Biomedical and public health studies on susceptibility to post-traumatic stress disorder

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SUMMARY

Traumatic stress exposure can induce the development of mental disorders such as post-traumatic stress disorder (PTSD), as well as physical ill-health, resulting in a decreased quality of life and increased disease burden, both economic and medical. As timely and appropriate treatment can prevent chronicity and disability, and hence result in a better quality of life, it is necessary that the identification of those at increased risk and susceptible to develop PTSD are known. Additionally, early diagnosis and management should be the priority once a person is known to be exposed to traumatic stress. Over the past decade, the focus of research has become more on the identification of susceptibility factors, including epigenetics and biomarkers studies.

This thesis aims to address the gaps of knowledge in the understanding of the association between epigenetic mechanisms, gene activity, and differential susceptibility to PTSD. It also aims to identify the public health measures that can be effectuated for the prevention of PTSD and how biomarkers may support these measures. Accordingly, the thesis discusses the possible ways that can aid in the early identification and detection of PTSD resulting from traumatic stress, and the possibility of developing biomarkers of increased susceptibility. It also discusses how this early detection can help with early intervention, and if early enough, prevention. Application of such models, with findings from future research to establish cost-effective measures, can greatly enhance the patient's quality of life and decrease the disease burden.

Chapter 2 summarized the recent studies and their findings on epigenetic and epigenomic changes associated with PTSD development. The identification of such changes can help identify patients at increased risk and hence intervene early with the application of preventive measures. These epigenetic changes can be applied in real-life practice once proven reliable and cost-effective.

In **Chapter 3**, we conducted a transcriptomic analysis on participants of the Prospective Research in Stress-Related Military Operations (PRISMO), a cohort of Dutch military members deployed to Afghanistan for 4 months, who experienced trauma and developed PTSD, those who did not develop PTSD and healthy (unexposed) individuals. We aimed to replicate previous findings, as well as discover new differential expression patterns of blood mRNA for the detection of PTSD susceptibility. Among the important genes implicated in PTSD from our study, *FOSB*, *SLC13A4* and *NPR3* were upregulated, while *TBC1D16* was downregulated. We demonstrated that a transcriptome profile of PTSD vulnerability at a post-traumatic time point may offer new perspectives for additional follow-up research and should be addressed with more precision.

In **Chapter 4**, we aimed to provide for the first-time an investigation of the involvement of RNF39 in traumatic stress and PTSD. Recently, RNF39 has been implicated as a potential

modulator in stress, however, no investigation to date has been done to ascertain its role. Through the social defeat animal model of PTSD, we demonstrated higher expression of RNF39 in dentate gyrus fibres of the hippocampus in animals exposed to traumatic stress, as well as a correlation between stress-induced anhedonic behaviour and RNF39 expression in these animals. Our study paves the way for translational studies with larger human cohorts to assess the exact role of RNF39 in PTSD and its applicability as a biomarker.

In **Chapter 5**, the identification of the most important and common stressors, and the main factors that can affect the response to traumatic stress were discussed together with the the socio-economic model for disease prevention, and the potential of its application in the prevention of PTSD. The model comprises four levels, with the individual level at its core, up to the relationship, community, and societal levels. From a practical point of view, the thesis discussed examples of preventive measures at each level of the model, the three types of prevention, namely primary, secondary and tertiary prevention, by applying real-life examples of applicable interventions and programs. For integration, the latest treatment modalities used for PTSD are inventoried, and how these interventions can contribute to enhanced quality of life and decreased disability.

To wrap up the thesis, **Chapter 6** reviewed the most recent advances and discoveries in PTSD development, treatment and prevention, and emphasising the current state of the art of biomarkers. We demonstrated the important involvement of psychological, environmental and social factors, in conjunction with biological factors in the induction and maintenance of the disorder. Of importance for diagnosis and treatment is the underlying disturbance in neurobiology, which includes neuroanatomical changes, neuroendocrine disturbances in molecules such as norepinephrine; serotonin; BDNF; NPY and oxytocin, in addition to the essential dysregulation in the HPA axis as a key player of stress regulation. The approach to treating the disorder involves both psychotherapeutic and pharmacological interventions. Although trauma-based psychotherapy is considered a first line of management, pharmacotherapy is also used in conjunction and in specific situations. Although the science of PTSD biomarkers still has a long way to go, we showed that most of the implicated biomarkers are actually reflective of the underlying neurobiological changes, substances, structural alterations, and responses associated with PTSD. For that, future research on PTSD should take into consideration all these aspects, starting from the pathophysiology, and how it can be translated into effective interventions and clinically meaningful biomarkers.