Unraveling the temporal dynamics between symptom and treatment variables in a lifestyle-oriented approach to anxiety disorder. A time-series analysis

Rogier Hoenders, Elske Bos, Joop de Jong, Peter de Jonge

Nederlandse samenvatting

Achtergrond: Er is steeds meer bewijs voor de positieve effecten van een gezonde leefstijl op de psychische gezondheid. Het meeste wetenschappelijk onderzoek hiernaar houdt echter slechts rekening met één leefstijlfactor, gaat voorbij aan de mogelijkheid van bidirectionele causaliteit en focust op gemiddelde groepsresultaten.

Methoden: In deze N=1 studie gebruikten we tijdreeksanalyse om de dynamische wisselwerking tussen symptomen en behandelvariabelen te ontrafelen in een multicomponent behandeling van een patiënt met een angststoornis. De belangrijkste behandelvariabelen waren de leefstijlfactoren lichamelijke activiteit en ontspanning.

Resultaten: De patiënt in dit onderzoek herstelde volledig. Multivariate tijdreeksanalyse toonde een complex patroon van dynamische relaties tussen symptoom- en behandelvariabelen. Het doen van ontspanningsoefeningen was voorspellend voor symptoomreductie, maar fysieke activiteit verergerde verrassend genoeg de klachten. Veranderingen in energie voorspelden veranderingen in angst. Bewijs voor bidirectionele causaliteit was tevens aanwezig: veranderingen in ontspanning werden gevolgd door veranderingen in energie, maar ook omgekeerd, hetgeen wijst op een positieve feedback loop.

Conclusies: Dit soort onderzoek is nuttig voor het verkrijgen van inzicht in de causale mechanismen die ten grondslag liggen aan de effecten van een gezonde leefstijl op de psychische gezondheid.

Trefwoorden
Angst, lifestyle, idiografisch onderzoek, tijdreeksanalyse, patiëntgerichte behandeling
Abstract

Background: Although there is increasing evidence for the positive effects of a healthy lifestyle on mental health, most studies only take into account a single lifestyle factor, ignore the possibility of bidirectional causality, and focus on average group results.

Methods: In the present single-subject study we used time-series analysis to unravel the dynamic interplay between symptom and treatment variables in a multi-component treatment of anxiety disorder. Main treatment variables were two lifestyle factors (physical activity and relaxation).

Results: The patient in this study recovered completely. Multivariate time-series analysis revealed an intricate pattern of dynamic relationships between symptom and treatment variables. Relaxation was predictive of symptom reduction but physical activity surprisingly worsened the symptoms. Changes in energy predicted changes in anxiety. Evidence for bidirectional causality was present as well, with changes in relaxation predicting changes in energy and vice versa, indicating a positive feedback loop.

Conclusions: This type of research is useful for gaining insight into the causal mechanisms underlying the effects of a healthy lifestyle on mental health.

Keywords
Anxiety, Lifestyle, Idiographic research, Time-series analysis, Personalized treatment

Introduction

There is increasing interest in, and evidence for, the beneficial effects of a healthy lifestyle, including diet, activity and relaxation, on mental health (Walsh, 2011). A strong relationship has been found, for example, between physical activity and mental health, in population-based as well as intervention studies (Morgan, 1997; Biddle et al., 2000; Penedo & Dahn, 2005; Pisinger et al., 2009). Most evidence for the beneficial effects of activity has been found in patients with depressive disorder (Craft & Landers, 1998; Lawlor & Hopker, 2001; Mead et al., 2009), although some effects in anxiety (O’Connor et al., 2000), and other psychiatric disorders (Gorczynsky & Faulkner, 2010) have been found as well. Relaxation practices like yoga, meditation, guided imagery, breathing, and progressive muscle relaxation have also been associated with improved psychological well-being, including reduced feelings of anxiety (Eppeley et al., 1989; Bindeman et al., 1991; Beck et al., 1994; Conrad & Roth 2007; Grossman et al., 2007; Craigie et al., 2008; Lolak et al., 2008; Brown & Gerbarg, 2009; Chiesa & Serretti, 2010; Walsh, 2011).

An important limitation of this research is that different lifestyle behaviors are usually studied in isolation. There are to our knowledge no studies on multiple-component approaches of improving health-related behavior in
psychiatric patients, and thus no studies that have investigated how different lifestyle behaviors interact in producing health gains. This may be important, as different health-related behaviors may reinforce or counteract each other. A second problem is that in most studies only unidirectional effects have been studied, i.e. how lifestyle behaviors affect mental health. The possibility of reverse causality, i.e. that psychological symptoms influence the readiness to engage in health-related behaviors, is rarely accounted for. Moreover, conventional studies generally show treatment effects at the group level, while at the individual level great differences in efficacy or effectiveness exist. Finally, little is known about the causal mechanisms by which lifestyle interventions exert their effect. The typical intervention study has measurements before and after the intervention, but not in between. As a result, little can be concluded about the process of change and how improvements are established (Hilliard, 1993; Molenaar & Campbell, 2009). The present study is an attempt to address the above issues. We investigate the temporal relationships between health-related behaviors and symptoms of psychological distress in a patient receiving a multi-component treatment for anxiety disorder. Our aim is to unravel the dynamic interplay between lifestyle behaviors and outcomes using a single-subject time-series approach. In this approach, multiple repeated measurements are assessed within a single individual and idiosyncratic series are analyzed by means of time-series analysis (Lütkepohl, 2006; Brandt & Williams, 2007). Capitalizing on the power of the multitude of repeated measurements, such studies can give a detailed and person-tailored account of the dynamic relationships between several variables and the temporal order and reciprocity of their effects, therewith greatly enhancing the potential to draw causal inferences (Hilliard, 1993; Molenaar, 2004; Barlow & Nock, 2009).

**Methods**

**Participant**
The participant (called “Alex” in this paper) was a 56-year-old man with a 25-year history of recurrent episodes of anxiety, well controlled by 40 mg of paroxetine (a selective serotonin reuptake inhibitor; SSRI), at the cost of substantial side effects (impotence, 10 kg weight gain and heavy sweating). Because of these side effects, Alex had tapered his use of paroxetine successfully in 2006 with the aid of his therapist (RH, the first author). In the fall of 2008 he was readmitted to our outpatient center 1, because of a relapse of anxiety after accepting a job for the first time in many years. He had been unemployed for 2 years because of his symptoms and because his wife had died of breast cancer, after which he had to take full parental responsibility for his 4 daughters aged 10 to 18. Just before his readmission he was told that his oldest daughter carries the same breast cancer gene as his wife. He experienced a general feeling of anxiety and fear, and mild depressive symptoms but no specific phobias or panic attacks. He also had

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many physical symptoms like fatigue, low energy and nausea. The clinical diagnosis did not fulfill the criteria for any specific anxiety disorder. Anxiety Disorder NOS and cluster C personality traits (DSM-IV; American Psychiatric Association, 2000) were diagnosed by RH.

**Study design**
The study had a naturalistic design; the treatment followed the regular course of treatment as given at the center. Alex recorded symptom and treatment variables on a daily basis by means of a self-report registration form. These recordings were part of the lifestyle intervention. Daily completion of the registration form started as soon as the treatment started, on October 23, 2008, after the intake interview. Alex continued his recordings until June 15, 2009 resulting in a series of 236 assessment points. After termination of the therapy Alex gave his informed consent for the use of his data for research and publication.

**Treatment**
The treatment was explicitly multifactorial. A bio-psychosocial approach was adopted, in which lifestyle interventions and psychiatric counseling were combined with selected psychotropic medication or nutritional supplements (Hoenders et al., 2010). The treatment started with lifestyle interventions targeting relaxation and physical activity. After identifying the most prominent symptoms (low energy and anxiety), Alex was instructed to score the intensity of these symptoms daily, together with the time spent on relaxation practices and physical activity. This was done because results of behavioral interventions are known to improve when patients keep track of their own behaviors and get feedback on them from their therapist. Daily self-monitoring enhances self-observation and control, which in turn may foster responsibility and motivation for treatment (Quenter et al., 2002). Alex did not want to start again with regular medication because of the side effects. Therefore, RH suggested inositol, a naturally occurring compound that is a member of the B-vitamin family. There is evidence for its effectiveness in anxiety-related disorders and depression (Belmaker & Levine, 2008). The effective dosage is 12-18 g (Settle, 2007). In the second half of the study period Alex switched to paroxetine again, for reasons that will be addressed in the Results section. Paroxetine is registered for treating depression and anxiety-related disorders. The recommended dosage of paroxetine is 20-60 mg.

During the entire study period, Alex and RH had regular therapy contacts. They had 17 contacts in total, varying in duration from 5 to 50 minutes (mean = 33 min). During these contacts Alex and RH discussed his registration and RH advised and commented on them, reinforcing healthy lifestyle changes. He further employed an eclectic supportive psychotherapeutic approach, focusing on unconditional positive regard, adjusting to Alex’s needs and preferences and helping him to regain a sense of control. RH consistently endorsed Alex’s initiatives and decisions regarding
his own treatment (for instance his initiative to adjust RH’s general lifestyle advice to his personal situation and his wish to be medicated with ‘natural medicines’), to strengthen the therapeutic relationship and Alex’s sense of self-management.

Assessment
The study variables were assessed daily by means of a registration form. The form consisted of 7 columns, two in which Alex recorded his daily levels of energy and anxiety (range 0-10), two for registering the type of relaxation practices and physical activity, and two for the time he spent on it (in minutes). In the seventh column Alex could mark special events. The Energy score refers to the patient’s morning energy level, because the morning was the time of day Alex could estimate this level most accurately. The Anxiety score refers to the average anxiety level experienced during the day. The Relaxation score denotes the time spent on relaxation-related techniques like yoga and mediation. The Activity score denotes the time spent on physical activities including walking, gardening and household activities.

Statistical analysis
The statistical analyses were done by one of the authors (EB), who was blinded to treatment outcomes. Univariate time series were investigated using time-series regression analysis, to examine trends over time (Ostrom, 1990). Time-series regression accounts for the fact that repeated observations tend to be serially correlated (autocorrelation) by fitting autoregressive moving average (ARMA) models to the residuals. To investigate the dynamic relationships between the different variables, we used Vector Auto Regressive modeling (VAR) (Lütkepohl, 2006; Brandt & Williams, 2007). VAR was originally developed by Sims (1980) in econometrics and since then has also been used in fields like meteorology, sociology, political science, and neuroimaging. In the field of psychiatry, VAR has only been used occasionally (e.g., Dugas et al., 2009). An attractive feature of VAR is its ability to investigate bidirectional influences between variables without having to make a priori assumptions about the direction of the effects. By separating the dynamic part of the model (the relationships between the lagged values of the variables) from the simultaneous part (the relationships between the contemporaneous values), the model allows to make inferences about the temporal order of the effects and thus about causality (Brandt & Williams, 2007). A further advantage is that VAR allows for feedback effects and for indirect links between variables, i.e. that the effect of one variable on another runs via a third variable. This makes the VAR approach very suitable for studying mechanisms of change.
A VAR model is a multivariate autoregressive model that consists of a set of unrestricted regression equations for a system of two or more variables (Brandt & Williams, 2007). All variables in the system are treated as endogenous, which means that they can be both determinant and outcome. Each of the endogenous variables is regressed on its own lagged values and
the lagged values of the other variables. The error terms, called innovations or shocks, should be serially uncorrelated but can be contemporaneously correlated. In VAR, the coefficients in the regression equation cannot be interpreted individually, because they are part of a system in which all elements are dynamically related to each other. Therefore, VAR is usually accompanied by the techniques of Granger causality testing, impulse response analysis and forecast error variance decomposition, which give an indication of the system’s dynamic behavior (Brandt & Williams, 2007).

In the present study, a 4-variable VAR was used, modeling the temporal dynamics of Energy, Anxiety, Relaxation and Activity. To account for the potential effects of inositol and paroxetine, we added two control variables denoting the dosages of these drugs to the model. These control variables were considered exogenous to the system (which means that they may influence the system but cannot themselves be influenced by the system). A variable denoting the treatment contacts (0/1) was also included as an exogenous variable, but as it did not contribute significantly to the model it was removed from the final model. After estimation of the VAR, we examined whether the coefficients of some parameters could be constrained (set to 0; Lütkepohl, 2006). The VAR was re-estimated after placing each constraint. Parameters with the lowest t-values were constraint first. The procedure was continued until a p-value of 0.300 was reached. We checked whether the final VAR model was correctly specified using diagnostic tests on stability and residual autocorrelation (Lütkepohl, 2006).

A two-tailed alpha level of 0.05 was used to determine statistical significance. Bootstrapped 95% confidence intervals were used for the error bands of the impulse response functions (Lütkepohl, 2006). Analyses were performed in STATA 11.

**Results**

Figure 1 shows the time series of daily energy and anxiety levels, and the time spent on relaxation practices and physical activity. Alex completed the registration form every single day, yielding a unique series of 236 consecutive daily observations with no missing values. He engaged in relaxation practices and physical activities almost every day (see Figure 1). The relaxation practices he recorded most often were yoga and meditation. Occasionally, he recorded massage and singing in a Russian choir. The physical activities he recorded were walking, gardening, housekeeping, and swimming. Walking was the activity he registered most often. The average daily time spent on Relaxation during the study period was 66 minutes (SD = 28, range 0-150). The average time spent on Activity was 52 minutes (SD = 30, range 0-150). Energy scores ranged from 2 to 7 (mean = 4.72, SD = 1.15). Anxiety scores were between 0 and 7 (mean = 1.42, SD = 1.36).

After a baseline phase of 8 days Alex started to use 2 g inositol, increasing the dosage to 4 g after another 8 days. After 90 days, he lowered the dosage to 2
g and stopped inositol intake two weeks thereafter. Alex did not come near the supposed efficacy threshold (10-12 g) for inositol at any moment during the study period. He did not suffer from any side effects but decided to stop because he regarded the effect, though present, as too slow and too weak, and now felt more confident to try paroxetine again because of previous success. The prospect of suffering the side effect of impotence was less problematic for him at this time because his girlfriend had ended their relationship and he did not feel like engaging a new one in the near future. Alex started with 10 mg paroxetine 2 days after he stopped using inositol, gradually increasing the dosage to 40 mg in 4.5 weeks. He continued to take 40 mg paroxetine until the end of the study period.

![Graph](image)

**Figure 1.** Daily ratings of Energy and Anxiety (range 0-10), and Relaxation and Activity (minutes) from October 23, 2008 until June 15, 2009 (236 days). The bar at the top of the graph shows the period in which the participant used inositol and paroxetine.

On Christmas Day, Alex started to add alprazolam to his medication, at his own initiative. Alprazolam is a benzodiazepine that is used as an anxiolytic.
Alex used this drug before and had some leftover. He discussed this initiative with his therapist, who accepted it because this medicine is appropriate for short-term use in anxiety. Moreover, endorsing Alex’s initiatives was in line with the supportive treatment approach and the intention to help Alex regaining a sense of self-determination and control. During the next 3 months, Alex took 1 to 3 tablets of 0.25 mg alprazolam on days he felt the need to do so. He recorded his use of the drug on the registration form. He used alprazolam on 38 days in total. Most often he used 1 tablet; sometimes he used 2 or 3 tablets. Since an effect on Energy and Anxiety can be expected from taking this drug, a variable denoting the number of alprazolam tablets was added to the VAR model as a control variable. We also included the first lag of this variable to account for possible lagged anxiolytic effects.

Special events
According to the registration form, the days around Christmas had been very burdening, leading to a sharp increase in anxiety symptoms (see Figure 1). Alex told his therapist that he had had a major crisis during these days as a result of a coincidence of stressful events: getting back to work, worries concerning his daughters, and the Christmas period with its many social happenings bringing back memories of his deceased wife. To control for possible confounding effects due to this unusual time of the year, we included a dummy variable denoting the Christmas period (coded ‘1’ for the 10 days around Christmas and ‘0’ otherwise) as an exogenous variable to the VAR model.

Course of symptom and treatment variables
We first examined overall trends in the four time series over the whole study period. As can be seen in Figure 1, the Energy scores showed a gradually increasing trend over time, while the Anxiety scores gradually decreased, the Christmas period being a major exception. We examined whether these trends were significant using time-series regression analysis, modeling a linear trend. As the Energy and Anxiety series showed heteroskedasticity (non-stationary variances), we used the natural logs of these variables to stabilize the variances (Brandt & Williams, 2007). The linear trend was significant in the models for Energy (B = 0.002, p = 0.005), Anxiety (B = -0.006, p = 0.000) and Activity (B = -0.071, p = 0.013). Thus, Alex showed a significant increase in Energy and a significant decrease in Anxiety over time, while his Activity levels gradually diminished during the study period. This overall pattern of symptom relief was in line with RH’s clinical impression and Alex’s own experience of gradual recovery.

Estimation of the VAR
We determined how many time lags were needed in the VAR model (a “lag” 2 Likelihood Ratio test, Final Prediction Error, Akaike Information Criterion; Hannan-Quinn Information Criterion, and Schwarz Bayesian Information Criterion.
optimal lag length can be found using lag-length selection criteria\textsuperscript{2} (Lütkepohl, 2006). Most of these criteria suggested an optimum lag length of 2, some suggested including 1 lag. We tested both a 1- and a 2-lag VAR, but as the former showed considerable residual autocorrelation, we proceeded with the 2-lag model.

Next, the VAR with 2 lags was estimated. Table 1 presents the final VAR model in which the 4 endogenous variables (Energy, Anxiety, Relaxation, Activity) were modeled as a function of their own previous values (lags 1 and 2), the previous values of the other endogenous variables, and the control variables. As can be seen in the table, both the Energy and Anxiety series showed important positive autocorrelation: the first and second lags of these variables significantly predicted their own current values. Some positive autocorrelation was also detected in the Relaxation series. The Activity series did not show significant autocorrelation. Besides these autoregressive effects the variables showed some lagged correlations with each other. The second lag of Energy was related to current Anxiety scores: higher levels of Energy were followed by lower levels of Anxiety two days later. A trend for the reverse effect was also present, with increases in Anxiety being related to decreases in Energy the next day. Lagged values of Relaxation were positively related to Energy and negatively to Anxiety; the more time Alex engaged in Relaxation, the higher his Energy and the lower his Anxiety levels the next day. A reverse effect from Energy to Relaxation was present as well: higher Energy levels were followed by more time spent on Relaxation the next day. Lagged values of Activity were also associated with Energy and Anxiety. The nature of these relationships, however, was contrary to what we had expected; higher levels of Activity were related to lower Energy and higher Anxiety levels the next day.

Inositol and paroxetine were significantly related to Energy and Anxiety as well. Higher dosages of inositol and paroxetine were associated with more Energy and less Anxiety. Alprazolam was related to all 4 endogenous variables. More alprazolam tablets were taken on days with less Energy and more Anxiety, and taking this drug went along with reduced levels of Relaxation and Activity. The presumed anxiolytic effect of this benzodiazepine could be observed the day after; the first lag of alprazolam was negatively related to Anxiety. Finally, a strong relationship was found between the Christmas period and Anxiety.

**Granger causality**

In time-series analysis, the temporal ordering of events can be used to empirically distinguish between leading and lagging variables. This distinction is the basis of a definition of causality called ‘Granger causality’ (Granger, 1969). A variable X ‘Granger causes’ Y if past values of X improve the prediction of Y (beyond past values of Y and other variables in the system) (Lütkepohl, 2006). We performed Granger tests to investigate whether there was Granger causality present in our system.
Table 2 (p. 21) shows the results of these tests. The table shows that the relationship between Relaxation and Energy was bidirectional: past Relaxation levels predicted current Energy scores ($p = 0.035$), but also the reverse was true ($p = 0.002$). Past Relaxation levels also tended to predict current Anxiety scores ($p = 0.062$). Past Energy levels predicted current Anxiety scores ($p = 0.039$), and a trend for the reverse effect, from Anxiety to Energy, was present as well ($p = 0.072$). Activity influenced both Energy and Anxiety ($p = 0.011$ and $0.031$), but was not itself affected by any of the other variables. Thus, Activity was exogenous to the system.

Contemporaneous correlations

We subsequently calculated the contemporaneous correlations between the endogenous variables, using the residuals of the VAR model (Brandt & Williams, 2007). These correlations represent the immediate relationships between the variables, i.e. on the measurement days itself. Table 3 shows that the highest contemporaneous correlation was between Energy and Anxiety; these variables were negatively correlated with each other ($r = -0.338$). The other correlations were positive but small.

Table 1. VAR estimates for the 2-lag model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Anxiety</th>
<th>Coefficient</th>
<th>Relaxation</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (lag 1)</td>
<td>0.420***</td>
<td>0</td>
<td>0.455***</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Energy (lag 2)</td>
<td>0.214***</td>
<td>-0.226*</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anxiety (lag 1)</td>
<td>-0.049*</td>
<td>0.433***</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anxiety (lag 2)</td>
<td>0</td>
<td>0.240***</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Relaxation (lag 1)</td>
<td>0.035*</td>
<td>-0.060*</td>
<td>0.154*</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Relaxation (lag 2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Activity (lag 1)</td>
<td>-0.038*</td>
<td>0.064*</td>
<td>0</td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td>Activity (lag 2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Control variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Coefficient</th>
<th>Coefficient</th>
<th>Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inositol</td>
<td>0.019*</td>
<td>-0.048**</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Seroxat</td>
<td>0.003*</td>
<td>-0.009***</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>-0.044*</td>
<td>0.142***</td>
<td>-0.129*</td>
<td>-0.132*</td>
</tr>
<tr>
<td>Alprazolam (lag 1)</td>
<td>0.022</td>
<td>-0.111***</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Christmas</td>
<td>0.053</td>
<td>0.281***</td>
<td>0</td>
<td>0.235</td>
</tr>
</tbody>
</table>

Note. Energy and Anxiety are natural log-transformed variables. Relaxation and Activity are scaled in hours. Coefficients denoted with 0 are constraint parameters. Control variables are exogenous to the system. Number of observations = 234. \( \text{-}p < 0.10, \text{*}p < 0.05, \text{**}p < 0.01, \text{***}p < 0.001. \)
Table 2. Granger causality tests

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relaxation $\rightarrow$ Energy</td>
<td>4.46</td>
<td>0.035*</td>
</tr>
<tr>
<td>Activity $\rightarrow$ Energy</td>
<td>6.43</td>
<td>0.011*</td>
</tr>
<tr>
<td>Anxiety $\rightarrow$ Energy</td>
<td>3.25</td>
<td>0.072</td>
</tr>
<tr>
<td>Energy $\rightarrow$ Anxiety</td>
<td>4.27</td>
<td>0.039*</td>
</tr>
<tr>
<td>Activity $\rightarrow$ Anxiety Relaxation $\rightarrow$ Anxiety</td>
<td>4.65</td>
<td>0.031*</td>
</tr>
<tr>
<td>Activity $\rightarrow$ Anxiety</td>
<td>3.49</td>
<td>0.062</td>
</tr>
<tr>
<td>Energy $\rightarrow$ Relaxation</td>
<td>9.19</td>
<td>0.002**</td>
</tr>
<tr>
<td>Anxiety $\rightarrow$ Relaxation</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Activity $\rightarrow$ Relaxation</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Energy $\rightarrow$ Activity</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Anxiety $\rightarrow$ Activity</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Relaxation $\rightarrow$ Activity</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Note. Tests denoted with (-) were not performed because the parameters involved were constrained. A significant $\chi^2$-value implies that the first variable “Granger causes” the second variable. Thus, the first variable is considered to have causal impact on the second variable (whether the impact is positive or negative cannot be derived from this table, but becomes clear from the sign of the estimates in Table 1 and the form the Impulse Response Functions below). $-p < 0.010$, $*p < 0.05$, $**p < 0.005$. For all tests df = 1.

Table 3. Contemporaneous correlations

<table>
<thead>
<tr>
<th></th>
<th>Energy</th>
<th>Anxiety</th>
<th>Relaxation</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>-0.338</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relaxation</td>
<td>0.109</td>
<td>0.059</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td>0.077</td>
<td>0.116</td>
<td>0.120</td>
<td>-</td>
</tr>
</tbody>
</table>

Impulse Response Functions

The regression coefficients of a VAR can only be interpreted as part of a system of variables that are dynamically related to each other. Impulse Response Functions (IRFs) allow tracing out the dynamic impacts of changes in each of the endogenous variables over time. They do so by visualizing the impact of an isolated shock in one of the variables to the other variables, thus showing how these innovations are propagated through the system. IRFs only take into account the time-lagged relationships between the endogenous variables. Orthogonalized Impulse Response Functions (OIRFs) are variants of IRFs that take into account the contemporaneous correlations between the variables as well (see Brandt & Williams, 2007). OIRFs assume that a specific ordering is chosen for the direction of the contemporaneous
relationships. If no theory is available guiding this choice, the results of alternative orderings can be presented. The critical point in VAR is that the decision about this ordering can be made explicit and can be evaluated after accounting for the dynamics in the data (Brandt & Williams, 2007). In the present study, we know that the Energy scores refer to Alex’s morning energy levels and the Anxiety scores to his average anxiety level during the day. We further know that Alex did his relaxation practices generally at earlier times of the day than his activities. Thus, a reasonable ordering for the innovations in the variables within the same day is that changes in Energy precede changes in Anxiety, which precede changes in Relaxation, which precede changes in Activity. This is the ordering of our first choice (Order 1: Energy—Anxiety—Relaxation—Activity). We investigated alternative orderings as well. Figure 2 (p. 23) shows the OIRFs for Order 1. The upper row shows the impact of a shock in Energy. The first graph of this row shows the response of Energy to its own shock. This response is positive and persists over many days, slowly decaying to 0 after about 10 days. The same pattern of strong persistence can be seen in the response of Anxiety to the Energy shock (2nd graph of 1st row). We see a significant direct decrease in Anxiety that slowly diminishes during the following days. The next two graphs show that a shock in Energy also results in a direct increase in Relaxation and Activity. This effect is not significant for Activity, but becomes significant after 1 day for Relaxation. The latter effect decays slowly to 0 after 1 week.

The second row shows the impact of a shock in Anxiety. An increase in Anxiety is followed by a decrease in Energy the next day, which becomes significant after 3 days and persists over several days. Strong persistence can also be seen in the response of Anxiety to a shock to itself. We further see that the Anxiety shock has a positive impact on Relaxation and Activity, but this effect is short in duration and only significant for Activity. Thus, on anxious days, the participant spent more time than average on physical activities.

The third row shows the impact of a shock in Relaxation. The responses of Energy and Anxiety to this shock are initially 0, which is a natural result of the chosen ordering in which changes in Relaxation follow after changes in Energy and Anxiety within the same day. The impact of the shock in Relaxation becomes visible after 1 day, when an increase in Energy and a decrease in Anxiety can be observed. These effects become significant later, as the confidence intervals become smaller. Both effects persist during the next days, slowly dying out after about 10 days. The response of Relaxation to a shock to itself is short in duration and disappears after 2 days. The response of Activity to the Relaxation shock is not significant.

The lowest row shows the impact of a shock in Activity. An innovation in Activity leads to a decrease in Energy and an increase in Anxiety the next day. Also these effects gradually taper off to 0 after several days. The Activity shock further leads to a delayed decrease in Relaxation. This must be an indirect effect, as the Activity parameters in the VAR equation for Relaxation
Figure 2. Orthogonalized Impulse Response Functions for a 4-variable VAR with 95% bootstrapped error bands. Responses are considered significant if their error bands do not include 0. Energy and Anxiety are natural log-transformed variables. Relaxation and Activity are scaled in hours. Order 1: Energy–Anxiety–Relaxation–Activity. Responses are plotted over a 10-day horizon.

were both set to 0 because they did not contribute significantly to the model. Presumably, this effect runs via reductions in Energy. Finally, there is no persistence in the response of Activity to its own shock after the first day.

Cumulative Impulse Response Functions
The accumulated impact of a shock over time is calculated by computing Cumulative Orthogonalized Impulse Response Functions (COIRFs). The results showed that an isolated one-time shock of 1 SD in the natural logs of Energy (corresponding to a 10% increase in Energy) results in a total reduction in Anxiety of 44% over 10 days. The same Energy shock leads to a total increase in Relaxation of about ¼ hour over that period. The response of Activity to the Energy shock is negligible. A shock of 1 SD in Relaxation (about ½ an hour) leads to a total increase in Energy of 6% and a total decrease in Anxiety of 11% over 10 days. A similar shock in Activity on the other hand results in a total decrease in Energy of 7% and a total increase in Anxiety of 13% over the same period.
Alternative orderings
We also considered OIRFs for alternative orderings of the contemporaneous correlations. The results appeared to be rather robust to different orderings. The main differences resulted from converting Energy and Anxiety in the ordering, which is not surprising because these two variables showed the largest contemporaneous correlation. However, these differences did not change the results in a fundamental way.

Discussion
This study aimed to unravel the dynamic relationships between psychological symptoms and the health-related behaviors intended to improve these symptoms. These relationships turned out to be characterized by bidirectionality, lagged influences, indirect effects, and feedback loops, both between symptoms and behaviors as well as among them. The present time-series design with its many data points enabled us to disentangle these complex effects. These would have gone unnoticed in conventional group studies, as the small number of measurements and the aggregation of data across individuals in such studies obscures relevant information on the dynamic interdependencies between variables (Hilliard, 1993; Molenaar & Campbell, 2009; Dugas et al., 2009).

The results showed that this patient’s symptoms and behavior were interrelated in an intricate way. One important finding was that energy and relaxation mutually reinforced each other. Changes in relaxation tend to be followed by changes in energy, but also the other way around. Furthermore, both energy and relaxation were predictive of anxiety. Anxiety in turn was predictive of energy, particularly in the longer run. This suggests an intricate system of indirect effects and positive feedback loops, which may form a target for initiating a positive spiral. Once initiated, such a spiral may bring about a cascade of small but relevant increments in healthy behaviors and reductions of symptoms. It is precisely this potential cascade effect that makes the results meaningful. Although the isolated effects of changes in individual variables may be small, the eventual effects can be large because of the way these changes propagate through the system and mutually reinforce each other. Moreover, in daily life changes are often not isolated and once only but occur in concert and more frequently.

The effect of relaxation on anxiety seemed to be a delayed one. The present-day correlation between relaxation and anxiety was low and the effect after 1 day was not yet significant. The OIRF showed a significant favorable effect of relaxation on anxiety only after a few days. This suggests that the direct effects of relaxation on anxiety are small in this patient, but that the indirect effects, presumably via increments in energy, are larger. A more immediate connection seemed to exist between energy and anxiety. The contemporaneous correlation between these symptoms was moderately large. Furthermore, past energy levels influenced current anxiety scores and also a
trend for the reverse effect was present. So, energy and anxiety seemed to mutually reinforce each other.
A striking result was that activity seemed to worsen the patient’s symptoms. Increases in activity were followed by decreases in energy and increases in anxiety. The results further showed that activity had a negative effect on relaxation. These findings could possibly have large implications for everyone promoting lifestyle behavior for (mental) health and assuming that all ‘healthy behavior’ is healthy for anyone. This might not be the case. In this patient exercise was not beneficial, at least not in the short run. Maybe Alex did his activities in the wrong way, for example by not respecting his limits. That might have stirred up an already overactive stress response system. In several mental disorders including anxiety, the stress response systems (the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS)) are hyperactive (Wolkowitz, 2001; Mantella et al., 2008). Prolonged or excessive activation of these systems can lead to excessive anxiety and fatigue (McEwen, 2000; Wolkowitz, 2001; Heim et al., 2000). Anxiety and fatigue (lack of energy) were Alex’s two main problems. Exercise represents a physical stressor that activates the stress response systems (McEwen, 2008; Mastorakos, 2005). Whereas sustained physical conditioning is associated with a decreased stress response to exercise, in untrained individuals or when applied inappropriately the response is relatively high (Howlett, 1987; Mastorakos, 2005).
Interestingly, relaxation practices such as yoga and meditation are known to do the opposite. They down-regulate the stress response systems (Astin, 1997; Brown & Gerbarg, 2009; Chiesa & Serreti, 2010), stimulate a relaxation response by increasing parasympathetic nervous system activity (Hoffman et al., 1982; Innes et al., 2005; Benson, 2009), and improve subjective measures of fatigue (Brown & Gerbarg, 2009). Possibly, in some circumstances or in some type of individuals, relaxation practices are more beneficial than exercise. Similar evidence has been reported by some other authors (Ross & Thomas, 2010; Streeter et al., 2010). By down-regulating the stress response systems, relaxation practices may create a window of opportunity for dynamic interactions to instigate a positive feedback loop that advances recovery.
Inositol as well as paroxetine had positive effects, decreasing anxiety and increasing energy. The design, however, did not allow drawing any conclusions about the effectiveness of these drugs, as there was no good control (baseline period too short, no predefined intake schedule, and too little variation in dose). There are some strong experimental designs for testing the effectiveness of treatments in single subjects (e.g., Guyatt et al., 1986; Ottenbacher, 2001), but these were not applied here.
According to RH’s clinical impression, another important factor in Alex’s recovery was the promotion of his sense of control. Yoga and meditation are thought to be beneficial not only because of their relaxing effects, but also because they cultivate feelings of self-regulation and control (Astin, 1997; Shapiro et al., 2006). Further, during the treatment sessions RH consistently
endorsed Alex’s initiatives and decisions regarding his own treatment, which seemed to have strengthened the therapeutic relationship and Alex’s self-efficacy. Research has shown that treatment is most effective when patients are actively involved in treatment decisions (e.g., Nikles et al., 2005; Ryan & Deci, 2008) and when therapists and interventions are matched to the patient’s worldview, preferences, and motives (Prochaska et al., 1992; Rothwell et al., 2007). Also evidence-based medicine (EBM) defines patient preference as one of three pillars in decision making (Sackett et al., 2000). The most important limitation of this study is that the results cannot be generalized to a larger patient population because we used a single-subject design. Broader generalization can be established by systematic replication, gradually expanding the population to patients with different profiles (Hilliard, 1993; Ottenbacher, 2001). It should be noted however that generalization of group-averaged results to individuals, as is implicitly done in nomothetic research designs, is often not justified (Molenaar, 2004). The study has also several strong features, including its naturalistic design, the high-intensity data set, and the innovative analytic techniques, which allowed us to catch sight of the intricate dynamic processes involved in psychophysiology and behavior. We feel this kind of research may be useful for improving our understanding of the complex mechanisms underlying the effects of a healthy lifestyle on mental health and individual differences therein, and may prove valuable for identifying the critical elements of the psychotherapeutic process.

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