, the importance of hypoxia–ischaemia as a mechanism underlying psychiatric syndromes, in association with the maternal immune activation and microglial activity, and its link to the immune system disturbance was discussed. Finally, the aims and outline of the thesis were presented.

Chapter 2 presents a cross-sectional study, in which peripheral pro- and anti-inflammatory cytokine balance (IFN-γ, TNF-α, IL-2, IL-4, IL-5, and IL-10) was examined using flow cytometry in euthymic bipolar patients (medication-free (n = 16) and lithium-monotherapy (n = 15)), in comparison to age and gender matched healthy controls (n = 16). While there was no difference between medication-free and healthy controls in circulating cytokine profile, TNF-α and IL-4 concentrations in euthymic bipolar patients on lithium-monotherapy were higher than in both the medication-free euthymic bipolar patients and healthy controls. Given that, it is plausible to speculate that the pro-inflammatory state reported in manic and depressive episodes resolves in euthymia, and lithium exerts a complex immune-modulatory action by increasing both pro- and anti-inflammatory cytokines, thereby also emerging as a confounding factor while investigating the disease-related pathogenesis of bipolar disorder.

Chapter 3 presents a study investigating the possible association between circulating TNF-α concentration assessed using enzyme-linked immunosorbent assay and long-term lithium response assessed using ALDA lithium response scale in 60 euthymic bipolar patients (17 with good lithium response, 23 with partial lithium response, 20 with poor lithium response). TNF-α concentrations in patients with a poor response to lithium were higher than in patients with a good response; both Criterion A (the degree of improvement over the course of lithium treatment) and total ALDA lithium response scale scores (Criterion A subtracted by Criterion B assessing the causality between improvement and lithium treatment) were negatively associated with TNF-α concentrations after controlling for the *a priori* selected confounders. These findings indicate that circulating TNF-α concentration may impact on the clinical response to lithium and a continuous immune imbalance in poor lithium responders may be related to treatment resistance.

Chapter 4 presents a study investigating the possible association between peripheral markers of an ongoing chronic pro-inflammatory process (soluble tumor necrosis factor receptor-1 (sTNF-R1), soluble interleukin-6 receptor (sIL-6R) and soluble interleukin-2 receptor (sIL-2R)) and persistent subsyndromal symptoms in bipolar disorder in a sample consisted 22 euthymic bipolar patients with subsyndromal symptoms and 23 euthymic bipolar patients without subsyndromal symptoms and 23 well controls. sTNF-R1 and sIL-6R concentrations were increased in both patients with and without and without subsyndromal symptoms in comparison to that in well controls, also after controlling age and sex, however there was no difference in sTNF-R1 and sIL-6R concentrations between patients with and without subsyndromal symptoms. These findings indicate that the pro-inflammatory shift might be evident in bipolar patients compared to well controls, but subsyndromal symptoms are not associated with additive increasing effects.

Chapter 5 presents an 8-week, prospective study investigating the impact of anti-TNF-α (infliximab) infusion on disease activity, quality of life, fatigue and depressive symptoms along with its possible relation to immune parameters, and the tryptophan availability (tryptophan/competing amino acids) in 15 patients with Crohn's Disease. The findings were: (i) scores of depression scales were decreased after anti-TNF-α infusion and this effect was to a degree, but not entirely, reducible to disease activity; (ii) there was no change in the tryptophan availability after anti-TNF-α infusion and neither scores of depression scales, nor immune parameters were associated with tryptophan availability; (iii) immune activation was higher in patients with current/past depressive disorder. These findings indicate that anti-TNF-α infusion in patients with Crohn's Disease reduces depressive symptoms, in part independently of disease activity, and that the effect on depressive symptoms is not associated with immune-induced changes in tryptophan availability to the brain, as estimated indirectly by serum tryptophan/competing amino acids ratio.

Chapter 6 presents a literature overview on the effect of electroconvulsive therapy (ECT) on the immune system. The literature search identified limited number of studies. Although inconsistency in findings and methodological issues –statistical power and consideration of confounding factors impacting cytokine concentrations– preclude definitive conclusion; the findings suggest that a single session of ECT induces an acute, transient immune activation, whereas repetitive ECT treatment results in long-term down-regulation of immune activation.

Chapter 7 presents a prospective study investigating the impact of ECT on the metabolites in tryptophan-kynunerine pathway (tryptophan (TRP), kynunerine (KYN), kynurenic acid (KYNA), 3-hydroxykynurenine (3-HK), 3-Hydroxyanthranilic acid (3-HAA), 5-Hydroxyindoleacetic acid (5-HIAA), KYN/TRP, KYNA/KYN, KYNA/3-

HK, 5-HIAA/ KYN), in association with ECT-related alterations in depressive symptoms in 23 patients with unipolar or bipolar depression. The findings were: (i) KYNA, KYNA/3-HK, KYNA/KYN and KYN/TRP concentrations increased over time; (ii) KYN and KYN/TRP were negatively associated with total HDRS scores; (iii) Baseline TRP metabolite concentrations did not predict time to ECT response. Notwithstanding its limitations, this study highlights the impact of ECT on TRP-KYN pathway with a shift toward neuroprotective side, which may play a role in its mechanism of action.

Chapter 8 presents a gene-environment interaction study investigating in a general population sample of 334 females in 180 twin pairs whether associations between obstetric complications (OC) and expression of psychopathology were moderated by selected single nucleotide polymorphisms (SNPs) in genes that were previously shown to be associated with hypoxia-response regulation and schizophrenia. SNPs in *AKT1* (rs1130233), *BDNF* (rs11030101), *CHRNA7* (rs3087454), *GABRB2* (rs1816072), *PLXNA2* (rs752016, rs841865, rs2478813), *RELN* (rs7341475), *RGS4* (rs2661319), and *YWHAE* (rs28365859) moderated the associations between OC and the Symptom Checklist-90-Revised (SCL-90) total scores. In addition, there were significant main genetic, and interactive effects on subscales of the SCL-90, but not on neurocognitive tests. When SNPs per gene were analyzed together in one model per gene, only the variants in *AKT1* showed a statistically significant interaction with OC on SCL-90 total, depression, and psychoticism scores. The findings suggest that the interaction between hypoxia-response genes and OC influences the expression of mental ill health in general, and not just the expression of schizophrenia-specific psychopathological dimensions.

Chapter 9 provides an overview of the findings and discusses them in the light of the current evidence. The findings derived from the studies in this thesis investigating the role of aberrant immune functioning in mood disorders from different perspectives are integrated to elucidate possible underlying immune-related mechanisms in the pathogenesis of mood disorders; and to provide directions for future research.