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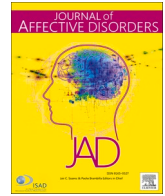
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Dynamic time warp analysis of individual symptom trajectories in depressed patients treated with electroconvulsive therapy

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ABSTRACT

Background: Although electroconvulsive therapy (ECT) effectively improves severity scores of depression, its effects on its individual symptoms has scarcely been studied. We aimed to study which depressive symptom trajectories dynamically cluster together in individuals as well as groups of patients during ECT using Dynamic Time Warp (DTW) analysis.

Methods: We analysed the standardized weekly scores on the 25-item abbreviated version of the Comprehensive Psychopathological Rating Scale (CPRS) in depressed patients before and during their first six weeks of ECT treatment. DTW analysis was used to analyse the (dis)similarity of time series of items scores at the patient level (300 'DTW distances' per patient) as well as on the group level. Hierarchical cluster, network, and Distatis analyses yielded symptom dimensions.

Results: We included 133 patients, 64.7% female, with an average age of 60.4 years (SD 15.1). Individual DTW distance matrices and networks revealed marked differences in hierarchical and network clusters among patients. Based on cluster analyses of the aggregated matrices, four symptom clusters emerged. In patients who reached remission, the average DTW distance between their symptoms was significantly smaller than non-remitters, reflecting denser symptom networks in remitters than non-remitters ($p=0.04$).

Limitations: The assessments were done only weekly during the first six weeks of ECT treatment. The use of individual items of the abbreviated CPRS may have led to measurement error as well as floor and ceiling effects.

Conclusion: DTW offers an efficient new approach to analyse symptom trajectories within individuals as well as groups of patients, aiding personalized medicine of psychopathology.

1. Introduction

Major depression and bipolar disorder are common mental disorders with one year prevalences of 4.4% and 1.5% respectively, and rank amongst diseases with the highest global burden of disease. (Clemente et al., 2015; Collaborators and 2017) Due to differences in aetiology, depressive episodes are highly heterogeneous among patients translating in diverse symptom trajectories and prognosis. (Kelley et al., 2018) A variety of predictors of depression recovery has been identified in large cohorts with or without treatment, from demographic variables, to stressful life-events or specific symptoms of depression (e.g., demographic, personality traits, and life event variables). (Keller et al., 2007; Lux and Kendler, 2010) Moreover, distinct risk factors were associated with improvement of distinct symptoms over time. For example, stressful life events were associated with the items of the PHQ-9 'concentration' and 'suicide' but not with 'self-blame' or 'depressed'. (Fried et al., 2014) These findings suggest that the mere use

of sum scores of depression severity scales may obscure meaningful differences in trajectories of individual symptoms. (Fried et al., 2014; van Eeden et al., 2019)

An alternative view to the oversimplified sum scores (Fried and Nesse, 2015) is that individual symptoms of depression directly affect other symptoms (i.e., network hypothesis of depression) and therefore do not follow a similar trajectory over time. (Bringmann et al., 2015; Fried et al., 2016) The network hypothesis conceptualises depression as a 'complex dynamic system' rather than a 'generic latent variable model'. The network of symptom-symptom interactions is thought to evolve during treatment (such as with ECT). (Cramer et al., 2016) Moreover, symptoms may follow markedly different paths between patients. Graphs are used to represent (potential causal) relationships (as edges) between symptoms (as nodes). However, despite the increasing interest in the interaction of symptoms, the majority of network analyses have focussed on cross-sectional networks derived from groups of patients. (Belvederi Murri et al., 2018; Park and Kim,

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2020) To understand causal interaction between symptoms, longitudinal analyses may help to uncover similarities and differences of symptom dynamics over time, even within individual patients. (Borsboom & Cramer, 2013) This may deepen our understanding of depression as a complex dynamic system. (Borsboom, 2017; Borsboom and Cramer, 2013; Cramer et al., 2016)

Several innovative studies focussed on such dynamics by using lag-1-time analyses. (Borsboom and Cramer, 2013; Bringmann et al., 2015; Epskamp et al., 2018; Fisher, 2015; Fisher et al., 2017) Group-level approaches often assume that symptom dynamics are approximately similar in each patient. The patient-level idiosyncratic approach in which the interactions between symptoms may be different in each patient implies a more personalized approach. (Fisher, 2015) Only a few studies have applied such longitudinal approaches to individual patients. (Epskamp et al., 2018; Fisher, 2015; Fisher et al., 2017) Despite the advantages of time lag analyses, a disadvantage is that when shifts in time correspond over longer or shorter periods than a single preceding time-interval, they are no longer recognised as being associated. We therefore propose an alternative, with more ‘elastic’ distance measures through ‘Dynamic Time Warp’ (DTW), (Giorgino, 2009) which may enable the study of between-item dynamics over a range of time intervals.

Electroconvulsive therapy (ECT) is an effective treatment option for depression with response rates of 60-80%, especially for patients with treatment-resistant depression and depression with psychotic features. (Kho et al., 2003) Although the trajectories of sum scores on severity measures have been studied in patients treated with ECT, (Cinar et al., 2010; Petrides et al., 2001) we are not aware of studies that focused on the trajectories of individual symptoms during ECT treatment. Symptom dimensions of Montgomery-Åsberg Depression Rating Scale (MADRS) were the focus of a study among 110 depressed patients. (Veltman et al., 2018) Although all three symptom dimensions showed a rapid improvement during ECT treatment, the ‘mood’ dimension showed the steepest decline.

In the present study, we therefore aim to explore trajectories of individual symptoms by analysing the weekly individual scores on the 25-item abbreviated version of the Comprehensive Psychopathological Rating Scale (CPRS) (Goekoop et al., 1992; Montgomery and Asberg, 1979; Tyrer et al., 1984) in 133 depressed patients treated with ECT, during the first six weeks of treatment using the novel approach of DTW analysis. These analyses were conducted both on the patient-level as well as on the group-level. We hypothesize that such an analysis will yield different dimensions of symptoms than cross-sectional analyses have, and that more densely connected networks are prone to critical transitions (i.e., tipping points) and have a higher chance of changing from a depressed state into a euthymic state. (Cramer et al., 2016)

2. Methods

2.1. Study population

In this retrospective cohort study, we included depressed inpatients who were treated with ECT at the Department of Psychiatry of the Leiden University Medical Center (LUMC) in the Netherlands between January 2009 and January 2019. These patients met criteria of a major depressive disorder (MDD) or a depressive episode as part of a bipolar disorder, diagnosed by a psychiatrist according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)*. The diagnoses were confirmed through the MINI International Neuropsychiatric Interview – Plus 5.0.0 (MINI-PLUS 5.0.0) (Sheehan et al., 1998) and by assessment by a psychiatrist of the LUMC. In case of more than one ECT treatment episode in the LUMC between January 2009 and January 2019, only the first episode fulfilling the inclusion criteria was included. Patients with primary psychotic disorders or catatonia, or the inability to complete questionnaires (in Dutch) were excluded from our analyses. For inclusion, patients must have Routine Outcome

Monitoring (ROM) measurements during at least four of the first six weeks of treatment, including the baseline assessment before the start of ECT. The Medical Ethics Committee decided that this analysis was not subject to the Medical Research Involving Human Subjects Act (WMO), and did not require a formal review because it concerned a retrospective status study (registration number G19.036).

2.2. Electroconvulsive therapy procedures

Antidepressants and mood stabilizers were tapered off and ECT was performed twice weekly according to the Dutch Guidelines, (van den Broek et al., 2010) using a brief pulse (0.5-1.0 msec) constant Thymatron IV system (Somatix Inc., Lake Bluff, USA). Unilateral or bifrontotemporal ECT was applied according to the decision of a psychiatrist based on the clinical characteristics and treatment history. The stimulus dose was calculated by stimulus titration during the first ECT session or in case of contra-indications of titration (e.g., age >75 years or severe somatic comorbidity) the age titration method protocol was used as described in the manual accompanying the Thymatron ECT machine. (Abrams and C.M., 1989) During the following ECT sessions the stimulus dose was titrated if necessary. Etomidate lipuro was the anaesthetic drug of choice (0.2-0.3 mg/kg), and propofol (1.5-2.0 mg/kg) was used when etomidate was not well tolerated. Succinylcholine (0.5-1 mg/kg) was used as a muscle relaxant. If the clinical condition worsened or if no clinical improvement was seen after eight unilateral treatments, a switch to bifrontolateral ECT was made. ECT was continued until no further improvement was observed for two weeks after an initial response, or if there was no response to treatment after at least 8 unilateral and 8 bilateral sessions.

3. Measurements

We used the weekly ROM assessment and medical records to gather demographic data, including age, gender and somatic diagnoses at baseline, as well as data on psychiatric diagnosis, duration of the depressive episode, presence of psychotic features, number of prior depressive episodes and prescribed medication at time of admission.

At baseline and weekly follow-up, the CPRS was completed for evaluation of the treatment. The original CPRS consists of 65 items and was constructed to quantify the effect of treatment on various psychiatric disorders. (Asberg et al., 1978) The abbreviated CPRS consists of the MADRS, (Montgomery and Asberg, 1979) the Brief Anxiety Scale (BAS) (Tyrer et al., 1984) and a scale that assesses psychomotor inhibition (REM), (Goekoop et al., 1992) resulting in 25 items, each on a 0-6 Likert scale, with higher scores indicating a higher severity. A trained research nurse performed the ROM assessments weekly on a non-ECT day as part of routine clinical care. The abbreviated CPRS has the advantage of being a partial observer-based questionnaire that is suitable for weekly administration. In case of a missing assessment, these scores were omitted for that particular week. Because we analysed the (dis)similarity of changes during each subsequent assessment (i.e., improvement or deterioration) within each individual patient, DTW handled missing assessments rather well. Only after we had constructed each distance matrix for each patient (i.e., idiographic approach), we combined the different distance matrices together in the nomothetic approach using distatis analysis.

3.1. Statistical analysis

Frequency distributions for categorical variables and means with standard deviations (SD) or medians with interquartile ranges (IQR) were used to describe the baseline characteristics.

We used DTW to calculate distances between each pair of symptoms within each patient. (Berndt and Clifford, 1994) DTW is an approximate pattern detection algorithm that measures dissimilarity between two temporal sequences. It uses a dynamic (i.e., stretching and compressing)

programming approach to minimize a predefined distance measure, in order for the two time-series to become optimally aligned through a warping path. The ‘optimal’ alignment minimizes the sum of distances between aligned elements. The DTW function computes the alignment with a symmetric continuity constraint, implying that arbitrary time compressions and expansions are allowed, and that all elements must be matched. We used the step pattern ‘symmetricP0’ and the global constraint of a ‘Sakoe-Chiba’ window band of 1 around main diagonal (Fig. 1). (Sakoe and Chiba, 1978) This implied that only changes in symptom scores that were maximally 1 time points away (plus or minus 1 weeks) were used within the chosen warping window. As a result, items with the best alignment, having a more similar slope and other dynamics (i.e., changes that co-vary over time) resulted in the smallest distance. All item scores were standardized (i.e., z-scores) before the DTW analysis, as some (e.g., “11. Compulsive thoughts”) tended to score lower on average than other items (e.g., “4. Anhedonia”). This prevents clustering together of symptoms that tend to have a similar average score across patients. Only to ease the interpretation of the DTW technique in Fig. 1, we used unstandardized item scores to visualize the distance calculation in this individual patient.

We analysed the temporal dynamics of each of the 25 time series of individual CPRS items in a distance matrix by using a DTW technique, resulting in $n(n-1)/2 * 133 = 39,900$ calculated ‘DTW distances’. An example of the analysis by DTW technique of patients 7 is shown in Fig. 1. Fig. 1A shows the scores at all items at baseline and during the first six weeks of treatment. The items ‘pessimistic thoughts’ and ‘apparent sadness’ were chosen for this example and the trajectories of the symptoms were plotted in Fig. 1B. The dotted lines illustrate the warped (i.e., elastic) modification of one item to get the scores of the other item, representing the DTW-distance. To calculate the DTW

distance, a matrix was constructed in which the x-axis contains scores of ‘pessimistic thoughts’ and the y-axis contains the scores of ‘apparent sadness’ (Fig. 1C). The distance between the items was calculated for the matrix for each time-point, on basis of the ‘symmetricP0’ step pattern recursion shown in Fig. 1C using the r “parDist” function (with method=“dtw”).

Items that remained at the lowest level of 0 throughout all the up to 7 assessments were omitted, as such items tend to cluster (spuriously) together. The DTW distances between each symptom pair in each patient were grouped in a distance matrix containing 300 distinct distances per patient. Per patient a dendrogram is given to represent the distance between the dynamics of the 25 symptoms in that patient.

The R package ‘qgraph’ was then used to visualize symptom networks and to compute centrality measures. In each symptom network, a node represents an individual item. Associations between nodes are represented with grey edges, in which thicker lines represent stronger associations and items in the centre of the network represent items that are represented as core to the depression network (all distances were positive). The edges between symptoms were all positive as a dissimilarity between a pair of items (i.e., $1 / \text{distance}$) could not have negative values.

The centrality index was calculated per item and shown in a graph per patient. The centrality represents the number and strength of the associations that each item has with other items. Thus, the higher the centrality of a symptom, the stronger that symptom was dynamically linked to the other symptoms within that patient.

Next, we focused on nomothetic group-level analyses using ‘Distatis’ analysis. (Abdi et al., 2005) A Distatis analysis is a technique for combining multiple distance matrices in order to construct compromise plots for which all results of the separate distance analyses are used to

A. a-CPRS item score over time in one patient

Time(weeks)	0	1	2	3	4	5	6
1 Autonomic disturbances	3	4	2	1	2	0	0
2 Aches and pains	4	2	0	3	2	2	4
3 Inner tension	0	0	0	0	0	0	0
4 Anhedonia	3	2	4	4	2	4	4
5 Inability to feel	2	0	0	0	0	0	2
6 Sadness	3	3	2	2	1	2	2
7 Pessimistic thoughts	5	4	1	3	3	4	3
8 Suicidal thoughts	3	0	0	0	0	2	2
9 Hypochondriasis	4	1	0	0	0	2	2
10 Worrying over trifles	0	0	0	0	0	0	0
11 Compulsive thoughts	0	0	0	0	0	0	0
12 Phobias	0	0	3	2	0	0	0
13 Hostile feelings	5	2	4	3	3	3	4
14 Lassitude	0	0	1	0	2	1	0
15 Concentration difficulties	2	0	0	2	2	2	2
16 Reduced appetite	2	0	1	1	2	2	2
17 Reduced sleep	2	1	0	2	1	1	2
18 Derealization	3	2	2	2	2	2	3
19 Depersonalization	5	4	3	4	2	4	4
20 Apparent sadness	6	2	3	3	2	3	4
21 Lack of appropriate emotion	2	0	0	0	0	0	2
22 Observed autonomic disturbances	6	3	4	3	3	4	4
23 Reduced speech	4	2	2	0	1	2	0
24 Slowness of movement	0	0	0	0	0	0	0
25 Observed muscular tension	0	0	3	0	0	0	0

C. Step pattern and constraint,

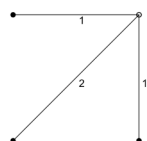
‘symmetricP0’ step pattern recursion:
 $g[i,j] = \text{minimum of}$

- $g[i-1, j-1] + 2 * d[i, j]$
- $g[i, j-1] + d[i, j]$
- $g[i-1, j] + d[i, j]$

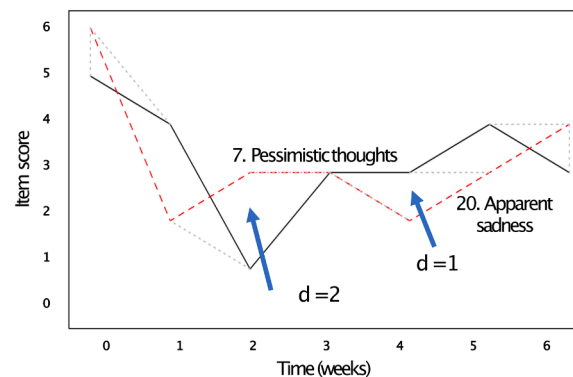
$d = \text{local distance}$
 $g = \text{stretched distance}$

Sakoe Chiba Band:

- window size = 2
- constraints on the alignment, limiting the warping scope



B. Scores of items 7 and 20 over time, with DTW alignment



D. Optimal DTW warping route

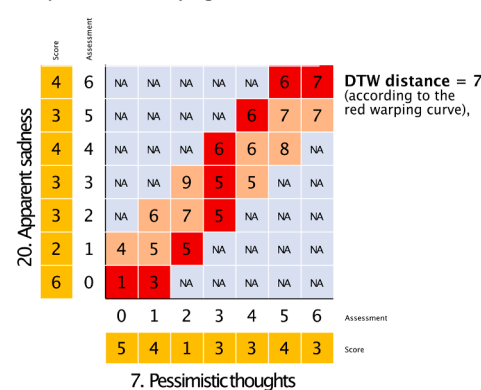


Fig. 1. Example of DTW analysis of a single patient no P7, showing [A] (unstandardized) scores of the individual symptoms in time; timepoint “0” is baseline, [B] trajectories of symptom 7 “Pessimistic thoughts” and symptom 20 “Apparent sadness”, [C] calculation of DTW distance based on a ‘symmetricP0’ step pattern and a Sakoe Chiba Band of 1 (thus plus or minus 1 weeks), and [D] the optimal warping route between symptom 7 “Pessimistic thoughts” and symptom 20 “Apparent sadness, yielding a DTW distance of 7.

calculate the position in the plot (i.e., three-way principal component analysis). This results in a two dimensional plane in which the distance between the symptoms corresponds with the compromise of differences in dynamics of symptoms based on multiple analyses, which represent their consensus. This technique was used to visualise symptom dimensions. We estimated the optimal number of clusters by a scree plot, and using the elbow method based on the percentage of variance explained as a function of the number of clusters. Next, a hierarchical cluster analysis was applied according to ‘Ward.D2’ clustering methods. (Murtagh and Legendre, 2014) With ‘Ward.D2’ the total within-cluster variance was minimized, and the dissimilarities were squared before cluster updating. This hierarchical clustering was visualized in a dendrogram.

To check the robustness of clustering of symptoms with a different approach, all distances matrices were averaged over the patients, weighted for the number of time points and these assessments were done for each of the patients (ranging from 4 through 7 time points), resulting in 300 mean distances. The distance matrix of the total group was used to visualize the group-level symptom network.

We aimed to compare network density between remitters and non-remitters. The average DTW distance among all symptom trajectories for each patient individually was calculated. Symptoms that scored consistently zero were deleted before this average distance was calculated for that particular patient, as all such symptoms would result in distances of zero. Shorter average DTW distances reflected denser interconnections between symptoms and longer average DTW distances reflected looser longitudinal connectivity between symptoms. In order to investigate the relationship between network-density and reaching remission, we calculated the residuals of the regression analysis, that also included the number of assessments and the CPRS sumscore in the model. These residuals were plotted using box plots according to whether remission was reached, and a Wilcoxon signed-rank tests was used to compare the average DTW distance among the two samples.

The trajectories of mean individual item scores during ECT treatment on the group level were analysed using multilevel regression analysis using the ‘lme4’ package (with time as a categorical variable), and presented this in a graph.

To validate our findings of the symptom dimensions further, our sample of 133 patients was randomly split into two samples of 67 and 66 patients. Using the Procrustes algorithm (from the R Package ‘networktools’) networks were obtained (based on each of the two average distance matrices). The congruence coefficient was calculated for the two distance matrices.

The baseline table was constructed using SPSS version 25 (IBM Corp Released 2017, IBM SPSS Statistics for Windows, Version 25). For all other calculations we used RStudio (R version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria, 2016. URL: <https://www.R-project.org/>), with main packages ‘dtw’ (version 1.20.1), ‘parallelDist’ (version 0.2.4), ‘DistatisR’ (version 1.0.1), ‘qgraph’ (version 1.6.2), and ‘networktools’ (version 1.2.1).

4. Results

4.1. Demographic and clinical characteristics

The baseline characteristics of the 133 patients are shown in Table 1. The mean age was 60.4 (standard deviation [SD] 15.1, range 20 to 87) years and the majority was female (64.7%). The mean score on MADRS at baseline was 31.3 (SD 8.0) points, indicating moderate to severe depression. The mean number of assessments per patient was 6.2 (819 assessments to be analysed in 133 patients). There were 112 instances in which the time interval was larger than 1 week.

Table 1

Baseline sociodemographic and clinical characteristics.

	Estimate (n=133)
Age, mean (SD)	60.4 (15.1)
Male gender, no. (%)	47 (35.3%)
Diagnosis:	
- Unipolar depression	103 (77.4%)
- Bipolar depression	30 (22.6%)
Disease duration (months), median (IQR)	11 (5 – 24)
Psychotic features, no. (%)	48 (36.1%)
Depression severity scores (vCPRS), mean (SD):	
- MADRS subscale	31.3 (8.0)
- Brief anxiety subscale (BAS)	17.9 (6.4)
- Inhibition subscale	6.9 (4.0)
MMSE, median (IQR; n=65/133; 48.9%)	28 (24 – 29)

Baseline sociodemographic and clinical characteristics. Abbreviations: SD denoted standard deviation; IQR = interquartile range (P_{25} , P_{75}); no. = number; MADRS = Montgomery Åsberg Depression Rating Scale (i.e., sum of items 3, 4, 6, 7, 8, 14, 15, 16, 17, and 20); BAS = Brief Anxiety Scale (i.e., sum of items 1, 2, 3, 9, 10, 12, 13, 17, 22, and 25); Inhibition scale (i.e., sum of items 5, 20, 21, 23, and 24)

4.2. Individual patient analyses (idiographic approach)

Fig. 2 shows that idiographic analysis in two depressed patients (P80 and P114) who received ECT. Panels A show the trajectories of each sample-standardized item over time during the first 6 weeks of ECT treatment according to the 3 most parsimonious clusters. Panels B present the clustering of the symptoms in dendrograms. Panels C show the individual’s symptom networks. Panels D show the centrality indices of all symptoms. These idiographic results for all individual 133 patients are presented in the accompanying PDF (see Supplementary Figure 1).

Example 1. P80 was a 43-year old female with a depressive episode in a bipolar I disorder without psychiatric comorbidity. Trajectories of the 20 individual symptoms are shown (as 5 items remained at the level of 0 throughout follow-up). She was treated with 16 bilateral ECT sessions and partial remission was achieved followed by a short hypomanic period. Lithiumcarbonate and nortriptyline were started and the patient was transferred to another psychiatric hospital for resocialization.

Example 2. P114 was a 68-year old male with unipolar depression without psychiatric comorbidity. He mentioned sadness and worry as his main depressive symptoms at hospital admission. He was treated with five unilateral right ECT sessions and fifteen bilateral ECT sessions and complete remission was achieved. Nortriptyline and lithiumcarbonate were started and the patient was transferred to another psychiatric hospital for resocialization.

4.3. Group-level analyses (nomothetic approach)

Based on the scree plot (Fig. 3A) and the dendrogram (Fig. 3B) based on hierarchical clustering after Distatis analysis of all 133 distance matrices, we identified four main dimensions of symptoms: 1] core depressive symptoms (with 9 items: ‘anhedonia’, ‘apparent sadness’, ‘sadness’, ‘inner tension’, ‘observed muscular tension’, ‘concentration difficulties’, ‘pessimistic thoughts’, ‘worrying over trifles’, ‘lassitude’), 2] retardation (with 8 items: ‘reduced speech’, ‘observed autonomic disturbance’, ‘slowness of movement’, ‘hostile feelings’, ‘suicidal thoughts’, ‘lack of appropriate emotion’, ‘phobia with avoidance’, ‘inability to feel’), 3] vegetative symptoms (with 4 items: ‘reduced sleep’, ‘reduced appetite’, ‘aches and pains’, ‘autonomic disturbances’), and 4] dissociation/compulsions (with 4 items: ‘hypochondriasis’, ‘derealization’, ‘compulsive thoughts’, ‘depersonalization’). Fig. 3C shows the network plot based on the average distance matrix. The two compromise plots (of the first against the second compromise factor in Fig. 3D, and of the first against the third compromise factor in Fig. 3E) similarly spread the items into its 4 symptom dimensions, which

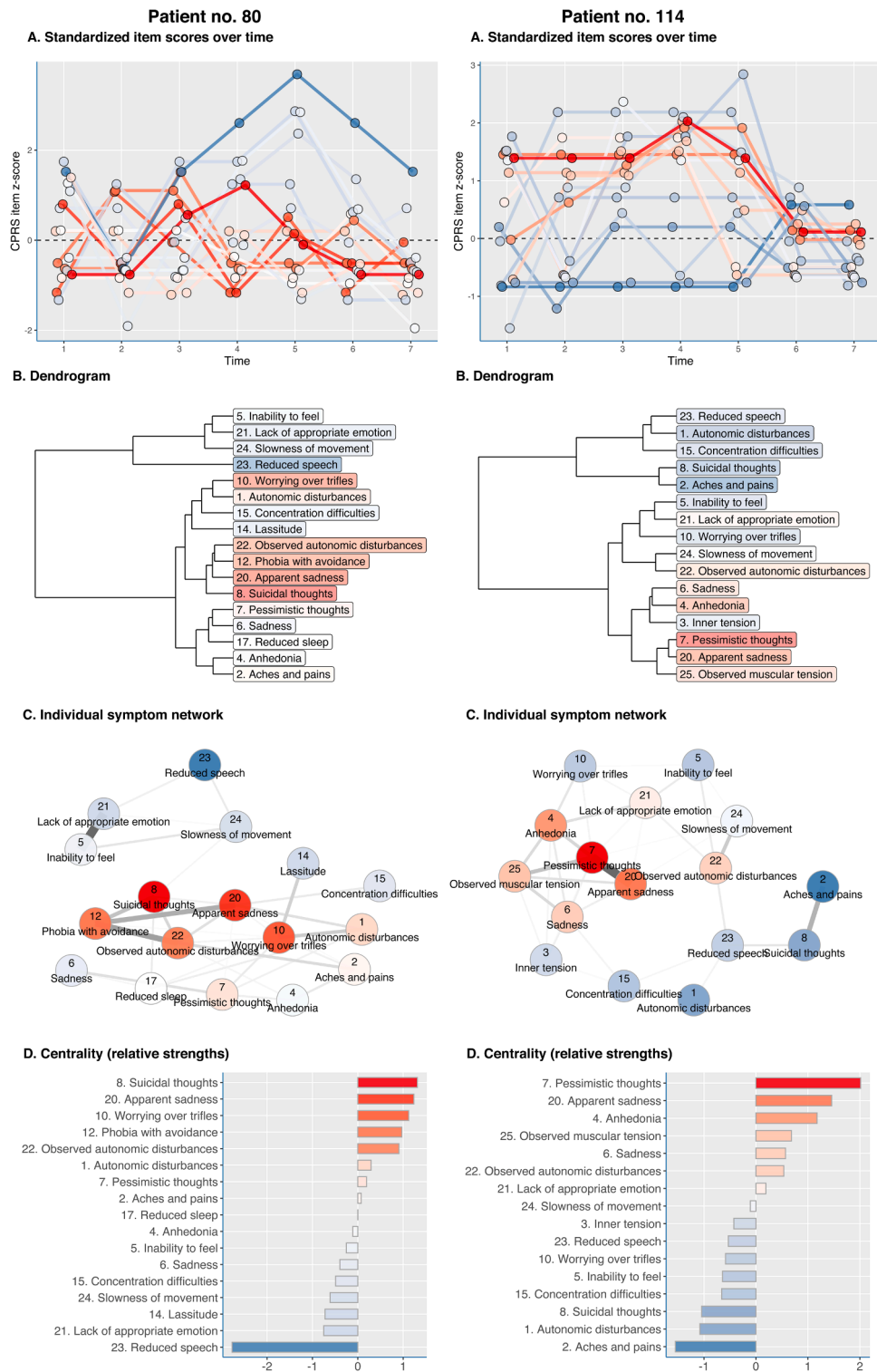


Fig. 2. Idiographic DTW analysis of a single patient no P80 and P114 (see Supplementary PDF), showing [A] trajectories of the standardized individual symptom scores over time; timepoint “1” is baseline, [C] dendrogram based on the individual’s distance matrix, and [C] Network based on the individual’s distance matrix, [D] relative strengths of individual items for the individual patient presented in a graph.

corroborates with the symptom dimensions found in the network plot.

The trajectories of the average item scores are shown in supplementary Figure 1. The items of the ‘core depressive symptoms’ dimension had on average the highest mean scores during the whole ECT course compared with the other symptoms. The scores on ‘dissociation and compulsion’ were relatively low in our sample and showed smaller mean changes during the ECT course. Apparent sadness was the

symptom with the highest mean value over time, and the steepest decline, but retained one of the highest mean scores after 6 weeks. There were some marked exceptions. ‘Concentration difficulties’ tended to improve relatively slower as compared to the other 24 items, probably as a side effect of ECT.

To validate our findings of 4 symptom dimensions further, our sample of 133 patients was randomly split into two samples of 67 and 66

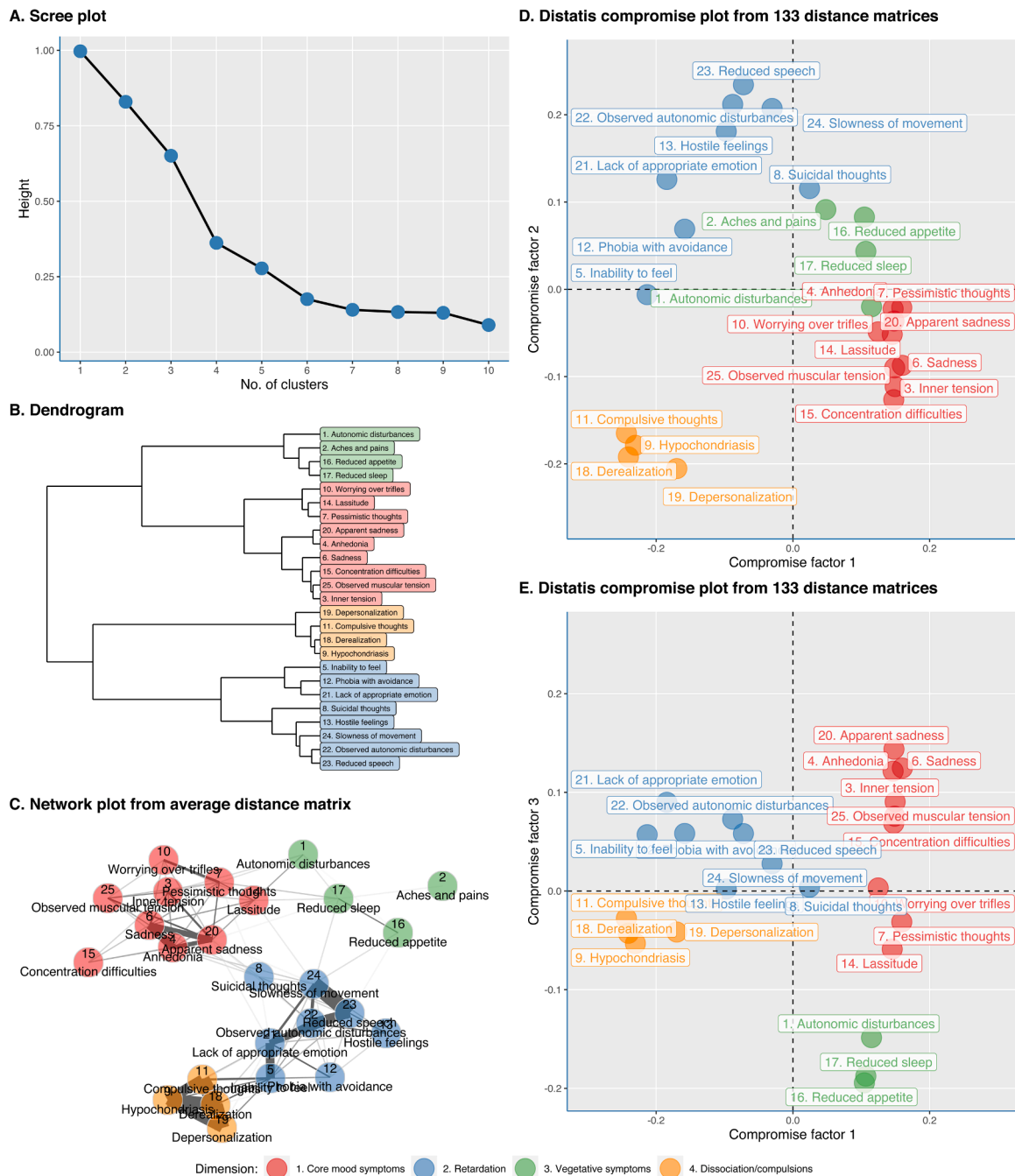


Fig. 3. Group-level DTW analysis of symptom clusters with [A] scree plot of Eigenvalues, [B] the dendrogram based on the distance matrix averaged over all 133 patients, [C] symptom network based on the average distance matrix, [D] Distatis compromise plot for the 25 individual items based on all 133 distance matrices, for which the first and second compromise factors are plotted, and [E] Distatis compromise plot for which the first and third compromise factors are plotted.

patients. These analyses confirmed the robustness of the 4 symptom dimensions in Supplement Fig. 2, with a high congruence coefficient of 0.994, indicating large similarity between the symptom networks of both patient samples.

Finally, we compared the average DTW distance among patients who reached remission after ECT treatment (n=79) versus those who did not (n = 54; Fig. 4). Remitters had a significantly smaller distance than non-remitters, reflecting denser interconnections between symptoms than in non-remitters (p=0.043).

5. Discussion

The results of our analyses in 133 depressive patients treated with

ECT show that the trajectories and clusters of all individual depressive symptoms vary substantially between patients during treatment. These differences may unmask clinical information which is typically not visible when only the sum scores of symptom severity scales are presented. (Fried and Nesse, 2015) We were able to cluster the individual CPRS symptoms at the individual level, and also at the group level, which revealed four symptom clusters on basis of their similar dynamics over time. This clustering was robust as shown by the similar findings in two samples after a random sample split of our patients, and the Distatis analysis and the average distance network also revealed similar symptom dimensions in the total sample. We assume that the clustering of symptoms is the result of (potential causal) interactions between symptoms especially with in each of the symptom clusters. (Cramer et al.,

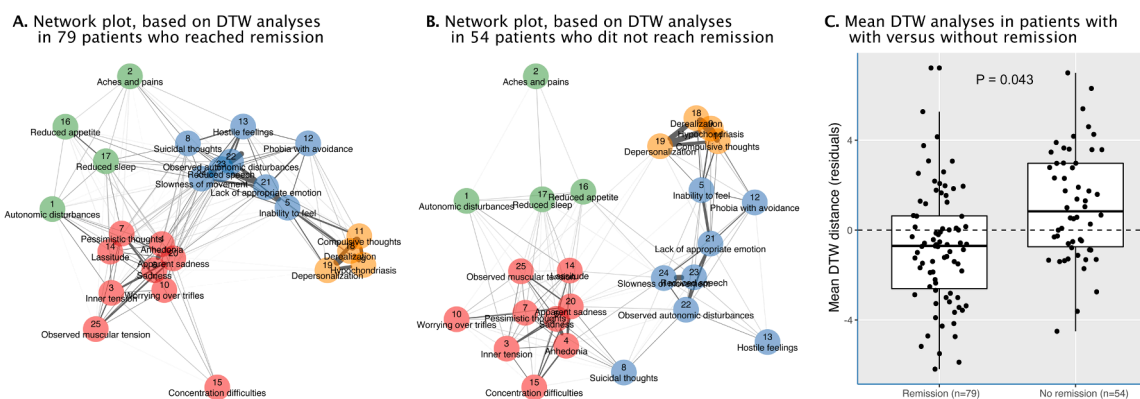


Fig. 4. Analysis of remitters versus non-remitters with [A] averaged network structure of patients who reached remission, [B] averaged network structure of patients who did not reach remission, [C] box plot analysis of mean DTW distance of residuals (adjusted for the number of assessments and CPRS sum score before the start of ECT) within the networks of remitters versus non-remitters.

2016) For example, core mood symptoms covaried together, with improvements in one symptom being accompanied by improvements of other symptoms within the same cluster. However, we cannot exclude the possibility that some clustering of symptoms could also be the result of shared underlying emotional constructs, from which the several items tap, like “slowness of movement” and “reduced speech” that may have resulted both from inhibition.

The network structure of remitters had on average a lower mean DTW distance. Strongly connected networks may represent more unstable networks, with higher chances of critical transitions (e.g. tipping points) than more loosely connected networks (Scheffer et al., 2009). This may imply a larger vulnerability for psychiatric disease, because an ‘activated symptom’ in one part of the network may result in a faster cascade of effects through other nodes in such a densely connected symptom network (Borsboom, 2017). Paradoxically, it may also imply that patients with such networks are also more ‘vulnerable’ to a transition into recovery, particularly under the influence of ECT treatment. Previous studies have studied characteristics of remitters versus non-remitters of depression upon ECT (van Diermen et al., 2018) but the only consistent predictive symptom for remission was the existence of psychotic features before start of treatment. In contrast to our findings, a study on the association between baseline network connectivity and remission of depression found that a lower symptom connectivity was advantageous on the prognosis (van Borkulo et al., 2015). However, this network connectivity was measured cross-sectionally which reflects a different kind of interactions between symptoms other than the dynamic symptom interactions through time as was assessed in the current study. As it could be hypothesized that the result of a dynamic analysis of symptoms is rather stable for a given patient, then the symptom network prior to the start of treatment will be quite similar to the symptom network during and after treatment. Clinically, an analysis of the dynamic interactions of a patient’s symptoms could be performed prior to ECT or another form of therapy as a potential aid and predictor of outcome. This hypothesis should be tested in future clinical studies.

Our patient-level analyses may guide future research on personalized medicine. It may help to reveal the dynamic relationship between symptoms in a particular patient. These findings are in line with those recently published by Hebbrecht et al (Hebbrecht et al., 2020) for the Hamilton Rating Scale for Depression in 255 depressed inpatients. These networks differed substantially from patient to patient, and revealed which symptoms had the strongest connectivity (due to a similar course over time) to each other and which symptoms may act as bridge symptoms in a particular patient. Intervening on central symptoms that are connected to many different symptoms could benefit that specific patient, which could lead to a more efficient decrease of the whole connectivity of the symptoms network (Borsboom and Cramer, 2013). Intervening on non-central symptoms would likely be less effective for

that particular patient. DTW enables direct visualisation of dynamic interaction of symptoms within individual patients, which may represent mechanistic causal interactions of symptoms (Borsboom, 2017; Fried and Nesse, 2015). DTW analysis may enable the visualisation of personalized symptom network. This individual network may represent potentially causal interactions, as suggested in the complex dynamic systems model (Borsboom, 2017; Borsboom and Cramer, 2013; Cramer et al., 2016) in which there is symptom-symptom interaction and interactions are also subject to change over time (Robinaugh et al., 2020). Understanding the individual patient’s characteristic interaction of symptoms, also referred to as the idiosyncratic structure of symptoms (Fisher, 2015; Fisher et al., 2017) could be an important step towards personalized medicine (Fried et al., 2017).

DTW is a new analytical technique to compare trajectories of depressive symptoms over time. It is a technique that has been widely used in artificial intelligence to accommodate sequences that are similar but out of phase, such as in computed speech recognition and robotic applications, and was introduced in 1994 for database studies (Berndt and Clifford, 1994). The technique has only rarely been used previously for analysis in medicine (Giannoula et al., 2018). Techniques other than DTW have analysed emotion dynamics previously (Dejonckheere et al., 2019). Although most studies used cross-correlation analyses to assess the factor structure of severity scales, other have assessed the coherence of time series of symptoms using cross-correlation analysis (de Vos et al., 2017; Lydon-Staley et al., 2019; Snippe et al., 2017; Wigman et al., 2015). This enabled the study of density of symptom networks and its association with depression (Lydon-Staley et al., 2019; Wigman et al., 2015) but findings were not always consistent (de Vos et al., 2017). The use of cross-correlation analysis would be applicable in our study under the assumption that, for example, a decrease in symptom A causes an equally large decrease in symptom B at the same assessment, if they were linked. In general, we do not expect this assumption to always hold, because a change in symptom A may cause only a partial change, or change in a lower or higher velocity of change in symptom B, which only later results in a measurable change. In such situations, DTW may prove valuable.

Studies with a factor analytic approach on cross-sectional data of the full CPRS in patients with depression (Goekoop et al., 1992) or schizophrenia (Lindstrom and Lindstrom, 1996) resulted in only a partly consistent clustering of symptoms than that found in the current study based on DTW analysis of time series. A cluster of emotional dysregulation was found in patients with depression that showed a large overlap with the core depressive symptoms in our study, but also had many additional items (Goekoop et al., 1992). In schizophrenic patients, (Lindstrom and Lindstrom, 1996) ten symptom factors were found using the CPRS, that showed hardly any overlap with any of our dimensions, which may be ascribed to the different disease category that was

studied. Studies including other questionnaires than the CPRS found factor structures that showed some overlap. In cross-sectional analyses, the three symptom clusters (i.e., core emotional, sleep, and atypical) were consistently found in depressed patients, (Chekroud et al., 2017) which overlapped in part with our dynamic symptom dimensions of ‘core depressive symptoms’, ‘retardation’, and ‘vegetative symptoms’. It is important that symptom dimensions are assessed through the dynamic analysis of time series of symptoms, as factor structures of symptoms are likely to change over time in patients treated for depression (Bagby et al., 2004; Fried, van Borkulo, et al., 2016).

We found that the mean scores on the item 20 ‘apparent sadness’ were the highest throughout the first 6 weeks of ECT treatment, but showed a rapid and continual mean decline starting immediately after the start of ECT. The stability of relatively high scores of concentration difficulties (shown in the forest plot of Fig. 4) may be due to the side effect of ECT on cognitive functioning. Cognitive side effects of ECT include anterograde amnesia for recently learned information and retrograde amnesia for previously learned information. (Semkovska and McLoughlin, 2010)

The present study has several strengths. We used an observational design which enabled us to study the clustering of trajectories of individual symptoms during an effective treatment, as our focus was not to prove the effectiveness of the ECT. The analysis on the patient level provided new insight on the within-person idiosyncratic interaction of symptoms in time and may help to construe a bridge between evidence-based medicine and patient-centred personalized medicine. Currently, physicians already practice an efficient form of personalization by taking into account the patient’s symptom profile as well as the safety and tolerability of the different treatment options. (Demyttenaere, 2016) Making use of a DTW analysis of the symptom profile may yield extra empirical support.

6. Limitations

There are some limitations that need to be discussed. First, we selected up to only seven assessments during the first six weeks of treatment, whereas highly intensive time series (e.g., daily assessments or experience sampling method (ESM)) would have been preferable for such an analysis. Initial and final points of the series cannot be warped and must match, which may have resulted in some symptoms which started either high to cluster together (Cluster ‘core depressive symptoms’), similar to those starting low (i.e., Cluster ‘dissociation and compulsion’). A linear trend in the model for each item could be included to reduce this effect. A second limitation is the use of a crude items score scale that ranged from 0 through 6, causing notable measurement error as well as floor and ceiling effects. Symptoms that started with high scores tended to cluster together despite the use of standardized item scores. Finally, many different step patterns can be used, including asymmetric ones, which may enable the study of changes in one item preceding the change in another item, resulting in directed symptom graphs. (Giorgino, 2009)

7. Conclusion

We conclude that the clustering of symptom trajectories in severely depressed patients showed large variability. This per-patient and per-item variability may reflect the heterogeneity of depression and the delicate (causal) relationships between symptoms. We recommend integrating such DTW analysis on the dynamic symptom network to the personalized medicine approach (Fried et al., 2017) in observational as well as intervention studies. Our findings need to be replicated in larger study samples, with smaller time intervals (such as in Ecological momentary assessment (EMA) or ESM), and over longer observation periods which should also include the dynamics of symptoms before the start of treatment. We expect that knowledge about the aetiology of idiosyncratic structures (Fisher, 2015; Fisher et al., 2017) may lead to

new insights and (psychotherapeutic) treatment options to improve the disease outcome of individual patients.

Conflict of Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.06.068.

References

- Abdi, H. V. D.; O’Toole, A.J.; Edelman, B. (2005). DISTATIS: The Analysis of multiple Distance Matrices. Proceedings of the IEEE Computer Society. International Conference on Computer Vision and Pattern Recognition.
- Abrams, R. S., C.M. (1989). ECT instruction manual. 3rd ed. Somatics Inc.
- Asberg, M., Montgomery, S.A., Perris, C., Schalling, D., Sedvall, G., 1978. A comprehensive psychopathological rating scale. *Acta Psychiatr Scand Suppl*(271), 5–27. Retrieved from. <https://www.ncbi.nlm.nih.gov/pubmed/277059>.
- Bagby, R.M., Ryder, A.G., Schuller, D.R., Marshall, M.B., 2004. The Hamilton Depression Rating Scale: has the gold standard become a lead weight? *Am J Psychiatry* 161 (12), 2163–2177. <https://doi.org/10.1176/appi.ajp.161.12.2163>.
- Belvederi Murri, M., Amore, M., Respingo, M., Alexopoulos, G.S., 2018. The symptom network structure of depressive symptoms in late-life: Results from a European population study. *Mol Psychiatry*. <https://doi.org/10.1038/s41380-018-0232-0>.
- Berndt, D. J., & Clifford, J. (1994). Using dynamic time warping to find patterns in time series. AAAI-94 workshop on knowledge discovery in databases, 229–248.
- Borsboom, D., 2017. A network theory of mental disorders. *World Psychiatry* 16 (1), 5–13. <https://doi.org/10.1002/wps.20375>.
- Borsboom, D., Cramer, A.O., 2013. Network analysis: an integrative approach to the structure of psychopathology. *Annu Rev Clin Psychol* 9, 91–121. <https://doi.org/10.1146/annurev-clinpsy-050212-185608>.
- Bringmann, L.F., Lemmens, L.H., Huibers, M.J., Borsboom, D., Tuerlinckx, F., 2015. Revealing the dynamic network structure of the Beck Depression Inventory-II. *Psychol Med* 45 (4), 747–757. <https://doi.org/10.1017/S0033291714001809>.
- Chekroud, A.M., Gueorguieva, R., Krumholz, H.M., Trivedi, M.H., Krystal, J.H., McCarthy, G., 2017. Reevaluating the Efficacy and Predictability of Antidepressant Treatments: A Symptom Clustering Approach. *JAMA Psychiatry* 74 (4), 370–378. <https://doi.org/10.1001/jamapsychiatry.2017.0025>.
- Cinar, S., Oude Voshaar, R.C., Janzing, J.G., Birkenhager, T.K., Buitelaar, J.K., van den Broek, W.W., 2010. The course of depressive symptoms in unipolar depressive disorder during electroconvulsive therapy: a latent class analysis. *J Affect Disord* 124 (1–2), 141–147. <https://doi.org/10.1016/j.jad.2009.11.002>.
- Clemente, A.S., Diniz, B.S., Nicolato, R., Kapczinski, F.P., Soares, J.C., Fermo, J.O., Castro-Costa, E., 2015. Bipolar disorder prevalence: a systematic review and meta-analysis of the literature. *Braz J Psychiatry* 37 (2), 155–161. <https://doi.org/10.1590/1516-4446-2012-1693>.
- Collaborators, G.D., 2017. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 390 (10100), 1211–1259. [https://doi.org/10.1016/S0140-6736\(17\)32154-2](https://doi.org/10.1016/S0140-6736(17)32154-2).
- Cramer, A.O., van Borkulo, C.D., Giltay, E.J., van der Maas, H.L., Kendler, K.S., Scheffer, M., Borsboom, D., 2016. Major Depression as a Complex Dynamic System. *PLoS One* 11 (12), e0167490. <https://doi.org/10.1371/journal.pone.0167490>.
- de Vos, S., Wardenaar, K.J., Bos, E.H., Wit, E.C., Bouwmans, M.E.J., de Jonge, P., 2017. An investigation of emotion dynamics in major depressive disorder patients and healthy persons using sparse longitudinal networks. *PLoS One* 12 (6), e0178586. <https://doi.org/10.1371/journal.pone.0178586>.
- Dejonckheere, E., Mestdagh, M., Houben, M., Rutten, I., Sels, L., Kuppens, P., Tuerlinckx, F., 2019. Complex affect dynamics add limited information to the prediction of psychological well-being. *Nat Hum Behav* 3 (5), 478–491. <https://doi.org/10.1038/s41562-019-0555-0>.
- Demyttenaere, K., 2016. Taking the depressed “person” into account before moving into personalized or precision medicine. *World Psychiatry* 15 (3), 236–237. <https://doi.org/10.1002/wps.20362>.
- Epskamp, S., van Borkulo, C.D., van der Veen, D.C., Servaas, M.N., Isvoranu, A.M., Riese, H., Cramer, A.O.J., 2018. Personalized Network Modeling in Psychopathology: The Importance of Contemporaneous and Temporal Connections. *Clin Psychol Sci* 6 (3), 416–427. <https://doi.org/10.1177/2167702617744325>.
- Fisher, A.J., 2015. Toward a dynamic model of psychological assessment: Implications for personalized care. *J Consult Clin Psychol* 83 (4), 825–836. <https://doi.org/10.1037/ccp0000026>.
- Fisher, A.J., Reeves, J.W., Lawyer, G., Medaglia, J.D., Rubel, J.A., 2017. Exploring the idiographic dynamics of mood and anxiety via network analysis. *J Abnorm Psychol* 126 (8), 1044–1056. <https://doi.org/10.1037/abn0000311>.
- Fried, E.I., Epskamp, S., Nesse, R.M., Tuerlinckx, F., Borsboom, D., 2016. What are ‘good’ depression symptoms? Comparing the centrality of DSM and non-DSM symptoms of depression in a network analysis. *J Affect Disord* 189, 314–320. <https://doi.org/10.1016/j.jad.2015.09.005>.

- Fried, E.I., Nesse, R.M., 2015. Depression sum-scores don't add up: why analyzing specific depression symptoms is essential. *BMC Med* 13, 72. <https://doi.org/10.1186/s12916-015-0325-4>.
- Fried, E.I., Nesse, R.M., Zivin, K., Guille, C., Sen, S., 2014. Depression is more than the sum score of its parts: individual DSM symptoms have different risk factors. *Psychol Med* 44 (10), 2067–2076. <https://doi.org/10.1017/S0033291713002900>.
- Fried, E.I., van Borkulo, C.D., Cramer, A.O., Boschloo, L., Schoevers, R.A., Borsboom, D., 2017. Mental disorders as networks of problems: a review of recent insights. *Soc Psychiatry Psychiatr Epidemiol* 52 (1), 1–10. <https://doi.org/10.1007/s00127-016-1319-z>.
- Fried, E.I., van Borkulo, C.D., Epskamp, S., Schoevers, R.A., Tuerlinckx, F., Borsboom, D., 2016. Measuring depression over time . . . Or not? Lack of unidimensionality and longitudinal measurement invariance in four common rating scales of depression. *Psychol Assess* 28 (11), 1354–1367. <https://doi.org/10.1037/pas0000275>.
- Giannoula, A., Gutierrez-Sacristan, A., Bravo, A., Sanz, F., Furlong, L.I., 2018. Identifying temporal patterns in patient disease trajectories using dynamic time warping: A population-based study. *Sci Rep* 8 (1), 4216. <https://doi.org/10.1038/s41598-018-22578-1>.
- Giorgino, T., 2009. Computing and Visualizing Dynamic Time Warping Alignments in R: The dtw Package. *Journal of Statistical Software* 31 (7), 1–24. <https://doi.org/10.18637/jss.v031.i07>.
- Goekoop, J.G., Hoeksema, T., Knoppert-Van der Klein, E.A., Klinkhamer, R.A., Van Gaalen, H.A., Van Londen, L., Zwinderman, A.H., 1992. Multidimensional ordering of psychopathology. A factor-analytic study using the Comprehensive Psychopathological Rating Scale. *Acta Psychiatr Scand* 86 (4), 306–312. <https://doi.org/10.1111/j.1600-0447.1992.tb03271.x>.
- Hebbrecht, K., Stuivenga, M., Birkenhager, T., Morrens, M., Fried, E.I., Sabbe, B., Giltay, E.J., 2020. Understanding personalized dynamics to inform precision medicine: a dynamic time warp analysis of 255 depressed inpatients. *BMC Med* 18 (1), 400. <https://doi.org/10.1186/s12916-020-01867-5>.
- Keller, M.C., Neale, M.C., Kendler, K.S., 2007. Association of different adverse life events with distinct patterns of depressive symptoms. *Am J Psychiatry* 164 (10), 1521–1529. <https://doi.org/10.1176/appi.ajp.2007.06091564> quiz 1622.
- Kelley, M.E., Dunlop, B.W., Nemeroff, C.B., Lori, A., Carrillo-Roa, T., Binder, E.B., Mayberg, H.S., 2018. Response rate profiles for major depressive disorder: Characterizing early response and longitudinal nonresponse. *Depress Anxiety* 35 (10), 992–1000. <https://doi.org/10.1002/da.22832>.
- Kho, K.H., van Vreeswijk, M.F., Simpson, S., Zwinderman, A.H., 2003. A meta-analysis of electroconvulsive therapy efficacy in depression. *J ECT* 19 (3), 139–147. Retrieved from. <https://www.ncbi.nlm.nih.gov/pubmed/12972983>.
- Lindstrom, E., Lindstrom, L.H., 1996. A subscale for negative symptoms from the Comprehensive Psychopathological Rating Scale (CPRS): a comparison with the Schedule for Assessment of Negative Symptoms (SANS). *Eur Arch Psychiatry Clin Neurosci* 246 (4), 219–223. <https://doi.org/10.1007/BF02188957>.
- Lux, V., Kendler, K.S., 2010. Deconstructing major depression: a validation study of the DSM-IV symptomatic criteria. *Psychol Med* 40 (10), 1679–1690. <https://doi.org/10.1017/S0033291709992157>.
- Lydon-Staley, D.M., Xia, M., Mak, H.W., Fosco, G.M., 2019. Adolescent Emotion Network Dynamics in Daily Life and Implications for Depression. *J Abnorm Child Psychol* 47 (4), 717–729. <https://doi.org/10.1007/s10802-018-0474-y>.
- Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134, 382–389. <https://doi.org/10.1192/bjp.134.4.382>.
- Murtagh, F., Legendre, P., 2014. Ward's Hierarchical Agglomerative Clustering Method: Which Algorithms Implement Ward's Criterion? *Journal of Classification* 31 (3), 274–295. <https://doi.org/10.1007/s00357-014-9161-z>.
- Park, S.C., Kim, D., 2020. The Centrality of Depression and Anxiety Symptoms in Major Depressive Disorder Determined Using a Network Analysis. *J Affect Disord* 271, 19–26. <https://doi.org/10.1016/j.jad.2020.03.078>.
- Petrides, G., Fink, M., Husain, M.M., Knapp, R.G., Rush, A.J., Mueller, M., Kellner, C.H., 2001. ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. *J ECT* 17 (4), 244–253. <https://doi.org/10.1097/00124509-200112000-00003>.
- Robinaugh, D.J., Hoekstra, R.H.A., Toner, E.R., Borsboom, D., 2020. The network approach to psychopathology: a review of the literature 2008–2018 and an agenda for future research. *Psychol Med* 50 (3), 353–366. <https://doi.org/10.1017/S0033291719003404>.
- Sakoe, H., Chiba, S., 1978. Dynamic Programming Algorithm Optimization for Spoken Word Recognition. *IEEE Transactions on acoustics, speech, and signal processing ASSP-26*, 43–49.
- Scheffer, M., Bascompte, J., Brock, W.A., Brovkin, V., Carpenter, S.R., Dakos, V., Sugihara, G., 2009. Early-warning signals for critical transitions. *Nature* 461 (7260), 53–59. <https://doi.org/10.1038/nature08227>.
- Semkowska, M., McLoughlin, D.M., 2010. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. *Biol Psychiatry* 68 (6), 568–577. <https://doi.org/10.1016/j.biopsych.2010.06.009>.
- Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59 (Suppl 20), 22–33 quiz 34–57. Retrieved from. <https://www.ncbi.nlm.nih.gov/pubmed/9881538>.
- Snippe, E., Viechtbauer, W., Geschwind, N., Klippel, A., de Jonge, P., Wichers, M., 2017. The Impact of Treatments for Depression on the Dynamic Network Structure of Mental States. Two Randomized Controlled Trials. *Sci Rep* 7, 46523. <https://doi.org/10.1038/srep46523>.
- Tyrer, P., Owen, R.T., Cicchetti, D.V., 1984. The brief scale for anxiety: a subdivision of the comprehensive psychopathological rating scale. *J Neuro Neurosurg Psychiatry* 47 (9), 970–975. <https://doi.org/10.1136/jnnp.47.9.970>.
- van Borkulo, C., Boschloo, L., Borsboom, D., Penninx, B.W., Waldorp, L.J., Schoevers, R.A., 2015. Association of Symptom Network Structure With the Course of [corrected] Depression. *JAMA Psychiatry* 72 (12), 1219–1226. <https://doi.org/10.1001/jamapsychiatry.2015.2079>.
- van den Broek, W. W. B., T.K.; de Boer, , D.; Burggraaf, J.P.; van Gemert, B.; Groenland, T.H.N.; Kho, K.H.; Stek, M.L.; Verwey, B.; van Vliet, I.M.; van Waarde, J.A.; Wijkstra, J. (Werkgroep elektroconvulsie therapie). (2010). Guideline Elektroconvulsie therapie, second revised edition. 1–200.
- van Diermen, L., van den Amele, S., Kamperman, A.M., Sabbe, B.C.G., Vermeulen, T., Schrijvers, D., Birkenhager, T.K., 2018. Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis. *Br J Psychiatry* 212 (2), 71–80. <https://doi.org/10.1192/bjp.2017.28>.
- van Eeden, W.A., van Hemert, A.M., Carlier, I.V.E., Penninx, B.W., Giltay, E.J., 2019. Severity, course trajectory, and within-person variability of individual symptoms in patients with major depressive disorder. *Acta Psychiatr Scand* 139 (2), 194–205. <https://doi.org/10.1111/acps.12987>.
- Veltman, E.M., van Hulten, S., Twisk, J., Dols, A., van Exel, E., Stek, M.L., Rhebergen, D., 2018. Differences in Speed of Response of Depressive Symptom Dimensions in Older Persons During Electroconvulsive Therapy. *J ECT*. <https://doi.org/10.1097/YCT.0000000000000506>.
- Wigman, J.T., van Os, J., Borsboom, D., Wardenaar, K.J., Epskamp, S., Klippel, A., Wichers, M., 2015. Exploring the underlying structure of mental disorders: cross-diagnostic differences and similarities from a network perspective using both a top-down and a bottom-up approach. *Psychol Med* 45 (11), 2375–2387. <https://doi.org/10.1017/S0033291715000331>.