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Dynamics of the human stress system in depression

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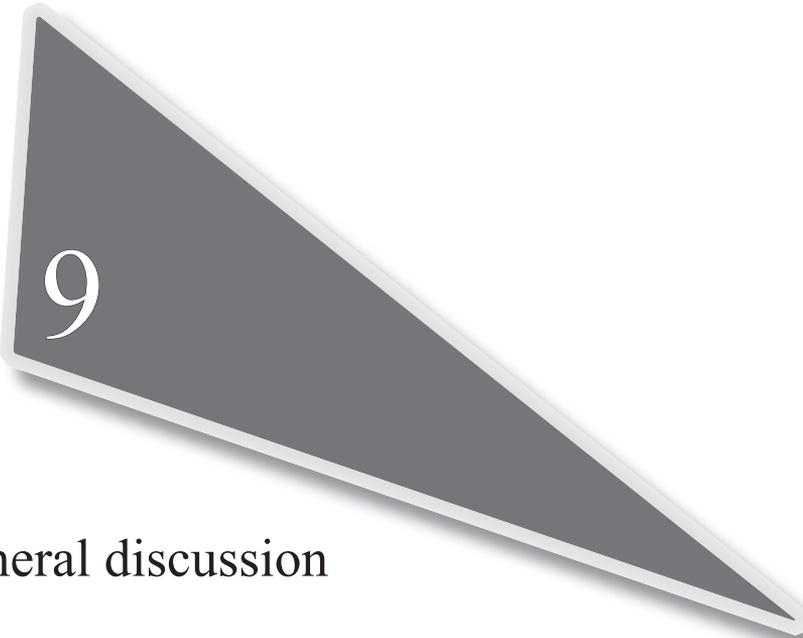
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General discussion

While many experts have the opinion that the hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the pathophysiology of depression, there is great uncertainty about what that role exactly is (e.g. 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 this thesis, I focused on the temporal dynamics of HPA axis functioning, which is a rather unexplored topic in depression research. To do so, I combined prospective group studies over several years with intensive sampling strategies in individuals in daily life. In the first part, I assessed whether long-term changes and daily life dynamics of the HPA axis account for some of the inconsistent findings with regard to HPA axis (re)activity at the group level (Chapter 2 and 3). I also assessed the temporal dynamics of cortisol and affective states in depressed and non-depressed individuals in daily life (Chapter 4 and 5). In the second part, I took another route to examining the role of HPA axis functioning in depression. Research suggests that physical activity is a potent antidepressant, as well as an activator and modulator of the HPA axis. This led me to examine whether and how HPA axis functioning mediates the relationship between physical activity and depression (Chapter 6 – 8). In the current chapter, the findings of the individual chapters are summarized and integrated and critical considerations, practical considerations as well as future directions are discussed.

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

Summary and key findings

Both increased and decreased reactivity has been found in depressed samples (e.g. Burke et al., 2005). Epidemiological as well as neurobiological evidence suggests that this may be due to differences in depression history. Therefore, in Chapter 2, I studied in a population sample of adolescents whether chronicity of depressive problems (20% with the highest levels of depressive symptoms) influenced the cortisol response to psychosocial stress. Data from cortisol samples collected during and after a standardized social stress task showed that, compared to adolescents without depressive problems, adolescents with acute depressive problems had an increased cortisol response to psychosocial stress, while adolescents with chronic depressive problems had a reduced cortisol response to psychosocial stress. This is the first indirect support for the hypothesis that HPA axis reactivity to psychosocial stress changes with progression of depression.

Similar to results on HPA axis reactivity, results on HPA axis activity (measured under baseline conditions) have been found to be heterogeneous. While HPA axis reactivity is usually assessed under highly standardized conditions in laboratory settings, the study of HPA axis activity is usually not: measurements are often done by the participant at home. In daily life, cortisol levels fluctuate heavily, because they

are influenced by many different time-varying factors, including circadian rhythm, ultradian rhythm, sleep time, time of waking up, and food intake (e.g. Gibson et al., 1999; Kudielka, Hellhammer, & Wust, 2009; Lightman & Conway-Campbell, 2010). Hence, when assessing between-group differences in HPA axis activation, it is important to measure and take into account this within-person variability in order to acquire reliable results (Hruschka, Kohrt, & Worthman, 2005). Nevertheless, there are almost no studies that do so (Peeters, Nicolson, & Berkhof, 2004; Stetler & Miller, 2011). In Chapter 3, I studied the relationship between cortisol levels and depression in 15 depressed individuals and their 15 non-depressed matches, who collected saliva three times a day for thirty days ($T=90$). This number of measurements is large enough to account for within-individual variation. The results showed that, on average, the depressed group had higher cortisol levels than the non-depressed group. However, when depressed individuals were compared to their non-depressed matches, the percentage of depressed individuals with higher levels than their match did not differ from chance (about 50%). Further, intra- and interindividual variation in cortisol was large. Hence, the group-level results did not generalize to individuals in this sample. To conclude, depression was a poor predictor of individual cortisol levels.

A more general limitation of previous studies is that they were all performed at the group level, which means that the results cannot be generalized to the intra-individual level (i.e. the level at which mechanisms operate). Fluctuations in cortisol may serve as a crucial link between daily life experiences and the subsequent emotional responses and the accompanying behaviours. By definition, such “mechanistic” processes should be studied within individuals over time. This can be done by applying an intensive time-series approach, with many repeated measurements within individuals. In Chapter 4, the practical implications of using a time-series approach were discussed. In Chapter 5, I took this approach to study the temporal dynamics between cortisol and affective states in the daily life of depressed and non-depressed individuals. The results showed that there are large individual differences in the temporal order and the sign of the relationship between cortisol and affective states. These individual differences suggest that there are differential ways to deal with daily life stress.

HPA axis functioning as a marker for depression: a dead end?

The results described in Chapter 2 and 3 show that, to some extent, daily life fluctuations and long-term changes in HPA axis functioning underlie the inconsistencies in the literature regarding (dys)functioning of the HPA axis in depression. However, even when accounting for these factors, individual differences remained present, as was made explicit in Chapter 3. Relatively little variation in cortisol was explained by depression, making it difficult to discriminate depressed from non-depressed individuals by means of their cortisol levels, despite of a matching procedure on gender, age, BMI and smoking, and excluding confounding factors such as pregnancy and alcohol abuse. Even in the high-end range of cortisol, there were both depressed and non-depressed individuals with such values. Many other factors have also been related to HPA axis functioning, such as physical fitness, oral contraceptives (Bouma, Riese,

Ormel, Verhulst, & Oldehinkel, 2009; Rimmele et al., 2007), but also depression characteristics such as severity and type of depression (Lamers et al., 2012; Peeters et al., 2004). Perhaps, when all these factors would be controlled for, depressed individuals could be discriminated from non-depressed individuals based on their cortisol patterns. But clearly, depressed individuals cannot easily be identified using one or a few cortisol samples. Use in clinical practice is therefore ruled out currently.

Whether cortisol patterns can ever be used for diagnostic or prognostic purposes for depression in clinical practice also depends on technical and statistical advancements. Perhaps they can be useful in combination with other (bio)markers. The literature and expertise on the development of complex prediction models with multiple predictor variables is growing, but up till now, such models have rarely made it to clinical practice (Moons, Altman, Vergouwe, & Royston, 2009). Furthermore, more advanced automatic subcutaneous sampling devices which can sample cortisol at 10-minute intervals for several days without effort of the patient may become available in the future. This would make it more feasible to get a reliable estimate of someone's average cortisol level or to assess cortisol dynamics. However, such a device may be costly at first (Bhake, Leendertz, Linthorst, & Lightman, 2013). Taken together, research into the use of cortisol as marker for depression is reaching a dead end. Perhaps, statistical and technical advances may bring this area of research back on track.

HPA axis dynamics: from 'inconvenient' to 'important'

The results of Chapter 2 and 3 add to the body of literature showing that the dynamics of the HPA axis are important to take into account when assessing group-level associations between HPA axis functioning and depression (e.g. Hruschka et al., 2005). But beyond being an inconvenient confounder that should ideally be controlled for, Chapter 2 and 5 in particular suggest that HPA axis dynamics is an interesting topic in its own right. First of all, in Chapter 2, differential HPA axis reactivity to psychosocial stress with progression of depression was found, suggesting that depression and HPA axis functioning interact over time. Because of the semi-longitudinal design (i.e. multiple assessments of depressive symptoms, one assessment of HPA axis reactivity), it cannot be inferred from these findings what is cause and what is consequence. But together with the observation that the chance to become depressed increases with every subsequent episode (Kendler, Thornton, & Gardner, 2001; Kendler, Thornton, & Gardner, 2000; Morris, Ciesla, & Garber, 2010; Post, 1992) and reduced hippocampal size with progression of depression (Lorenzetti et al. 2009), the findings point in one direction. That is, depressive episodes and the accompanied stress can cause changes in the brain, such as hippocampal atrophy (Lorenzetti, Allen, Fornito, & Yücel, 2009). Consequently, this leads to reduced negative feedback of the HPA axis and hyporeactivity of the HPA axis (Sapolsky, 2000). In turn, this may increase the risk to become depressed again. Furthermore, individual differences were found in the temporal relationship between cortisol and affective states, in the sign, the direction and timing of the effects (Chapter 5). Interestingly, some depressed individuals showed decreases in positive as well as negative affect in response to cortisol, while an increase in

negative affect was expected. This result fits with the idea of a biphasic response to stress (Gilbert, 2001; Henriques, 2000; Selye, 1976). According to this idea, the first response to a threat is to invigorate behavior. This can be done by increasing negative emotions (e.g. irritability, aggression, fear). However, if such a response does not work eventually (i.e. the threat does not dissipate), the second response is to immobilize, to prevent a too far deviation from the preferred physiological state (allostatic overload) (Gilbert, 2001; Selye, 1976). Speculatively, some of the findings in Chapter 2 and 5 (i.e. hyporeactivity of the HPA axis in individuals with chronic depressive symptoms and decreased emotional responses to cortisol in some of the depressed individuals) may represent physiological/behavioural responses in a later stage of continued chronic stress. I will elaborate on this below, using recent insights into the HPA axis as a dynamic system.

Various experimental studies, supported by simulation studies, have shown that the HPA axis is a dynamical system, with circadian and ultradian rhythms that are important for maintaining homeostasis, stress responsiveness, and optimal metabolic and cognitive function (Lightman & Conway-Campbell, 2010; Spiga, Walker, Terry, & Lightman, 2014; Spiga & Lightman, 2015). Although the presence of ultradian rhythms of cortisol have been known for quite some time, their importance for health and disease has only become clear more recently (Lightman & Conway-Campbell, 2010). In humans and rats (in which ultradian rhythms have been studied mostly), cortisol fluctuates with approximately 1-hour rhythms, and tissues that are regulated by cortisol require oscillating concentrations of cortisol for optimal responses (Spiga et al., 2014).

HPA axis dynamics have been modelled in two simulation studies and successfully tested against empirically derived experimental data (Markovic, Cupic, Vukojevic, & Kolar-Anic, 2011; Walker, Terry, & Lightman, 2010). Subsequently, the model has been used to predict what happens to HPA axis functioning under various levels of chronic stress, as indexed by (continuously) elevated levels of CRH. It predicted that this induces qualitative changes to HPA-axis dynamics, such as changes in amplitudes and frequencies of ultradian oscillations. Specifically, it was found that at moderate levels of chronic stress, the ultradian cortisol rhythm speeds up and HPA axis responsiveness increases, whereas at high levels of chronic stress, the ultradian rhythm slows down and HPA axis responsiveness decreases, up to a level that responsiveness is lost. A similar pattern was found for rats: rats that were infused with constant levels of corticosterone showed a suppressed ACTH response to stress, compared to rats infused with vehicle and pulsatile corticosterone (Sarabdjitsingh et al., 2010a; Sarabdjitsingh et al., 2010b). Hence, the available evidence suggests that both increased and decreased HPA axis reactivity can occur under stressful circumstances, and that severe, chronic stress generally leads to decreased reactivity and loss of ultradian and circadian rhythmicity.

It is not known whether changes in HPA axis dynamics (by varying levels of chronic stress) are reversible or (partly) irreversible. As mentioned above, tissues require oscillating concentrations of cortisol for optimal functioning. Changes in the dynamics cause alterations in receptor localization, rates of chemical reactions and transporting processes in different brain regions, such as the hippocampus, amygdala and pre-frontal cortex (De Kloet, Joëls, & Holsboer, 2005; Joëls & Baram, 2009; McEwen, 2008). Some of these processes may result in long-lasting changes (e.g. hippocampal damage). Hence, the conditions for returning to the original physiological state have changed, such that a simple cessation of stress is not enough to return to the original dynamic equilibrium (Markovic et al., 2011). Because of that, even after stress has terminated a new (less dynamic) state may arise, with a less efficient dynamic regulatory mechanism (Markovic et al., 2011). As a consequence, allostatic overload, i.e. the incapability of the HPA axis to cope with the “external pressure” (McEwen, 2000), may be reached more easily.

Taking these results back to my own findings, individuals with chronic depressive problems may have reached a state in which enduring chronic stress has not only temporarily reduced HPA axis reactivity, but has also changed HPA axis dynamics into a system that is less flexible as a whole, and more often crosses the boundaries (also termed adaptive capacity, e.g. Koolhaas et al., 2011), causing wear and tear of the body (allostatic load) (McEwen, 2008). This makes them vulnerable for future stress-related diseases. Speculatively, such individuals may also ‘chose’ more often for an immobilization strategy in the face of stress, instead of becoming active, to prevent a too far deviation from the preferred physiological state, which may explain the decreased negative affective responses to cortisol in some of the depressed individuals.

To conclude, the findings presented here, and those of others, suggest that HPA axis dynamics play an important role in the pathophysiology of depression. Future studies with larger samples, combining intensive sampling strategies with yearly follow-up assessments, may assess whether reduced cortisol responses to stress and decreased emotional responses to cortisol are the result of chronic stress, and whether this goes together with other characteristics of a ‘worn out’ HPA axis. Also, they may assess the long-term adaptive capacity of the HPA axis, i.e. the possibility that shifts in HPA axis dynamics due to chronic stress return to a more dynamic equilibrium, by the passage of time or by treatment. Lastly, it may be further examined whether losing dynamics, thereby reaching a state of allostatic overload, also marks the beginning of a disease state, such as depression.

PART 2: HPA AXIS FUNCTIONING AS A MEDIATOR OF THE RELATIONSHIP BETWEEN PHYSICAL ACTIVITY AND DEPRESSION

Summary and key findings

Exercise training not only reduces HPA axis reactivity to physical, but also to psychosocial stress. This finding has led researchers to pose the idea that HPA axis reactivity may play a role in the antidepressant effects of exercise (e.g. van der Rot, Collins, & Fitterling, 2009). In the second part of this thesis, I examined whether physical activity, a potent activator and modulator of the HPA axis, exerted antidepressant effects, and whether these effects were mediated by HPA axis functioning. Specifically, in Chapter 6, I examined whether exercise habits predicted somatic and affective symptoms cross-sectionally and two years later, and whether this pathway was mediated by the cortisol response to a standardized social stress test (the same as used in Chapter 2). Similar to a study of Stavrakakis et al. (2012), a relationship was found between exercise and affective but not somatic symptoms of depression. While exercise habits were negatively related to HPA axis reactivity to psychosocial stress, the latter was not related to affective symptoms. Because of the findings in Chapter 2, I also repeated the analysis without the participants with chronic depressive problems, but this did not change the results.

Cortisol may also play a more immediate role in the beneficial effect of physical activity on depression, by influencing affective states in daily life. In Chapter 7, it was firstly addressed whether physical activity influenced positive and negative affective states in depressed and non-depressed individuals in daily life. This appeared to be so in a subset of individuals, of which some were depressed and some were not. Interestingly, the direct effect of physical activity on positive affect was positive for nearly all individuals, while the direct effect on negative affect was more variable (i.e. both positive and negative effects). Furthermore, the lagged effects of physical activity on positive and negative affect were heterogeneous as well. Those individuals who significantly benefitted from physical activity in terms of their affect, were further examined in Chapter 8. Specifically, it was examined whether cortisol mediated the relationship between physical activity and affective states. Little support was found for this hypothesis, because a mediatory pathway was found in only one out of nine individuals.

Can we exclude HPA axis functioning as a potential mediator of the relationship between physical activity and depression?

No support was found for HPA axis functioning as a mediator of the relationship between physical activity habits and depressive symptoms (Chapter 6). No other studies examined a mediatory pathway of the HPA axis between long-term exercise habits and depressive symptoms. However, one other study (also in adolescents) assessed the effect of an 8-week physical activity intervention on depressive symptoms and 24-hour cortisol levels. They found an antidepressant effect of physical activity, and physical activity was also associated with reduced 24-hour cortisol levels (Nabkaso-

rn et al., 2006). However, it is unclear whether reduced cortisol levels were a cause or consequence of depressive symptoms, or neither of these options. In the study of Chapter 8 also no support was found for a mediatory pathway through cortisol in the relationship between daily life physical activity and affective states. One other study in humans assessed cortisol as a mediator of the short-term relationship between physical activity and mood. In particular, these researchers examined (psychosocial) stress-induced cortisol and mood responses after physical activity (Zschucke, Renneberg, Dimeo, Wüstenberg, & Ströhle, 2015). They did not find a mediatory pathway, however, they found another thing: physical activity increased positive affect acutely, and this in turn was related to a reduced cortisol response to subsequent psychosocial stress. To conclude, the results of the few available studies suggest that cortisol and affect can both be influenced by physical activity, but they do not support a mediating role of cortisol.

In this thesis, it was hypothesized that chronic or acute physical activity would reduce HPA axis (re)activity, and that this in turn would reduce depressive symptoms. The complex dynamics of the HPA axis in health and disease as described in the previous section challenge this hypothesis. First of all, according to the previously described dynamic behavior of the HPA axis, reduced HPA axis reactivity may mean many things. It may indicate reduced perception of stress, by for example increased coping or increased perception of controllability, but it may also indicate reduced adaptive capacity. Hence, whether a lower stress response is beneficial for health depends on the conditions under which it is lowered. Furthermore, the evidence for reduced HPA axis reactivity in physically fit, compared to non-fit individuals comes mainly from healthy, non-depressed individuals (Rimmele et al., 2009; Rimmele et al., 2007), presumably with high adaptive capacity (i.e. sufficient HPA axis dynamics). It cannot be a priori assumed that physical activity has the same effect in depressed individuals. Hence, physical activity may still improve HPA axis functioning via other ways than reducing the stress response, and this may depend on the current state of HPA axis dynamics of the participant. Another option is, as described above, that physical activity immediately increases affective states via other mechanisms than the HPA axis, and that this reduces psychological stress and the accompanied physiological response. This in turn reduces allostasis and prevents allostatic overload, thereby positively impacting on other systems, such as the immune system. Future time-series studies may sample over shorter intervals, taking into account ultradian rhythmicity, to better understand the effect of physical activity on the HPA axis, as well as the influence of HPA axis functioning on affective states. Moreover, target systems of the HPA axis, such as the immune system could be assessed as well.

GENERAL

Methodological considerations and limitations

In Chapter 2 and 6, group designs were used to assess long-term relationships. Hence, some individual differences may have gone unnoticed. Moreover, the (semi)-longitudinal designs were not optimal for assessing changes over time. In Chapter 2, other evidence, such as kindling or sensitization (i.e. the chance to become depressed increases with every subsequent episode, Kendler et al., 2001; Kendler et al., 2000; Morris et al., 2010; Post, 1992) and reduced hippocampal size with progression of depression (Lorenzetti et al. 2009), also point towards changes in the HPA axis over time in depressed patients. Nevertheless, it is still possible that the differences in HPA axis reactivity constitute a depression-predisposing trait that is present from early childhood (e.g. Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). Assessing whether HPA axis reactivity changes over time within individuals is a big challenge; individuals should be repeatedly assessed for stress reactivity. This can be done under standardized conditions or in daily life. In case of the first option, a standardized stress task should be used repeatedly. However, repeated stress tasks have the problem that the task becomes more predictable to the participant with every repetition, and hence perceived stress decreases (Koolhaas et al., 2011). In the case of the second option, participants take part in several intensive time-series studies to assess their average (individual) stress-reactivity for every study period. This requires much perseverance from the participants. Moreover, for every assessment period, many cortisol samples per person need to be analyzed ($T > 50$), which requires a large budget. As also discussed in the section ‘Intensive time-series approaches in psychoneuroendocrinological research: Practical challenges and possible solutions’, future innovations may increase feasibility of the intensive time-series approach for psychoneuroendocrinological research.

In Chapter 5, 7 and 8, I used a time-series design with 90 measurements per individual, which has the great strength that associations can be assessed within individuals over time. However, the studies had a small sample size, meaning that the findings could not be generalized to the population at large. Only with many replications of single-subject studies, general laws can be uncovered (Lamiell, 1998). Related to this is the limitation that there were too few subjects to identify meaningful subgroups of individuals with similar associations. If the groups would have been larger, we could have assessed more thoroughly why individuals differed in their temporal relationships.

A final important limitation is the notion that the results of the time-series models were sometimes strongly influenced by outliers. Although we tried to accommodate this by using dummy variables for outliers in the VAR models, this suggests that in some cases, at least for cortisol, longer time-series would be necessary to get more reliable models. Currently, not much is known about the minimum number of measurements required for performing time-series analysis on cortisol data. While simula-

tions have been successful with >30 measurements (Lütkepohl, 2005), the reliability probably depends highly on the parameters under study, and the intervals over which these parameters are sampled. With the current sampling design (3 measurements a day), the ultradian rhythm was not adequately controlled for. This introduced additional noise. In sum, longer time series are advised if cortisol is sampled three times a day like in the MOOVD study.

Advantages of the time-series approach in psychoneuroendocrinological research

In ecological momentary assessment studies, effects are usually assessed contemporaneously or over one specific time lag by means of mixed-model analysis. This may give the false impression that one variable influences the other in a certain way, while over longer time periods the net effect is negligible or even the opposite. A great advantage of the time-series approach is that it allows to assess in detail the temporal relationship over multiple lags at once and the net effect over a certain time period (Lütkepohl, 2005). If cortisol is sampled frequently enough, rapid as well as slow effects of natural fluctuations in cortisol on other fluctuating factors (e.g. emotions, behaviors), and vice versa, can be estimated precisely. This advantage is illustrated in the following hypothetical example. An ecological momentary assessment study with hourly measurements indicates that an increase in cortisol levels results in reduced negative affect one hour later in a male participant. Based on these results, he would be given the advice to engage in stressful activities to improve his mood. However, further examination of effects at higher lags suggests that over 2 - 3 hours an increase in cortisol leads to an increase in negative affect. To examine whether the net effect over time is positive, negative or negligible, impulse response function analysis is used. The results show that an impulse in cortisol induces a decrease after 1 hour, and an increase in negative affect after 2- 3 hours. In addition, negative affect increases further over the next couple of hours (because of positive autocorrelation in negative affect), resulting in a large and positive net effect after 6 hours. Hence, based on these results, the best advice to this man would be to avoid engaging in stressful activities, not engaging in them. Taken together, time-series analysis and the accompanied tools, seem ideal for further exploration of the dynamic interplay between natural fluctuations in cortisol and daily life emotions and behaviours.

At the group level, relationships in daily life have been found to be predictive of future depressive episodes and treatment response (Wichers, 2014). These predictions may be improved, by using a bottom-up approach, first estimating relationships at the individual level with time-series analyses, and thereafter finding common patterns for (sub)groups of individuals (Molenaar & Campbell, 2009). Furthermore, the dynamics of daily life relationships (including, but not confined to cortisol), as captured by the impulse response function analyses, have not been previously used to predict clinical outcome, and may be of value in this respect as well.

Intensive time-series approaches in psychoneuroendocrinological research: Practical challenges and possible solutions

In the MOOVD study, the collection of data for one participant involved preparation of the study materials, an introduction interview (about 2 hours), four visits to the participants' homes to collect saliva samples (30 min – 4 hours), four visits to the lab (1 hour), a final interview session (30 min), and making a short report about the participants' daily behaviors, thoughts and feelings, and their temporal relationships (2-3 hours). Especially the weekly visits to the participant's homes for saliva collection and the construction of feedback make it time consuming, compared to other types of studies. Future time-series studies may need larger samples of participants to search for meaningful subgroups of individuals. For these studies, it would be useful to reduce the investment for researchers, without putting more work in the hands of the participants. Luckily, progress is being made in the areas of research and technology. For the electronic questionnaires, a PsyMate was used that needed programming for every participant, and the data were stored on a computer only after the participant completed the study. At this moment, mobile phones are being used in most studies to collect data (e.g. HowNutsAreTheDutch, Blaauw et al., 2014). In this way, participants can fill out electronic questionnaires easily, and the results are automatically (in real-time) collected and stored in an online database. In that same study, personal reports are automatically created by built-in web-based software. Although personal feedback is not a necessary feature for conducting idiographic research, it may be beneficial for the motivation of the participant to (thoroughly) complete the study. For the long-term collection, storage and analysis of cortisol saliva samples, there are no time-saving solutions available yet. Nevertheless, progress is being made in this field as well. For example, an automated sampling system has been developed, which can collect timed samples of microdialysis fluid over 24 hours in individuals living their everyday lives (Bhake et al., 2013). Similar to salivary cortisol, subcutaneous tissue contains free unbound cortisol, which is not bound to carrier proteins and has access to tissues and their receptors. This means that it is suitable as a substitute for salivary cortisol measures. Possibly, in the near future similar systems will be manufactured that can last longer than 24 hours.

Another challenge is the analysis of time-series data of a large number of individuals (i.e. larger than in the MOOVD study). Where a nomothetic study requires one or a few analyses to be conducted in a sample of participants, idiographic studies requires at least one analysis to be conducted for every participant. For example for Chapter 5, I conducted 60 different analyses, which is still feasible. However, if there would have been 100 participants instead of 30, which is required to differentiate between subgroups of individuals, I would have had to run 200 individual analyses. This would already be much less feasible. Fortunately, also in this respect progress has been made. For example, a special analysis package called GIMME has been written to find meaningful subgroups of individuals with common dynamic models (Moleenaar, 2013). A drawback of this package is that it uses information about the direction of the relationship to establish the dynamic models, but not about the sign of the

relationships under study. Hence, individuals with similar dynamic models may have opposing effects of one variable on the other. While in some research areas signs of relationships may not be that relevant, in psychology and psychiatry they often are. Thus, only for answering particular research questions about directionality of effects this package may be useful. Another advancement in the field of time-series analysis is the development of AutoVar, web-based software that automates the steps that would otherwise be performed manually during vector autoregression (VAR) analysis (Emerencia et al., 2014). This application underlies the automated personalized feedback that is generated in the HowNutsAreTheDutch study. Although AutoVar provides the basis to run VAR analysis, as of to date, some more advanced options are still missing with regard to analysis (e.g. log transformation for one or a few variables in the system, finding common pathways in groups of individuals) and results (e.g. providing results of impulse response function analysis). Possibly, in the near future these and many more functionalities will be incorporated, so that AutoVar can also be used for other purposes than automated feedback.

A problem that pertains to both manual and automated time-series analysis is the lack of variation in some of the variables under study. Time-series analysis requires variation in the measures under study. However, for some individuals the variables of interest barely fluctuate. For example, in Chapter 5 some non-depressed individuals lacked variation in negative affect. Therefore, no statements could be made regarding the influence of negative affect on cortisol for these individuals. In our study, the lack of variation in negative affect was easily detected, because this was accompanied by a high skewness; non-depressed individuals tended to score consistently low on negative affect, and this could not be resolved with a log transformation. Hence, these individuals were excluded from the analysis. However, a variable can also be rather normally distributed and still have little variation. In the AutoVar program previously described, these variables are now identified by using the mean square of successive differences (MSSD), which is a measure that combines autocorrelation and variability in one score. Identifying non-fluctuating variables is important to prevent conducting analyses with potentially misleading results. Most ideally, however, one would want to prevent all together that an analysis cannot be performed. Therefore, when designing a diary study, it is important to include variables in the diary that 1) are of relevance to the research question; and 2) are expected to fluctuate in all individuals of the examined study (sub)samples.

A final and important challenge is the financial part of assaying large numbers of saliva samples for cortisol or other biomarkers. For the MOOVD study, almost all of the available budget was spent on assaying cortisol, α -amylase and melatonin. While there were 54 participants that completed the study, due to financial constraints only for 30 of them assays could be conducted (which equals 2700 samples). This is a problem that is not easily tackled. One thing that can help to reduce the price is to collaborate with researchers from the laboratory department, which also brings some expertise on (clinical) chemistry in the team. In any case, a good advice is to

be informed early during the setup phase of the study on pricing, so that funds can be collected early in the process.

Clinical relevance

The results of this thesis suggest that depression research and treatment could benefit from a more individualized (tailor-made) approach. For example, in Chapter 5, different processes were at play in different individuals; cortisol increased negative affect in some individuals, but not in others. Hence, a particular physiological process may induce depressive symptoms in only a subset of individuals, and this may depend on the individual's genetic makeup and past experiences. In addition, there may be multiple physiological processes that (potentially) induce depressive symptoms. This possibility, of personalized etiological pathways to depression cannot be explored in group studies, because effects are aggregated. Intra-individual analyses may provide further insight into personalized etiological pathways to depression.

In Chapter 8, some individuals benefitted from physical activity in terms of their affect, while others did not. Possibly, physical-activity based interventions can also benefit from a more personalized approach. Although this idea is appealing, the application of tailor-made interventions in clinical practice needs additional work. In the case of physical activity, future intensive time-series studies in larger groups of individuals could identify subgroups that benefit most from physical activity. It can be subsequently addressed what it is that determines why these individuals benefit and others do not. In addition, time-series approaches could be implemented in clinical care (e.g. while on a waiting list), using automated time-series analyses and personalized feedback, which are already available for research purposes (Emerencia et al., 2014). This feedback can aid clinicians in the decision whether to implement physical activity interventions for depressed mood or not.

Conclusions

In the previous Chapters, it became clear that HPA axis dynamics constitutes more than inconvenient temporal variance that should be dealt with when examining the role of HPA axis functioning in depression. The dynamic behaviour of the HPA axis itself, and particularly the loss of dynamics, may play a key role in the development and progression of stress-related disorders, such as depression. This idea needs further examination, so there are many new opportunities for research in this area. New types of study designs with high frequency sampling within individuals may fit this line of research better than traditional nomothetic designs with a few observations, because they have the tools to examine various aspects of these dynamics. However, ultimately, many repeated measurements on many individuals should be combined. Having the best of both worlds (i.e. the inter- and intra-individual approach), HPA axis dynamics can be compared within individuals over time as well as across individuals, and thereafter linked to depression onset, progression and remission.

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