The emotional power of glucocorticoids: towards a better understanding of the effects of glucocorticoids on emotions and neuropsychiatry

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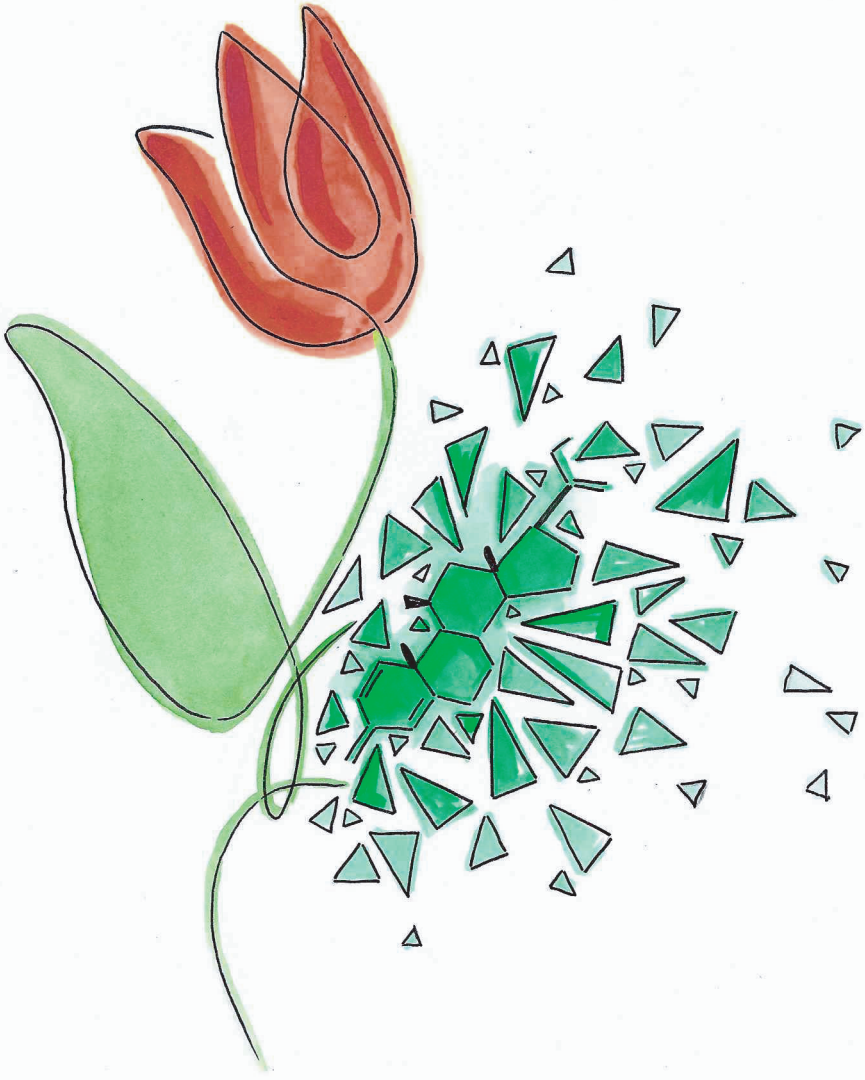


CHAPTER 1

General introduction and outline

GENERAL INTRODUCTION

Stress is our body's natural response to changes in our environment, which helps us to adapt to these changes. In modern society, stress has acquired a somewhat negative connotation and often gets mentioned in the same breath as burnout and other stress-related mental health disorders, like depression and anxiety. Indeed, both stress and mental disorders are highly prevalent nowadays. Stress has become part of our everyday life and it is well established that it can affect our mental health (1). In 2019, mental health disorders were seen in 1 out of 8 people according to the World Health Organisation, of which anxiety and depression were the most common (2). In 2020, during the COVID-19 pandemic these numbers got even higher, with an increase of 26% and 28% in one year for anxiety and depression, respectively (3). It appears reasonable to infer that stress has a negative undertone.

However, adapting to change is not only inevitable but often useful, and our stress response is essential for adaptation to a changing environment. It is mainly when stress becomes chronic, or the stress response is somehow impaired (for example by medication) that it can negatively affect our health (4). This chapter provides an overview of the stress response system. In addition, medication affecting the stress response and stress-related psychopathology are introduced. Furthermore, hypotheses and possible solutions for the neuropsychiatric adverse effects of medication affecting the stress response are discussed.

The stress response

The stress response in the body is mediated by two hormonal systems; the more rapid sympathetic nervous system (SNS) and the slower hypothalamic pituitary adrenal (HPA) axis. The SNS is a network of nerves that get activated immediately upon stress or danger to allow the 'fight-or-flight' response. Activation of the SNS causes the release of noradrenaline (NA) in the brain stem, which leads to increased NA release from sympathetic nerves and the release of adrenaline by the adrenals. Noradrenaline and adrenaline act on multiple tissues, including the heart, lungs, eyes, liver and digestive system; all working together to fight-or-flight from threat (5).

Of more importance in this thesis is the HPA-axis (**Fig. 1**), which has a slower response time, but with more prolonged effects. The HPA-axis is pivotal in the regulation of a stress response and its activation causes a series of hormonal events: corticotrophin-releasing hormone (CRH) is released by the hypothalamic paraventricular nucleus (PVN) to induce release of adrenocorticotropic hormone (ACTH) in brief bursts by the anterior pituitary. This triggers the production and secretion of glucocorticoids by the adrenal

glands (6, 7). In humans the glucocorticoids produced are cortisol and corticosterone. Cortisol is the primary stress hormone and its circulating levels are about 20-fold higher than those of corticosterone. However, the ability of cortisol to penetrate the brain is less than that of corticosterone (8). A properly controlled stress response includes a relative rapidly activated HPA-axis and efficient termination after successful adaptation (9), in which the actions of the receptors to which cortisol can bind play an important role. In this thesis, we will mainly focus on the effects of glucocorticoids on the brain.

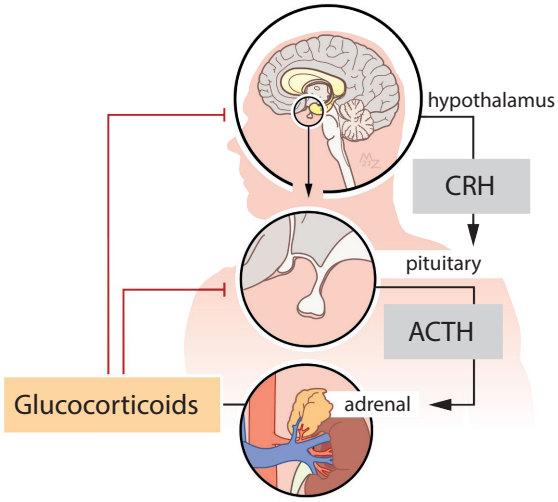


Figure 1. The hypothalamic pituitary adrenal (HPA)-axis.
In the brain, the hypothalamic paraventricular nucleus (PVN) releases corticotrophin-releasing hormone (CRH) to induce the release of adrenocorticotropic hormone (ACTH) by the pituitary. ACTH induces the production and secretion of glucocorticoids by the adrenals. The negative feedback loops (red arrows) suppress HPA-axis activity at the level of the PVN and pituitary.

Cortisol receptors

Cortisol exerts its effects by binding to two types of receptors: the mineralocorticoid receptor (MR) and glucocorticoid receptor (GR). Together these receptors are responsible for all the effects of cortisol in the body. MR has a high affinity for cortisol, which means that already with lower or basal cortisol levels the MR is occupied by hormone. This makes MR important in the early phase of the stress response, which includes the appraisal process and memory retrieval (1). GR has a lower affinity for cortisol and is bound when cortisol levels are higher, for example during stress. GR is therefore important in the termination phase of the stress response, and behavioural adaptation (1). Termination of the endocrine stress response is facilitated by the GRs via two negative feedback loops that suppress the production of cortisol. First, at the

level of the PVN where the production of CRH is suppressed, which results in a lower drive to release ACTH from the pituitary and subsequently the cortisol production by the adrenals. Second, at the level of the pituitary where ACTH production and release are suppressed (**Fig. 1**) (10-12). The negative feedback loops are essential for bringing the cortisol level back to normal, basal levels after a stress response.

MR and GR each have their own roles in the stress response. This is reflected by the different tissue expression of these receptors; GR is widely expressed in the body, while MR has a more restricted tissue-specific expression. In the brain, MR is mainly expressed in the prefrontal cortex, amygdala and hippocampus (in the limbic system) which integrate multimodal information about the environment with previously stored experience. GR is expressed in most brain regions, including the limbic system, the PVN, and the cell bodies of ascending projection from the brain stem that affect HPA-axis activity (13). The fact that the limbic system is involved in processing and regulating emotion and memory already indicates the importance of MR in stress-related psychopathology. This latter will be described in more detail later in this chapter.

MR and GR are nuclear receptors and mediate their effects by regulating gene expression in different ways (14). In this thesis, the classical action of direct binding of the receptors to the DNA was evaluated: upon binding by their ligand (e.g., cortisol), the nuclear receptor complex translocates from the cytoplasm to the cell nucleus. The DNA contains glucocorticoid response elements (GRE) to which the GR and MR bind with their DNA binding domain (DBD) to regulate gene transcription via recruitment of coregulator proteins that impinge on the basal transcription machinery (**Fig. 2**). The DBD of MR and GR are very similar and therefore they recognize the same GREs and they share several target genes (15). Next to these shared target genes, they also have their own unique MR-specific and GR-specific target genes (16). This further emphasizes their own role in the stress response.

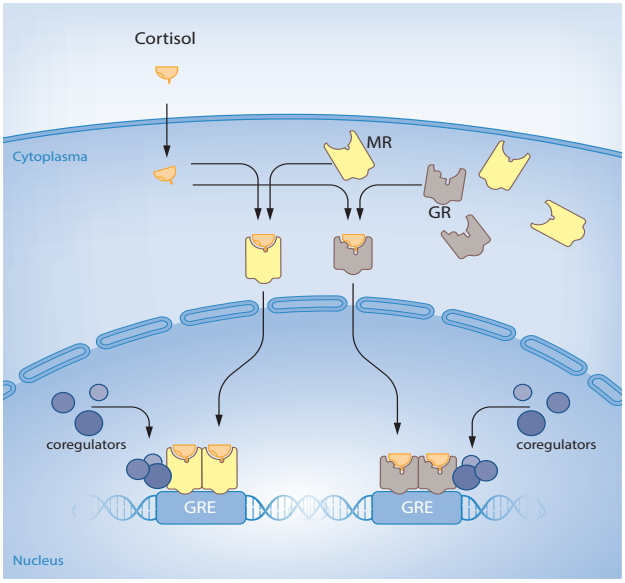


Figure 2. GR and MR signaling and binding on the DNA.
The nuclear mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) are located in the cytoplasm of a cell. When the receptors are bound by their ligand, e.g. cortisol, the complex (receptor and ligand) translocates from the cytoplasm to the nucleus of a cell. In the nucleus it starts to recruit coregulators and these help the complex to bind the DNA and to regulate gene expression. The complex binds to the DNA on the glucocorticoid response elements (GRE). This allows the receptors to regulate target genes for MR and/or GR.

Aldosterone

MR is not only activated by cortisol, but also by another endogenous hormone: aldosterone. Aldosterone is involved in the body's salt and water regulation and therefore in the regulation of blood pressure (17). Aldosterone levels in the blood are approximately 500-fold lower than cortisol levels, which makes it more difficult for aldosterone to bind to the MR. Aldosterone specificity for MR is regulated by an enzyme called 11β hydroxysteroid dehydrogenase type 2 (11βHSD2). In aldosterone selective tissues, e.g., the kidneys, the enzyme converts cortisol into cortisone. Because cortisone is unable to bind to receptors, this conversion enables aldosterone to bind to the MR. Aldosterone-selective neurons expressing 11βHSD-2 have a restricted distribution in the periventricular regions and the brainstem nucleus tractus solitarii. There is another form of this enzyme called 11β hydroxysteroid dehydrogenase type 1 (11βHSD1). This isoform works in the other direction: it converts cortisone into cortisol amplifying glucocorticoid action and is found in the liver and hippocampus (18-20).

Synthetic glucocorticoids

In physiological conditions, cortisol exerts negative feedback on the HPA-axis to prevent excessive activation of the system. However, also synthetic glucocorticoids can influence HPA-axis activity. Synthetic glucocorticoids are used worldwide for their anti-inflammatory effects in the treatment of various conditions, including immune diseases and several forms of cancer. The annual prevalence of their systemic use is established between 0.5% and 3% (21-23). In lung and skin conditions, there is an additional widespread glucocorticoid use via inhalers and cremes. A few examples of synthetic glucocorticoids are prednisolone, methylprednisolone and dexamethasone. Most synthetic glucocorticoids have strong potency at the GR, causing their anti-inflammatory effects (24). The potencies to activate MR are much lower and this helps to prevent the unwanted adverse effects of MR activation, such as hypertension and imbalance in fluid-electrolyte. However, GR and MR binding affinities still differ substantially between these synthetic compounds (**Fig. 3**) (25).

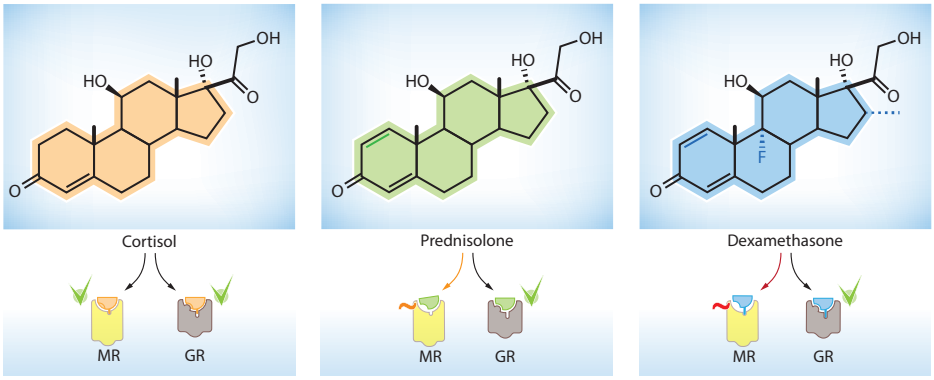


Figure 3. Structural formulas of cortisol, prednisolone and dexamethasone.
The structural formulas of synthetic glucocorticoids are very similar. Their differences determine their different affinity for MR and GR.

With their potent ability to activate GR, synthetic glucocorticoids activate the negative feedback loop of the HPA-axis, mostly at the pituitary level. This results in suppressed ACTH production and release, and subsequently suppressed cortisol production. Because the affinity of synthetic glucocorticoids is substantially lower for MRs they cannot easily compensate for the lack of cortisol, which is a high affinity MR ligand. This is predicted to result in low occupancy of the MRs after synthetic glucocorticoid use (26). Low dose synthetic glucocorticoids poorly penetrate the blood-brain barrier and with the cortisol production suppressed, both MRs and GRs in the brain are underactivated. However, higher doses synthetic glucocorticoids can penetrate the

blood-brain barrier (27, 28). With the HPA-axis still being suppressed, the GRs in the brain can be bound by the synthetic glucocorticoids, while the MRs will still be unoccupied. Taken together, in the brain, high dose synthetic glucocorticoids causes overactivation of GR, underactivation of MR and/or an imbalance in the activation of MR and GR (26).

Stress-related psychopathology

Inappropriate endocrine stress responses like prolonged, blunted or excessive HPA-axis activation are thought to increase the risk for stress-related psychopathology, like anxiety and mood-disorders, such as depression and bipolar disorder, dysthymia and burn-out (1, 29-35). While these disturbed responses can lead to significant disturbances in emotions, these can vary per individual, in severity from mild to severe symptoms, and in duration from transient changes to prolonged conditions (36).

The effect of excessive exposure to cortisol – GR overactivation – is evident in patients with active Cushing's disease, who chronically have excessive endogenous cortisol levels caused by ACTH-producing pituitary adenomas. In these patients, psychopathology is often observed, such as major depression, anxiety disorders and mania; a condition in which excessive high level of energy, mood or behavior is displayed. Interestingly, the risk for psychopathology is still enhanced even after long-term remission, which points to long lasting or perhaps 'programming' effects of cortisol (37, 38). The use of a GR antagonist (a GR blocker) in these patients, can reduce psychotic depressive symptoms during active disease (39).

In contrast, MR activation seems to be protective in psychopathology. One line of research showed that in postmortem brain tissue of major depression disorder patients, suicide victims, schizophrenia and bipolar disorder patients, decreased MR expression was found (40-44). Another proposition is that low MR activity leads to loss of its tonic inhibition of the HPA-axis, which results in elevated cortisol levels that subsequently increases the risk for major depressive disorder (45, 46). Genetic research has found a common gain-of-function MR gene variant that is associated with a lower risk of depression and enhanced optimism – interestingly mainly in women (47). Additionally, another study confirmed the increased MR expression of this MR haplotype and demonstrated more efficacious cortisol and ACTH responses to a physiological stressor (48), and yet another study established that this haplotype had higher scores on implicit happiness, indicating a stress resilient phenotype (49).

The role of MR and GR in stress-related psychopathology is also reflected in the effect that high dose synthetic glucocorticoid has on the receptors. While synthetic

glucocorticoids are very efficacious in the treatment of certain diseases, high dosage can cause many side effects that include behavioral, cognitive and neuropsychiatric adverse effects. Neuropsychiatric adverse effects include depression, anxiety, mania, delirium and even suicidality (50-52). It is important to mention that not every patient treated with synthetic glucocorticoids develops neuropsychiatric adverse effects. There are also patients that do not develop any side effects, or who develop only strong somatic side effects without any psychological effects. The latter argues against a genetically determined higher sensitivity of the main target of the glucocorticoids, the GR, as the explanation for the occurrence of psychological side effects.

The MR refill hypothesis

The underactivation of the MR, that comes with synthetic glucocorticoid treatment may play a role in the development of neuropsychiatric side effects. A solution might be to add a low dose of cortisol to synthetic glucocorticoid treatment. The additional cortisol can then bind to the empty MRs and receptor occupancy and/or balance will be restored (**Fig. 4**).

In fact, this is a testable hypothesis: several experiments in rodents and human have shown that empty MRs can be refilled with corticosterone or cortisol, respectively (53). In humans, for example, prolonged treatment with dexamethasone may enhance negative feelings, like anger and sadness, while co-treatment with cortisol was able to counteract many of these negative feelings (54). This effect is likely caused by the reactivation of MR.

Reactivation of the MR with cortisol is now considered as a potential way to ameliorate neuropsychiatric adverse effects of synthetic glucocorticoids in a clinical setting. A clinical trial investigated this MR refill hypothesis in pediatric leukemia patients who were treated with dexamethasone. In this patient group, dexamethasone-related adverse effects are well known and encompass mood, sleep, behavior and cognition (55-60). Next to the dexamethasone treatment, the patients received co-administration of cortisol or placebo. With cortisol cotreatment the psychological adverse effects and sleep-related difficulties could be alleviated (61). The latter is the first study to investigate a rather safe intervention to reduce dexamethasone-related adverse effects and with promising results. However, recently a new randomized controlled trial in the same study population was published and found that hydrocortisone had no effect in reducing clinically relevant dexamethasone-induced neurobehavioral problems (62). A complicating factor is that in the latter trial reported a very substantial placebo effect, and this may have masked putative beneficial effects of cortisol add-on.

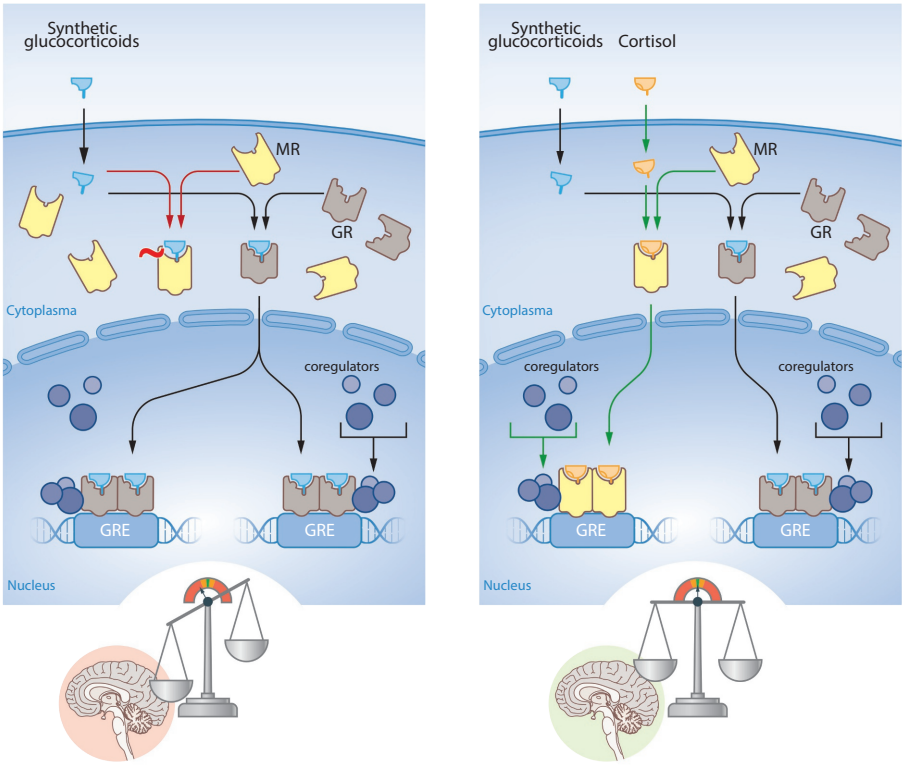


Figure 4. MR refill hypothesis.
High dose synthetic glucocorticoids cause overactivation of GR, underactivation of MR and/or an imbalance in the activation of MR and GR in the brain. Reactivation of the MR with cortisol might ameliorate neuropsychiatric adverse effects of synthetic glucocorticoids. Additional cortisol can bind to the empty MRs and receptor occupancy and/or balance will be restored.

Using psychopathology symptom networks

The relationships between (synthetic) glucocorticoids and mood will be central in this thesis. However, the analysis of mood is not trivial. Classically, much research relies on the use of questionnaires (or clinical observations) that lead to an overall score on a number of axes. Nowadays psychopathologies are more and more seen as complex dynamic systems, in which symptoms may interact, influence and cause each other. In other words: symptoms may also be causal ingredients for mental disorders (63). Mental disorders are thus seen as a network with causally connected symptoms, which change and adapt over time. Network analysis can be used to create and understand the network of symptoms.

Whereas the use of network analysis in psychiatry focuses on mental disorders, this thesis focuses on the use of network analysis on mood in healthy subjects, physically ill subjects and depressed patients. In a network, symptoms or mood items are represented as nodes, and these are connected through edges that represent the association between the connected symptoms or mood items (63). For example, due to a stressor, a person is suffering from insomnia for several nights, the sleep loss will cause the person to experience fatigue. Subsequently, if the fatigue is long lasting, the person might also start to experience concentration problems. These symptoms can trigger the development of major depression: insomnia → fatigue → concentration problems → depressed mood (**Fig. 5**). These four symptoms are part of the items on which the diagnosis for major depression is based (64).

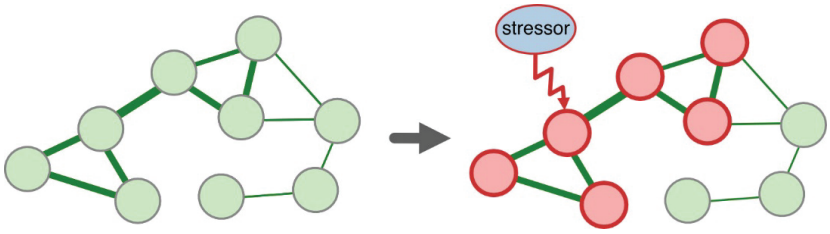
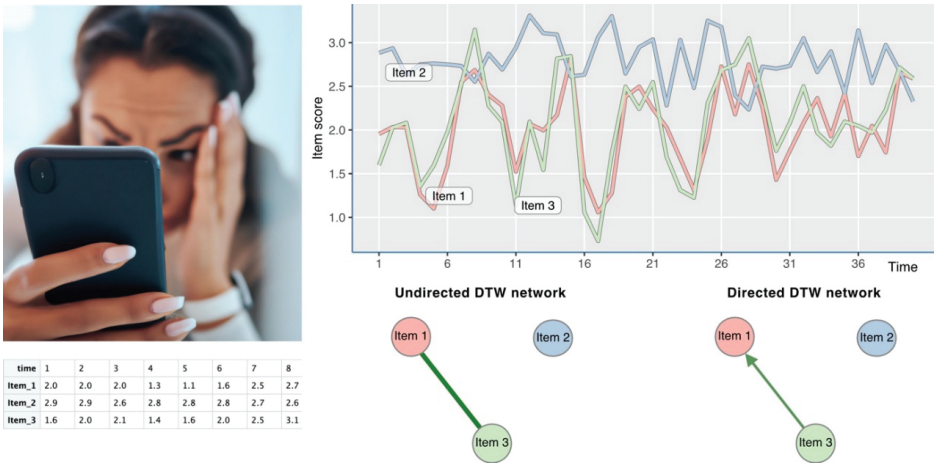


Figure 5. Example of a network of components of mental health.
In a network symptoms or mood items are represented as nodes, and these are connected through edges that represent the association between the connected symptoms or mood items. A stressor may trigger changes in one node that in turn may trigger changes in other associated nodes, which may result development of disease or disorder. (Picture by courtesy of Dr. Erik Giltay).

A diagnosis based on an overall score may thus not be highly informative. Instead, the process where symptoms cause each other is more of interest, and for that an important factor is time. One sleepless night may not immediately result in excessive fatigue the next day. On the other hand, a time interval of a year might be too large to identify possible symptom or mood connections. Currently, research started to focus on ecological momentary assessments (EMA). With EMA, time-series data can be collected, in which individuals report their behavior, state of affect, and daily context several times a day for multiple consecutive days in their natural environment (65, 66). Time-series data like that can also capture how symptoms or mood change over time. The change over time is called the temporal dynamics, and this may play an important role in the development of psychopathology (**Fig. 6**).



time	1	2	3	4	5	6	7	8
Item_1	2.0	2.0	2.0	1.3	1.1	1.6	2.5	2.7
Item_2	2.9	2.9	2.6	2.8	2.8	2.8	2.7	2.6
Item_3	1.6	2.0	2.1	1.4	1.6	2.0	2.5	3.1

Figure 6. Ecological momentary assessments (EMA) to investigate symptom or mood changes over time. *EMA data can be collected with use of an app on a phone or tablet. Daily, or several times a day one could be asked to fill out short questionnaires in order to collect information on how symptoms or mood items change over time. With Dynamic Time Warping (DTW) the temporal dynamics of symptoms or mood items can be analysed in an undirected, and directed method, of which the latter shows the direction of an association. (Picture by courtesy of Dr. Erik Giltay).*

A relatively new statistical method that takes into account the temporal dynamics, is called Dynamic Time Warping (DTW). DTW can identify which symptoms or mood items change together over time, and are likely to precede or affect each other (**Fig. 6**). The DTW analysis can be done on an individual level and on group level, this makes DTW a promising tool for personalized care, since symptoms can differ between individuals and can follow a different trajectory in the development of psychopathology (67-70). This approach may help in understanding the potential causal relationships between symptoms and can inform treatment strategies. For instance, if DTW reveals that changes in sleep patterns consistently precede changes in mood, it suggests that addressing sleep issues might be a crucial aspect of treatment.

OUTLINE OF THIS THESIS

As is evident from this chapter (**Chapter 1**), stress is essential for adaptation to a changing environment, however, dysregulation in the stress response can result in stress-related psychopathology. The aim of this thesis is to gain more insight into the role of cortisol and synthetic glucocorticoids in emotions and neuropsychiatric adverse effects. In **Chapter 2,** we first map the relationship between endogenous cortisol and emotions in depressed and non-depressed individuals, using network analysis and DTW. The neuropsychiatric adverse effects of synthetic glucocorticoids have been known for years, but their use is often inevitable. Yet, many aspects of these neuropsychiatric effects remain ill-understood. In **Chapter 3** we provide an overview of the available studies investigating neuropsychiatric adverse effects of glucocorticoids. In **Chapter 4** the network analysis of emotional state is further investigated in a case series of patients using synthetic glucocorticoids because of T-cell lymphomas of the skin. We investigate the underlying mechanisms of neuropsychiatric effects of dexamethasone by focusing on the MR and GR status in post-mortem human brain in **Chapter 5**. In **Chapter 6** we describe a multicenter randomized clinical trial to investigate the hypothesis that reactivation of MR could alleviate psychiatric adverse effects of dexamethasone. This trial is ongoing and patients are still being included. Finally, the results from these studies and their implications are discussed in **Chapter 7**.

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