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The temporal dynamics of cortisol and affective states in depressed and non-depressed individuals

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ABSTRACT

Objectives: Cortisol levels have been related to mood disorders at the group level, but not much is known about how cortisol relates to affective states within individuals over time. We examined the temporal dynamics of cortisol and affective states in depressed and non-depressed individuals in daily life. Specifically, we addressed the direction and timing of the effects, as well as individual differences.
Methods: Thirty depressed and non-depressed participants (aged 20–50 years) filled out questionnaires regarding their affect and sampled saliva three times a day for 30 days in their natural environment. They were pair-matched on age, gender, smoking behavior and body mass index. The multivariate time series (T = 90) of every participant were analyzed using vector autoregressive (VAR) modeling to assess lagged effects of cortisol on affect, and vice versa. Contemporaneous effects were assessed using the residuals of the VAR models. Impulse response function analysis was used to examine the timing of effects.
Results: For 29 out of 30 participants, a VAR model could be constructed. A significant relationship between cortisol and positive or negative affect was found for the majority of the participants, but the direction, sign, and timing of the relationship varied among individuals.
Conclusion: This approach proves to be a valuable addition to traditional group designs, because our results showed that daily life fluctuations in cortisol can influence affective states, and vice versa, but not in all individuals and in varying ways. Future studies may examine whether these individual differences relate to susceptibility for or progression of mood disorders.

1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis adapts the body to stress conditions by mobilizing energy and inhibiting non-emergency processes such as sleep, sexual activity, and growth (Chrousos, 2009). This system is vital for survival, and also thought to play an important role in the onset and progression of depression (e.g. Holsboer and Ising, 2010). By some, the HPA axis is even referred to as the final common pathway for most of the symptomatology of depression (e.g. Bao et al., 2008). This proposition is supported by the indirect evidence that stressful life events, which are capable of triggering the HPA axis, often precede depressive episodes (e.g. Kendler et al., 2000).

Cortisol is an end product of the HPA axis. Because of its numerous targets in the body, among which are brain areas involved in emotional reactivity, it is much researched in the context of depression. Many of these studies have been observational, of which the results were assessed in a meta-analysis by Stetler and Miller (2011). They concluded that, overall, there seems to be a tendency towards increased cortisol levels in depressed samples, albeit with considerable heterogeneity between studies. Observational studies with a single or a few measurements are useful to detect general patterns and traits in the population. However, cortisol has a highly dynamic nature (e.g. Booij et al., 2015), and the negative affect experienced by depressed individuals shows daily and context-dependent variation as well (e.g. Myin-Germeys et al., 2009; Wirz-Justice, 2008). Hence, these studies do not reveal information about the dynamic relationship between cortisol and depressive symptoms in daily life (Hamaker, 2012).

Depressive symptoms are characterized by increases in negative affect and decreases in positive affect (Clark and Watson, 1991). Improvement of depressive symptoms might therefore rely on lowering negative affect as well as on increasing positive affect in depressed individuals. Peeters et al. (2003) studied associations between negative affect and cortisol in daily life using an experi-

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ence sampling protocol (ESM) (Csikszentmihalyi and Larson, 1987). Besides having high ecological validity, ESM has the added benefit that the small time interval between measurements reduces recall bias (de Vries and Csikszentmihalyi, 2006; Telford et al., 2012). In short, Peeters et al. (2003) found that negative affect was related to higher cortisol levels in the healthy but not the depressed group. van Eck et al. (1996) did a similar study in healthy individuals with low and high levels of perceived stress, including measures of both positive and negative affect. Regardless of the perceived stress level, they found a positive association between negative affect and cortisol, and no associations with positive affect. In a larger sample from the general population, however, Smyth et al. (1998) did find a negative association between positive affect and cortisol.

The design and analytical methods that were used in these studies did not allow statistical inference about the direction of the relationships. Experimental evidence showing that exposure to stressful situations increases cortisol levels (Dickerson and Kemeny, 2004; Kirschbaum and Hellhammer, 1989) favors the idea that increases in negative and/or reductions in positive affect precede increases in cortisol. As such, in many ESM studies the results are interpreted in this way (e.g. Adam, 2006; Peeters et al., 2003; van Eck et al., 1996). On the other hand, studies in rats have shown that increased cortisol levels may precede increases in negative affect (Lightman and Conway-Campbell, 2010). Thus, the relationship may also be reversed to what is generally assumed, or reciprocal.

In the above-mentioned ESM and experimental studies, effects were estimated over a limited time frame (e.g. minutes up to several hours). This restrains knowledge about the dynamics of the relationship and about the *net* effect of cortisol on affect over a longer time frame, and vice versa. Studies into the autocorrelation of negative and positive emotions (emotional inertia) in depressed versus non-depressed individuals suggest that depressed individuals show relatively large autocorrelation in both positive and negative affect, compared to non-depressed individuals (e.g. Koval et al., 2012; Kuppens et al., 2010). This suggests that an initial subtle change in affect to an increase in cortisol may eventually result in a relatively large net change over a longer time period, especially for depressed individuals. With regard to the response pattern of cortisol, evidence suggests that the cortisol response to stress is cyclic (i.e. fluctuating around a certain set point) (e.g. Schubert et al., 2006, 2003, 2012). This may relate to cortisol's crucial role in the maintenance of the body's homeostasis. To our knowledge, no study has examined the temporal aspects of the relationship between affect and cortisol in detail, that is, including the direction of the effects, potential feedback loops, and the time period over which the effects take place.

Recently, sophisticated regression techniques for the analyses of time-series data have become available in the field of psychiatry. These techniques are suitable for explaining variance within single individuals instead of variance in the population. With sufficient data points ($T > 60$), time-lagged associations between variables as well as the temporal ordering of the effects can be assessed in detail, at the level of the individual. Moreover, so-called 'impulse-response functions' can be used to predict how an increase in one variable can work through the system over time to result in dynamic changes in other variables. This approach can reveal the timing and direction of the effects, as well as possible feedback loops (Brandt and Williams, 2007).

Adopting an intensive time-series approach has another benefit. Because individuals are examined one by one, individual differences that would go unnoticed in group designs can be revealed. Depression can present very differently in different individuals, with regard to both symptoms and severity (van Loo et al., 2012). In addition, various studies suggest that only a subgroup of depressed individuals (e.g. individuals with melancholic depression) has increased cortisol levels (Lamers et al., 2012; Sachar et al., 1970), and that other subgroups (e.g. individuals with severe or chronic depression) may even show the opposite association (Booij et al., 2013; Burke et al., 2005; Oldehinkel et al., 2001). Because of such heterogeneity, associations at the group level may be small and seemingly irrelevant, whereas in certain individuals the association may be large and meaningful. The present study complements the available literature in a unique way by examining the temporal dynamics of cortisol and mood in daily life, and potential individual differences therein. For this purpose, we adopted an intensive time-series approach in which we monitored 30 pair-matched depressed and non-depressed participants three times a day for 30 days in their natural environment.

Because group-level evidence has been found both for an influence of affective states on cortisol and of cortisol on affective states, we did not adopt specific hypotheses about the direction of the relationship within individuals. Rather, the study was designed to explore whether the relationship between cortisol and affect is bidirectional for all individuals, or whether for some individuals the relationship is particularly evident in one direction. Furthermore, we examined whether individual differences in the sign and size of the relationship between cortisol and affect were related to individual differences in depression characteristics. Finally, with regard to the temporal dynamics of the effects, we hypothesized that the response of affect to an increase in cortisol would show a steady increase or decrease over time, particularly in depressed individuals, resulting in a large net change over several days. Regarding an increase in affect on cortisol, we hypothesized that it would result in cyclic response pattern of cortisol, resulting in a relatively small net effect over several days.

2. Methods

2.1. Participants

The sample was part of the 'Mood and movement in daily life' (MOOVD) study, which was 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. Of the 62 participants who started the study, 4 participants dropped out early. Another 4 participants completed the study but did not have enough valid physical activity or diary measurements ($T < 60$). This could be due to non-compliance, technical problems, or protocol violations. This left 54 participants for further study. Participants with and without a depressive disorder were pair-matched on gender, smoking, age, and BMI. The present study was based on the subsample for which cortisol and α-amylase concentrations had been determined, consisting of 15 matched pairs. They were the first participants completing the study, and did not differ significantly from the remaining participants on BDI score, gender, age, BMI and smoking status ($p > 0.05$). All matched pairs had the same gender and smoking status, while age and BMI differed on average 3.1 years (SD = 2.4) and 3.4 kg/l^2 (SD = 2.6), respectively. We discarded the data of one depressed participant because of extreme values of cortisol, presumably due to a chronic infection, leaving 29 participants for the analysis. Pairs are numbered 1–15; numbers with a D refer to the depressed participants, and numbers with an N refer to the non-depressed participants.

The depressed participants were recruited from patient groups of the Psychiatry Department of the University Medical Center Groningen (UMCG) and the Center for Integrative Psychiatry (CIP) in Groningen, The Netherlands. The non-depressed participants