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Detecting nonlinearity in the associations between depression and cortisol

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Chapter 6

Discussion

The aim of the research presented in this thesis was to gain more insight into the etiological factors that are associated with expressions of depression. Findings from previous studies in this field have shown mixed results, which may have been caused by two factors. First, these studies rely on analysis techniques that assume linear relationships between variables, which may have led these studies to miss key non-linear associations. Second, these studies follow a nomothetic, group-based approach, which may be unable to account for the large differences that exist within a strongly heterogeneous target-group. The research in this thesis is based on the assumption of nonlinear relationships and the application of idiographic techniques that are based on nonlinear dynamical systems theory. More specifically, time series of physiological and diary data were analyzed with embedding-based techniques. Most of these techniques had been previously used in ecology and physics, but not in mental health research. The used data came from studies that were previously conducted by others and analyzed by using linear techniques (Booij et al., 2015; Bouwmans et al., 2015; van Ockenburg et al., 2016). In this chapter, I will summarize and discuss the findings that were presented in the previous chapters.

Summary

The main nonlinear techniques that were used were CCM (Chapter 2) and SMAP (Chapter 3, 4, and 5). These techniques were combined with dewdrop embeddings to combine data of several participants and with bundle embeddings to account for repeating diurnal patterns in the time series. The techniques were applied to time series of urinary cortisol (Chapter 4), urinary cortisol and NA (Chapter 2) and salivary cortisol and NA (Chapter 3 and 5).

I started with an analysis of possible nonlinear associations between 24-h urinary free cortisol and NA (Chapter 2). These data were obtained from a study by van Ockenburg et al. (2016). The associations were studied by applying CCM and dewdrop embeddings. The CCM technique allows for finding causal associations in multivariate nonlinear time-series

data, while dewdrop embeddings allow for combining time series from several participants in a nonlinear context, which may make it possible to detect whether participants share common dynamical parameters. The CCM results showed that nonlinear dynamical associations between cortisol and NA may be present in some participants. However, further analyses also showed that noise and influential points had considerable impact on the results. Furthermore, CCM could not reveal the exact nature of the associations: it showed that there may be an association, but it did not show the sign of the relationship. In an attempt to find common dynamics within a group of participants, we combined their time-series data, using the dewdrop-embeddings technique. The dewdrop results indicated that combining the time series did not lead to stronger associations between cortisol and NA. This may be an indication of heterogeneity between the participants.

To obtain more information about the relationship between cortisol and NA I conducted another study, in which I applied SMAP on time series of salivary cortisol and NA of depressed and non-depressed participants (Chapter 3). These data were obtained from the MOOVD study (Booij et al., 2015; Bouwmans et al., 2015). Univariate and multivariate models were compared to explore the association between cortisol and NA. In almost half of the participants, the predictions improved when multivariate models were used instead of univariate models. This may indicate that cortisol and NA are part of the same dynamical system. The association between cortisol and NA was stronger in the depressed group, although the results showed considerable inter-individual heterogeneity within both groups. This study also showed that the presence of daily recurring patterns complicates interpretation of the results because of the additional variance that is caused by the repeating pattern itself. To take the diurnal pattern into account, I combined SMAP with bundle embeddings in a univariate study on urinary cortisol data (Chapter 4). These were the same data as used in chapter 2. The bundle-embedding approach was compared with a non-bundled approach and an approach in which time series were corrected beforehand by using a linear correction method that removed the extra variance that was caused by the diurnal pattern. The study showed that the bundling approach may be a worthwhile extension of current nonlinear and linear methods to correct for recurrent temporal patterns. It also showed that cortisol values during the day may be subject to influences from more variables than is the case for night cortisol.

The combination of SMAP and bundle embeddings was subsequently applied in a multivariate study on salivary cortisol and NA (Chapter 5), using the same data that were used in Chapter 3. The results showed that morning cortisol was better predicted with multivariate SMAP (with NA included), while prediction of afternoon and evening-cortisol values did not benefit from such inclusion. This may be indicative of a relationship between NA and the initial peak of cortisol, followed by an autonomous cortisol decay during the afternoon and evening. This may be related to the anticipation hypothesis of the cortisol awakening

response (CAR), which states that an increased CAR prepares a person for the anticipated demands for that day (Adam et al., 2006). An increased NA score on the previous day may be one of the factors that play a role in this anticipation process.

Techniques

Embedding-based prediction

The applied techniques use embeddings to predict values in the time-series data. A comparison between the predicted and the real values was used as a measure of prediction performance of the applied model. By comparing the performance of different models, information was obtained about the optimal model parameters. These included the optimal embedding dimension, the optimal lag between values from the time-series and the optimal width of the Gaussian curve in the case of SMAP. For multivariate embeddings that were constructed from time series of several variables, the models also produced information about possible associations between those variables. There are however limitations to the range of values that can be used for the parameters: choosing a large value for the embedding dimension or the lag reduces the number of embedding points that can be obtained from the time series. Given the – in general – relatively short lengths of time series that are used in the psychophysiology research-domain, this puts a restriction on the maximum value of the embedding dimension. Especially in the case of missing values, a high dimension results in a considerable number of embedding vectors that have to be discarded. Imputation techniques that are commonly used in linear analysis are not suited for nonlinear techniques because they assume linear relationships by definition.

CCM

The CCM technique was described in Chapter 2. It is based on the nonseparability of nonlinear data, which implies that time-series data of a variable that is nonlinearly coupled to another variable also contains information about that latter variable. At the time of the start of my research, CCM was a new technique that had mainly been applied to data from marine systems (Sugihara et al., 2012; Ye et al., 2015). The technique had been proven to be effective with ecological time series as short as 35-40 measurements (Sugihara et al., 2012, supplementary material). My study used time series consisting of 126 measurements, spanning 63 days. My results showed CCM results that were quite sensitive to the selected embedding dimension and lag size. This sensitivity decreased when outliers were removed from the time series. Additional analyses, using simulated logistic-map data, also showed that observational noise had a large influence on CCM results. This influence was strongly reduced when the simulated time-series length was increased to 200 time points. A complicating factor with regard to my analyses is that NA was constructed as a sum score of several items. I do not know how CCM and nonlinear-dynamical methods in general be-

have when analyzing sum-score data instead of measurements of continuous variables as this has not been extensively investigated. It may be that summing up the Likert-type item variables (a linear operation) decreases the amount of nonlinearity in the data. Furthermore, sum-score data may still be semi discrete, so not fully continuous, which further complicates nonlinear analysis. Further analyses, possibly from simulation studies, are needed to get more insight into the feasibility of using nonlinear-dynamical methods with sum-score data.

Dewdrop embeddings

Dewdrop embeddings allow for combining time series from several participants. In my analyses the use of dewdrop embeddings did not lead to improvements in the prediction accuracy. This might be an indication of heterogeneity between the participants. Compared to a study that used dewdrop embeddings to analyze ecological field data (Hsieh et al., 2008), my study combined relatively few time-series. Furthermore, the ecological time series that were used in Hsieh's study all originated from the same ecological system. The question is whether the participants from my study can be regarded as being part of the same dynamical system. On the one hand, these participants did not share a common background, and did therefore not operate within the same system. On the other hand, one can argue that they share the same biological architecture, and may therefore show the same dynamics. My results seem to support the first consideration. It would be interesting to conduct a dewdrop study on participants that do share a common environment – for example, persons from the same household –, but the problem that then arises is that it would be difficult to find groups that are sufficiently large to construct the actual dewdrop embeddings.

SMAP

SMAP was described in Chapters 3, 4, and 5. It turned out to be the most versatile technique because it allowed for analyzing time-series data in various ways along a continuum, ranging from fully linear to fully nonlinear. In the linear domain, SMAP results are similar to VAR results. An important practical difference though, is that the VAR technique has already been used extensively in a lot of different fields, while SMAP had only been used sporadically at the time of my research (e.g., Deyle et al., 2013; Hsieh et al., 2005; Sugihara et al., 1996). VAR has been included in major statistical software suites and has been well documented. SMAP is more experimental and lacks additional tools to prepare the data before analysis and analyze the results afterwards. For example, it is possible to do a VAR analysis with categorical data, by using dummy variables. For now, this is impossible in SMAP, as it assumes that variables are continuous. Still, the presented studies

highlighted some positive features of SMAP, such as its ability to analyze data with possible nonlinear features, and its ability to analyze periodic data in a unique way by combining it with bundle embeddings.

I combined my SMAP analyses with a bootstrapping approach. This made it possible to obtain probability-density distributions for SMAP's parameters, without assuming any parametric form. Using the bootstrap distribution, CIs and NRMSEs were calculated, to be used in further analyses. The bootstrapping approach had already been used for CCM analyses (Clark et al., 2015). The results from my analyses showed distributions that were non-normal and slightly asymmetric, justifying the choice to use bootstrapping.

Bundle Embeddings

The bundle-embedding approach was described in Chapters 4 and 5. When synchronization between systems takes place, with one system strongly forcing the other, this may result in repeating patterns in the time series of the forced system. This gives rise to additional variance in the time series, which has to be addressed when carrying out analyses. In such cases, it may be better to take the state of the forcing system into account when constructing the embeddings for the forced system (Stark, 1999). This is attained by creating separate embeddings for the forced system for each possible state of the forcing system. In Stark's paper, these are called 'bundle embeddings'. An advantage of using bundle embeddings is that the problem of additional variance is addressed without having to correct for the repeating pattern directly in the time series. Traditionally, such corrections are usually carried out by applying linear methods (e.g., detrending by subtracting the mean value), which may remove any nonlinear features that are present in the data. The bundle-embedding's advantage however, comes at the cost of having fewer embedding vectors in each embedding, resulting in a lower reliability of the results for each bundle embedding separately, than for a single embedding that contains all vectors, but that does not adjust for temporal patterns. This implies that this technique can only be applied when time series are of sufficient length, again stressing the importance of collecting long time-series data when the aim is to investigate non-linear associations.

Cortisol is known to vary according to a diurnal pattern. In the analyses in Chapter 4 and 5, I attributed the diurnal pattern to synchronization with external parameters (e.g., sunlight, the daily alarm clock, etc.). In other words, cortisol is synchronized to the clock. Consequently, I constructed separate cortisol-embeddings for each possible state of time of day. In Chapter 4, this resulted in night embeddings and day bundle-embeddings, and in Chapter 5, in morning, afternoon and evening bundle-embeddings. An interesting result in Chapter 5 was that the most optimal bundle embeddings for morning cortisol had higher dimensions than those for afternoon and evening cortisol. This was interpreted as morning cortisol being influenced by more factors than afternoon or evening cortisol, sug-

gesting that cortisol's morning value is influenced by events of the day before, but that its decay during the day follows a more autonomous pattern. Such insights could not have been obtained from carrying out an analysis on the full embedding only. Interestingly, the bundling approach could also be introduced in regular, linear VAR analyses, as a means of correcting for repeating patterns without altering time-series values. Of course, nonlinear features will not be observable with this method, but it would allow for obtaining different parameter sets for different phases within the pattern. To the best of my knowledge, the combination of VAR and bundle embeddings has not yet been explored.

Embedding parameters

I adopted two different approaches to determine the optimal values for the lag size and the embedding dimension. In Chapter 2, I used the simplex technique (Sugihara & May, 1990) to conduct an exhaustive search within a bounded parameter space. This technique was chosen because the subsequent CCM analyses used a similar method to carry out predictions. The results showed that the simplex projections did not produce a clearly optimal set of embedding parameters. Instead, the prediction strength of the simplex projection varied only slightly with embedding dimension or lag size, with only a very modest optimum (i.e. the optimal value was hardly distinguishable from its adjacent values, or more than one optimal value could be found). Maybe as a result, the parameter values for the most optimal embeddings in the CCM-analyses were often different from the simplex results. I would therefore suggest to always compare the results for several parameter combinations and find out if prediction values vary smoothly and consistently with the parameter combinations. If not, it may be that there is a large influence of outliers or noise. However, further research on simulated data would be needed to draw definitive conclusions about this relationship.

The aim of Chapters 3 and 5 was to analyze differences in the prediction results between univariate and multivariate embeddings, using the SMAP technique. Here, the approach was to use univariate analyses to find a set of optimal embedding parameters. The multivariate embedding was constructed by expanding the optimal univariate embedding by adding values from the time series of the second variable. Another possibility would have been to find the optimal embedding parameters for the univariate and multivariate embedding separately, but I think that this would considerably increase the probability of running into a multiple comparisons problem (Benjamini, 2010), because the number of multivariate embeddings to choose from would increase considerably. The results from Chapter 2 showed that in some cases, a changed parameter value (e.g., the embedding dimension) resulted in very different results. This would increase the probability of finding a significant difference in prediction strength between a univariate embedding and a multivariate embedding with very different parameters. Therefore, the choice was made to build further on the parameters that were determined in the univariate analysis. To analyze the

multiple comparisons problem in more depth, it would be interesting to extend the studies from Chapters 3 and 5 with analyses over all possible parameter combinations and examine if the results vary smoothly over the parameter space.

In the SMAP technique, the theta parameter makes it possible to apply a range of models on a continuum from completely global to local. The results from Chapter 3 showed that the prediction strength of SMAP varies smoothly with the value of theta, making it relatively easy to find its optimal value. In the multivariate analyses in Chapters 3 and 5, the value for theta was not kept the same between the univariate and its corresponding multivariate embedding. The reason for this was that the multivariate embedding contained one more variable than the univariate embedding, effectively increasing the dimension by one. This may change the relative distances between embedding points, which means that the optimal value for theta should also be re-established. The precise relationship between theta and addition of a, possibly nonlinear, variable has not yet been determined. It would be interesting to do a simulation study to gain more insight into the value of theta when embeddings are expanded with additional variables.

Outliers

To correct for outliers, values that deviated more than 2.5 SDs from the mean were removed from the time series before embedding construction. In future analyses, it would be interesting to compare this approach with more sophisticated ways of removing outliers from nonlinear time series (e.g., Galeano & Peña, 2013).

Nonlinearity

It is difficult to draw definitive conclusions about the presence of nonlinearity in the data that was used in my studies. The CCM results from Chapter 2 show a clear convergence for at least one participant, suggesting nonlinearity (Clark et al., 2015; Sugihara et al., 2012). However, these analyses did not yet take the cyclic pattern of cortisol into account. It is not yet clear to what extent such patterns can influence the CCM results. Interestingly, the SMAP study in Chapter 5, which used bundle embeddings to correct for the cyclic pattern, did show a better performance of local models when predicting morning-cortisol values. This may be an indicator for the presence of nonlinearity (Sugihara et al., 1996). It would be interesting to use CCM on the data that were used in Chapter 5, in combination with bundle embeddings to find out if strong convergence can be observed. That would provide additional evidence for the presence of nonlinearity. So far, the combination of CCM and bundle embeddings has not yet been attempted. Taken together, the results from Chapters 3, 4 and 5 definitely do suggest that linear methods might not always be the most optimal choice for analyzing psychophysiological time-series data.

Causality

This thesis explored two different methods to analyze causal relationships between variables in nonlinear dynamical systems. The CCM method was discussed in Chapter 2. Causal relationships that are found with CCM may be regarded as a distinct form of causality, applicable to nonlinear dynamical systems (Sugihara et al., 2012). Its largest difference with more common forms of causality (e.g., GC) is that it does not rely on linear correlations to detect associations within data. In Chapter 3, possible causal relationships between variables were analyzed with SMAP. The contribution of a predictor variable was assessed by comparing predictions where the predictor variable was left out of the total set of predictor variables with predictions where it was included. As such, it is comparable to GC causality, which is applicable in the linear domain. However, when some of the system's variables are of a stochastic nature, it is not directly possible to draw conclusions about the direction of causality with SMAP. In that case, improved SMAP prediction of a variable Y , after inclusion of predictor variable X , may be indicative of either Y being nonlinearly coupled to X , X being stochastic and nonlinearly coupled to Y , or X having a GC influence on Y . The discussion in Chapter 3, explored these possibilities in more detail. It showed that additional considerations need to be taken into account before definite conclusions about the direction of causality can be made when using SMAP. Further studies, based on simulated data, could provide more insight into the relationships between results from different methods and the inferred causal directions within a system.

Nomothetic knowledge

The methods described in this thesis used individual time-series data to analyze relationships between variables within a person. These types of studies primarily lead to idiographic knowledge that applies to the individual only. Additional steps were needed to obtain nomothetic knowledge that is generally valid from these idiographic results. The approach that was used in this thesis was to use the individual time-series methods to obtain idiographic summary statistics (such as the NRMSE and SD), which were subsequently aggregated on the group level to obtain some kind of nomothetic conclusion. This pooling approach is often used in analyses of extensive individual time-series data of groups of individuals (Booij et al., 2016; Stavrakakis et al., 2015). Chapter 2 also showed how, in the nonlinear domain, it might be possible to use dewdrop embeddings to derive nomothetic conclusions, without first doing analyses on the individual level. Instead of aggregating individual results, the dewdrop method combines individual time series before embedding-construction. Dewdrop embeddings may be better suited to truly detect whether individuals share the same nonlinear dynamical system, whereas the pooling approach would only

provide conclusions based on the final outcome of individual analyses, by means of a linear aggregation operation. Dewdrop embeddings were only briefly studied in Chapter 2, but it may be worthwhile to study this method more extensively.

Strengths and limitations

The research that is described in this thesis has several strengths. One of the main strengths is the use of intensive idiographic time-series data, making it possible to draw conclusions on the individual level. Another strength is the application of nonlinear methods to study data that may possess nonlinear features that are impossible to capture with traditional linear methods. A specific strength of the SMAP method is its nonparametric nature. It is not necessary to make a priori assumptions about the underlying system. Another strength of SMAP is its versatility: it has the ability to analyze data in a linear as well as a nonlinear way, with the possibility to gradually change between the two. The application of bundle embeddings is another specific strength as it allows for studying data with recurrent patterns, without having to correct the time series beforehand, using operations that may eliminate any relevant non-linear associations.

The same factors that can be considered strengths are also responsible for the limitations of this research. SMAP, CCM, dewdrop embeddings and bundle embeddings are quite new in the field of psychophysiological research. Much has still to be learned about the influence of noise and influential points. There are no well-established procedures for determining optimal time-series lags or the number of dimensions when constructing the embeddings. Furthermore, these methods rely on intensive time-series data of sufficient length and granularity. In a time-series context, granularity – the level of detail in the data – is directly related to the length of the time interval between successive measurements. When working with human participants, it is difficult to obtain long and detailed time-series data because data collection spans a long period of time and measurements need to be taken frequently. Especially for vulnerable subjects (e.g., depressed patients) this may be too burdensome. Fortunately, recent technological developments have made it easier and more feasible to sample physiological and psychological variables at high frequency over extended periods (see below).

Future developments

Ideally, the nonlinear embedding-based techniques should be easily accessible from standard software packages. The R library that is described in the appendix is a first attempt at reaching this objective. However, as was mentioned earlier, more research is needed to

establish the exact conditions under which these methods can be used. Furthermore, the methods that were used to find the optimal embeddings or SMAP-parameters may need to be analyzed more extensively, using simulated data.

The described embedding-based methods can currently only be used with continuous data. To be able to handle ordinal questionnaire-data, several variables need to be combined to obtain quasi-continuous sum-score variables. It would be interesting to find out whether it is possible to use the ordinal variables directly, without grouping them together in a sum-score. If that is possible, it would greatly enhance the applicability of embedding-based methods in the behavioral sciences, where ordinal self-report assessments or rating scales are commonly used.

In the last decade, promising developments have taken place in the field of data-sampling. Many biological variables can now be more easily measured than ten years ago (Poudineh et al., 2021). As a result, it has become much easier to obtain long time-series with a high granularity, which greatly enhances the statistical significance of the outcomes of embedding-based techniques.

Concluding remarks

We are living in an age in which an ever-increasing amount of real-life psychophysiological longitudinal data can be collected. We know that these data may potentially contain nonlinear and cyclical associations that may inform our understanding of the mechanisms underlying mental-health problems. These associations cannot be optimally analyzed with the conventional, linear techniques and it is necessary that we consider suitable and targeted techniques to obtain valid insights into the non-linear associations involved in the etiology of psychopathology. The techniques that are described in this thesis may still be very new and in a developing phase, but combined with recent developments in data sampling, they may provide a means to overcome the limitations of linear techniques and may provide a powerful addition to the available tools for time-series analysis. These techniques' ability to obtain idiographic information can lead to new insights in the field of psychopathology and can help to overcome the heterogeneity that plagues group-based studies.

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