Modeling the brain

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General Summary

The overarching aim of this thesis was to explore the interplay between the mutlifaceted aspects of stress and cognition. Over the last decades, research focus has been shifted towards a transdiagnostic, dimensional approach, which investigates constructs (and their dimensions) that are not bound to traditional categorical classifications but cut across different disorders. To gain insight into the dimensionality of mental disorders and health, the primary outlook of **chapters 2, 3, 4, 5** and **6** was to investigate mechanisms underlying the interaction between the various dimensions of stress and cognition.

In **chapter 2**, we investigated the effect of acute stress on a cost (i.e., physical effort) and benefit (i.e., monetary reward) reinforcement learning task testing healthy participants that were allotted to either acute stress or no stress control condition. We found that acute stress reprioritized learning to maximize monetary rewards over learning to minimize the expenditure of physical effort. Using computational modelling, we demonstrated that this learning strategy can arise when reward and effort learning rates are afforded equal importance. Pupillometry analyses showed a link between cost and benefit learning with activity of neuromodulators such as dopamine and noradrenaline. These results provide an initial step in explaining how acute stress could act both beneficially and detrimentally. Specifically, it suggests that prioritizing rewarding over costly things could confer immediate benefits (e.g., reaching a valuable goal despite a high action cost) but, probably depending on the context, might also be detrimental (e.g., substance use relapses under acute stress).

In **chapter 3**, we evaluated how transdiagnostic factors linked to psychopathology (i.e., perceived chronic stress, anhedonia, impulsivity, energy) are associated with alterations in learning about the costs and benefits of actions in the general population, utilizing a simplified version of the task used in chapter 2 for online research purposes. We observed that elevated levels of perceived chronic stress and impulsivity were consistently associated with reduced accuracy in the task, which could be explained by a selective reduction in learning from reinforcement (not punishment). The other factors, namely anhedonia and energy, were not associated with various task performance metrics. These results highlight how interindividual differences related to susceptibility for psychopathology may contribute to cognitive mechanisms that support goal-directed behaviour. In addition, this work illustrates some challenges associated with data collection via online platforms and suggests the use of a single device type when conducting online research.

In **chapter 4**, we investigated the roles of dopamine and noradrenaline - two stress-related catecholamines - on performance in a value-based decision-making task, during which participants could earn monetary rewards in exchange for physical effort. Healthy volunteers were assigned to placebo, propranolol (β-noradrenaline receptor antagonist) or haloperidol (dopamine D2 receptor antagonist) according to a randomized double-blind placebo-controlled design and 150 minutes post-administration (~time max), they completed the cost-benefit decision-making task.

Preliminary results indicate that low-dose haloperidol may temporarily increase response at the cost of reduced acceptance over time, while propranolol might increase sensitivity to effort cost. Future computational modelling can provide further insights into mechanisms that may mediate these effects.

In **chapter 5**, we used network analyses to explore the relationship between COVID-19 related stressors and changes in mental well-being in adults living in the Netherlands and Belgium during the initial phase of the COVID-19 pandemic. Results illustrate that worries about the pandemic were associated with elevated distress and low positive mood, which, in turn were associated with other components of mental well-being, such as energy, motivation, and loneliness. Time-lagged network analysis – which illustrates how variables predict each other in subsequent measurement windows (e.g., from day 1 to day 2), identified worries about COVID-19 to be temporally associated with the reciprocal interplay between heightened distress and low positive mood. The outcome of this study points to psychological mechanisms associated with changes in mental well-being during COVID-19, which, in the long run, could result in poorer mental health outcomes and may provide an explanation for the increased prevalence of affective/stress-related disorders reported during the pandemic.

Chapter 6 presents a summary of preclinical and clinical findings on curcumin as a potential cognitive enhancer. Results demonstrated that animal studies show beneficial effects on improving cognitive functions both on molecular and behavioral level, however, human studies remain mixed regarding curcumin's effects on cognition. This review highlights the difference in findings between preclinical and clinical research regarding curcumin. It suggests that improving curcumin's bioavailability and conducting homogenized clinical trials are required to bridge this translational gap. Because curcumin is a natural, widely available compound with mild side effects, we propose that it warrants further investigation.

Finally, **chapter 7** discusses the main findings, strenghts, limitations and suggestions for future research. Although there is still a long way to go, findings from the current thesis provide some steps for the long term goal of adopting dimensional conceptualizations that could lead to a comprehensive understanding of the full spectrum of mental disorders and health. Future research exploring further both biological and behavioral functioning of the different dimensions as well as their interactions, will help put more pieces together.