Modeling the brain

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Stress is ubiquitous in people's lives, affecting mental well-being and various cognitive functions. Everyone has experienced stress, difficulties concentrating, or reduced motivation at some point in their lives. These symptoms do not necessarily reflect the presence of a mental disorder. However, their prolonged or intense presence is highly associated with a range of mental health problems either as risk factors or as symptoms. Impairments in one of these transdiagnostic constructs (i.e., excessive stress, cognitive deficits, motivational decline) can impact vocational, personal, every-day functioning and can pose a considerable financial burden for society. For instance, past research has estimated that the total costs of stress-related problems worldwide range from $221 million in Australia to $187 billion in the USA (Hassard et al., 2018). In addition, a recent study estimated that in the Netherlands an episode of sick-leave due to stress-related problems amounts to €19,151 on average for Dutch employers (Wolvetang et al., 2022). Thus, increased insight into the different dimensions of these constructs is essential to improve our understanding about transdiagnostic clinical phenomena, which could lead to better treatment options in the future and benefit not only people who experience such problems but also society as a whole.

For this reason, this thesis evaluated the interaction of different dimensions of these transdiagnostic constructs, particularly stress (acute, chronic, COVID-19 related), cognitive aspects of motivational impairments (reward and effort processing during learning and decision-making) as well as cognitive skills (e.g., memory), in accordance with the approach of a unified framework for understanding mental disorder and health as a continuum. Improving transdiagnostic dimensional models could inform interventions in two major ways. The first one is conceptual, since they could provide an explanation on why or which pharmacological agents, as well as psychotherapeutic interventions, are effective for multiple diagnostic groups. The second one is more practical, as they could provide biological targets or psychological dimensions that could be targeted through specialized interventions and have an impact across many conditions (Krueger & Eaton, 2015).

However, implementing transdiagnostic approaches into clinical practice might be challenging as it depends crucially on developing a clear framework as well as assessments and interventions that can replace or supplement their diagnostic counterparts (Fusar-Poli et al., 2019). In this thesis we focused on some sub-components of this complex process. However, complexity should not be equated with vagueness. Therefore, we highlight that we should be very specific when referring to different dimensions (e.g., acute vs chronic stress instead of stress as an umbrella term) because they can result in different biological and behavioral effects as observed in chapters 2 and 3 and discussed in chapter 7.

Another challenge of transdiagnostic approaches is to achieve a more detailed understanding of the circuitries and molecular mechanisms involved in the maladaptive behavioral manifestations in both healthy and dysfunctional states. This would allow identification of systems that are sensitive to dysregulation, and that may be considered candidate targets for future pharmacological and non-pharmacological treatments. For instance, catecholamines, such as dopamine (DA) and noradrenaline (NA), are involved in the pathogenesis of many (mental) disorders and are targets

of multiple pharmacological interventions but they can also be altered in healthy states (chapter 2). Disentangling and/or finding their complementary action could be informative for the development of better, pharmacological treatment strategies (chapter 4). Therefore, continued research on stress and the motivational functions of DA and NA could shed light on the neural circuits underlying some of the motivational symptoms observed in health and psychopathology and could promote the development of novel treatments for these symptoms. In addition, several biological underpinnings are being explored for the treatment of cognitive impairments, which are also present across multiple disorders as well as healthy aging (Abramovitch et al., 2021; Amor et al., 2014; Kim et al., 2015). Particularly, biological pathways such as inflammation and oxidative stress, as discussed in chapter 6, deserve more attention, especially considering that in addition to cognitive deficits they underly a plethora of (mental) disorders.

Next to pharmacological treatments, psychological interventions are equally important. As stated in chapters 2, 3, 4 reward and effort processing dysfunction (in learning and decision-making) is observed in many stress-related disorders. Providing a mechanistic explanation about these processes with the use of computational models could be beneficial for psychotherapeutic interventions. For instance, cognitive-behavioral approaches, such as behavioral activation therapy (Farchione et al., 2017), that encourage effort expenditure/ approach behavior in order to experience rewarding emotions, can be effective on many people that experience decline in motivated behavior (with or without a neuropsychiatric diagnosis). The underlying theory is that re-engagement with various activities, such as work, social interactions, hobbies, which may have been limited due to the clients' condition, will prove to be more enjoyable and less effortful than initially anticipated. As a result, a series of positive prediction errors might gradually adjust clients' expectations regarding the costs and benefits associated with their actions (Zald & Treadway, 2017). For example, exploring how measures of reinforcement learning and RPE signals can be utilized to predict which groups of people might show better prognosis to such treatment can be of high interest. Another relevant intervention for people that experience, for instance, problems with cost benefit decision-making could be motivational interviewing (Miller & Rollnick, 2013). The aim of this approach is to alter subjective costs and benefits associated with behavioral change, allowing the subjective value of a more adaptive behavior to surpass that of maladaptive behaviors (Zald & Treadway, 2017). Moreover, network analyses (chapter 5) can provide key symptoms or clusters of symptoms that could be potential targets for interventions. Exploring how interaction of symptoms contributes to psychopathology could be informative for the development of treatments that target specific symptoms even before psychiatric disorders arise. However, since not everyone who experiences certain symptoms will develop mental disorders, we should highlight that more research is needed to delineate when symptom dynamics might contribute to psychopathology.

Importantly, besides the wide range of patient groups affected by stress exposure, as already mentioned in the thesis (from people with depression and anxiety to Alzheimer's disease), transdiagnostic approaches can also have an important impact in the non-clinical population with subclinical symptoms. Thus, developing tools that could distinguish between different transdiagnostic dimensions could promote further awareness on vulnerable, non-clinical groups and contribute to improving their well-being. Considering the broad target group of this approach,

improving transdiagnostic conceptualization, and exploring related treatment strategies is very important, not only for both clinical and non- clinical population but also for the general health care, economy, and job market worldwide.

Lastly, we have already taken steps to disseminate results of this thesis to the scientific community, so that others can expand on these ideas in the future. This work has been presented in several scientific meetings. In addition, all studies described in this thesis use open science practices. All published papers used open-access publishing, ensuring unrestricted accessibility to a wide range of readers. In addition, research data and source code are publicly available in online repositories with links provided in each paper. This facilitates free access to the data, promoting transparency and enabling reproducibility of results. Additionally, availability of these sources fosters replicability and enhances the ability of researchers to validate the findings.

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