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Experts in the field share the opinion that functioning of the hypothalamic-pituitary-adrenal (HPA) axis, the major neuroendocrine stress system of the human body, plays a pivotal role in the pathophysiology of depression. In the literature, many statements like the following can be found: “The HPA axis is considered to be the ‘final common pathway’ for a major part of the depressive symptomatology” (Bao, Meynen, & Swaab, 2008, p. 535). “… elevation of adrenocortical stress hormones has been recognized as a depression-associated feature for decades” (Holsboer & Ising, 2010, p. 90). “There is little doubt that cortisol plays a central role in the onset and course of major depression disorder (MDD)…” (Herbert, 2013, p. 449). However, there is great uncertainty over exactly what that role may be (Herbert, 2013). This uncertainty is illustrated by the overall inconsistent literature regarding the relationship between indices of HPA axis functioning and depression across observational studies in humans (e.g. Burke, Davis, Otte, & Mohr, 2005; Stetler & Miller, 2011).

In the first part of this thesis, I will seek explanations for some of these inconsistent findings and shed new light on the role of HPA axis functioning in depression. I will do so by focusing on the dynamics of HPA axis functioning in depression, which has been a rather unexplored topic so far (e.g. Peeters, Nicolson, & Berkhof, 2004). I combine prospective group studies over several years with intensive sampling strategies in individuals in daily life. This allows for the examination of long-term changes at the group level and daily life dynamics within individuals.

Physical activity is a potent activator and modulator of the HPA axis (e.g. aan het Rot, Collins, & Fitterling, 2009; Hackney, 2006). Interestingly, this form of physical ‘stress’ seems to have a positive influence on mood states and depressive symptoms (e.g. Kanning, Ebner-Priemer, & Schlicht, 2013; Rimer et al., 2012). In the second part of this thesis, I will explore whether physical activity reduces depressive symptoms via long-term changes in HPA axis functioning and daily life fluctuations in cortisol. This may increase insight in the role of the HPA axis in depression, and provide clues to optimize the antidepressant effect of physical activity.

PART 1: THE TEMPORAL DYNAMICS OF HPA AXIS FUNCTIONING IN DEPRESSION

A role for the HPA axis in depression?
Depression is a common psychiatric disorder, with an often chronic or recurrent course and far-reaching consequences for individuals’ quality of life and future opportunities (Meyer-Lindenberg & Weinberger, 2006). Core symptoms are depressed mood and anhedonia (i.e., loss of interest or pleasure), of which at least one should be present. Various other symptoms can occur, whereof several should be present to qualify for Major Depressive Disorder (MDD) according to the DSM-IV. Symptoms should be present for at least two weeks.
Depressive episodes are often preceded by acute or chronic psychosocial stress, particularly the first episode (Kendler, Thornton, & Gardner, 2000). Psychosocial stress is a potent activator of the hypothalamic-pituitary-adrenal (HPA) axis (Mason, 1968). The HPA axis is a vital system that helps the body adapt to stressful situations by mobilizing energy resources and inhibiting non-emergency processes such as reproduction (Chrousos, 2009). Upon a stressful stimulus, the neurons in the paraventricular nucleus of the hypothalamus release corticotropin-releasing hormone and vasopressin, which migrate to the pituitary portal system. There they promote the synthesis and excretion of adrenocorticotropic hormone into the bloodstream. Once arrived at the adrenal cortex, this hormone stimulates the release of cortisol. As the final effector of the HPA axis, cortisol acts on many target organs in the periphery, but it also functions as a negative-feedback signal at several levels of the HPA axis (Figure 1) (De Kloet, Joëls, & Holsboer, 2005). Furthermore, cortisol acts on several limbic structures implicated in emotional processing, of which some also activate or inhibit the HPA axis (Gold, Drevets, & Charney, 2002; J. LeDoux, 2003).

**Figure 1** Schematic representation of the release of cortisol upon activation of the HPA axis, and cortisol’s targets in the central nervous system. ACTH = Adrenocorticotropic hormone, CRH = Corticotropin-releasing hormone, VP = Vasopressin. Striped lines with pointy arrows and dotted lines with oval arrows indicate activating and suppressing influences on the secretion of cortisol, respectively. Continuous lines represent connections between the hypothalamus and other brain areas.
The finding that psychosocial stress activates the HPA axis has led to a series of studies on HPA axis functioning in hospitalized depressed patients (Mason, 1968). In the early 1960’s the first articles appeared that reported HPA axis alterations in depressed patients, such as resistance to the suppressive effects of dexamethasone on plasma cortisol levels, and altered diurnal cortisol rhythms (e.g. Butler & Besser, 1968; Carroll, Martin, & Davies, 1968; Sachar, Hellman, Fukushima, & Gallagher, 1970). Two other alterations which were found are still the subject of many studies to date: increased HPA axis activation and decreased HPA axis reactivity to stress (Burke et al., 2005; Stetler & Miller, 2011). A recent meta-analysis of 40 years into HPA axis activation in depression concluded that, overall, there was a tendency for increased cortisol levels in depressed groups. However, it was also noted that the results varied considerably across studies, with some studies even showing opposite results (Stetler & Miller 2011). In a meta-analysis on HPA axis reactivity to stress it was concluded that, overall, there seems to be a tendency towards reduced instead of increased HPA axis reactivity to psychosocial stress in depressed groups, but results also varied considerably across studies (Burke et al., 2005).

**HPA axis (re)activity in depression: potential sources of inconsistencies**

The inconsistencies in the literature may at least in part be the result of some limitations of these studies. Most studies into the relationship between HPA functioning and depression to date used only one or a few samples of cortisol per participant (Stetler & Miller, 2011). However, cortisol fluctuates strongly in daily life and is influenced by time-varying factors, such as circadian and ultradian rhythm, stressful events, physical activity and food intake (e.g. Gibson et al., 1999; Kudielka, Hellhammer, & Wust, 2009; Lightman & Conway-Campbell, 2010). When within-subject variability (i.e. a person’s variation over time in a variable, see Figure 2) is not adequately dealt with, the estimation of between-individual variation is hampered (Hruschka, Kohrt, & Worthman, 2005). Hruschka et al. (2005) nicely illustrated that many measurements are often necessary for assessing between-individual variation in cortisol with adequate power. This notion also holds for the assessment of subgroups of depressed individuals, for example, individuals with different types of depression (e.g. Gold & Chrousos, 2002; Lamers et al., 2012).

The lack of repeated assessments over longer time periods in most of the studies is another potential source of inconsistencies. There is some evidence that the relationship between depression and HPA activity is dynamic. For example, the relationship between psychosocial stress and the onset of a depressive episode weakens with every subsequent episode, likely due to sensitization to stress (Kendler, Thornton, & Gardner, 2001; Kendler et al., 2000; Morris, Ciesla, & Garber, 2010; Post, 1992). Also, brain structures which are tightly connected to the hypothalamus, such as the hippocampus, seem to decrease in volume with progression of depression (Frodl et al., 2008; Lorenzetti, Allen, Fornito, & Yücel, 2009). Long-term changes in reactivity of the HPA axis to stress may therefore occur with progression of depression as well.
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Observational studies often make use of a 2-dimensional slice of the data cube. Namely, they measure several variables in multiple individuals, but only once in time.

Cortisol dynamics in daily life: a link between experiences and emotions

In the previous section, I addressed limitations of studies assessing the relationship between HPA axis (re)activity and depression. Related to this is a more general point that cross-sectional studies cannot say anything about mechanistic processes. For example, if a cross-sectional study shows that cortisol levels are positively related to depression, this does not necessarily mean that more cortisol leads to more depression within individuals. Only under very strict circumstances can results based on between-individual variation be translated to the within-individual level, and these circumstances are hardly ever met (Molenaar & Campbell, 2009). Hence, for studying the etiology of depression, longitudinal studies are required.

Over the past years, evidence has accumulated suggesting that depression is the result of a dynamic interplay between ‘micro-level’ daily life experiences and behavior over time (Wichers, 2014). Daily life experiences may trigger cortisol release. Cortisol acts on various brain areas within hours after being released, including limbic areas and the prefrontal cortex, which are implicated in cognitive and emotional processing (Figure 1). Besides regulating its own release via these areas, it modulates functioning of these areas in other ways. For example, it enhances the amygdala’s preferential processing of negative over positive emotional stimuli (e.g. Henckens, van Wingen, Joels, & Fernandez, 2010). Cortisol could therefore be a crucial link between daily life experiences and emotions, and the accompanied emotion-driven behaviors. Studying cortisol in relation to these emotions in daily life may further contribute to the understanding of the role of HPA axis functioning in depression.
A number of studies have examined cortisol in daily life in relation to momentary affective states (for a discussion about the similarities and differences between mood, emotions and affect, see Box 1), by means of an experience sampling method (ESM) (e.g. Peeters, Nicholson, & Berkhof, 2003; van Eck, Berkhof, Nicolson, & Sulon, 1996). Besides having high ecological validity, ESM has the added benefit that the small time interval between measurements reduces recall bias (de Vries & Csikszentmihalyi, 2006; Telford, McCarthy-Jones, Corcoran, & Rowse, 2012). In a study of Peeters et al. (2003), a differential relationship was found between cortisol and affective states in depressed versus non-depressed groups, namely a positive association in the non-depressed group, and no association in the depressed group. However, because of the group-based approach, it is not known whether this is generally true for depressed individuals, or only for some; group-based longitudinal studies aggregate individual regression terms and the same regression model is imposed on all subjects rather than modeling the dynamic relationship for each subject individually. Hence, meaningful individual differences in this relationship may have gone unnoticed. Moreover, the nature of the design and analytical methods that were used in this study did not allow statistical inference about the direction of the relationship. Finally, it is not clear whether, in the specific analyses, the between-individual variation was adequately separated from the within-individual variation. Hence, the exact nature of the temporal relationship between cortisol and affective states in daily life remains to be discerned.

Recently, techniques for the analysis of time-series data have become available in the field of psychology. These techniques are suitable for explaining variance within single individuals instead of variance in the population. Moreover, with sufficient data points (T>60), time-lagged associations between variables as well as the temporal ordering of the effects can be assessed at the level of the individual (Brandt & Williams, 2007). Because individuals are examined one by one, processes can be studied at the within-subject level and individual differences that would be obscured in group designs can be revealed (Rosmalen, Wenting, Roest, de Jonge, & Bos, 2012). In this thesis, I applied a time-series approach to study the temporal dynamics between cortisol and affect.
Affect is not necessarily the same as emotion, but draws many similarities. In the current literature, two different definitions of affect are present. The first is that ‘affect is a neurophysiological state consciously accessible as a simple primitive non-reflective feeling most evident in mood and emotion but always available to consciousness’ (LeDoux, Barrett, & Russell, 2014; Russell, 2009). According to this definition, affect is a key element of mood and emotions (i.e. “core affect”; Figure A, left). In standard text books, however, affect is often defined as an umbrella term for affective phenomena, such as emotions and moods (e.g. Totterdell & Niven, 2014) (Figure A, right). Where emotions are often intense feelings that are usually directed at something or someone and last shortly, moods are longer lasting and more diffuse, and unlike emotions they are typically not directed at any specific event (Totterdell & Niven, 2014; Wilhelm & Schoebi, 2007).

Although the two definitions of affect have quite different meanings, in practice they appear not to be that different, because many complex affective phenomena are highly correlated to core affect (Yik, Russell, & Steiger, 2011). Most studies using “momentary affect” include more complex affective phenomena in their item list which are specifically relevant to depression, such as feeling guilty or hopeless. In this thesis, I mostly used core affect items, but also included some more complex affective phenomena. These items were averaged to form a positive and negative affect scale (Bylsma, Taylor-Clift, & Rottenberg, 2011). Furthermore, because we assessed momentary affective states, we probably captured a mixture of emotions and moods and other affective phenomena that are present in an individual at that moment (Figure B).
PART 2: HPA AXIS FUNCTIONING AS A MEDIATOR OF THE RELATIONSHIP BETWEEN PHYSICAL ACTIVITY AND DEPRESSION

The antidepressant effect of physical activity: a role for the HPA axis?

Given the presumed role of the HPA axis in the onset or progression of depression (e.g. Bao et al., 2008; Herbert, 2013; Holsboer & Ising, 2010), some of the existing interventions against depression may exert their effect (at least partly) via the HPA axis. Studying the role of HPA axis functioning in relation to candidate interventions (i.e. those that are known to affect HPA axis functioning) may 1) provide knowledge that may be used to further optimize the treatment in terms of effectiveness, 2) aid in determining the general role of the HPA axis in the pathophysiology of depression. One intervention against depression of particular interest is physical activity. Meta-analyses suggest that physical activity interventions of several weeks are effective in reducing depression, although some caution is required because methodological robust studies show smaller effects (Rimer et al., 2012). There is some evidence for short-term effects as well: physical activity seems to improve affective states within the context of daily life (Kanning et al., 2013), which may subsequently prevent or ameliorate depressed mood (e.g. Geschwind et al., 2011; Wichers et al., 2010). Besides its positive effects on depressive symptomatology, it has few side effects and the costs are low (Daley, 2008).

Physical activity is a potent activator and modulator of the HPA axis (e.g. Hackney, 2006). Physical activity induces an acute cortisol response. However, physical activity training results in reduced cortisol responses in the long run, not only to physical activity, but to psychosocial stress as well (Rimmele et al., 2007). Furthermore, subtle fluctuations in cortisol may play a role in the effect of physical activity on affective states in daily life. In rats, running during or shortly after exposure to a stressor reduced stressor-induced cortisol secretion (Starzec, Berger, & Hesse, 1983). In turn, this reduction in cortisol may alter functioning of emotional circuits in the brain and, hence, influence affective states (Salmon, 2001; Sarabjit Singh et al., 2010). In this thesis, I assessed whether and how the HPA axis mediates the relationship between physical activity and depression.

OUTLINE OF THE DISSERTATION

In this thesis, I combined prospective group studies over several years with intensive sampling in daily life of depressed and non-depressed individuals. Prospective group studies were conducted in the ‘Tracking Adolescents’ Individual Lives Survey (TRAILS) cohort, and intensive sampling studies in daily life were conducted in the Mood and Movement in Daily life (MOOVD) sample (see Box 2 for details about these study samples). In the first part of this thesis, I used these data to make inferences about the dynamics of HPA axis functioning in depression, and individual differences therein. In the second part of this thesis, I assessed whether and how HPA axis
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functioning mediates the relationship between physical activity and depression over several years, and from moment to moment.

I examined potential explanations for some of the inconsistencies with regard to HPA axis functioning in persons suffering from depression. Specifically, in Chapter 2, I examined the relationship between chronicity of depressive problems and HPA axis reactivity to psychosocial stress in adolescents (TRAILS focus sample). In Chapter 3, I assessed between- and within-individual variation in cortisol (t=90) in matched depressed and non-depressed individuals (n=30) (MOOVD study).

Examining the dynamic relationship between cortisol and affective states in daily life may increase understanding of the role of the HPA axis in depression. Because this question regards temporal processes within individuals, I chose for a within-individual analytical approach (i.e. time-series analysis). This approach requires specific sampling protocols. Chapter 4 described how stress biomarkers can be optimally sampled for time-series analysis. In Chapter 5, I examined the dynamic relationship between cortisol and positive and negative affect in daily life in depressed and non-depressed individuals (MOOVD study).

In chapter 6, I examined whether adolescents’ exercise habits prospectively predicted HPA axis responses to psychosocial stress, and whether this subsequently predicted somatic and affective symptoms of depression (TRAILS focus sample). In Chapter 7, the temporal relationship between physical activity and affective states in daily life of depressed and non-depressed individuals was assessed (MOOVD study). For those individuals with significant direct or lagged effects of physical activity on affective states, I assessed in Chapter 8 whether cortisol mediated this relationship. Finally, in Chapter 9 the findings of the previous chapters were integrated and discussed.


**BOX 2: STUDY DESIGNS**

*The TRAILS study*
For two of the studies in this thesis (Chapter 2 and 6) we used data from a focus sample of the TRacking Adolescents’ Individual Lives Survey (TRAILS), a prospective cohort study of Dutch adolescents with bi- or triennial measurements from age 11 to 24. This study was set up to learn more about the etiology and course of mental health problems in the Dutch population. The first measurement wave was in 2001-2002 (age ± 11 years), with 2230 children enrolled in the study. Up till now, 5 waves have been completed. For a detailed description of the TRAILS cohort, please see De Winter et al. (2005) and Oldehinkel et al. (2008). For this thesis, we used data from wave 2 (age ± 13.5 years) and wave 3 (age ± 16 years). Specifically, we used a focus sample of 715 adolescents who agreed to participate in a series of laboratory tasks additional to the usual assessments at wave 3. One of those tasks was a social stress test to assess psychological and physiological responses to stress. Among other things, cortisol was assessed.

*The MOOVD study*
For Chapter 3, 4, 5, 7, and 8 we used data from the Mood and Movement in Daily life (MOOVD) study, which we set up to investigate the dynamic relationship between (physical) activity and mood in daily life, and the role of several biomarkers therein. Participants (age 20-50 years) were intensively monitored in their natural environments for 30 days, by means of electronic diaries, actigraphy, and saliva sampling, resulting in a total of 90 measurements per individual. This number is sufficient to perform time-series analysis for single individuals. Of the 62 participants who started the study, 8 participants dropped out early or did not have enough valid physical activity or diary measurements (T<60). This left 54 participants for further study. Participants with and without a depressive disorder were pair-matched on gender, smoking, age, and BMI. For this thesis, 15 matched pairs (the first subsample for which cortisol concentrations had been determined, because they enrolled in the study first) were used.
REFERENCES


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Part 1

The temporal dynamics of HPA axis functioning in depression