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Detecting nonlinearity in the associations between depression and cortisol

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Chapter 1

Introduction

With an estimated lifetime prevalence of 12%, mood disorders are among the most prevalent disorders worldwide (Kessler et al., 2009). In the Netherlands, the lifetime prevalence of developing any mood disorder is 14.4% for men and 26.1% for women (de Graaf et al., 2012). Besides having a major impact on the well-being of the affected person, mood disorders put a heavy burden on society as well (Vos et al., 2017). In Europe, the total economic costs of mood disorders were more than 113,000 million euro in 2010 (Olesen et al., 2012).

Depression

Major Depressive Disorder MDD is the most prevalent specific mood disorder, showing lifetime prevalences in the Netherlands of 13-14% and 24-26% for men and women respectively (de Graaf et al., 2012). MDD is a serious illness that is characterized by persistent feelings of sadness or a lack of interest in almost all activities most of the day. These symptoms co-occur with other symptoms, such as: weight loss or gain, changes in appetite, insomnia or hypersomnia, psychomotor changes, fatigue, feelings of worthlessness or guilt, reduced ability to concentrate, and recurrent thoughts of suicide or suicide attempts. Together, these symptoms lead to a significant distress or impairment in daily life.

Depression is thought to be caused by an interplay between genetic factors, biochemical factors and cognitive-behavioral factors (Beck, 1967; Brown et al., 1973; Keller & Nesse, 2006; Keller et al., 2007; Lazarus & Folkman, 1984; Saveanu & Nemeroff, 2012; Teasdale, 1988). Cortisol is one of the biochemical factors that has been shown to be altered in depressed persons (Holsboer & Barden, 1996). Cortisol is a component of the hypothalamic-pituitary-adrenal HPA axis, which plays an important role in responses to stressful events. In healthy persons, in normal circumstances, cortisol levels show a circadian rhythm that starts with a sharp peak in the morning – the cortisol awakening response (CAR) – followed by a gradual decay during the day (Fries et al., 2009).

A meta-analysis by Stetler and Miller (2011), comprising hundreds of studies, showed a general tendency of increased cortisol levels in depressed individuals, indicating hyperactivation of the HPA axis. It also showed that the degree of hyperactivity varied considerably across patient groups. Other studies showed that there may actually be hypoactivation of the HPA axis in individuals with chronic or recurrent depression (Holsen et al., 2011).

Depression has also been associated with changes in the dynamics of cortisol. Some studies have found a flatter diurnal pattern in depressed individuals (Gartside et al., 2003; Weinrib et al., 2010), whereas another study found a steeper slope (Booij et al., 2013), and some studies found no change at all (Maes et al., 1998; Vreeburg et al., 2009). In short, the exact relationship between cortisol's dynamics and depression remains inconclusive.

Classification challenges

The classification of mental disorders has been a subject of intensive discussion and has changed numerous times in history. Mental disorders are not easily categorized in mutually exclusive non-overlapping sets of symptoms and causes. Many disorders share etiological pathways or show comorbidity with other disorders (Clark et al., 2017; Kessler et al., 2005). In addition, patients with the same disorder show a large heterogeneity in their symptom profile, in the course of their illness and in their reactions to treatments (Fried, 2015; Kessler et al., 2005, 2017; Sullivan et al., 1998; Van Loo et al., 2012; Wardenaar et al., 2014).

Research into the causes of depression is hindered by such heterogeneity. Traditional research methods aimed for nomothetic knowledge about disorders. Nomothetic knowledge is knowledge that is 'true in general', independent of the particular (in this case, the individual). In the medical sciences, such knowledge is mostly based on cross-sectional group studies, using inter-individual analysis-techniques. In such studies, data of individuals within a group is combined into aggregated results – for example: an average or a median value. Comparing such results with aggregated results of other groups will only reveal differences that are 'true on average' (Lamiell, 1998). Given the within-group differences – due to the heterogeneity that was mentioned in the previous paragraph – group-based studies may be of limited use when studying the symptoms, the underlying mechanisms and the treatment of disease in individual persons. Instead, it is better to first study the dynamics within an individual, to obtain dynamical rules that are valid for that particular individual. This – so-called – idiographic approach leads to knowledge that is true for the individual. In a later stage, it may be possible to look for common characteristics between individuals, in order to arrive at nomothetic knowledge.

Research in the past usually followed the opposite direction; there has been a tendency to generalize results from group studies to the individual level. More specifically, if an inter-individual study showed an association between two variables, it was assumed that the same association held within a single individual. Especially the last decades there has been a growing recognition of the fact that this kind of generalization is not necessarily valid (Hamaker, 2012; Molenaar, 2004; Nesselroade, 1991; Rosmalen et al., 2012). Only when the statistical properties conform to a pair of strict conditions, this generalization from the group level to the individual level is valid. These conditions are known as the classical ergodic theorems (Hamaker et al., 2005; Molenaar, 2008; Molenaar & Campbell, 2009). The first condition is the condition of homogeneity, which states that the statistical parameters for each subject have to be the same; in other words, it assumes a homogeneous population. The second condition is the condition of stationarity, which states that the statistical parameters have to be time independent. It is not difficult to find cases where this condition will not be met. Examples are: human developmental processes, learning processes, and other processes where change is a key characteristic.

The idiographic approach

More recent work has shown a shift towards longitudinal, idiographic studies (Hamaker & Wichers, 2017). Commonly used analysis techniques for these kinds of studies use time-series data of individual subjects and apply statistical methods to draw conclusions about relationships between variables and the change in these relationships over time within the individual.

The shift towards an idiographic approach to mental disorders has been accompanied by a change in the view on what constitutes a mental disorder. Traditionally, mental disorders were thought to be a state, caused by biological and psychosocial factors, working independently of each other and together causing the disorder (Molenaar, 2004). However, in reality such factors are never independent. Instead, they will mutually influence each other and change over time. Currently, research into mental disorders increasingly represents disorders as networks of factors (Kendler et al., 2011), with each factor having the capability of changing all the other factors. The process of finding out what constitutes a disorder then consists of identifying all possible factors, analyzing how they mutually influence each other, and compare results between healthy persons and persons with the disorder.

Studying networks of dynamically changing factors necessitates the use of analysis-methods that are able to capture changes over time. Although statistical methods such as repeated measurements ANOVA or linear mixed models are capable of detecting change over time, they do so by comparing aggregated group-data. For the idiographic approach, it is necessary to use methods that are capable of detecting change within the person,

using individual data consisting of many measurements over time. One such method is Vector Auto Regression (VAR), a multivariate linear analysis-technique, which uses time-series data of several variables and is able to find out how strongly one variable is correlated to the other (Brandt & Williams, 2007). It does so by establishing statistical parameters that describe the relationship between the value of a variable and previous values of itself and the other variables. This method has for example been used to study the relationships between: physical activity and depression (Kumagai et al., 2019; Rosmalen et al., 2012), biological stress markers and depression (Booij et al., 2015), eating behavior and depression (Christian et al., 2023; Wild et al., 2010), and mood states and paranoia (Oorschot et al., 2012). These studies have shown large inter-individual differences in the temporal associations within the time-series data, thereby showing that the first ergodic condition – the condition of homogeneity – is not met.

Causality

The presence of a statistical association between two variables is an important prerequisite for causality (Hill, 1965; Kraemer et al., 2001; Rothman & Greenland, 2005). While group-based studies search for such associations between or within groups, idiographic studies have to rely on associations within the individual. Another indicator of causality is a change in the behavior of a variable when different conditions are applied, for example in randomized controlled trials (RCT), used in group-based medical research. In idiographic studies, the VAR technique allows for both: it can show the values of the time based correlations between variables within individual time-series, and it is possible to study these correlations both in the presence or absence of one or more conditions. The VAR technique also allows for a new type of causality, called Granger Causality (GC) (Granger, 1988). Instead of analyzing the time-based correlations in the presence or absence of a condition, this type of causality relies on differences in the correlations when including or leaving out earlier values of other variables from the same time-series data, thereby showing temporal dependencies between variables.

Nonlinearity

Methods such as VAR are based on linear correlations over time in the factors' time-series data. A linear correlation implies a linear relationship between factors: the change in one factor can be represented as the sum of the changes in the other factors, each multiplied by a constant that represents the strength of the influence. However, many systems in nature are not linear (Scheffer, 2020). In such systems, the temporal change in one variable cannot be represented as the sum of linear changes in the other variables. Instead, some variables may have to be combined in different mathematical ways, for example by multiplication or division. In other words, their dynamics are controlled by nonlinear equations. In such – nonlinear dynamical – systems, linear correlations between time series may be absent,

or may change over time, causing linear methods to be inadequate to find the existing relationships between the factors (Sugihara et al., 2012). Applying linear methods to time-series data from nonlinear dynamical systems may lead to the detection of correlations when there is no causal relationship, or to nondetection of correlations when there is a causal relationship.

To analyze time-series of nonlinear dynamical systems, several methods are available, for instance: recurrence plots (Kantz & Schreiber, 2004), threshold autoregressive models (De Haan-Rietdijk et al., 2016), markov switching state space models (Hamaker & Grasman, 2012) and embedding-based models (Von Oertzen & Boker, 2010). Each of these methods has its specific advantages, but this thesis uses methods that are based on nonlinear embeddings because: a) they offer the possibility to detect causality within nonlinear time-series data (Sugihara et al., 2012), b) some of these techniques show similarities with regular VAR-analyses (Sugihara, 1994), and c) they had already been successfully applied within other fields of research, but not yet within the field of psychophysiology. For the purpose of this thesis, these embeddings can be roughly regarded as shapes that are formed by tracing a path through a space of variables. See Figure 1.1. That is, each dimension (or axis) of that space represents a variable that is obtained from time-series data. Each point on the path represents a combination of values of several variables at one point in time. Going to the next point on the path is equivalent to proceeding to the next point in time. An explicit time-dimension is absent, implying that the path is not bound to moving in one direction along a time axis. This makes it possible for the path to return to a region where it had been before. As a result, each point in an embedding can contain neighbor points from completely different moments in time. In many cases, the direction of the path through a point is almost similar to the direction of the path that is going through a neighbor point, implying that the future at one point in the embedding can be predicted by observing the paths that go through its neighbors. Using this property, several techniques have been invented that overcome the problem of ambiguous correlations that plague the linear techniques when applied to nonlinear data. For example, GC relies heavily on linear correlations between variables and may therefore be inadequate to use for the analysis of nonlinear data. A nonlinear-embedding based alternative is convergent cross mapping (CCM) (Sugihara et al., 2012), which analyzes how well predictions hold across different embeddings. Another nonlinear technique, sequentially weighted logistic maps (SMAP) (Sugihara, 1994), can be used as an alternative for VAR. In cases where there is synchronization between two systems, fixed repeating patterns may be observed over time. Linear techniques typically try to compensate for this by adding an extra variable that represents the state of the other system (e.g., time of day [TOD]). For nonlinear techniques, this is not possible. A nonlinear alternative is the use of bundle embeddings (Stark, 1999), where a single embedding is split in several smaller embeddings according to the other system's state. Another nonlinear technique, dewdrop embeddings (Hsieh et al., 2008), can be used when there is a need to combine the time series of several subjects. This may be used to

find out if some subjects share the same dynamics. These techniques are largely based on techniques that were developed by Sugihara and his team. When the studies for this thesis were conducted, some nonlinear techniques were already being applied in the field of psychology (Guastello et al., 2008; Steenbeek & van Geert, 2007; Van Geert, 2009), but to my knowledge, the CCM, SMAP, dewdrop and bundle embedding techniques were new to this field.

OUTLINE OF THE DISSERTATION

Studies after the possible associations between cortisol and depression have shown mixed results. This may be caused by the application of group-based techniques on a largely heterogeneous population and the possible presence of nonlinear contributions in the acquired data. In this dissertation, I have applied embedding-based nonlinear techniques to analyze idiographic time-series data. These data were obtained in earlier idiographic studies that were conducted at the Interdisciplinary Center Psychopathology and Emotion regulation (ICPE) at the University Medical Center Groningen (UMCG).

In Chapter 2, I present a study using CCM to analyze the association between urinary cortisol and NA, using data that were obtained by van Ockenburg et al. (2016). Dewdrop embeddings were used to combine data of several participants and a simulation was carried out to study the stability of the method.

In Chapter 3, I describe a study that used SMAP to analyze the association between salivary cortisol and NA. Data for this study were obtained by Booij et al. (2016) and Bouwmans et al. (2015). I examined whether nonlinear predictions would give more accurate results than linear predictions and tried to find out if SMAP could be used to obtain information about causality. In Chapter 4, I describe a study that combined SMAP with bundle embeddings, to obtain univariate predictions for cortisol. The data for this study were the same as the data that were used for the analyses in Chapter 2. I examined which method gave more accurate predictions: unbundled embeddings, bundled embeddings, or data that was corrected for TOD patterns.

In Chapter 5, I describe a study that combined SMAP with bundle embeddings to obtain multivariate predictions for cortisol and negative affect (NA). The data for this study were the same as the data that were used for the analysis in Chapter 3.

In Chapter 6, I integrate and discuss the findings of the previous chapters. I developed an extensive amount of software to carry out the analyses. I wrote the main part in in C. For ease of use, I developed an R package around the C functionality. Appendix I provides the user manual for this R package.

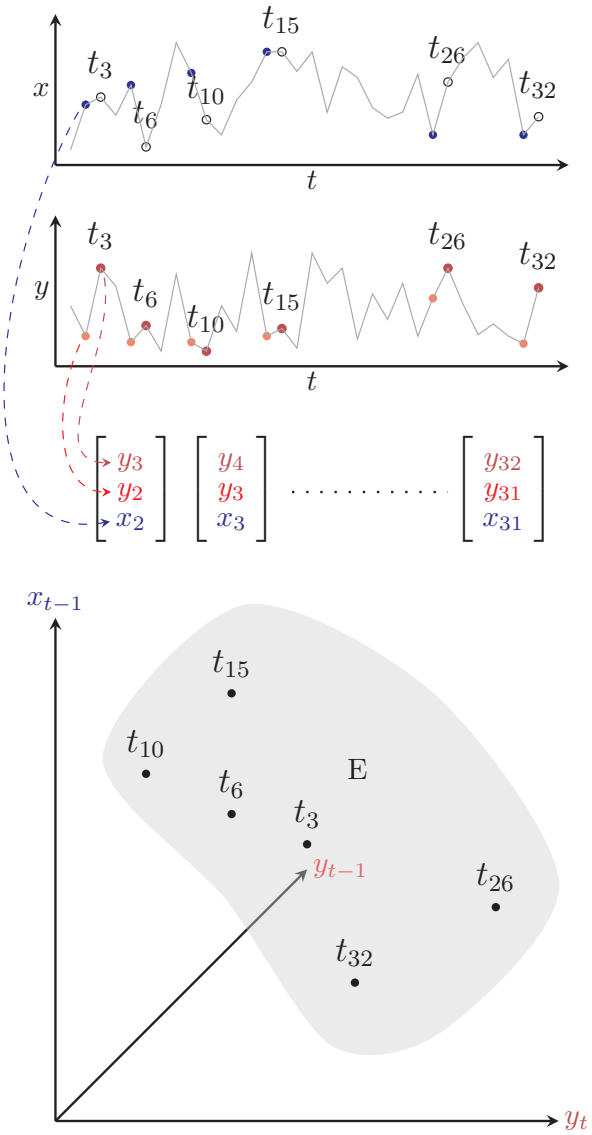

Figure 1.1: Construction of a three-dimensional multivariate embedding.

Three-dimensional coordinate vectors are produced from time series $x(t)$ and $y(t)$. The scalar components of each vector are obtained by taking lagged values of x at time $t-1$, and of y at t and $t-1$. The embedding E is the set of all generated coordinate vectors. A dynamical path, connecting subsequent vectors in the embedding, has been omitted for the sake of clarity.

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