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A new science of mental disorders: Using personalised, transdiagnostic, dynamical systems to understand, model, diagnose and treat psychopathology

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ABSTRACT

The core ideas of a 10-year research program ‘New Science of Mental Disorders’ are outlined. This research program moves away from the disorder-based ‘one-model-fits-all’ approach to treating mental disorders, and adopts the network approach to psychopathology as its foundation of research. Its core assumption is that dynamically interacting symptoms *constitute* the disorder. Our goal is to further develop the network approach by studying (1) dynamic networks of symptoms and other variables (i.e., elements) in a large number of individuals with a wide range of mental disorders from a transdiagnostic perspective (network-based diagnosis; *mapping*), including both Ecological Momentary Assessment (EMA) and digital phenotyping, (2) the transdiagnostic mechanisms reflecting potential causal relations among elements of the networks by performing experimental (pre-)clinical studies (*zooming*), and (3) the effectiveness of personalised network-informed interventions (*targeting*). Challenges to overcome in this research program are discussed, which relate to data collection (e.g., selection of EMA variables) and data analyses (e.g., power considerations), the development and application of network-informed diagnoses and network-informed interventions (e.g., what characteristic(s) of the network to target in interventions), and the implementation in clinical practice (e.g., train therapists in the use of networks in therapy).

In spite of the overwhelming scale of mental disorders (~26% lifetime prevalence worldwide), there is a large gap between the need for treatment and its provision, all over the world. Mental disorders are far less likely to receive treatment than physical illnesses (Clark, 2018; Layard & Clark, 2015). If mental disorders are treated, the success rates of interventions are modest, in both adults and adolescents, across the full range of mental disorders (Holmes et al., 2018; Reynolds, Wilson, Austin, & Hooper, 2012). Many patients do not, or only scarcely, benefit from treatment, and others soon relapse after an initial success: Even relatively good short-term outcomes of treatment are no guarantee of good long-term outcomes. For example, if recovery is defined as no longer meeting the diagnostic criteria of a mental disorder and seeking

little or no treatment for the mental disorder during a follow-up period, only about 40% of patients achieve sustained recovery (Clark, 2018; Layard & Clark, 2015). So, the sad reality is that many patients with mental disorders do not receive treatment at all and, if they are treated, roughly 60% either do not respond to treatment or relapse within a year.

The modest outcomes of treatment suggests that we do not yet fully understand the maintenance mechanisms of mental disorders and therapeutic working mechanisms (Holmes et al., 2014, 2018). Treatments are largely disorder-based and often follow a “one-model-fits-all” approach within each specific DSM5 mental disorder category. Research to enhance psychological treatments is argued to be ‘scandalously under-supported’ (‘Therapy deficit’, 2012). Whereas mental disorders

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account for a larger burden of disease in developed countries than, for example, all forms of cancer put together (Layard & Clark, 2015), the amount of research funds and investments spent on researching psychological therapies is disproportionately small (Chisholm et al., 2016; ‘Therapy deficit’, 2012). This contrasts with evidence that returns on scaling-up financial investments in treatment research for mental disorders by far outweigh the costs (Chisholm et al., 2016).

Recently, the Dutch government invested nearly 20 million euros in research to enhance psychological treatment through the “Gravitation” programme of the Dutch Research Council (www.nwo.nl). A consortium of researchers¹ in the Netherlands studies transdiagnostic, dynamic networks of mental disorders and the effectiveness of individually tailored network-based interventions. The fundamental ideas of this ten-year research program, entitled “New science of mental disorders”, will be outlined here. Its main ambition is to develop a novel approach to understand, diagnose and treat mental disorders. The ambitious program goes beyond common practises in several ways by its transdiagnostic focus on dynamic, within-person networks of symptoms and other relevant variables (i.e., network of elements).

1. Current classifications do not always reflect reality

Mental disorders are classified in the widely used Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association (APA), and in the International Classification of Mental and Behavioural Diseases (ICD), published by the World Health Organisation (WHO). The DSM (currently 5th edition; APA, 2013) describes 22 categories of mental disorders, each of them including several separate clinical diagnoses. The ICD (currently 11th edition; WHO, 2019) is largely overlapping. DSM and ICD diagnoses are mainly based on clinical consensus. In many countries, treatment recommendations, as well as reimbursement by health insurance companies, are determined by the gold standard DSM or ICD classifications. The classification manuals advanced the field tremendously, but they have also been criticised for their lack of reliability, validity, and clinical utility (e.g., Borsboom, 2008; Lilienfeld, 2014).

First, the DSM and ICD have their roots in medicine and are based on a ‘common cause’ framework, assuming that a mental disorder consists of symptoms that all follow from one or more underlying causes. This explains the persistent search for underlying, mainly biological causes and final common pathways for specific mental disorders. The focus on separate disorders in ICD and DSM leads both science and treatments to concentrate on separate clinical diagnoses and their unique causes. However, as Hyman (2021) extensively discusses, recent empirical evidence does not support the distinct categories approach to psychopathology, nor a clear-cut distinction between healthy and ill. Instead, psychiatric disorders should be viewed as ‘heterogeneous quantitative deviations from health’ (p. 6); risk factors and symptoms are continuously distributed in the population. Despite decades of diagnosis-driven research, approaches that have tried to identify specific causes for specific categories of mental disorders were largely unsuccessful (Borsboom, Cramer, & Kalis, 2018; Hyman, 2021).

Second, comorbidity is the rule rather than the exception: Mental disorders frequently co-occur; at least half of the people with mental disorders receive two or more diagnoses (Cramer, Waldorp, van der Maas, & Borsboom, 2010; Kessler, Chiu, Demler, & Walters, 2005; Kim & Eaton, 2015; Lilienfeld, 2014; Nolen-Hoeksema & Watkins, 2011; Sauer-Zavala et al., 2017). Meanwhile, the current focus in clinical

science and practice is predominantly on thinly sliced diagnoses: A researcher studies and a clinician treats a single DSM-disorder, despite the high degree of comorbidity.

2. Transdiagnostic turn

Over the past decade, there has been an increasing focus on transdiagnostic research (e.g., Dalgleish, Black, Johnston, & Bevan, 2020; Harvey, Watkins, & Mansell, 2004; Insel et al., 2010; Mansell, Harvey, Watkins, & Shafran, 2009; Nolen-Hoeksema & Watkins, 2011; Sauer-Zavala et al., 2017; Seligman, 2014). Transdiagnostic models focus on shared processes causing and maintaining multiple or comorbid disorders. These processes can be linked to symptoms of multiple mental disorders, across categories of disorders, and could therefore explain comorbidities among mental disorders.

Seligman argues that when giving up categorical symptom diagnoses and instead focusing on underlying transdiagnostic processes, “those transdiagnostic processes become the real disorders” (Seligman, 2014, p. 2). The experimental study of such processes, mechanisms, and interventions is increasing. For example, studies investigate transdiagnostic biases in cognitive processing, negative thinking, rumination, and sleep problems (e.g., Dolsen, Asarnow, & Harvey, 2014; Duyser et al., 2020; McLaughlin, Wisco, Audio, & Hilt, 2014). Also, some modular transdiagnostic treatments have been developed for emotional disorders (Barlow et al., 2017).

There are also collaborative initiatives of large-scale consortia for transdiagnostic research, such as the Research Domain Criteria (RDoC) project launched by the National Institute of Mental Health (NIMH) (Cuthbart & Insel, 2013; Insel et al., 2010). RDoC is a transdiagnostic research framework to study mental illnesses by shared dimensions. Each RDoC domain contains several constructs reflecting negative valence systems (like threat, loss and frustration), positive valence systems (like reward responsiveness and reward learning), cognitive systems (like attention, perception and cognitive control), systems for social processes (like social communication and the understanding of others), arousal and regulatory systems (like sleep-wakefulness and arousal) and sensorimotor systems (like motor actions).

Deficits in these transdiagnostic systems may be responsible for dysfunctions shared by several mental disorders, such as sleep problems or biases in attention. RDoC integrates information from genes, molecules, cells and circuits to physiology, behaviour and self-reports. The focus is on conceptualising mental disorders as brain disorders, and it is mostly biologically oriented. The framework reflects a dynamic research strategy that aims to clarify basic biological, cognitive and behavioural processes, but it is not meant to serve as a diagnostic guide or to replace current diagnostic systems. Further transdiagnostic initiatives are on the way, such as the Hierarchical Taxonomy of Psychopathology (HiTOP; Kotov, Krueger, & Watson, 2018).

3. The network approach of mental disorders

The network approach to psychopathology is a theoretical framework to explain the existence, development and maintenance of mental disorders (e.g., Borsboom, 2008, 2017; Borsboom & Cramer, 2013; Borsboom et al., 2018; Boschloo et al., 2015; Cramer & Borsboom, 2015; Cramer et al., 2016; Fried, 2015; Fried & Cramer, 2017). It is embedded in a wider framework of systems science and network science (e.g., Hayes, 2020; Robinaugh, Hoekstra, Toner, & Borsboom, 2020; Schiepek, 2009, 2020). The core assumption of the network approach is that the complex system of dynamically interacting symptoms constitutes the disorder. This contrasts with the common cause view where an underlying, latent categorical or dimensional entity causes a number of symptoms.

From this perspective, psychological and medical conditions may differ from each other, as fittingly expressed by McNally (2016, p101): “A person can have cancer, yet be currently asymptomatic, whereas it

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makes no sense to say that an asymptomatic person has depression". From the network perspective, symptoms are not the output of one underlying pathogenic pathway, they rather are the input for, and driver of, other symptoms. Thus, symptoms reinforce each other. They do not *reflect* a mental disorder: they *constitute* it. This turns the common definition of a symptom as indicating a disease upside down (Borsboom, 2017; Borsboom & Cramer, 2013; Fried & Cramer, 2017), giving them the role of independent, causal agents.

Overall, the network approach assumes spreading activation to be the engine that drives the mental disorder: Connected elements synchronise, maintain each other actively in vicious cycles (Bakker, 2019), and become a self-sustaining entity. Mental disorders thus represent stable states in a dynamical network structure (Borsboom, 2017). Perturbations from outside this network, like adverse life events, can trigger a phase transition into an alternative stable state (Van de Leemput et al., 2014). The likelihood and nature of such transitions may depend on the resilience of the system —characteristics of the network that determine how long it takes for a system to move from a healthy state to a disordered state. (Lunansky et al., 2021; Scheffer et al., 2018). Network characteristics that may determine a system's resilience include the number of feedback relations, the ease with which symptoms are activated in the first place, and the strengths of connections in a network (Cramer et al., 2016). If the interactions between symptoms are strong enough, an alternative state itself can become resilient, so that removing the factor that triggered the transition does not suffice to bring the system back to the healthy state; a phenomenon known as hysteresis (Cramer et al., 2016). Effects such as hysteresis imply that even if the stressors that initially shifted a system to such an alternative state are taken away, the system may nonetheless persist in this state.

The network approach also sheds an entirely different light on the question of why mental disorders are highly comorbid. These networks are transdiagnostic by nature; if two disorders share a symptom, such as for example fear that is shared between anorexia nervosa and anxiety disorders, the symptom may operate as a bridge between the two disorders, connecting two or more networks into one single system (Fried et al., 2017; Jones, Ma, & McNally, 2021). From this point of view, high levels of comorbidity are not methodological artefacts, but result from real patterns of complex relations that do not respect diagnostic boundaries: In this sense, comorbidity is an intrinsic feature of mental disorders, rather than a nuisance.

The network approach initially focused on symptoms exclusively, but was extended considerably over the past years. One crucial development was to embrace the importance of relevant biopsychosocial variables beyond symptoms, such as life events (Borsboom, 2017), biological variables such as inflammation levels (Fried et al., 2020), and momentary social circumstances. Note that mixing different levels of explanation (e.g., subjective experience and biology) may require multi-layered networks (Riese & Wichers, 2021). Conceptually, such variables can be distinguished into those that are part of the network structure itself (for instance, refusing offers of high caloric food at work several times a day may trigger an eating binge later), and those that influence the network from the outside, that is, the external field (for instance, being employed in a job that requires many night shifts may disrupt sleep and lead to insomnia; Borsboom, 2017). To reflect this broader perspective, throughout this paper we refer to elements, which includes symptoms and other variables that are relevant in dynamic network structures of psychopathology. So, elements can be defined as variables involved in causing and maintaining psychopathology, including, but not limited to, symptoms of mental disorders, reflecting both nodes of the network and variables affecting the network from the outside.

Another extension was to acknowledge that the common cause and the network perspectives need not be mutually exclusive (e.g., Fried & Cramer, 2017; Fried 2020). To understand how symptoms emerge and give rise to other symptoms in a network, a useful notion might be to consider different types of causes lying on a spectrum from 'proximal' to

'distal'. Proximal causes are directly related to the mechanisms driving symptoms and might mostly feature as a node or an edge in the network. They are useful targets for treatment. By contrast, distal causes (e.g., genes, personality, social economic status, early adversity) are indirectly related to the (mechanisms driving) symptoms, and might mostly be situated outside the network (external field) or be viewed as a common cause. They are sometimes useful indicators for prevention. For example, a general tendency to experience negative affect, as commonly represented in the personality factor neuroticism, may represent a constant or slowly evolving variable that influences the liability of a person to develop the clinical symptom of depressed mood (Lunansky, van Borkulo, & Borsboom, 2020).

The search for proximal causes may benefit from experimental research, whereas the search for distal causes may benefit from epidemiological or longitudinal research (Roiser, 2015; Rutter, 2013). Building on a long tradition of experimental psychopathology research, our project aims to advance our understanding of proximal causes in the transition from normal to abnormal processes and the other way around. As to whether these causal relations solely reflect central nodes in the network, edges between elements, or (partly) latent constructs is still an issue for empirical testing. Hybrid statistical models are under development to allow for the analysis of data featuring both potential common causes and relations among elements (Epskamp, Rhemtulla, & Borsboom, 2017).

A third recent extension to the network literature was to close the gap to other fields such as basic network science and systems science (Fried & Robinaugh, 2020; Olthof et al., 2020; Robinaugh et al., 2020). These fields have a rich tradition in operationalizing, investigating, and modelling a wide variety of targets as complex systems, including ecosystems, the stock market, and the weather. The common view is that studying particular elements of systems can be helpful, but the micro-level will not be sufficient to understand the macro-level behaviour of such systems (Pessoa, 2021; Scheffer et al., 2018). Closing the gap between network approaches to psychopathology and these adjacent areas in the complexity literature allows for the use of ever-growing theoretical and statistical toolboxes to better conceptualise and investigate networks, such as the immense literature on early warning signals to predict transitions of systems into alternative stable states (e.g., from a healthy to a depressed state; Scheffer et al., 2018; Van de Leemput et al., 2014).

4. Network studies

After the network approach to mental disorders was introduced as a theoretical framework more than a decade ago, empirical network studies have become increasingly common in psychopathology research (Contreras, Nieto, Valiente, Espinosa, & Vazquez, 2019). Such studies have applied statistical network models to mental health data. In a recent paper (Robinaugh et al., 2020), network investigations for a large number of different mental disorders were reviewed. Examples include mood disorders (e.g., Fried et al., 2020), anxiety disorders (Tsuruta et al., 2017), eating disorders (e.g., Levinson, Vanzhula, & Brosf, 2018), and substance use disorders (e.g., Rhemtulla et al., 2016).

However, most studies so far have estimated networks for cross-sectional data for groups of patients (Robinaugh et al., 2020), often focused on a single mental disorder, and often only included self-reported symptoms. This focus on single disorders and self-reported symptoms, measured once, cannot provide insights into processes bridging diagnostic boundaries. Moreover, relying on between-subjects data fails to take into account personalised dynamic processes and mechanisms within individuals, who likely differ from each other, even if they share the same diagnosis (Fried & Cramer, 2017).

Importantly, not all work has focused on single disorders in cross-sectional data. Increasingly, network models are being estimated on time series data (e.g., Bringmann et al., 2013; Levinson, Vanzhula, & Brosf, 2018; Spanakis, Weiss, Boh, & Roefs, 2016) and span comorbid

disorders (e.g., Levinson, Brosiof et al., 2018; McNally, Mair, Mugno, & Riemann, 2017). The inclusion of participants with different diagnoses and the measurement of a wide range of symptoms and other variables, not restricted to one’s primary diagnosis, permits the study of how comorbidity arises between disorders in a network perspective. Time series data obtained in multiple participants, combined with appropriate statistical models, allow us to disentangle the between-subjects and within-subjects variance (Hamaker, Kuiper, & Grasman, 2015). This can tell us to what degree relations among elements of mental health networks differ from each other across people, across different types of people (e.g., by age or gender), or across different types of DSM-defined disorders (Fried & Cramer, 2017). Disentangling nomothetic relations that hold for most people, versus idiographic relations that are unique to certain individuals, is crucial if we want to keep the promise of the network approach as a new paradigm for the treatment of mental disorders (e.g., see Gates & Molenaar, 2012; Gates, Lane, Varangis, Giovanello, & Guskiewicz, 2017).

Accordingly, network-informed diagnoses and network-based interventions, tailored to the individual patient, might prove to be a real game changer in clinical psychology, but awaits further research. The estimation of transdiagnostic, dynamic networks in a large number of individuals allows for investigating inter-individual differences in network structures, and can, in a second step, also be used to explore whether these individuals can be clustered based on their network structures, and explore how these clusters relate to traditional diagnoses (see Fig. 1). If we know a person’s critical elements on a transdiagnostic level, have an understanding of how these interact, and can study to what degree such processes reflect maintenance mechanisms, we may be

able to formulate a treatment indication based on the network, and to develop individually tailored interventions to provide relief and ultimately cure the mental disorder.

5. Why dynamic networks may change the field

Our research project aims to test the applicability and usefulness of the network approach in clinical practice. We will further develop the network approach by studying the dynamics of networks in individuals with mental disorders from a transdiagnostic perspective, and by critically testing its value and usefulness for personalised diagnosis and treatment in mental health care. Our research program consists of three main layers (see Fig. 2). The first layer, *mapping*, studies the dynamics of complex individual networks across a broad range of mental disorders to provide network-informed diagnoses, aims to discover clusters of people with similar networks, and relate individual networks to traditional DSM-5 and ICD classifications (see Fig. 1). The second layer, *zooming*, is a series of mostly experimental (pre-)clinical studies into transdiagnostic mechanisms reflecting the putative causal relations among elements of the networks. Finally, the *targeting layer* examines the effectiveness of personalised network-informed interventions.

6. Mapping: network-informed diagnoses

For network-informed diagnosis and treatment, we first need insight into a host of variables in the daily life of the patient (e.g., Spanakis, Weiss, Boh, & Roefs, 2016; Spanakis, Weiss, Boh, Kerkhofs, & Roefs, 2016; Wichers, 2014). We will examine which symptoms and other

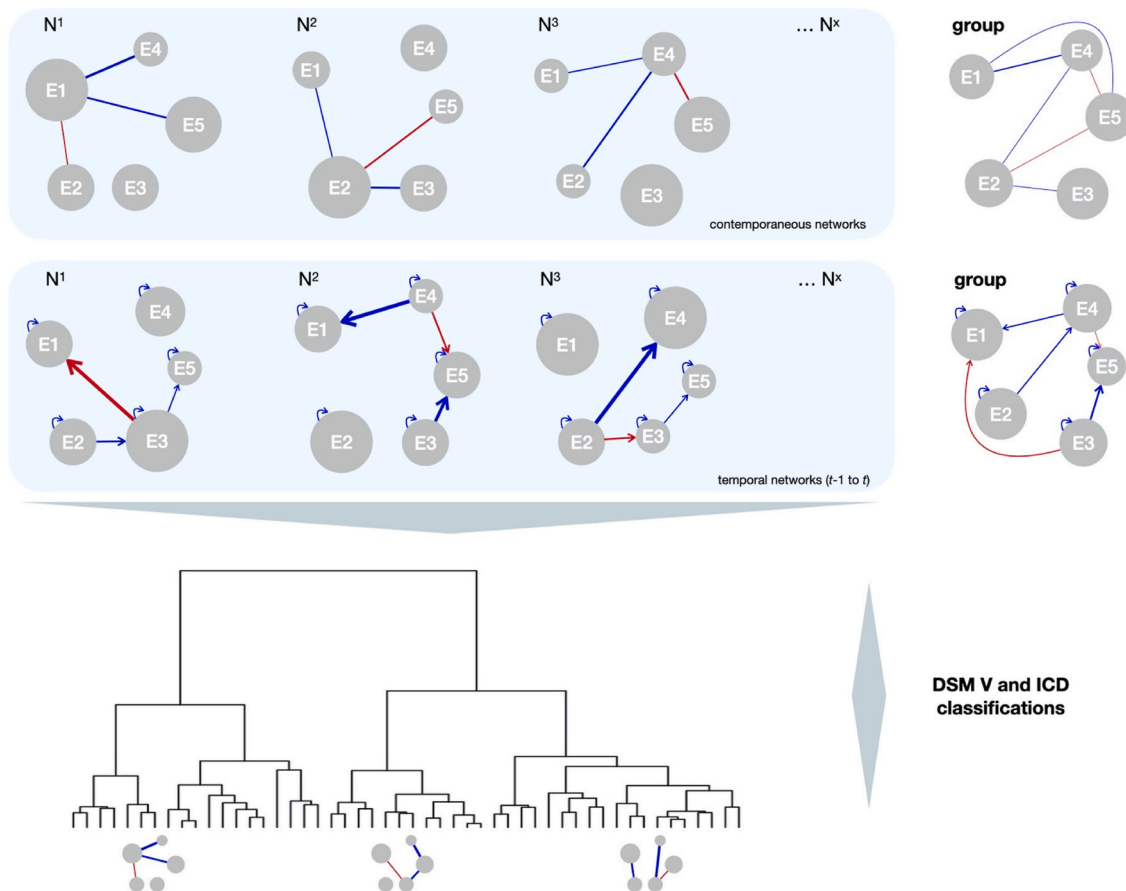


Fig. 1. Graphical illustration of idiosyncratic and group-level contemporaneous (time point t) and temporal (from time point $t - 1$ to t) network, clustering into network structure types, and relating network structures to DSM-5 and ICD classifications. Note that blue lines reflect positive relations, whereas red lines reflect negative relations. Line thickness reflects strength of the relation. Node size reflects the score on that element, with larger nodes reflecting higher scores. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

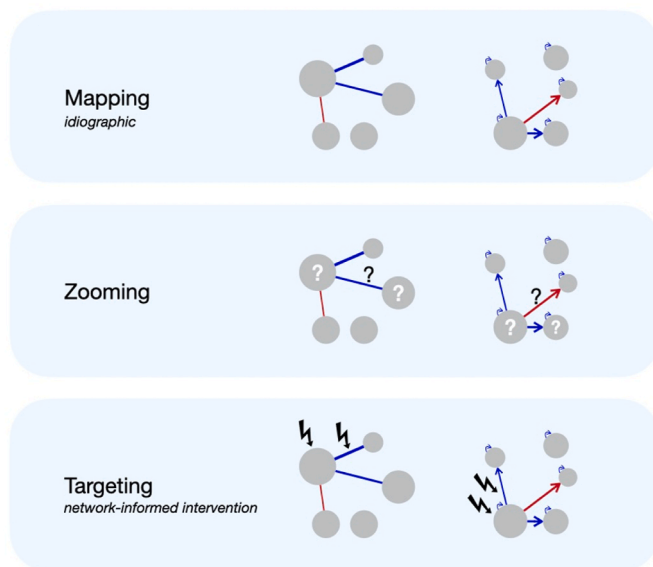


Fig. 2. Graphical overview of the research program 'New Science of Mental Disorders'. Note that blue lines reflect positive relations, whereas red lines reflect negative relations. Line thickness reflects strength of the relation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

elements (e.g., social circumstances, geolocation, physical activity) are involved in a patient's network, how elements are associated, and how variables in the external field (e.g., life events) influence the network. That is, in addition to a traditional DSM-5 diagnosis, for each individual patient, a network is constructed, providing insight into the mental problems of each participant, without strict diagnostic categorization. In addition, we will investigate if clusters of similar networks can be discovered, and if networks (partly) coincide with DSM-diagnoses (see Fig. 1).

6.1. Time series data collection

To address these aims, we will estimate idiosyncratic dynamic networks for a large number of patients with a broad spectrum of mental disorders on time-series data collected via smartphones and wearable technology, including ecological momentary assessment (EMA), sensors (e.g., physical activity, sleep quality), and other forms of digital phenotyping (e.g., time spent online, time taken to respond to text messages, etc.; Huckvale, Venkatesh, & Christensen, 2019; Insel, 2018). Important considerations that guide our data-collection are the precise selection of EMA items, that is, assessing a broad range of (transdiagnostic) variables while keeping participant burden within acceptable boundaries, the timing and number of measurements for an optimal tracking of processes in time, and the inclusion of relevant variables from the external field (e.g., life events).

Whereas advantages of EMA include the high ecological validity, the reduction of recall bias, and the possibility to assess participants with relatively high frequency, a disadvantage is that answering questions several times a day for a longer period of time can be burdensome for participants, which may reduce their compliance and the quality of answers (Myin-Germeys & Kuppens, 2021; Vachon et al., 2019). Because we aim to study (trans)diagnostic networks in a wide spectrum of mental disorders, a first challenge was to select the optimal set of variables (elements) to assess, covering the main problems of the spectrum. Selection of variables for this project was recently completed, and was based on three sources of information: (1) empirical and theoretical literature and DSM-5, (2) a questionnaire administered to expert clinicians, and (3) focus groups with expert clinicians for each category of

disorders. In the questionnaire, participants were asked to mention the most relevant variables to assess multiple times per day, once per day, and once per week, for each category of disorders they treat, as well as transdiagnostically. There was much overlap in mentioned variables across categories of disorders, which provided a natural limitation on the number of variables to be included in the measurement protocol. The information of the focus groups was used to check if any relevant variables had been missed by the questionnaires. The final set of variables was determined by two raters.

To make gaining nomothetic insights into transdiagnostic networks possible as well, all participants will answer most questions, with only some questions adapted to information that participants provide in a baseline questionnaire. For example, only people who smoke will be asked daily about their smoking behaviour. A next challenge is statistical power, that is, to collect sufficient measurements per participant per variable to reliably estimate personal networks, especially when these feature more than just a few nodes. It was recently shown (Mansueto, Wiers, van Weert, Schouten, & Epskamp, 2021) that with between 75 and 100 measurements of each variable per participant, it is only possible to reliably estimate a network with approximately 6 nodes, although this will of course depend on the true structure as well as the particular network estimation methods used. As our goal is to estimate individual transdiagnostic networks, the number of nodes will be larger, and therefore the number of EMA-measurements per variable per person needs to be larger. We currently aim for a 4-week measurement period with 8 measurements per day (224 measurements per variable per person). In addition, sensor technology and digital phenotyping will provide data with a (much) higher frequency. For the digital phenotyping variables, an important consideration is of course the safeguarding of the privacy of our participants. The collected EMA data can be used to test the validity of the digital phenotyping variables, a research area which is still quiet in its infancy.

6.2. Time series data analyses

Common statistical models to estimate networks in time-series data include the Vector Autoregressive (VAR) model (Bringmann et al., 2013), Group Iterative Multiple Model Estimation (GIMME; Beltz & Gates, 2017), and Dynamic Structural Equation Modelling (DSEM; Asparouhov, Hamaker, & Muthen, 2017). The VAR model is our point of departure because it is currently the most widely used statistical model in network studies on psychopathology. In VAR modelling, each variable at a certain time point is regressed on all other variables at the previous time point including the variable itself. This analysis delivers a temporal, intra-individual network (idiographic approach) with connections between variables that represent predictive relations: for example, negative mood at timepoint $t - 1$ predicts binge eating at timepoint t . The approach also allows us to estimate the same predictive relations at the level of a group (nomothetic approach). In addition, so-called contemporaneous networks can be estimated to learn which elements are associated at the same timepoint (e.g., sadness at timepoint t is related to anxiety at timepoint t) (Epskamp et al., 2018). The latter relations may point to network links that operate at a different time scale than that implied by the spacing between time points sampled. For example, if one samples once a day, but some of the variables in the network operate on a faster time scale (e.g., hallucinations \rightarrow anxiety, which may operate on a shorter time scale), then the relation between these variables may end up in the contemporaneous network.

As VAR models have identified limitations (Bringmann, 2021; Bringmann et al., 2022), one important goal is to optimise the analysis of psychological time series data, recognising the problems and idiosyncrasies of psychological data as compared to traditional domains of time series modelling like econometrics and biology. More specifically, until now, most research on personalised networks in psychopathology mainly focused on affective states and symptoms. As we intend to go beyond these symptoms, and intend to include variables that develop

over different time periods, our analysis methods need to be able to deal with data that are collected on different time-scales (e.g., location can be continuously monitored), which is not possible to model with standard VAR models. In addition, VAR models assume that the network structure does not change over time (assumption of stationarity), whereas an important goal in our research is to study if and how networks change over time due to treatment. One suggested way of dealing with this issue is time-varying VAR models, which do allow for network-changes over time (Bringmann, Ferrer, Hamaker, Borsboom, & Tuerlinckx, 2018; Haslbeck & Waldorp, 2020), but can only be estimated when a sufficient number of data points is available. To optimise data analysis of time series data, we will look beyond VAR models as well.

Another challenge is the modelling of connections of variables within the network to variables in the external field (e.g., life events), as well as the modelling of moderation and mediation, as the relationships (edges) between network-elements may be mediated or moderated by other elements of the network or of the external field, such as biological markers, environmental variables, and predispositions (Haslbeck, Borsboom, & Waldorp, 2020).

6.3. Network-informed diagnoses

An important goal of the mapping study is investigating whether individual network-informed diagnoses are feasible. Every single individual network may reflect an idiosyncratic interplay of symptoms and other elements, thereby providing starting points for intervention. The reliability of network-informed diagnoses is another issue: Do we obtain a similar network-informed diagnosis when we gather data at another time? Moreover, do diagnoses of well-educated clinicians align with the network-informed diagnoses? So, the feasibility of network-informed individual diagnosis remains a challenge. Note that these questions are relevant and important, but can be asked for traditional DSM diagnoses as well.

A second goal of the mapping study is investigating if networks of individual patients can be grouped according to network structure, and investigating if and how (categories of) individual networks relate to traditional DSM-5 diagnoses (Wigman et al., 2015). If we can successfully group personalised networks in this data-driven way, a challenge is to examine whether these detected groups can be viewed as some kind of standard categories. Another possibility is that these personalised networks prove to be so idiosyncratic, that either grouping is not possible, or that grouping another set of individualised networks – of another group of patients – leads to an entirely different categorization. Note that if personalised networks turn out to be easily and consistently grouped, and the grouping mimics the DSM categories, the estimation of networks does not have added value for diagnostics.

7. Zooming: causal relations between network elements

The network paths between nodes (i.e., the edges) that we obtain in observational studies *may* point towards causal processes, but—despite some unfortunate claims in the growing network literature—a significant edge between two nodes does not necessarily imply a causal connection between the nodes (Fried, 2020). Causal relations between symptoms/elements cannot necessarily be inferred from intervention studies either. That is, when clinicians therapeutically target specific elements of an individual's network, the intervention may lead to other, non-intended, changes as well, an issue known as the fat-hand problem² in the philosophy of causality literature (Eronen, 2020; Kästner & Andersen, 2018; Scheines, 2005). For example, when targeting anxiety, binge drinking may improve as well. This is a desired outcome in

therapy, but it is difficult to tell whether recovery was hastened by first reducing the anxiety, the binge drinking, or both. Note that simultaneous improvements across one or more nodes in addition to the target node may still be informative, though it does not permit drawing conclusions about a causal role of the targeted element.

To tackle these questions about specific mechanisms and timing, our research project is enriched with a 'zooming' layer with a focus on in-depth experimental laboratory studies, unravelling the mechanisms by which one network element may cause another. The zooming studies intend to isolate key (transdiagnostic) causal mechanisms, which may be positioned on the network edges. Laboratory-based experimental and (pre-)clinical studies into the main processes that may drive connectivity between network elements will be performed. These precision studies of edge manipulations will provide information on causal mechanisms of change. A goal of the experimental zooming studies is also to develop effective interventions on specific nodes and edges. In other words, we aim to understand how to best control the system with a somewhat slimmer hand. Zooming studies will, for example, include research on emotional memory, disordered desires, cognitive control, mind-body associations and the mutual influence of networks between people such as parents and children.

For example, the studies on emotional memory assume that aversive learning experiences lie at the core of a broad range of mental health conditions, from anxiety disorders, post-traumatic stress disorder (PTSD), and mood disorders to substance use disorders and eating disorders to personality disorders (Arntz, 2020; Brewin, Gregory, Lipton, & Burgess, 2010; Kindt, 2014). This hypothesis is rooted in a long tradition of experimental research showing a causal link between aversive learning and the formation of fear memory, which subsequently shapes one's beliefs and behaviour. It is also illustrated by findings that childhood adversities, such as emotional abuse and neglect, are strongly associated with an increased vulnerability for developing psychopathology (Arntz, 2020).

The network hypothesis of psychopathology is actually in stark contrast with established theories of psychopathology, in which mental representations (e.g., schemas, cognitions, emotional memory) are assumed to lie at the root of a broad range of mental health conditions. These mental representations are not only assumed to play a critical role in the aetiology of psychopathology, but they are also common targets in psychotherapy. In line with the idea that the common cause and the network perspective need not be mutually exclusive (e.g., Fried & Cramer, 2017; Fried 2020), we will test whether emotional memory can best be conceptualised as a node or an edge in the personalised networks, or whether emotional memory is actually a latent construct or even a partial common cause of a broad range of mental conditions. In addition, it will be tested whether treatment effects can best be explained by changes in mental representations. Intuitively, there are numerous scenarios imaginable in which emotional memory plays a role in psychopathology, but the challenge is how to measure emotional memory—a hypothetical latent construct—independently of symptoms. That is, intrusions are for instance indicative of emotional memory, but are also a key symptom of PTSD. Even if emotional memory overlaps with the symptoms and is not a causal factor, it may still be a latent or 'intervening' variable that helps in summarising the relations between symptoms (Bringmann & Eronen, 2018). Such an abstraction tool may be of great value for the field, given that the neuroscience and psychological science of memory have already provided many new insights from which effective treatments could be derived.

Another example of zooming studies is research on network characteristics themselves, to study the forecasting of (re)lapses and gains. Complex dynamical systems can have tipping points at which a sudden shift to another state occurs, for example, from a state where a person is partly in remission to a relapse. Forecasting such transitions successfully may have strong implications for effective prevention and intervention. It is possible to extract so-called *early warning signals* (EWS) from intensive time-series data to forecast a critical transition, such as a

² "Thanks to Kevin Kelly, such interventions are called "fat-hand," the analogy being reaching to move a particular piece in chess but knocking over others because of a fat hand." (Scheines, 2005, p. 931).

relapse or gain (Olthof et al., 2020; Scheffer et al., 2009, 2012). For example, it was demonstrated that EWS in the network of a depressed person preceded a clinical transition into a depressed state (Wichers, Groot, Psychosystems ESM Group, & EWS Group, 2016; Van de Leemput et al., 2014), and this was recently replicated (Wichers, Smit, & Snippe, 2020). These EWS included changes in autocorrelations and variances of network elements as the system approached a tipping point. It has been shown in other fields that homogeneous and strongly connected networks are more likely to show these sudden critical transitions (Cramer et al., 2016).

The notion of critical transitions fits well with clinical observations of sudden gains – that is, improvement of a mental disorder occurring non-linearly, in a more sudden way (Hayes, Laurenceau, Feldman, Strauss, & Cardaciotto, 2007; Hosenfeld et al., 2015). Recently it was shown in a large sample that EWS predicted the occurrence of sudden gains and losses in a 4-day predictive window (Olthof et al., 2020). In our project, EWS (e.g., increased temporal autocorrelation and variance) will be extracted from each person's network structure, and related to changes in symptomatology. The innovative study of changes in network structure continuously over time within a single patient, requires long-term intensive time-series data. Note that even if EWS are present, it need not imply that these are strong and precise enough to inform interventions (Dablander, Pichler, Cika, & Bacilieri, 2020), and the translation of these findings to clinical practice requires further validation research. We will systematically explore which early warning signals within individual networks relate to later symptom transitions, taking into account recent recommendations to pre-define relevant symptom shifts, and choosing an optimal measurement protocol in terms of selected variables and observation period (Helmich et al., 2021).

8. Targeting: network-informed interventions

Understanding the dynamics of individual networks paves the way for new personalised network-based interventions, independent of any DSM diagnosis. The network perspective predicts that treatment is most effective if relevant elements of a person's network are targeted. Our 'targeting studies' provide a critical test of the value of dynamic networks for clinical science and practice. Experimental network-informed interventions will be compared to control interventions that are not network-informed. The control interventions offer the best available treatments for a particular DSM-diagnosis, and comparable evidence-based techniques are used across conditions. The only difference between conditions is the focus of intervention being based on the individual network or not. We will test if individually tailored network-based interventions are more effective, also in the long run, than current evidence-based treatments. Interventions guided by the individual patient's dynamic network of symptoms are expected to improve success and decrease relapse.

Network-based interventions aim to bring the malfunctioning system back to a healthier state. To develop these network-based interventions, the question arises which elements (nodes) and processes (edges) should be targeted for each person. Originally (e.g., Borsboom & Cramer, 2013; Borsboom, Cramer, Schmittmann, Epskam, & Waldorp, 2011; Fried et al., 2017), it was proposed that treatment should target the so-called most central (i.e. interconnected) nodes, a suggestion for which there is some empirical support (Elliott, Jones, & Schmidt, 2020; Robinaugh, Millner, & McNally, 2016; Rodebaugh et al., 2018).

There are many different ways to operationalize centrality, and common metrics in the field include degree, strength, closeness, expected influence, and betweenness (Bringmann et al., 2019; Jones et al., 2021). Of these measures, degree, strength, and expected influence centrality may hold the most promise (Bringmann et al., 2019; Jones et al., 2021). Degree centrality simply is the number of direct edges that a node has, whereas strength centrality also takes into account the strength (absolute value) of the relationships (i.e., weights of edges). Expected influence centrality is similar to strength centrality, but in

addition takes into account the sign (positive versus negative) of the edge, resulting in a measure of positive connectivity. Recently, centrality measures to specifically identify bridge symptoms were developed (Jones et al., 2021), improving upon the practice of identifying bridge symptoms by visual inspection of a network.

There are discussions on how useful such centrality metrics are, and whether these indices, originally developed in the field of social networks, can readily be applied to psychological networks (Borgatti, 2005; Bringmann et al., 2019). One relevant difference between social and psychological networks is that in social networks the edges are observable, in that, for example, people can be interviewed about relationships (edges) between them (nodes). So far, edges in psychological networks have only been statistically estimated. This relates to the next point, of whether relations among elements in networks can and should be interpreted as so-called flow-processes. For psychological networks, parallel flow—one symptom affecting multiple others simultaneously—seems the most likely option, which can be likened to the flow of emails, with people (nodes) sending emails to multiple people (parallel) in their contact list (other nodes; Bringmann et al., 2019). However, it is questionable—even in social networks—if flow processes are actually underlying the edges. There is nothing literally flowing between symptoms, it is unclear what processes are located at the edges. Also other assumptions of centrality metrics are likely not met, such as node distinctiveness and node exchangeability. That is, there is likely multicollinearity between symptoms/elements, and not all elements of a psychological network are comparable. Certain symptoms are surely more severe than others, which makes sense to consider as well in the selection of the most important element (Bringmann et al., 2019). As ways forward, Bringmann et al. (2019) propose to (1) develop new centrality measures, (2) to use 'old' measures of variable importance, which were developed for the statistical models that are used to estimate psychological networks, or (3) to abandon the idea of centrality, as the focus on distinct symptoms or elements may not be ideal or realistic, also given the fat-hand problem (Erronen, 2020), the likelihood that interventions affect more than the targeted node alone. Instead, the focus might better be on the network as a whole, and mental disorders might better be defined as a complex system network (Bringmann et al., 2019).

A recent study (Bastiaansen et al., 2020) provides a nice illustration of how complex the selection of treatment targets actually is. These authors crowdsourced ESM data of one individual patient to 12 independent research teams, and asked these teams to analyse the data and indicate what targets for treatment should be. The variation in analytical approaches and recommendations for treatment targets was strikingly large. There was large variety in both the number and the nature of selected targets for treatment. Several issues were highlighted by these authors to solve before ESM data can reach full potential in the clinic. Identified issues include (1) if treatment targets should be based on the mean intensity of symptoms and/or on centrality indices, or other aspects (2) what variables to include in the analyses (other than symptoms), and (3) what other information is necessary to provide the ESM data with more context, such as clinical theory and expertise.

For our targeting study—investigating if network-based interventions are more effective than current treatments, not informed by networks—we will carefully select the optimal network characteristics to inform the intervention, based on latest insights. Crucially, we will also examine which network characteristics are most informative for optimal treatment selection, leading to the best treatment response (Bastiaansen et al., 2020). For this decision, in-depth research into causal mechanisms that may connect elements of the network is also a necessity (see section *zooming*). In addition, we will test whether network-based interventions actually change the patients' individual network structures, whether network-based interventions do this differently than control interventions that are not network-informed, and whether network changes are associated with a corresponding relief of symptoms. Note that it is not sufficient to just observe that the patient has improved after treatment. To be able to conclude that the

patient improved *because of* the network-informed intervention, we need to observe change in the targeted network elements and edges.

Another challenge is to control for the techniques that therapists use in the network-informed interventions. Depending on the node or edge to intervene on, therapists preferably use evidence-based techniques. For example, if anxiety and avoidance are nodes with large outstrength and high intensity in a patient with anorexia nervosa, the therapist could target anxiety and avoidance by using tailored exposure techniques. If the node insomnia has a large outstrength, for example leading to negative mood, the therapist could use evidence-based insomnia treatment techniques, like cognitive behaviour therapy techniques. It is essential that therapists who conduct network-informed interventions indeed target the network and focus on the appropriate parts of the network. Continuous interaction is needed, tracking what techniques are used, what the focus of an intervention is, and whether the therapist is indeed adhering to intervening on the network. A challenge is to match the intervention techniques across interventions. If similar techniques are used in a control intervention but without network information, it is expected that the critical symptoms or elements will not be addressed, or will be addressed to a lesser extent, and therefore a control intervention will be less effective.

9. The implementation of network-informed diagnosis and intervention in clinical practice

If network-informed diagnoses and interventions are found to be significantly more effective than current evidence-based treatment protocols for DSM diagnoses, further challenges are related to implementation in clinical practice. A practical issue is whether it will be possible to estimate networks of individual patients within a relatively short time. For reliable estimation of a network, a relatively high number of measurements is needed (Mansueto et al., 2021), but that may not be desirable in clinical practice, as it can be experienced as a burden for the patient and delays treatment. However, patients are often on a waiting list during which EMA may take place, and they may also perceive such participation in EMA as the beginning of treatment. The estimation of personalised networks further demands specialised statistical knowledge. For the network approach to be adopted in clinical practice, it is essential to equip therapists with tools and training to relatively quickly obtain networks of their clients themselves, and to use these to guide their network-informed diagnoses and treatments. Therapists should also be educated and trained in the performance of adequate network-based interventions.

A future challenge is to convince the field, including institutions compensating mental health care, such as health care insurance companies, to revise, and even abandon a system that solely reimburses care for DSM-diagnosed disorders. It is advisable to inform and involve these institutions as soon as promising results are available, to show that network-informed mental health care is most likely more effective, also from a financial and economic point of view. Of course, this only becomes relevant when studies show that network-based interventions are more effective than current interventions, not merely non-inferior.

10. Conclusion

Starting from the foundation of the network approach to psychopathology, our multi-layered (*mapping, zooming, targeting*) research program intends to further develop this approach, and to critically examine if and how it can transform current clinical practice. The *mapping* layer estimates individual transdiagnostic dynamic networks in individuals, going beyond symptoms, including other potentially relevant variables—in the network and the external field—as well (i.e., elements), using both EMA and digital phenotyping. The *zooming* layer is aimed at understanding if and how relations between elements reflect transdiagnostic causal and maintenance mechanisms, which is crucial for drawing conclusions about causality. Finally, the *targeting* layer provides

the ultimate test, and examines if we can determine optimal targets in the network for interventions, and tests if network-informed interventions perform better than current treatment as usual. If our research supports the validity and effectiveness of this approach, the ultimate goal is the implementation of network-informed diagnoses and network-based interventions in clinical practice.

CRedit authorship contribution statement

Anne Roefs: Conceptualization, Writing – original draft, Visualization, Funding acquisition. **Eiko I. Fried:** Conceptualization, Writing – original draft, Funding acquisition. **Merel Kindt:** Conceptualization, Writing – review & editing, Funding acquisition. **Carolien Martijn:** Conceptualization, Writing – review & editing, Funding acquisition. **Bernet Elzinga:** Conceptualization, Writing – review & editing, Funding acquisition. **Andrea W.M. Evers:** Conceptualization, Writing – review & editing, Funding acquisition. **Reinout W. Wiers:** Conceptualization, Writing – review & editing, Funding acquisition. **Denny Borsboom:** Conceptualization, Writing – review & editing. **Anita Jansen:** Conceptualization, Writing – original draft, Funding acquisition, Supervision.

Declaration of competing interest

None.

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