University of Groningen

Dynamics of the human stress system in depression

Booij, Sanne

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Cortisol as a potential mediator
of the influence of physical activity
on affective states in daily life

S.H. Booij, E.H. Bos, P. de Jonge, A.J. Oldehinkel

ABSTRACT

Background
Using an intensive time-series approach, we explored whether fluctuations in cortisol mediate the relationship between physical activity and affective states in daily life at the individual level. We did so for nine individuals whose affect benefitted from physical activity as previously assessed in Stavrakakis et al. submitted.

Methods
The participants (age 20-50) wore accelerometers continuously, and filled out electronic diaries and sampled saliva three times a day for 30 days. For each participant, the amount of energy expenditure (EE; kcal/min) was summed across all sampling minutes over one day segment (i.e. 360 minutes per segment). The multiple time series of every individual (i.e. EE, cortisol, and positive or negative affect) were analyzed using vector autoregressive (VAR) modeling. Depending on the temporal relationship between physical activity and affect previously found, direct (i.e. within 6 hours) or direct and lagged (6 hours – 1 day) mediation effects were assessed.

Results & Conclusion
The results did not support a mediatory pathway from physical activity to affect via cortisol, because we found this mediation pathway in only one of the nine participants. Mediatory pathways over smaller time intervals, and individual differences in the mechanisms involved in the antidepressant effect of physical activity may explain the negative findings.

INTRODUCTION

Studies suggest a beneficial effect of physical activity on depressive symptoms, and in multiple ways. On the one hand, physical activity seems to have a long-term effect: exercise interventions of several weeks to months reduce depressive symptom levels afterwards (Rimer et al., 2012), and having an active lifestyle predicts low levels of depressive symptoms a few years later (Stavrakakis, de Jonge, Ormel, & Oldehinkel, 2012). On the other hand, there seems to be a short-term effect as well: physical activity can improve affective states within the context of daily life (Kanning, Ebner-Priemer, & Schlicht, 2013; Stavrakakis et al., submitted), which subsequently prevents or ameliorates depressed mood (e.g. Geschwind et al., 2011; Wichers et al., 2010).

The antidepressant effect of physical activity is poorly understood. One potential physiological mechanism involves the hypothalamic-pituitary-adrenal (HPA) axis, one of the major stress systems of the body that functions to maintain energy homeostasis. This system is thought to play an important role in the onset and progression of depression (e.g. Holsboer & Ising, 2010). Trained individuals show reduced cortisol responses to psychological stress, compared to non-trained individuals (Rimmele et al., 2007). Therefore, in a prospective cohort study, we tested the hypothesis that the HPA axis responses to psychosocial stress would mediate the relationship between exercise habits and depressive symptoms (Booij, Bos, Jonge, & Oldehinkel, 2014), but did not find support for such a mediatory pathway.

Instead of long-term changes in HPA axis functioning, subtle fluctuations in cortisol may play a role in the effect of physical activity on depressive symptoms, by influencing affective states in daily life. In rats, physical activity reduced cortisol secretion to ongoing or recent stressors (Starzec, Berger, & Hesse, 1983). In humans, physical activity reduced the cortisol response to subsequent psychosocial stress (Zschucke, Renneberg, Dimeo, Wüstenberg, & Ströhle, 2015). In turn, this reduction in cortisol response may alter functioning of emotional circuits in the brain and, hence, influence affective states (Salmon, 2001; Sarabdjitsingh et al., 2010). In a previous daily diary study with continuous actigraphy, we found that the influence of physical activity on affective states varied among individuals; while it positively influenced affect in some individuals, it did not do so in others (Stavrakakis et al., submitted). Furthermore, in some individuals, the effect of physical activity was relatively direct (i.e. physical activity levels in the past 6 hours influenced subsequent affect), while in others it was delayed. The origin of these individual differences is not well understood; among other things, genetic makeup, physical fitness, and contextual factors may play a role (e.g. Mata et al. 2010; Berlin et al. 2006; Harvey et al. 2010). Nevertheless, these findings highlight the importance of studying associations within individuals, instead of groups. Hence, we used an intensive time-series approach to explore whether fluctuations in cortisol mediate the relationship between physical activity and affect at the individual level, and we did so for those individuals of the previous study whose affect benefitted from physical activity (Stavrakakis et al. submitted).

In line with the previous study, physical activity was summed over 6 hour intervals, and direct (i.e. up to 6 hours) as well as lagged (6 hours – one day) effects were assessed. We expected the average direct and lagged effect of physical activity on cortisol to be negative. However, it is known that intense or prolonged physical activity may initially increase cortisol levels (e.g. Jacks, Sowash, Anning, McGloughlin, & Andres, 2002), before they return to baseline and even drop below that (e.g. Hackney & Viru, 1999). The reported dissipation time varies, but levels usually return to baseline after approximately 60 minutes (e.g. Harte, Eifert, & Smith, 1995; Shaner et al., 2014). Because of this combination of effects, we expected the direct effect to be weaker than the lagged effect. Finally, we expected a positive influence of cortisol on negative affect, and a negative influence of cortisol on positive affect.

METHODS

This study was conducted in a subsample of the participants of the 'Mood and movement in daily life' (MOOVD) study. Depressed and non-depressed participants (age 20-50, n=56) were intensively monitored in their natural environments for 30 days, by means of electronic diaries, saliva sampling, and continuous actigraphy. The multiple repeated measurements per individual (T=90) allowed assessing within-person temporal relationships between variables at the individual level. A previous study from our group, in the first 20 participants of this sample, revealed that in some individuals physical activity improved affective states, while in others there was no or even a negative influence (Stavrakakis et al., submitted). The sample of the present study consisted of the nine participants for whom we found a beneficial influence of physical activity on affective states. More specifically, physical activity reduced negative affect in three participants (participants 1-3), increased positive affect in five (participants 5-9), and did both in one (participant 4).

Participants completed questionnaires on an electronic diary, the PsyMate (PsyMate BV, Maastricht, The Netherlands) (Myin-Germeys, Birchwood, & Kwapil, 2011), for 30 days. The PsyMate was programmed to generate beeps at three predetermined moments a day with equidistant intervals of 6 hours (i.e. in the morning, the afternoon, and the evening). After every alarm beep, the participants were asked to fill out the electronic diary. Among other things, the electronic diary questionnaire contained 14 items on mood, which were adopted from Bylsma et al. (2011). From these items, rated on a 7-point Likert scale, positive and negative affect scores were computed by averaging the scores on the positive and negative affect items, respectively. Saliva was collected while completing the diary, by means of a synthetic collection device, the Salivette®. Participants were not allowed to eat or drink anything except water, nor to smoke or brush their teeth within 30 minutes before saliva sampling. Samples were analyzed by means of online-solid phase extraction in combination with isotope dilution liquid chromatography-tandem mass spectrometry (LC-MS/MS). Activity energy expenditure (EE) data from the ActiCal, which was worn throughout the total

study period, was used as a measure of physical activity. For each participant, the amount of EE (kcal/min) was summed across all sampling minutes over one day segment (i.e. 360 minutes per segment). This resulted in total EE per day segment (kcal/day segment). For further details about the ambulatory assessments regarding physical activity, see Stavrakakis et al. (submitted), and regarding cortisol sampling, see Booij et al. (2015).

The multiple time series of the nine individuals were analyzed using vector autoregressive (VAR) modeling. VAR analysis is especially suitable for investigating the dynamic relationships between two or more variables: inferences can be made about the temporal order of effects, which can involve bidirectional effects and feedback loops (Brandt & Williams, 2007). All three variables in the system (EE, cortisol, and negative or positive affect) were treated as endogenous, which means that they could be both determinant and outcome. Similar to Stavrakakis et al. (submitted), the maximum number of lags included in the models was set to three, which is equivalent to a period of one day. For more details about VAR modeling and a non-technical introduction, see (Brandt & Williams, 2007) and (Rosmalen, Wenting, Roest, de Jonge, & Bos, 2012), respectively.

To account for structurally lower EE values in the morning than in the afternoon and evening – participants spent part of the morning lying in bed – as well as for diurnal rhythms in mood, dummy variables for morning and evening were included in the model (afternoon served as a reference category). Variables for time and the square of time were included if this was necessary to render the series stationary. Total EE was divided by 100 to accommodate the difference in scaling between EE and the other measures. Because the distribution of cortisol was skewed, we chose to log transform cortisol. VAR model assumptions, namely stability of the model, independence, homoscedasticity and normality of residuals, were assessed using diagnostic checks (Lütkepohl, 2005). When one of the tests indicated a violation of the model assumptions, models were adjusted, re-estimated, and re-evaluated, in an iterative model-building process, until all assumptions were met.

To test the significance of the overall lagged effects, the Granger causality Wald test was used. This is a test for the directionality of the influence between two time series (Granger, 1969; Lütkepohl, 2005). The contemporaneous correlations between the variables were retrieved from the residuals of the final models. As the EE measure covered the 6-hour period directly before the saliva sampling, we consider this association as a direct effect of EE on cortisol. Also, cortisol samples reflect HPA axis activity 20 minutes earlier. Since saliva was sampled during the assessment of affect, we consider this association as a direct effect of cortisol on affect. Mediation was defined as a significant effect of EE on cortisol combined with a significant effect of cortisol on affect. If the effect of physical activity on affect in the previous study was lagged for a participant, both lagged and direct mediation effects were assessed (e.g. physical activity may directly influence cortisol levels, but cortisol may influence affective

states over longer time periods). If the effect was direct, only direct mediation effects were assessed (see, Stavrakakis et al. submitted). All analyses were done in STATA 11 using the suite of VAR commands (StataCorp, 2009).

RESULTS

Descriptive statistics
Descriptive statistics are displayed in Table 1.

Table 1. Descriptive statistics of the sample									
	ID1	ID2	ID3	ID4	ID5	ID6	ID7	ID8	ID9
Demographic									
Gender	F	F	M	F	F	F	M	F	M
Age	41	27	40	31	46	41	22	34	24
BMI	22.3	21.9	20.4	22.0	22.2	19.5	20.2	26.9	21.2
Lifestyle									
Self-report exercise (min/ week)	120	240	240	240	0	165	110	240	40
Clinical									
DSM-IV Depression	Yes	No	No	Yes	No	No	Yes	No	No
BDI-II	20	1	7	43	3	3	30	0	0
Ambulatory sampling									
				Mean (SD)					
PA (1-7)	4.48 (0.61)	5.27 (0.73)	4.90 (0.43)	1.22 (0.29)	5.41 (0.53)	5.48 (0.61)	3.70 (0.67)	6.08 (0.52)	4.17 (0.82)
NA (1-7)	1.36 (0.32)	1.51 (0.53)	1.52 (0.39)	5.28 (0.54)	1.04 (0.14)	1.15 (0.17)	2.79 (0.63)	1.05 (0.18)	2.64 (0.72)
EE (kcal/ day seg-ment)	385.4 (167.0)	277.5 (170.4)	241.7 (344.4)	199.2 (127.9)	259.0 (106.8)	294.3 (160.5)	294.1 (239.8)	369.1 (172.9)	122.3 (81.2)
Cortisol (nmol/l)	2.27 (2.56)	3.15 (2.66)	2.71 (1.92)	4.45 (4.73)	2.69 (1.92)	4.13 (3.51)	2.73 (2.22)	2.97 (2.98)	1.78 (1.41)

Note: ID= participant number, F= Female; M= Male; BMI= Body Mass Index; DSM= Diagnostic and Statistical Manual of Mental Disorders, BDI-II= Beck Depression Inventory; EE= energy expenditure; PA= positive affect; NA= negative affect

Mediation analyses

We found a mediation pathway from physical activity to affect via cortisol in one of the nine participants (ID 6; Table 2). Specifically, physical activity had a direct negative effect on cortisol and cortisol had a direct negative effect on positive affect. For two individuals, there was a (borderline) significant direct effect of physical activity on cortisol, but not of cortisol on affect (ID 2, ID 7). For both of the individuals, the effect of physical activity on cortisol was positive. Another three individuals showed a significant effect of cortisol on affect, but not of physical activity on cortisol (ID 3, ID 4, ID 9). For one individual this was a direct positive effect on negative affect (ID 3), for another this was a direct negative effect on positive affect (ID 9), and for the last person this was a lagged (t-1) negative effect on positive affect (ID 4: β = -1.88). Because the latter was the only significant lagged effect, all lagged effects were omitted from Table 2.

Table 2. Pathways from physical activity to cortisol, and from cortisol to negative and positive affect

	Physical activity -> cortisol	Cortisol -> negative affect
	r (direct effect)	*r (direct effect)*
1	-0.08	0.09
2	0.24*	-0.15
3	-0.04	0.25*
4	0.04	-0.08
	Physical activity -> cortisol	**Cortisol -> positive affect**
	r (direct effect)	*r (direct effect)*
4	0.06	0.00
5	-0.19†	0.14
6	-0.25*	-0.25*
7	0.21†	0.13
8	-0.07	0.00
9	-0.07	-0.22*

Note: Underlined values indicate a pathway from physical activity to affect through cortisol.
† p < 0.10, * p < 0.05

DISCUSSION

This study addressed the question whether cortisol mediates the influence of physical activity on affective states in daily life. For this purpose, we examined nine individuals for whom we had previously found a positive influence of physical activity on affective states (see Stavrakakis et al., submitted). The results did not support a mediatory pathway from physical activity to affect via cortisol, because for eight out

of nine individuals cortisol did not significantly mediate the relationship between physical activity and affect.

The one other study in humans that tested whether physical activity acutely influenced affective states via cortisol could not confirm this hypothesis either. Specifically, in this study it was tested whether exercise dampened subsequent psychosocial stress-induced cortisol responses, and whether this in turn enhanced mood after the psychosocial stress task (Zschucke et al., 2015). While they did find a buffering effect of physical activity on stress-induced cortisol release, this did not influence mood immediately after stress.

There may be several reasons why, for most participants, we did not find a cortisol-reducing effect of physical activity. First of all, these participants may have been physically active very often at intense levels immediately prior to saliva sampling. Because of that, both acute increases in cortisol and later decreases in cortisol may have been captured during the sampling period, resulting in small and non-significant average effects. Another (opposing) reason is that participants were not physically active enough. In the study of Zschucke et al., a reduced cortisol response to subsequent stress after exercise was found, but they also found an inverse relationship between the acute cortisol response to exercise and the cortisol response to subsequent stress. This suggests that an increase in cortisol during exercise is necessary for a cortisol-buffering effect later on. Given the daily life settings of our study and the characteristics (i.e. non-athletes) of the participants, it is more likely that the participants rarely reached high intensity activity levels than that they reached it very often. A final reason for the non-significant effect of physical activity that we found in most participants, is that physical activity may reduce cortisol in the context of (considerable) stress only. Because of the daily life settings of our study, some individuals in our study may have rarely encountered stress immediately before or after being physically active. The two previous studies (one in humans, one in rats) that assessed the influence of acute physical activity on cortisol both found a cortisol-reducing effect. However, they particularly assessed the preventive effects of physical activity on stress-induced cortisol (Zschucke et al., 2015) and the palliative effect of physical activity immediately after stress (Starzec et al., 1983).

For most of the individuals, the effect of physical activity on affect was direct, which means that it took place within the same six-hour measurement interval. Indeed, other daily diary studies have assessed the influence of physical activity on affective states at the group level over smaller intervals, and also found a positive influence of physical activity on affective states (Kanning et al., 2013). Moreover, effects of cortisol on brain areas involved in emotional reactivity on non-genomic or genomic actions, can be rather quick (from a few minutes up to a few hours) (De Kloet, Joëls, & Holsboer, 2005). Hence, with smaller sampling intervals, we might have found mediation effects for other individuals as well.

The finding of a mediatory pathway in only one participant may also be explained by different underlying mechanisms in different participants. In group studies, several potential physiological mechanisms have been studied and found to be associated with both physical activity and depressive symptoms, such as endorphins, glucocorticoids, monoamines, and neurotrophins (aan het Rot, Collins, & Fitterling, 2009). It is assumed that these factors produce the mood-enhancing effect of physical activity in all individuals in a similar way. But another option is that particular factors play a larger role in some individuals than in others. While this option is difficult to study in nomothetic group studies, intensive time-series studies including many individuals may shed some light on this matter.

The results must be interpreted in the light of several limitations. Firstly, cortisol may fluctuate (increase as well as decrease) because of physical activity, depending on the timing and intensity of the activity (e.g. Hackney & Viru, 1999; Jacks et al., 2002), hence effects of physical activity on affect may vary as a result as well. As argued above, however, it is not very likely that individuals exercised very intensively within an hour before the measurements often. Second, we used a very general measure of physical activity. Other measures of physical activity may have yielded different results, because the social context, the pleasurableness of the activity, and its intensity may play a role. A final limitation is that we had a very small sample size, because we only used individuals in which we previously found a positive influence of physical activity on affect. This small sample is suitable for testing a so-called "proof of principle", but the results are not generalizable to the general population.

To conclude, we explored whether fluctuations in cortisol may underlie the dynamic relationship between physical activity and affect in daily life. We found little evidence for this, since we found this relationship for only one participant out of nine. Existing evidence about acute effects of physical activity on cortisol and affect is scarce, emphasizing the need of studies like ours. Future studies may assess physical activity levels, cortisol and affective states over different, preferably smaller, time scales, and with multiple cortisol sampling after physical activity. Furthermore, they may address factors that potentially explain individual differences or alternative mediatory pathways.

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