Investigating the Complexity of Mental Health: Symptom Networks, Mechanisms of Change, and Digital Interventions

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I, Ciarán O’Driscoll confirm that the work presented in my thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Despite the high prevalence of mental health problems, we still have a limited understanding of how they develop and how to treat them effectively. Mental health problems are heterogenous with a myriad of potential symptoms and causes. This makes it difficult to develop treatments that are effective for everyone. With existing treatments, the mechanisms of change, are not well understood. This makes it difficult to develop new and improved treatments. I present a series of studies that explore the importance of considering the heterogeneity of symptoms and comorbidities in mental health conditions, through assessment and intervention and finally in developing a digital intervention.

In my first study I explore the functional relations among symptoms of depression and anxiety and compare networks for treatment remitters and those with persistent symptoms to identify potential prognostic indicators. In my second study I explore the dynamic process of symptom change during psychotherapy, illustrating how symptoms evolve and interact during psychotherapy. In my third study I investigated whether cognitive behaviour therapy and counselling for depression target different symptoms and explore the implications of modelling choices when quantifying change during treatment. In my fourth study I aimed to determine whether the associations between personality processes (e.g., mentalization, attachment, and emotion regulation) and psychopathological symptoms differed between diagnostic groups. In the final study I developed a just in time, digital behavioural health intervention targeting goal pursuit.

The studies suggest that transdiagnostic assessment and formulation of symptoms can inform clinical management and prognosis. I consider the implications my findings have for applied mental health contexts.

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Impact Statement

There is a lot of research on the effectiveness of psychotherapy, and while the results are generally positive, it doesn't work for everyone. Researchers and clinicians are interested in understanding the active ingredients in order to improve and refine psychological therapies. The problem is that it is not yet clear how psychotherapy works.

Change can occur at many levels; one level of expression is at the level of symptoms. Symptoms are a useful measure as they are both observable and salient to the experience of distress. Clinical psychology research has predominantly viewed psychopathology through the lens of disorders, where the measurement of disorder assumes a latent construct (e.g. depression or post-traumatic stress disorder). A person can reach a diagnosis through a myriad of symptom presentations. Although the symptom profiles may be different within disorders, these are assumed to be equivalent and the 'disorder' treated.

Network theory better fits with clinical practice where clinicians formulate the experience rather than attending to diagnosis. Specific symptoms (internal and external events) and the interaction between symptoms can uniquely impact the individual. Being able to track symptom changes over time may shed light on a part of the process of change. This approach also lends itself to a pandiagnostic or transdiagnositic understanding of psychopathology informing assessment, intervention and prognostics.

Informed by network theory and utilising network analysis, I have:

- Used data from six RCTs of depressed patients to explore the functional relations among symptoms of depression and anxiety and compared treatment remitters to those with persistent symptoms to identify potential prognostic indicators.
- Investigated the temporal dynamics of symptom change using data from 113,608 people who had engaged in psychotherapy for a broad range of mental health problems.
- Investigated the symptom specific effects of cognitive behavioural therapy compared to counselling for depression.

- Investigated how associations between personality processes (like mentalization, attachment, and emotion regulation) and psychopathological symptoms differ between different diagnostic groups (people with borderline personality disorder, people with affective disorders, and community controls).
- Developed, evaluated and implemented a personalised, just in time, digital behavioural health intervention to improve goal pursuit.

This work has stimulated, and pushed forward the research on symptom dynamics during psychotherapy, highlighting the importance to attending to symptom level assessment and considering a transdiagnostic approach. It has also led to recommendations on how to measure change during psychotherapy.

This research is spearheading a symptom focus within psychotherapy research and has stimulated debate about the use of these methods in large psychotherapy samples to identify processes relevant to specific subgroups. The methodological advances will benefit other clinical researchers, enhancing research capacity, knowledge, and skills of public, private and third sector organisations. This will contribute to improving health and wellbeing, where the findings and approaches influence the practice of clinicians and health services. Further to this, given the generalisability of some of the findings, given the large sample sizes, the findings could influence evidence-based policy making and public policies.

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CHAPTER 1

Background of the Problem

More and more people are going to psychotherapy. According to the National Institute of Mental Health, approximately 11% of people in the United States seek psychotherapy each year (National Center for Health Statistics, 2023) . In the UK, 1.9 million are expected to access psychological care each year by 2024 (Alderwick & Dixon, 2019). There has been extensive research on the effectiveness of psychotherapy, and while the results are generally positive, it doesn't work for everyone (Cuijpers et al., 2019). Researchers and clinicians are interested in understanding the active ingredients in order to improve and refine psychological therapies. The problem is, that it is not yet clear exactly how psychotherapy works.

Psychotherapy is not not a rigidly defined process, encompassing a single characteristic or set of characteristics. Varied approaches to psychotherapy have evolved from different philosophical positions and each holds different theories about how their approach to therapy works and brings about change. While therapeutic approaches may be empirically supported, in the most part, the theories themselves are not adequately supported by empirical evidence (Cuijpers et al., 2019). We may be able to show that change occurs, empirically, but not precisely how it occurs.

Available scientific literature suggests that most psychotherapeutic approaches have a similar impact (the dodo bird hypothesis) and this has led to the suggestion that change is due to 'common factors', or that comparable results can be achieved through different treatments (Cuijpers et al., 2019; Wampold, 2015).

Proponents of each of the various approaches to psychotherapy would likely agree that each approach helps people to understand their thoughts, emotions, and behaviours. Past experiences can affect present behaviour and people can get caught up in unhelpful or inflexible patterns of responding to experiences, both internal and external. All therapies hold the shared purpose of bringing about change.

All approaches also consider the relationship between therapist and person receiving therapy (the therapeutic relationship) to be an important factor that facilitates change. Better outcomes are associated with: a strong bond; having a shared understanding of the problem; and working on a clear goal. Within therapy the person experiences

care and empathy from another (Wampold, 2015). Change theoretically fits within a sequence: support, leading to learning and then to action (Lambert & Ogles, 2004) with a range of suggested common factors, such as cognitive change (Lemmens et al., 2016), mentalisation (Bateman et al., 2018) and mastery (Lambert & Ogles, 2004). The person comes with positive expectations, (or such expectations are shaped in therapy), so that during the therapy, the person becomes hopeful. Although what a person may 'do' in a session may vary, the activity of therapy aims to provide them with the means with which to cope with their distress.

Most approaches also aim to find ways to engage people to face internal experiences or situations that they avoid because they are uncomfortable or upsetting (Carey, 2011). Therapy often facilitates exposure to the things we would rather avoid. This may occur at each point of a person's engagement with therapy including: at the point of making the appointment; when sitting with the therapist; talking to them about feelings; exploring the past and or current difficulties in detail; and in making changes in day to day life. Through this process, the person is assisted and encouraged to learn to tolerate discomfort (or it may reduce over time), and the individual comes to think about their experiences differently (Carey,2011). The individual learns something new, adapts their responses, implements changes, re-evaluates and so on… Reducing avoidance brings about change.

The how

I've been feeling miserable for months. I've been going to work and contributing at home but it's a façade and it's draining. Outside of these duties I do nothing. I've been avoiding friends and have stopped doing things I used to enjoy. Simple things in my daily life no longer bring me the same level of joy. I find it hard to focus on what's going on around me. I'm mostly lost in thought, playing over past events: everything that went wrong and how I am to blame. I worry about the future: if things go on this way, will I lose my job, my partner, my home? I have been snappier and less affectionate to my partner, and they are concerned. They have said that something needs to change, suggesting I get help. I have brushed it off. I don't have the time or the energy. I am taking an anti-depressant medication. It helps, but not enough. I don't feel in control. I am trying to hold things together and it's not working.

I decide to try out therapy. I've been looking up therapists for some time but keep putting off calling one. Eventually, I arrange an appointment. On the day I dread it. I enter the room and sit across from this person. They ask questions, I answer as best as I can. It's difficult. I don't want to be there. They listen. At the end of the session, they summarise what I have told them. I listen, and I get the sense that I have been understood. I discuss how I would like things to be different and we jointly come up with a plan, both how we will use the sessions and what I will be working towards. I feel slightly hopefully.

Each week I meet my therapist. I never look forward it. They encourage me to discuss things I have been avoiding. It's uncomfortable and painful at times. I can see how events in the past have shaped the person I am now, and the way I think and feel about myself. I begin to understand why I feel the way I do. I can see how I became stuck, engaged in patterns, actions and reactions. I like this therapist. They seem caring, they appear interested in me, they seem to want to help, and I trust that they can.

I being to implement some changes, engaging in activities I have been putting off and dropping some habits that served or as a distraction or, as it happens, were making me feel worse. Some of my memories have less of hold over me. I can let things go. I can focus on the here and now. My partner is happier. Things that were uncomfortable at first, have become easier to engage with: talking about feelings, spending time with my friends. I feel ashamed that things got so bad and for so long. My therapist suggests there is still work to do, but I feel better. We agree that I have improved. Life for the most part is back to normal.

We can only really know the 'how', once we have the ability to measure it. When we can measure an event at a particular point in time, we begin to be able to explain the relationship between what is being done (intervention) and change (outcome). The event must change (i.e. reduction of avoidance) before there are changes in the outcome (symptoms) to demonstrate a causal, temporal relationship. If we expect the process of change to be sequential, we would need to be able show how change occurs at each point facilitating further change at the next point. This is a complicated pattern of external interactions both between therapist and client, and internally (within) for the client, unfolding over time, in the context of wider environmental

influences. Research to date has been hampered by studies that are too small or of poor quality, and which tend to be conducted by researchers who have a loyalty to a particular brand of therapy thereby often introducing bias (Fried, 2020).

Change can be influenced by psychotherapy, but it happens within the person. People are complex ‘systems’ (Borsboom, 2017). People are made up of many different parts: biological (ability and genetics), mental (thoughts and feelings), and social (life events, socio-demographics), each of which interact, impact, and adapt to one another and which can change over time. Our internal systems are constantly trying to maintain a balance, a state of equilibrium, satisfying the needs of all aspects of ourselves (for example, needs prompted by hunger, temperature or stress). We can readily understand how an external stressor (such as a loss) may have a profound effect on how we feel, think and behave. In addition, the underlying symptoms of our response to discomfort (for example, low motivation, worry and sleep deprivation), will each affect each other. At some points in this constantly active process, if we cross a certain internal or emotional ‘threshold’, our internal systems can shift into a different, self-sustaining state where the symptoms we experience actually drive each other (Hayes & Andrews, 2020). We can get stuck in this state (which we could call a disorder) and we may need assistance to get us out of that state (for example, therapy). An intervention can alter a specific symptom, and the change in one symptom can trigger changes in the others that produces a global change. Alleviation or alterations to some symptoms may have more power to trigger change or may be more susceptible to intervention. Being able to track symptom changes over time may shed light on a part of the process of change.

Changes relating to our wellbeing can occur at many levels (the molecular to societal); one such level is expressed through symptoms. A large percentage of change can or may in fact be attributable to factors outside of therapy (Buckman et al., 2022), so we would not be able (in most instances) to measure all relevant influences. Symptoms, however, are a useful measure of change as they are both observable and salient to the experience of distress. If someone is in therapy and their level of distress starts to decrease, that change can be observed in the transition between states (Hayes & Andrews, 2020). During a transition, we can look at and perhaps see, how symptoms are interacting and what is helping to facilitate the change. The individuals’ ‘system’ of symptoms may reorganize itself and develop as the symptoms interact, or it may reach

a critical point and transition into a different state (for example, from 'disordered' to 'healthy'). Change can be gradual or sudden, but it requires a significant shift to move the system out of a pathological state. These changes and transitions require sensitive and thorough measurement if we are to capture this process (Fried, 2020). The ability to capture the process though measurement assumes that we are in in fact able to measure the ‘what’ and ‘how’ accurately.

Many therapists will individualize their approach: mapping out the processes relevant to the person they are working with, identifying the external events that are impacting the person, identifying what might be keeping the processes going (both inside and out), and from there identifying ways to help. This is a theoretical approach. A group of different therapists presented with the same case may each come up with different formulations. Even if it were possible to assign this group the same client individually, if we desired to measure the ‘how’, we’d need to measure the distinct dynamics between therapist and client and the multiple procedures which can be implemented. As such, we can see that there are innumerable pathways to change, different for every client.

Mental health difficulties and how psychotherapy works are complex and not well understood. This makes it difficult to improve psychotherapy outcomes. Psychological therapies are an effective treatment for mental health difficulties, but there is room for improvement. Better understanding of mental health difficulties and how psychotherapy works could help to improve outcomes. Within this thesis I will suggest that this requires greater attention to the dynamic interaction between symptoms, and within person processes.

Theoretical Framework

There is a growing body of evidence that suggests that mental health difficulties can be informed by taking a transdiagnostic perspective (Dalgleish et al., 2020; Mansell, 2019). This means that different mental health disorders can share symptoms, and that this can affect treatment and diagnosis. There are several benefits to understanding mental health difficulties from a transdiagnostic perspective. First, it can help to improve treatment and prevention efforts, as it can help to target the underlying causes of mental health difficulties. Second, it can help to improve diagnosis, as it can help to identify which symptoms are most indicative of a particular mental health

disorder. Finally, it can help to reduce stigma, as it can help to show that mental health difficulties are not just “one thing” but can be experienced in different ways.

We tend to conceptualize mental health disorders, in line with diagnostic criteria such as that outlined in the Diagnostic and Statistical Manual (American Psychiatric Association, 2013). This conceptualisation reflects a common cause model which suggests that symptoms are interchangeable and passive, and indicators of an underlying disorder (Kendler & Campbell, 2009). Therefore, intervention should focus on this latent disorder variable. An alternative model, the network perspective, conceptualizes disorders as complex dynamic systems, where causal interactions between symptoms (within a network), are preferred to central casual pathways. Symptom interactions giving rise to mental disorders. Quantifiable symptoms take precedence over latent constructs (Borsboom, 2017), where no one symptom would be expected to predict an outcome (Cramer et al., 2016). Symptoms causally influence and potentially reciprocally reinforce one another (Borsboom & Cramer, 2013). Symptoms are important, autonomous causal agents and the 'disorder' is an emergent property.

This is not new to clinicians, where for decades a patient’s presentation has been formulated to consider the temporal and perpetuating factors to form an understanding of their distress. A functional analytic conceptualisation of a presenting problem will be idiosyncratic, specific to the patient and specific to event. This may lend itself to an overarch conceptualisation of the developmental factors, the triggering event, and pattern of behaviours that maintain distress over time. Network theory and associated network statistical approaches can formally model these associations. Though for the most part the literature focuses on symptom interactions, in the absence of environmental and developmental factors.

Within this system of psychopathology, ‘co-morbidity’ results from mutually reinforcing interactions between symptoms (Cramer et al., 2010). As there is no latent disorder, co-morbidity is explained or represented as the interaction between overlapping symptoms of ‘disorders’. The interaction between these symptoms can thus give rise to the expression of a myriad of other symptoms. While not characterised as disorders, symptoms may cluster together into communities and certain symptoms may form ‘bridges’ and connect these communities.

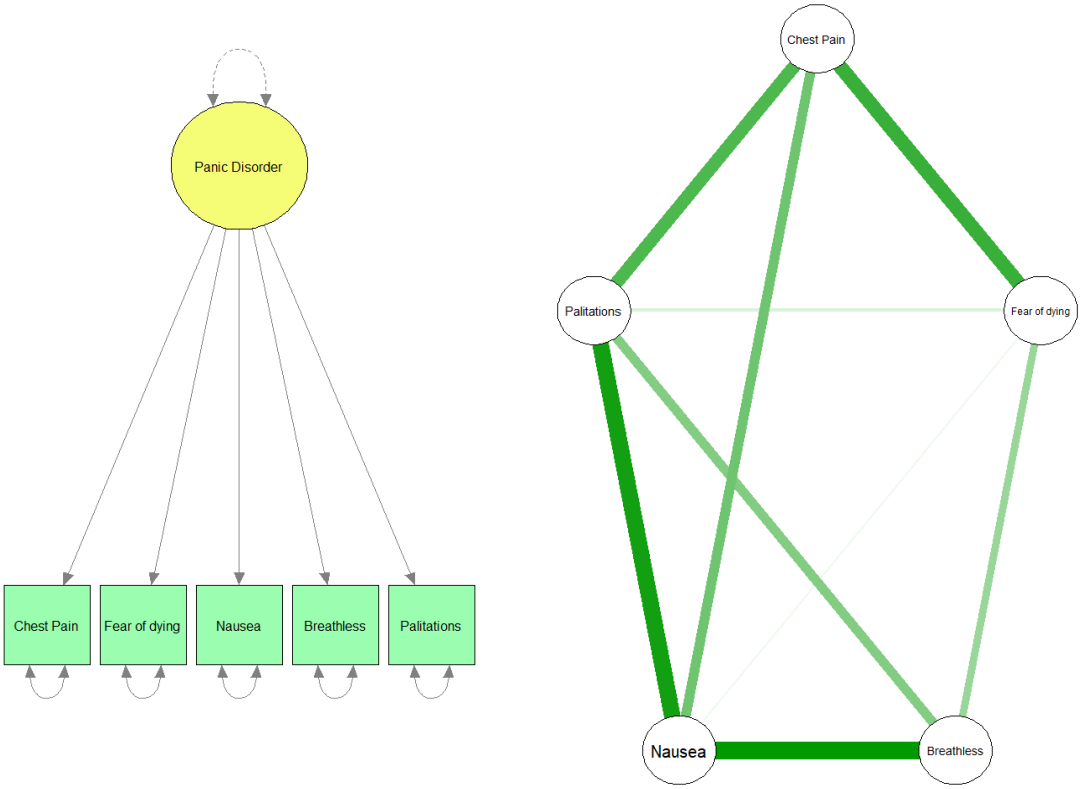

Figure 1. Visualisation of a simplified model of panic disorder. Common cause representation on the left, where the disorder causes the symptoms and a network representation on the right, where the emergence of panic disorder is a property of causal interactions between symptoms.

For instance, depression and anxiety have been modelled as symptom networks using cross-sectional and longitudinal data, demonstrating the interrelation between the symptoms of each disorder (Cramer et al., 2010; Heeren et al., 2018). Anhedonia, sad mood, anxiety, worry, fatigue and sadness have been shown to be predominantly central (Beard et al., 2016; Boschloo et al., 2016; Fried et al., 2016). While difference between subgroups emerge (Mullarkey et al., 2020; Santos et al., 2018), design, sample and variability arising from differing measurement also contributes to inconsistencies (Fried, 2017; Newson et al., 2020). When attempting to discriminate between groups for the purposes of identifying whom may benefit from treatment, there are varying results from network comparison studies, where it has been that suggested denser networks may be less likely to recover, (Van Borkulo et al., 2015).

However, these differences aren't always detected (Schweren et al., 2018) and require large sample sizes to detect any effect.

Similarly, sum score prediction models "conceal variability" within depression (Fried & Nesse, 2015). Symptoms not only show associations with other symptoms, but are likely to have variable associations with outcomes (Fried & Nesse, 2014; Gollan et al., 2012). Large-scale, multisite clinical and trial databases, coupled with innovative statistical methods can provide categorisation and treatment optimisation which provides immediate benefits by informing clinical decisions (DeRubeis et al., 2014; Dwyer et al., 2018; Fernandez et al., 2017). Symptoms level prediction models which include co-morbid indicators may offer a better model fit than sum-score models, with the relative importance of symptoms offering more information than severity of disorder alone and providing additional treatment and prognostic information.

The role of assessment in personalised treatment and improving outcomes.

We cannot improve what we cannot measure, and as such assessment is an important part of any treatment plan, as it can help to determine what the best course of action may be for a given individual. While nomothetic approaches can help us to identify what works best on average, or for specific groups of people, we also need to be able to employ idiographic approaches in clinical practice. By assessing a person's needs and goals, clinicians can develop a personalized treatment plan that is more likely to lead to positive outcomes. Current assessment procedures can be used to improve treatment and outcomes by providing more information about a person's individual needs. Taking a symptom level approach, an assessment of severity may help identifying specific symptoms that need to be addressed (e.g. those most affecting functioning), and inform a collaborative intervention plan that focuses on improving those symptoms. Tracking these symptoms over time, affords the opportunity to track changes and adjust treatment as necessary, however we can go further to track the momentary experience (i.e. ecological momentary assessment) which may also provide direct therapeutic benefits (Wichers, 2014) where self-monitoring provides the individual with greater awareness of their symptoms. Historically, idiographic approaches tended to be confined to case reports (Hoenders et al., 2012) but improvements in technology now allow us to employ intensive measurement across large samples to model both group level and individual level processes. Modelling

these processes are not straightforward (Bringmann, 2021; Rohrer & Murayama, 2023) requiring further methodological development before being suitable for clinical use. None the less, these methods offer the ability to tackle questions around mechanisms of change which have alluded researchers to date.

Statement of the Problem

There are large gaps in our knowledge of mental health difficulties and how psychotherapy works, which makes it difficult to improve psychotherapy outcomes.

Specific disorders are commonly perceived as unitary underlying diseases with a number of potential treatment options. However, patients differ in their symptom presentation and comorbidities. There are also large variations in treatment outcomes and associations of comorbidities with poorer prognoses, but limited understanding as to why, and little information to inform the clinical management of mental health problems. There is a need to improve our understanding of disorders, incorporating comorbidity, and consider the association of a wide range of symptoms with treatment outcomes.

The thesis will aim to provide a clinico-theoretical perspective rather than focusing solely on the statistical methods. Emphasis will be given to clinical translation.

Purpose of the Study

This thesis will use network theory and associated statistical methods to explore symptom interactions in the hope of contributing to our understanding of the nature of psychopathology, developing our understanding of ‘co-morbidity’, and how psychological interventions may target symptoms. The thesis will also look at how these methods can be applied in clinical practice both in terms of treatment choice and guiding personalised interventions.

Chapter 2 will investigate assessment of psychopathology using pre-post data from six randomised control trials for depression. Chapter 3 will explore symptom dynamics during psychotherapy, and Chapter 4, symptom specific effects of psychotherapy, both

using longitudinal data from primary care psychological services (IAPT). Chapter 5 will explore symptom overlap between disorders using cross sectional data. In Chapter 6, a pilot digital intervention study will use intensive longitudinal data to inform personalised interventions. In addition to exploring the impact of interventions on symptoms, the thesis will focus on methodological developments. Finally, in Chapter 7, the results from both a clinical and a methodological perspective, as well as the challenges of current approaches and future research directions will be discussed.

Significance of the Study

Network theory can inform psychological interventions by helping to identify how different symptoms are connected. This information can then be used to design interventions that target specific symptoms to achieve the desired outcome. As measurement improves, it will become possible to develop more personalised interventions. By providing individuals with targeted support that meets their specific needs we may overcome some of the limitations inherent in group design. By tailoring interventions to the unique circumstances of each individual, personalised approaches can more effectively address the underlying causes of problems and help people to manage their distress and achieve their goals.

A network theory of psychopathology could be used to make better decisions by identifying risk and protective factors for mental health treatment response. This could help to target interventions and prevention efforts more effectively. Additionally, a network approach could be used to map out the complex relationships between different mental health problems and their risk factors. This could help to create a more comprehensive understanding of mental health and how to best support people who are struggling with mental health issues.

This information can inform clinical practice through a shift in how we conceptualise disorders. Policymakers and service providers will also be able to use this knowledge to make more informed decisions about how to allocate resources and design services that are more effective and efficient. Clinicians, who already used formulation to guide interventions will find that they will be able to use this information to inform treatment decision making in an empirical and data driven way. With the development of

personalised digital interventions, the individual user will be able to use this knowledge to make better decisions about their own health and wellbeing. This will empower people to take control of their lives and make choices that are right for them.

Primary Research Questions

Over a number of studies, the thesis will investigate the multivariate interrelations and temporal dynamics of symptoms. How our assessment and treatment of psychological disorders need to consider symptoms over disorders.

Chapter 2

- How do symptom domains interact and do their patterns of interaction tell us anything about challenges that may present before the start of treatment, and are patterns of coupled change predictive of outcome?

Chapter 3

- Are there variations in intraindividual changes across different symptoms over the course of therapy?

Chapter 4

- Do interventions which are conceptually linked to specific symptoms have a differential impact on corresponding symptoms that could account for the distribution of treatment effect across the entire network?

Chapter 5

- Do associations between personality processes (e.g., mentalization, attachment, and emotion regulation) and psychopathological symptoms differ between diagnostic groups?

Chapter 6

- How feasible, acceptable, and effective is a just-in-time digital intervention in improving goal pursuit in a non-clinical sample?

Research Design

The thesis will primary model the data using network analytic approaches to answer the research questions.

Network analysis is a powerful visualisation tool for understanding the relationships between many variables. By representing each variable as a node and the relationships between those nodes as lines (edges), it is possible to see the interrelationships between the variables at a glance. Edges are weighted, where the thickness and saturation reflect the strength of the association. Network analysis can also be used to identify clusters or "communities" of related variables, and to find bridge symptoms (symptoms that connect different communities).

Within the networks, given the number of associations being estimated, to facilitate interpretation, conditionally independent (partial correlation) networks are estimated. The association between two variables is estimated after controlling for the influence of all other variables within the network (i.e. excluding shared variance of more than two variables). As a result, associations can be interpreted as direct or indirect.

In addition to this, due to the potential for a large number of spurious associations to be estimated, a regularisation is applied. This method applies a penalty equal to the absolute value of the magnitude of coefficient. This forces the coefficients to be small or equal to zero, which in turn results in a model that is more interpretable. This tends to maximise specificity at the cost of sensitivity (Epskamp, Kruis, et al., 2017), reducing the likelihood of false positives.

In addition to conditionally independent network modelling using cross sectional data, I will employ different network analytic methods relevant to the research questions posed. These will include models estimated in panel data and time series data (Epskamp, 2020; Haslbeck et al., 2020) and moderated network models, which take group differences into account (Haslbeck et al., 2019).

Assumptions, Limitations, and Scope (Delimitations)

As factor analysis has served a common cause model (i.e. the assumption of an underlying latent construct), the Gaussian Graphical Model (GGM) (Lauritzen, 1996) serves network theory. GGM and structural equation modelling (SEM) both model covariance structures and GGM shares similarities with factor analysis, path analysis and directed acyclic graphs (DAGs). However, the assumptions underlying the models are different. SEM assumes latent variables whereas GGM assumes interactions between observed variables. SEM assumes local independence: observed variables are independent of each other after conditioning on the latent variable(s). GGM does not, indeed expects this assumption to be violated, which is especially important when studying psychological phenomena, where direct causal effects, semantic overlap, and reciprocal interactions between variables are expected (Cramer et al., 2010; Robinaugh et al., 2019; Schmittmann et al., 2013). SEM takes measurement error into account, GGM does not, within network analysis observed variables tend to be measured using individual items. Within the DAG model there is the assumption that associations are acyclic (no feedback loops), whereas GGM assumes (or allows for) a cyclic relationship between variables.

GGM's are suited to exploratory analysis as they can provide insights into which variables are dependent on each other. However, they are not as well suited to causal discovery (Ryan et al., 2022), as the presence of an edge may suggest either a direct causal relationship or the presence of a collider structure (i.e. two variables both cause a third variable, conditioning on the third variable makes the two variables falsely dependent) (Pearl, 2000). When inferring casual relationships GGMs lie on a pathway between correlation and DAGs, where DAGs take causal inference a step too far (Epskamp, Rhemtulla, et al., 2017).

Estimating temporal networks (for instance, graphical vector-autoregressive models) does improve causal inferences, but are still limited in deriving true causal relationships between symptoms (Epskamp, 2020). The assumptions behind all these models are explored in more detail within each chapter.

Across the studies I will attempt to address the limitations posed by preceding methodology. For instance, in Chapter 2 when estimating a cross-sectional network

model, this does not represent a causal network. In Chapter 3, within the dynamic network model, I will be able to model temporal precedence. However, the transdiagnostic and pan-therapy approach in Chapter 3 obfuscates potentially clinically meaningful differences between therapies and between groups. Chapters 4 and 5 respectively address those limitations. Across all chapters the nomothetic analysis limits the ability to consider individual effects. By taking an idiographic approach in Chapter 6, temporal associations at the individual level can be explored while undertaking a micro-intervention.

The thesis spans several datasets and forms of measurement. All the group studies employ large samples to reliability estimate parameters of interest. Chapter 2 uses data from six randomised control trials for depression across the UK (n =2858), Chapter 3 and 4 uses data from psychological therapy services in London (n= 113,608, and n = 12756 respectively), Chapter 5 uses data from a large observational trial selecting people from a clinical and community population across the UK (N= 1386). Chapter 6 focuses on the individual where the intensity of measurement improves reliability, in the final sample n = 70, individuals provided 120 measurement each over a month period.

Summary

Despite the prevalence of mental health difficulties, there is still much that is not understood about these difficulties, how the psychological interventions we provide work and how to improve outcomes. This lack of understanding makes it difficult for practitioners to provide effective treatment, leading to a need for further research in this area. It is important to address these gaps in knowledge and how doing so can lead to improved mental health outcomes for individuals. This thesis aims to address the gaps in knowledge related to mental health difficulties and psychotherapy. In the following chapters I will present studies which aim to answer questions related to the assessment of psychopathology, symptom dynamics during psychotherapy, symptom-specific effects of psychotherapy, symptom overlap between disorders, and a pilot digital intervention study.

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CHAPTER 2

The importance of transdiagnostic symptom level assessment to understanding prognosis for depressed adults: analysis of data from six randomized control trials.

Abstract

Background: Depression is commonly perceived as a single underlying disease with a number of potential treatment options. However, patients with major depression differ dramatically in their symptom presentation and comorbidities, e.g. with anxiety disorders. There are also large variations in treatment outcomes and associations of some anxiety comorbidities with poorer prognoses, but limited understanding as to why, and little information to inform the clinical management of depression. There is a need to improve our understanding of depression, incorporating anxiety co-morbidity, and consider the association of a wide range of symptoms with treatment outcomes.

Method: Individual patient data from six RCTs of depressed patients (total n=2858) were used to estimate the differential impact symptoms have on outcomes at three post intervention timepoints using individual items and sum scores. Symptom networks (Graphical Gaussian Model) were estimated to explore the functional relations among symptoms of depression and anxiety and compare networks for treatment remitters and those with persistent symptoms to identify potential prognostic indicators.

Results: Item-level prediction performed similarly to sum scores when predicting outcomes at 3 to 4 months and 6 to 8 months, but outperformed sum scores for 9 to 12 months. Pessimism emerged as the most important predictive symptom (relative to all other symptoms), across these time points. In the network structure at study entry, symptoms clustered into physical symptoms, cognitive symptoms, and anxiety symptoms. Sadness, pessimism, and indecision acted as bridges between communities, with sadness and failure/worthlessness being the most central (i.e. interconnected) symptoms. Connectivity of networks at study entry did not differ for future remitters vs. those with persistent symptoms.

Conclusion: The relative importance of specific symptoms in association with outcomes and the interactions within the network highlight the value of transdiagnostic assessment and formulation of symptoms to both treatment and prognosis. We discuss the potential for complementary statistical approaches to improve our understanding of psychopathology.

Introduction

Psychological therapies and medication are effective treatments for depression (e.g., Arroll et al., 2016, Santoft et al., 2019). However, effect sizes have been modest and gains in treatment outcomes have plateaued (Cuijpers et al., 2010). Interventions for depression target a broad range of symptoms, and knowledge of 'what' is being intervened upon is not necessary to the delivery of most treatments, and poses problems for causal inference (Eronen, 2020). To improve interventions, we may need to improve our knowledge of the structure of depression (Fried et al., 2016).

Depression is heterogeneous in terms of aetiology and symptom profile (Cuijpers et al., 2012; Hardeveld et al., 2013; Simon and Perlis, 2010). Mood disorders are highly comorbid with anxiety disorders, and may share psychological and biological vulnerabilities (Brown and Barlow, 2009; Cummings et al., 2014). The risk of one disorder can increase the risk of another (Kessler et al., 2011) and the same end state may be achieved via many different paths (equifinality) (Kendler, 2013; Wichers, 2014).These disorders are not discrete entities and as such, neglecting the symptomatic heterogeneity discards potential insights (Fried and Nesse, 2015a).

There is strong evidence that different symptoms are not equivalent or interchangeable (Fried, 2017) and studies of individual symptoms in the last decade have brought important understanding. For example, individual symptoms may differ in response to treatment (Bekhuis et al., 2018; Boschloo et al., 2019), and have been shown to have a differential impact on functioning (Fried et al., 2019; Fried and Nesse, 2014; Gollan et al., 2012). Depression is a recurrent disorder with the probability of relapse strongly associated with the presence of residual depressive symptoms at the end of treatment (Buckman et al., 2018; Judd, 1999). Comorbid anxiety disorders are related both to worse treatment outcomes (Webb et al., 2020) and to an increased risk of relapse (Buckman et al., 2018). An assumed unidimensional view of depression, characterized by sum score (sum of symptom severity scores) measurement and prediction models conceals the variability within depression (Fried and Nesse, 2015b). Understanding the relative importance of co-morbid symptoms may offer more information than severity of disorder alone and provide additional treatment and prognostic information (Fried, 2017). Large-scale, multisite clinical trial data, coupled

with innovative statistical methods can provide categorisation and treatment optimisation to provide immediate benefits by informing clinical decisions (DeRubeis et al., 2014; Dwyer et al., 2018; Fernandez et al., 2017).

There is also value in studying the relations among these symptoms. Network theory posits that the relationships between common affective, cognitive, and somatic symptoms of these disorders, may reflect potential causal pathways and elucidate maintenance mechanisms (Borsboom, 2017). Depression and anxiety have been modelled as symptom networks using cross-sectional and longitudinal data, demonstrating the interrelation between the symptoms of each disorder, where co-morbidity results from mutually reinforcing interrelation between symptoms of each disorder (Cramer et al., 2010; Heeren et al., 2018a). Anhedonia, anxiety, worry, fatigue and sadness are predominantly influential symptoms in these networks (Beard et al., 2016a; Boschloo et al., 2016; Fried et al., 2016). The relationship between symptoms / mechanisms may help to predict outcome and potentially inform treatment targets and the development of treatments targeting specific mechanisms (Kendler and Campbell, 2009).

There are inconsistencies in the network literature exploring depression and anxiety, due to design, sampling, and variability arising from differing measurement (Fried, 2017; Newson et al., 2020). When attempting to discriminate between groups for the purposes of identifying whom may benefit from treatment, there are varying results from network comparison studies, where it has been suggested that densely connected networks may be less likely to recover (Van Borkulo et al., 2015). However, these differences are not always observed (Schweren et al., 2018a) and require large sample sizes to detect any effect. Past research has been conducted on small samples with low quality assessment of patients (or non-clinical samples) and lack of adequate consideration of co-morbidity (missing out on the wider spectrum of anxiety disorders) (Fried et al., 2016).

In this study I aim to:

1) Identify important symptoms for outcome by examining the (differential) impact of individual symptoms on prognosis for adults with depression that took part in randomized controlled trials after seeking treatment in primary care; and assess whether individual symptoms offer predictive value above sum scores.
2) Discern the functional relations among symptoms and clarify the interplay between highly co-morbid symptoms of depression and anxiety disorders.
3) Consider whether there are differences in the baseline symptom networks of patients that remitted vs those whose depression persisted, after treatment.

Method

Datasets

Data were drawn from a subset of the Dep-GP individual patient data (IPD) database (Buckman et al., 2020). The formation of the Dep-GP IPD dataset has been described elsewhere (Buckman et al., 2020). In brief, bibliographic databases were searched up to 29th April 2020 for RCTs of unipolar depressed adults seeking treatment for depression from a general practitioner/family physician and confirmed by the Revised Clinical Interview Schedule (CIS-R). Additional inclusion criteria for the present study were the use of the Beck Depression Inventory (2nd Edition) (BDI-II) (Beck et al., 1996a) at study entry. This ensured uniformity in the measurement of depressive and anxiety symptoms, chronicity of problems and determination of diagnoses including anxiety comorbidities.

Data on all individual patients from all six eligible RCTs were included in the current study, these were: COBALT (Thomas et al., 2012), GENPOD (Lewis et al., 2011), PANDA (Lewis et al., 2019), TREAD (Chalder et al., 2012), MIR (Kessler, David S. et al., 2018) and IPCRESS (Kessler et al., 2009).

Measures

Individual items from the BDI-II (Beck et al., 1996b); and individual symptom subscales of the CIS-R (Lewis et al., 1992), including duration of depression and anxiety which

have been shown to be independently associated with prognosis for depressed adults (Buckman et al., 2020).

Outcomes

The primary outcome was endpoint depressive symptoms at three to four months post-study entry. Five of the studies used the BDI-II at three to four months, and one used the PHQ-9. A continuous 'depression severity' score was developed by converting the responses on each measure to a latent trait depressive symptom severity score (PROMIS T-Score) (Choi et al., 2014), using the expected a posteriori parameter from a multidimensional item-response theory-based score conversion tool (Fischer and Rose, 2016). Depressive symptoms (PROMIS T-Score) at six to eight months post-study entry, and nine to twelve months were secondary outcomes.

As a sensitivity analysis, the BDI-II scores were used as outcomes for the three timepoints; (five studies at three to four months; four studies at six to eight months, and three studies at nine to twelve months).

Data analysis

All analyses were performed in R 3.6 (R Core Team, 2017) and Stata 16.0 (StataCorp, 2019). Analysis code is available from https://osf.io/wck6b/. The data that support the findings of this study are available from the lead author of the Dep-GP (JB) subject to agreement from the chief investigators or data controllers of the individual RCTs. Restrictions apply to the availability of these data, which were used under license for this study.

Pre-processing

Datasets were combined and pre-processed together. Missing data on individual items at study entry was imputed using nonparametric random forest imputation (missForest) (Stekhoven and Bühlmann, 2012). All items were investigated to ensure they met assumptions for inclusion in the network models, including assessing for: near zero variance; roughly equal variance of items; asymmetrical distributions; and collinearity. Items were removed if they violated assumptions across all studies. Where collinearity was identified, the respective pair of items were combined into a single variable using Principal Component Analysis (PCA) (Jones, 2018) if reasonable to

combine from a clinical perspective. Items were afterwards rescaled to their original Likert scale values to make variances comparable across items (Terluin et al., 2016).

Association with outcomes

We aimed to examine the differential impact of individual symptoms on outcomes; and assess whether individual symptoms offer predictive value above sum scores. Sum score totals were entered into a linear regression model, while the item severity scores were entered into an elastic net generalized linear model (ENR) (Friedman et al., 2010). ENR, a statistical method combining lasso and ridge regression approaches, minimizes overfitting and the use of ten separate, ten-fold repeated cross validation aids in assessing the effectiveness of the model. The item-level and sum-score models were compared using root mean squared error, mean absolute error and R^2.

As the item-level predictors were assumed to be correlated and that we wished to assess the explanatory power of individual predictors, we estimated the contribution of each item to the outcome prediction using Shapley Additive exPlanations (Lundberg and Lee, 2017), following ENR model estimation. Five hundred Monte Carlo repetitions were used to estimate each Shapley value. This metric is more accurate than other variable importance metrics when predictors are dependent (Molnar, 2019). Items with large Shapley values are 'important', indicating the relative contribution of an item to the model while accounting for correlated features in the data.

Network modelling

A Graphical Gaussian Model (GGM) aims to capture the direct effects (edges) between items while controlling for all other items in the network. A network was estimated by combining data from the six RCTs. The sample was then split into two networks (those with persistent symptoms vs. remitters: BDI-II score <10 at 3-4 months), the networks were re-estimated and compared using the network comparison test with 1000 iterations (van Borkulo et al., 2015).

We performed a number of analyses to test the robustness of the networks we estimated. While lasso (Tibshirani, 2016), regularized GGMs (Epskamp et al., 2012) are most frequently reported in the network literature, lasso specificity has recently

been shown to be lower than expected in dense networks with many small edges, leading to an increase in false positives (Williams and Rast, 2020). We also estimated an unregularized GGM procedure using the Extended Bayesian Information Criterion (EBIC) (Foygel and Drton, 2010). The best performing model (EBIC parameter) was selected to provide a conservative GGM estimation (high specificity; drop in sensitivity).

Chronicity of disorders has been shown to interact with symptom severity (Buckman et al., 2020; Lorenzo-Luaces et al., 2020). We corrected for the potential confounding effects of duration of depression and anxiety within the network models.

Combining data obtained from different studies holds the potential for between-study differences to influence estimation. A network estimation procedure (fused graphical lasso: FGL) (Costantini et al., 2019) has been designed to manage this issue, however, this involves estimating networks individually and penalizing between study differences. Where study size affects the estimation of edges, this can lead to penalization based on sample size rather than on true differences between the network structures (Fried et al., 2018). As such, it was decided to estimate based on the combined sample and to compare this to the FGL network (joint estimation using a fused penalty, and 10-fold cross validation), to assess the potential influence of group level differences.

Finally, the network model was tested for the stability of expected influence centrality and the accuracy of interrelations using a nonparametric bootstrapping procedure (1000 iterations) (Epskamp et al., 2018). For details of these see Chapter 2 Supplementary material.

We obtained two types of information from the resulting network structures. First, symptoms can form clusters or communities with other symptoms to which they are connected reflecting commonalities between them. We estimated the community structure by using a bootstrapped walktrap algorithm (Golino et al., 2020), investigated for item stability before selecting communities. Second, the overall connectivity of a symptom, i.e. its connection to other symptoms, can be quantified in a number of ways and is referred to as centrality. Some scholars have argued that activation of a central

symptom has the potential to activate associated symptoms in the network (Borsboom and Cramer, 2013), where symptom centrality is then interpreted as symptom importance, given that identifying such symptoms may have the potential to elucidate the processes underlying co-morbidity and implications for treatment. Within the context of communities specifically, symptoms which connected to more than one community are referred to as bridge symptoms. Within cross-sectional networks (as explored here), we refer to centrality as a statistical parameter, i.e. the strength of predictive associations between symptoms. Centrality does not automatically translate into clinical relevance (Bringmann et al., 2019) and cautious interpretation is warranted (Fried et al., 2018). It requires consideration of: how the symptoms activate within the network (flow or transfer); the conceptual similarity between symptoms; and whether there is missing information on the shared variance (Robinaugh et al., 2014). Symptom centrality was calculated using: Expected Influence (EI: strength of the relationships a given node has with other node); and the geometric mean of the Participation Ratio (PR) and Participation Coefficient (PC); and normalized bridge expected influence centrality (Jones et al., 2019). The PR quantifies the number and strength of edges, while the PC takes the community structure into account (Letina et al., 2019).

Results

	COBALT (N=469)	GENPOD (N=601)	MIR (N=480)	TREAD (N=361)	IPCRESS (N=295)	PANDA (N=652)	Overall (N=2858)
Baseline BDI-II total							
Mean (SD)	31.8 (10.7)	33.7 (9.67)	31.1 (9.91)	32.1 (9.24)	33.2 (8.80)	23.9 (10.3)	30.4 (10.5)
Median [Min, Max]	30.0 [14.0, 60.0]	33.0 [15.0, 60.0]	30.0 [14.0, 58.0]	31.0 [14.0, 57.0]	33.0 [15.0, 58.0]	23.0 [2.00, 54.0]	30.0 [2.00, 60.0]
Gender							
Female	339 (72.3%)	408 (67.9%)	332 (69.2%)	239 (66.2%)	200 (67.8%)	384 (58.9%)	1902 (66.6%)
Male	130 (27.7%)	193 (32.1%)	148 (30.8%)	122 (33.8%)	95 (32.2%)	268 (41.1%)	956 (33.4%)
Age							
Mean (SD)	49.6 (11.7)	38.8 (12.4)	50.7 (13.2)	39.8 (12.6)	34.9 (11.6)	39.7 (15.0)	42.5 (14.1)
Median [Min, Max]	50.0 [18.0, 74.0]	38.0 [18.0, 74.0]	51.0 [19.0, 84.0]	39.0 [18.0, 69.0]	34.0 [18.8, 74.6]	38.5 [18.0, 73.0]	42.0 [18.0, 84.0]
Employment Status							
Employed	206 (43.9%)	357 (59.4%)	237 (49.4%)	230 (63.7%)	178 (60.3%)	433 (66.4%)	1641 (57.4%)
Seeking employment	151 (32.2%)	123 (20.5%)	102 (21.2%)	48 (13.3%)	35 (11.9%)	73 (11.2%)	532 (18.6%)
Not seeking employment	112 (23.9%)	121 (20.1%)	141 (29.4%)	83 (23.0%)	82 (27.8%)	146 (22.4%)	685 (24.0%)
Education							
Degree or higher	95 (20.3%)	0 (0%)	95 (19.8%)	87 (24.1%)	102 (34.6%)	230 (35.3%)	609 (21.3%)
A-level or Diplomas*	123 (26.2%)	0 (0%)	135 (28.1%)	104 (28.8%)	88 (29.8%)	220 (33.7%)	670 (23.4%)
GCSE**	131 (27.9%)	0 (0%)	150 (31.2%)	102 (28.3%)	62 (21.0%)	145 (22.2%)	590 (20.6%)
None or Other	120 (25.6%)	0 (0%)	100 (20.8%)	68 (18.8%)	43 (14.6%)	57 (8.7%)	388 (13.6%)
Missing	0 (0%)	601 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	601 (21.0%)
Ethnicity							
White	459 (97.9%)	575 (95.7%)	469 (97.7%)	336 (93.1%)	281 (95.3%)	579 (88.8%)	2699 (94.4%)
Non-White	10 (2.1%)	26 (4.3%)	11 (2.3%)	25 (6.9%)	14 (4.7%)	73 (11.2%)	159 (5.6%)

*Table 1: Descriptive table of studies included in the dataset. Summary of included variables provided in supplementary materials. * International Baccalaureate equivalent ** High school diploma equivalent.*

Demographic details for the studies are presented in Table 1. Overall samples were comparable. The severity of depressive symptoms captured by BDI-II scores at baseline in the PANDA sample was lower than the other trials, reflecting the recruitment criteria. Descriptive results are reported in the supplementary materials.

Association with outcomes

In order to assess the utility of item level models, we compared them to sum score models. For all item level models (Table 2), the optimal shrinkage parameters for the ENR were selected via minimum cross-validated error criterion ($\alpha = 0.1$ and $\lambda = 0.05$). While models performed similarly at three to four months and six to eight months, the item level ENR regression model outperformed linear regression with BDI-II and CIS-R (sum of anxiety items) totals at the nine to twelve month time point. The sensitivity analysis performed similarly. Due to the absence of two studies (IPCRESS and PANDA) at the nine to twelve month endpoint, we reran the analyses for the earlier time points without these studies. This sensitivity analysis did not reveal any difference in the pattern of model performance.

Pessimism (Figure 1) was consistently the most important item; health anxiety was in the upper quartile at each time point; and concentration, failure/worthlessness, also in the upper quartile at three to four months; guilt and sleep at six to eight months; and somatic symptoms at nine to twelve months.

		PROMIS T-Score		
		RMSE	R^2	MAE
3 to 4 months N=2646	Items	0.925	0.146	0.730
	Sum scores	0.926	0143	0.730
6 to 8 months N=1297	Items	0.926	0.147	0.734
	Sum scores	0.924	0.146	0.735
9 to 12 months N=1110	Items	0.919	0.161	0.744
	Sum scores	0.935	0.126	0.753

Table 2: Performance of the regression models. Sum scores: BDI-II and CIS-R; RMSE root mean squared error; MAE mean absolute error; R^2 proportion of the variance explained.

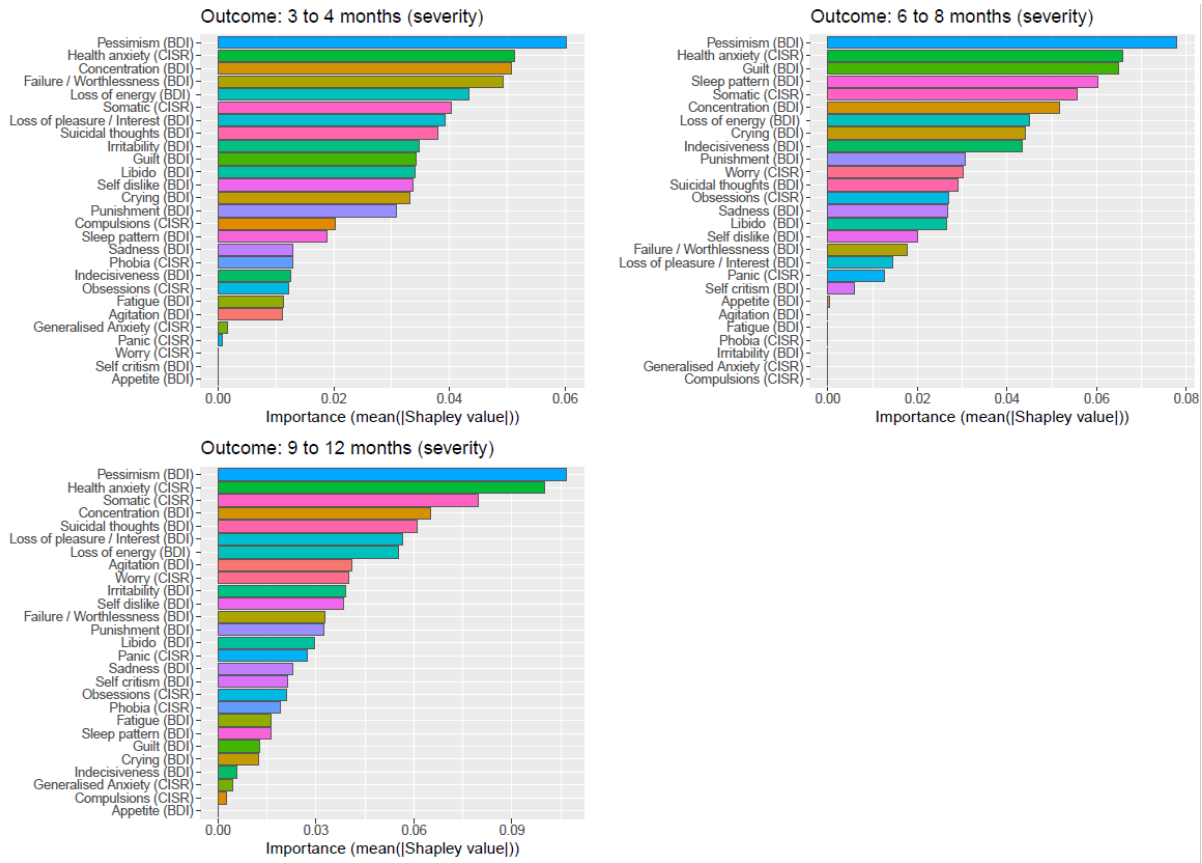

Figure 1: Shapley values for variable importance are plotted: (showing the difference contribution of items to predictions).

Network Modelling

For the individual items in the network model, near zero variance (e.g. due to floor and ceiling effects) was not observed. However, we saw asymmetric distributions (skew) on a number of items. As such, a Spearman covariance matrix was estimated and used to estimate the network model. Multi-collinearity was identified for two pairs of items (loss of pleasure with loss of interest, failure with worthlessness). New items were constructed using PCA for each pair. The optimal model for the network analysis was an unregularized GGM model using the EBIC.

A walktrap algorithm identified three symptom communities. The three communities split into anxiety items, depressive cognitions and depressive physical symptoms. Bridging EI elucidated three bridging symptoms between the communities: sadness and indecisiveness (from the physical symptoms community); and pessimism (cognitive symptoms community);

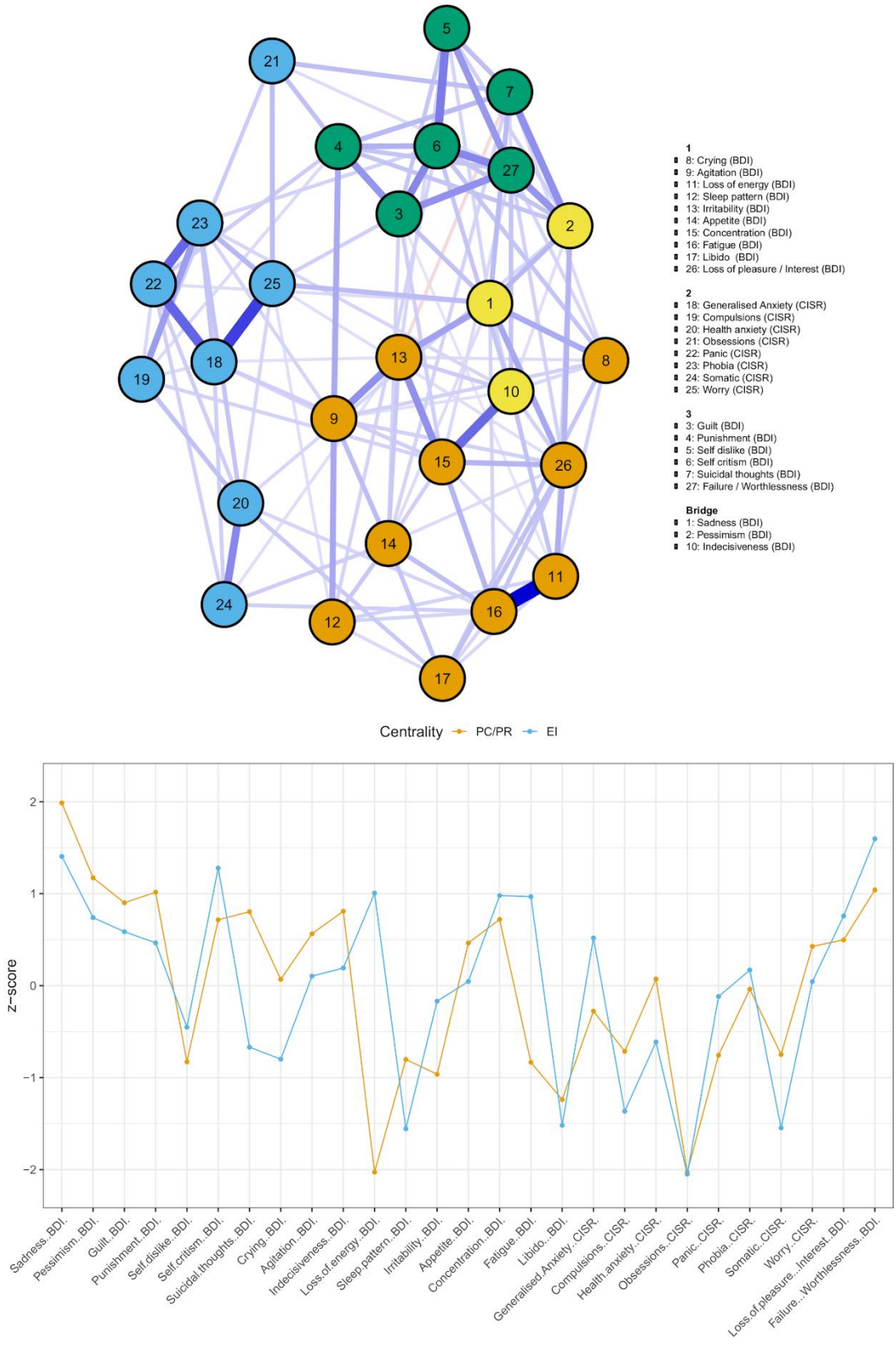

Figure 2: Network plot (top) with communities. Bridge symptoms are categorized separately, however sadness and indecisiveness fall into community 1, and pessimism into community 3. The thickness of the edges indicates to what degree items are related, and the colour of the edges indicates the relationship sign (i.e. positive = blue, negative = red). Centrality estimates: PC/PR and EI (bottom).

Centrality estimates (i.e. measures of the strength of connection to other items) are reported in figure 2. The EI correlation stability coefficient was high (0.75), suggesting that the ordering of items based on centrality remained the same after re-estimating the network with fewer cases (the probability the correlation between original centrality indices and centrality of networks based on subsets was 0.7 or higher) and can be reliably interpreted.

The estimates from the different metrics (EI and PC/PR) were correlated (r = 0.58). The most central symptoms were Sadness (PC/PR) and Failure/Worthlessness (EI). Failure/Worthlessness had a significantly higher EI centrality than twenty-one other symptoms (see supplementary material). The next most central nodes (EI) were sadness, self-criticism, and loss of energy (all z-score > 1), followed by concentration, loss of pleasure/interest, and fatigue (z-score > 0.96). While the next most central when using PC/PR were pessimism, failure/worthlessness, and punishment (all z-score > 1), then guilt, indecisiveness, and suicidal thoughts (all z-score > 0.80). Notably, while suicidal thoughts were highly central according the PC/PR metric (z-score = 0.80) it was much less central using EI (z-score = -0.67). Loss of energy displayed the opposite relationship, more central for EI (z-score = 1.01) than PC/PR (z-score = -2.03). Loss of energy and obsessions were jointly the least central nodes using PC/PR, and obsessions was also the least central when using EI.

Robustness checks suggest the resulting GGM was stable and accurate. Stability and accuracy plots, individual networks (with the fused penalty) and the fused network model are supplied in the supplementary materials. Mean severity was not significantly correlated ($p < 0.05$) with EI ($r = 0.21$) or PC/PR ($r = -0.05$), while the standard deviation was significantly correlated for both EI ($r = -0.56$) and PC/PR ($r = -0.41$). Symptom severity was not associated with nodes being interconnected, however differential variability may drive the centrality of nodes (Terluin et al., 2016).

The interrelation of the network and the FGL network were compared ($r = 0.72$), suggesting that between study differences had a small effect on network estimation. The network was corrected for the influence of duration of depression and anxiety, however the overall influence on edge estimation was negligible (interrelation between the corrected network and a network estimated without duration variables: $r = 0.997$). Overall, the resulting network model can be considered robust.

Network Comparison Test

Networks (unregularized) were compared (1000 iterations) for those who were classified as in remission (n= 956) and those who were not (n = 1466). Mean severity differences at baseline were significant for all items ($p<0.001$). The correlation between networks was high ($r=0.67$). While there were significant differences between edges, the overall networks (see supplementary material) did not differ in connectivity (global strength invariance: $p < 0.08$) and post hoc tests were not warranted. There was only evidence of one difference in centrality between the networks: somatic symptoms were more connected in the remitter network than the persister network ($p<0.001$).

Discussion

Individuals with depression also present with co-morbidity and this could present an issue for depression treatment. Understanding how symptoms influence one another across traditional diagnostic boundaries, and how they influence important outcomes, may provide insights relevant to the assessment and treatment of mood disorders. In this study we initially examined the differential impact of individual symptoms on prognosis and assessed whether individual symptoms offer predictive value above sum scores. The item level models of outcomes post-treatment and the sum score models were similarly associated with outcomes at three to four and six to eight months but explained considerably more at nine to twelve months. Pessimism was consistently the most important predictor of future outcomes (independent of its mean), indicating that the nature of the symptom rather than severity is responsible for this association. Secondly, we explored the functional relations among co-morbid symptoms of depression and anxiety disorders using network analysis. The symptom network comprised of three communities clearly clustering into: anxiety items; depressive cognitions; and depressive physical symptoms. The primary bridge symptoms between communities were sadness; pessimism; and indecision. The most central symptoms across both centrality metrics were sadness and failure/worthless. Finally, we analysed differences in the symptom networks at study entry for patients that remitted vs. those whose depression persisted, after treatment. Network

comparison revealed no overall differences in connectivity. Together, the present findings suggest the utility of item-level analysis.

Exploring the associations with treatment outcomes revealed that item item-level prediction methods performed similarly to sum scores, and outperformed sum score models at the nine to twelve month endpoint. It's not clear why there is a difference at this timepoint, while it was not due to attrition it could be due to random variation. It may also reflect the course of depression following intervention, or the cyclical nature of depression such that individual items are better at predicting the relapse or maintenance of symptoms after benefits of treatment have faded, or where an amelioration of symptoms occurred due to further treatment post-randomisation. There is an ongoing debate in the field whether the most central items derived from network models offer predictive utility (Elliott et al., 2020; Rodebaugh et al., 2018; Spiller et al., 2020). Pessimism was not only the best predictor across outcomes, it was a central item (ranked 2nd on PC/PR and 6th on EI centrality) that acted as a bridge between communities and showed strong associations with sadness and failure/worthlessness. Sadness, comparatively, did not predict well across time points. It is worth noting, that sadness falls within the physical symptom community and pessimism within the cognitive community. The amenability to act on an emotion (sadness), is understandably less than that of a cognition (pessimism), a target of cognitive therapy.

Symptoms of anxiety and depression clustered into separate communities with certain symptoms acting as bridges between communities. The bridge symptoms are statistically relevant and theoretically linked: indecision is a symptom in the classifications of both depression and generalized anxiety disorder; pessimism overlaps with worry (MacLeod et al., 1991); and the strong cross-community edge of sadness to worry, was similar to findings in other studies (Beard et al., 2016b; Price et al., 2019). The results therefore provide evidence that these bridging symptoms may be important in the emergence of comorbidity between anxiety disorders and depression.

Planned comparisons of networks at study entry for those whose depression would persist versus those who would be in remission, revealed no overall difference in connectivity, in contrast to Van Borkulo et al. (Van Borkulo et al., 2015), but similar to

Schweren et al. (Schweren et al., 2018a). This suggests that network density may not hold much prognostic value.

Overall, we found no correlation between centrality metrics and predictive importance. Failure / worthlessness was predictively important at three to four months, displayed high centrality and is suggested to be a key symptom in depression and anxiety (Heeren et al., 2018b). The predictive utility of health anxiety and somatic concerns may be considered alongside the observation from the network comparison where there was a difference in centrality with somatic concerns more connected in the remitter network. Health anxiety was in the upper quintile of variable importance across timepoints, but relatively unimportant in terms of centrality. Not surprisingly, given the conceptual overlap, with health anxiety, the strongest edge was with somatic concerns. As such, the degree of concern for one's health, or attention to somatic symptoms, whilst not playing a significant role within the maintenance of depression, may act as a motivational spur to engage with treatment (in this way enabling rather than disabling the individual). The absence of this anxiety may reflect an apathy about one's health which is not captured by the motivational item in the BDI. While the predictive modelling did consider the influence of each item independent of the other items, modelling the predictive value of individual items may be improved by examining the association between the changes at symptom level and the overall network (Papini et al., 2020; Robinaugh et al., 2016).

The network derived in this study provides empirical phenomena that can be explained by principles of network theory. This requires interpreting the network as a causal system, even though we cannot infer temporal relationship between symptoms and there is an absence of causal mechanisms within the external field (e.g. environmental factors) (Borsboom, 2017). These limitations apply to most of the findings in the network literature, although overinterpretation is common(Fried, 2020). Holding this in mind, we can consider possible pathways and mediating role of symptoms through the network. For example, taking suicidal ideation as a clinically severe symptom, we can identify the shortest path from worry (Law and Tucker, 2018) passing through sadness (bridge), and from loss of pleasure/interest (Ducasse et al., 2018) to suicidal thoughts, passed through pessimism (bridge). It is possible that any causal effect between these connections may be part of a longer pathway within the network highlighting a need for greater attention to be given to symptom interactions.

The statistical model investigates a symptom level, transdiagnostic conceptualization of the symptom interactions for individuals diagnosed with depression participating in RCTs. These interventions are based on biological or psychological theories, most notably Beck's cognitive of theory of depression (Beck, 1967). Clinically, pragmatism trumps theoretical completeness; simple interventions which achieve rapid change do not require a detailed appreciation of the potential underlying mechanisms. However, oversimplified theories may restrict the ability to identify causal patterns; and gaps emerge in practice where the model is suggested to not fit the patient (Roth and Fonagy, 2006). More process driven interventions targeting shared features of disorders have been developed (Barlow et al., 2016; Hvenegaard et al., 2020), yet there is no unifying theory. The findings presented may help bridge the gap between disorder specific theories and more transdiagnostic theories. Considering how symptoms may interact can help clinicians and researchers to understand underlying processes, and in turn to conceptualise their patients' difficulties in a way that supplements existing knowledge. A functional analysis which integrates the association between sadness and worry does not need to conceptualise the individual as having two disorders, but can consider how, for the individual, this interaction is being fueled and may be contributing to their distress.

The journey to develop models that provide both explanatory and predictive utility, will lead to greater understanding of psychopathology (Yarkoni and Westfall, 2017). While the analysis presented is primarily exploratory, it sets up clear testable hypotheses. Methods are currently emerging to help test hypotheses generated from network models (Rodriguez et al., 2020). These statistical methods may help inform how identifying pathways and targets may lead to improved treatments all dependent on better assessment of symptoms.

Strengths and Limitations

This study has clear strengths, making use of a large sample of individuals participating in RCTs for depression in primary care. The use of same assessment measures at study entry removed the need to harmonise data across different measures for the network. While this is less true of outcomes where issues of measurement errors arise from the use of PROMIS T-Score, the sensitivity analyses provided confidence in the results.

The demographic balance across samples may affect generalisability however five of the six trials were pragmatic trials more closely representative of patient populations. Most cases of depression are treated in primary care, and the studies being set in primary care, improve the potential generalisability to patients seen in this setting (McManus et al., 2016).

This study was limited to the use of aggregate/group level findings to inform within person processes. However, the presence of an RCT outcome variable affords us the ability to predict state transition, something difficult to ascertain on scale in idiographic research. The accuracy of the network is limited by the items included and those omitted. The network does not cover the breadth of co-morbidity of symptoms across psychopathology and is missing other environmental variables. There is also the possibility that the centrality of sadness particularly, represents a strong association with a latent variable rather than a specific role within the network (Hallquist et al., 2019).

The network models adjusted for duration of depression and anxiety, and a sensitivity analysis assessed for the influence of between study variability, adding robustness to the findings. While RCTs are used in the analysis, treatment arms were not factored in, and treated as equivalent when estimating outcome. This may make the findings generalizable where findings are applicable regardless of treatment offered especially as the treatments included reflect those commonly available in primary care. Controlling for treatment group within the outcome modelling and controlling for relevant covariates (e.g. age, gender and social economic status) would also have improved the robustness of the findings. Such adjustments would have been fitting where the emphasis was on developing the best predictive model, instead of comparing the predictive ability of symptoms vs. total scores. More comprehensive prediction modelling using the DEP-GP dataset has been conducted (Buckman et al., 2020). Additionally, our modelling did not include train/test split, as the whole sample was used in estimation of the network models. While a holdout dataset would have provided an unbiased evaluation of model fit, the cross-fold validation employed in the symptom level model offer a layer of robustness supporting the final model estimates (where overfitting presents an issue).

Single item symptom measurement will have unknown reliability and construct validity. Equally, the restricted range (e.g. a four point scale) may not adequately capture the range of symptom variance occurring in the sample. Symptom measurement on a broader scale may improve the prediction of changes over time.

Conclusions

Our study used samples from high-quality randomised controlled trials, and the findings can be generalised to adults with depression being treated in primary care. This study has reiterated the importance of assessing for both depressive and anxious symptoms among adults seeking treatment for depression, and that valuable information about prognosis can be gained by understanding the interrelations between individual symptoms; information which is not available when considering sum scores or baseline symptom severity alone. This may be particularly important to longer term outcomes from treatment. Treatment selection and application is often hampered by comorbid symptoms and considered to introduce 'complexity' (Kuyken and Tsivrikos, 2008). Considering the bidirectional relationship between symptoms, and associations which may be mediated by another symptom (e.g. a bridge symptom) may help to consider comorbidity as normative.

While specific symptoms and associations have been highlighted, the aim is not to offer simple heuristics to inform clinical judgement and decision making. The relative importance of the highlighted associations should not be overweighed. The aim is not to identify individual items, but to consider the network of interactions. The critical role of individual symptoms and their interactions give rise to the activation of the network through pathways and anxiety and depressive cognitive and physical symptoms may activate one another via these pathways. This network highlights how symptoms of depression and anxiety disorders influence one another. Clinically, there is a need for treatments to adequately assess and address comorbidity.

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CHAPTER 3

Transdiagnostic symptom dynamics during psychotherapy

Abstract

Background: Psychotherapy is an effective treatment for many common mental health problems, but the mechanisms of action and processes of change are unclear, perhaps driven by the focus on a single diagnosis which does not reflect the heterogeneous symptom experiences of many patients. The objective of this study was to better understand therapeutic change, by illustrating how symptoms evolve and interact during psychotherapy.

Method: Data from 113,608 patients from psychological therapy services who completed depression and anxiety symptom measures across three to six therapy sessions were analysed. A panel graphical vector-autoregression model was estimated in a model development sample (N=68,165) and generalizability was tested in a confirmatory model, fitted to a separate (hold-out) sample of patients (N=45,443).

Results: The model displayed an excellent fit and replicated in the confirmatory holdout sample. First, we found that nearly all symptoms were statistically related to each other (i.e. dense connectivity), indicating that no one symptom or association drives change. Second, the structure of symptom interrelations which emerged did not change across sessions.

Conclusion: These findings provide a dynamic view of the process of symptom change during psychotherapy and give rise to several causal hypotheses relating to structure, mechanism, and process.

Introduction

Psychotherapies are effective treatments for a broad range of common mental health problems, but do not work for a substantial proportion of patients (Cuijpers et al., 2021). It is still not clear how therapies work, or what the processes of change occur during psychotherapies (Cuijpers et al., 2019). This lack of knowledge is stifling the development of novel interventions that target the putative mechanisms maintaining the disorders, hence limiting the potential for improvements in patient outcomes. Dismantling studies and trials of individual treatment components can be informative, but have frequently been hampered by low-quality methodology (Lemmens et al., 2016). It is widely believed that different psychotherapies share several common causal mechanisms and operate in ways that are more similar than they are different (Barth et al., 2014; Carey, 2011; Horvath & Symonds, 1991; Norcross et al., 2017). Common factors, such as therapeutic alliance, are unlikely to improve our understanding of change (Cuijpers et al., 2019) and there is a need to focus on other mechanisms of change in psychotherapy (Kazdin, 2009; Mulder et al., 2017).

The development of psychotherapy treatments has, for the most part, been tied to specific diagnoses, yet this does not reflect clinical reality where co-morbidity is the rule rather than the exception (Lamers et al., 2011). The evidence-base for the effectiveness of psychotherapies comes from randomised control trials (RCTs) which largely focus on specific diagnoses (Kendler & Campbell, 2009). This assumes that treatments either target an underlying disease or target a specific set of symptoms commensurate with the diagnosis. In clinical practice, co-morbidity can present challenges for clinicians in selecting the most appropriate disorder-specific treatment, or the ordering of interventions to tackle the seemingly disparate presenting problems; this can lead to some comorbid presentations being labelled as ‘complex’. The presence of comorbidity is likely an artefact of the classification of disorders (Dalgleish et al., 2020; First, 2005) hence significant comorbidity exists within RCTs for depression (Buckman, Saunders, Cohen, et al., 2021) and is associated with treatment prognosis. While there are distinct features of diagnostic disorders, they are not discrete (Allsopp et al., 2019), with considerable symptom overlap across disorders (Haslam et al., 2012; Newson et al., 2020). Mapping symptoms across disorders reveals how this overlap can inform an understanding of the emergence of

co-morbidity (Van Borkulo et al., 2015). Symptom heterogeneity also occurs *within* disorders (Fried, 2017; Galatzer-Levy & Bryant, 2013), with potential both for variability in diagnosis, or reaching the same diagnosis without any symptom overlap (Olbert et al., 2014). A transdiagnostic approach to psychopathology (i.e. aiming to identify overarching processes, by addressing causality and mechanism), might help overcome these obstacles and facilitate the identification of processes of change (Mansell, 2019).

Modelling change (in symptoms for example) is a fundamental means by which we can better understand mental health problems and their treatment. Methodological approaches to understanding the processes of change during psychotherapies have largely considered symptomatic change as a shift in a latent construct (e.g. a difference in the sum score on a measure of depressive symptoms, as signalling a change in the latent construct of depression). This fits with the diagnostically congruent 'common cause' theoretical framework, which purports that symptoms are passive and interchangeable indicators of an underlying latent disease. Systems theory and network approaches (Borsboom, 2017) offer an alternative viewpoint, proposing that the disorder is an emergent property and that symptoms are autonomous causal agents (Borsboom & Cramer, 2013; Cramer et al., 2010). According to systems theory, causal interactions between symptoms and relevant external factors can give rise to emergent states of psychopathology. An external event (e.g. loss of job) or internal event (e.g. brain trauma), can activate the system (psychological, social and biological processes), and the system will respond (e.g. symptoms activating neighbouring symptoms). While individuals may exist in states of equilibrium, crossing certain thresholds may shift the system into different self-sustaining (attractor) states, so the system may be maintained through causal loops despite the absence of the initial stressor (Cramer et al., 2010; Schmittmann et al., 2013). If the psychotherapy activates change in an individual's distress, this change can be observed in transition between states. During a transition, the organization of the system and facilitators of change become apparent (Kelso, 1995). The system may reorganise and develop as the symptoms interact or may reach a critical point and transition into a different state (i.e. 'disordered' to 'healthy'). While change can be gradual or sudden, it requires significant disturbance to shift the system out of a pathological attractor state (Hayes & Andrews, 2020).

Investigations of the processes of change in large psychotherapy samples have typically focused on identifying profiles (Saunders, Buckman, et al., 2020a) of patients with differential outcomes and predictors of differential response trajectories (Saunders et al., 2019). Studies that have focused on symptoms have been hampered by the primary use of cross-sectional data where bidirectionality and statistical equivalence make inferences difficult (Fried, 2020). Cross-sectional data limits interpretation because they cannot provide evidence for directed relationships (over time); and in cross-sectional data, statistical equivalence (i.e. having multiple models that can fit the data identically), is a larger concern than in temporal data(Fried, 2020). Psychotherapy research has historically focused on between-person differences, either by comparing groups, or by studying correlations between individual characteristics (Molenaar & Campbell, 2009). Such relationships derived from group level analyses may not generalize to individuals (Fisher et al., 2018). To address these limitations, we will adopt a transdiagnostic, symptom level analysis, focusing on symptoms common across disorders, modelling change over time in a naturalistic setting of patients receiving psychotherapy. The modelling approach will also distinguish within-person variability (within a person over time and contexts), from between-person variability (stable traits and variations across persons) (Hamaker, 2012). Within this analysis, the term “within person” does not refer to true within person observations (i.e. of an individual person), but rather to the the within-person relationship of an average person (aggregated over people) (Epskamp et al., 2021).

This study will focus on the dynamics between common mental health symptoms during psychotherapy. We consider the modelled symptoms to represent an important part of a broader system and consider the interactive change and self-organisation of these signs and symptoms during the process of psychotherapy. The aim is to model transdiagnostic change, across therapies and across disorders, where the symptoms modelled reflect the core symptoms of depression and generalised anxiety in the DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*, 2013). These are dimensionally normative symptoms (e.g. tiredness, nervousness) and are diagnostic features of many disorders (Table 1). Some of these symptoms may be descriptively transdiagnostic while others could be considered mechanistically transdiagnostic (Harvey et al., 2004). Through identifying dynamics of symptom

change during psychotherapy, the results can inform theory on the structure of psychopathology and functional processes of change.

Symptoms	Generalised Anxiety	Depressive disorder	Schizo-phrenia	PTSD	Personality disorder - borderline	Bipolar	Anorexia	OCD	Insomnia	Panic Disorder	Specific phobia	Social Anxiety	
Feeling nervous, anxious or on edge	O		O	O	O	O	O	O		O	O	O	10
Not being able to stop or control worrying	O				O			O					3
Worrying too much about different things	O				O								2
Trouble relaxing	O		O	O		O				O			5
Restlessness	O	O	O	O		O							5
Becoming easily annoyed or irritable	O		O	O	O	O	O		O				7
Apprehensive expectation	O			O				O		O	O	O	6
Anhedonia		O	O	O				O					4
Feeling down, depressed, or hopeless		O	O		O		O		O				5
Sleep difficulties	O	O	O	O		O	O		O				7
Feeling tired or having little energy	O	O	O				O		O				5
Poor appetite or overeating		O	O				O						3
Feeling bad about yourself/ failure		O		O	O		O						4
Concentration	O	O	O	O		O			O				6
Psychomotor retardation/agitation	O	O	O	O		O							5
Suicidal ideation		O	O	O	O	O	O	O					7
Total	11	10	12	11	7	7	7	4	4	3	2	2	

Table 1: Symptoms captured by the PHQ-9 and GAD-7 mapped onto features of DSM-5 disorders

Methods

All methods were carried out in accordance with the Health Research Authority guidelines. NHS ethical approval was not required for this study (confirmed by the Health Research Authority July 2020, reference number 81/81). The data were provided by the IAPT services for evaluation as part of a wider service improvement project conducted in accordance with the procedures of the host institution and the NHS Trusts which operate the IAPT services (project reference: 00519-IAPT). At their initial contact with services all patients are informed that their data are sent to NHS Digital as part of national reporting, and may be used for research and service improvement by the services, and they are given the option to opt out of this if they wish. Only anonymised data from those patients that were considered to have opted-in for their data to flow in this way were included in the current project. No patient identifiable data were available to the research team.

Participants

We analyzed data from patients that received psychological therapy from eight Improving Access to Psychological Therapies (IAPT) services in the North and Central East London IAPT Service Improvement and Research Network (NCEL IAPT SIRN)(Saunders, Cape, et al., 2020) IAPT services provide evidence-based

psychological treatments for common mental health disorders and are mandated to collect outcome measures at each session, which has resulted in over 98% pre-post treatment data availability (Clark, 2018). In IAPT, high intensity therapy includes CBT, Behavioural Activation, Counselling, Interpersonal Psychotherapy, Short-term Psychodynamic Psychotherapy and EMDR, typically weekly for 10 to 16 session lasting 50 to 60 minutes, while low intensity therapy, tends to involve four to eight sessions of 30 minutes with practitioners guiding patients in the use of self-help material or computerized programmes based on CBT or Behavioural Activation (Shafran et al., 2021).

For this study, patients were included if they received a minimum of three psychological therapy treatment sessions and if data were available on all the individual symptom items from the requisite symptom measures (detailed below). Only data from the first six treatment sessions were analysed regardless of the total number of sessions a patient received if beyond six.

Measures

Each session patients completed: the Patient Health Questionnaire 9-item version (PHQ-9(Kroenke et al., 2001)) a brief measure of depressive symptoms; and the Generalized Anxiety Disorder Scale 7-item version (GAD-7; Spitzer et al., 2006)), a measure of generalised anxiety disorder symptoms.

Plan of analysis

The analyses involved estimating a panel graphical vector-autoregressive model (panel GVAR) in the training data and confirmatory models to test generalizability by: a) fitting the network model in the holdout sample; and b) testing for parameter invariance between datasets by implementing equality constraints (i.e. edges constrained to be equal between the training and holdout set). Finally, cross sectional networks were estimated to visualise the network structure at each timepoint.

Treatment length differs across modalities, and substantial change typically occurs early in psychotherapy (Catarino et al., 2020; Tang & DeRubeis, 1999), with a previous analysis in a similar sample indicating that the trajectory of change could be identified by the third session for most patients, and by the sixth session for the remaining patients (Saunders, Buckman, et al., 2020b). Temporal dynamics were modelled

across the first six sessions, chosen to capture these early causal dynamics during this period. The cap of six was also informed by the constraints of model complexity where convergence issues arise with each additional wave.

The dataset was randomly split (60:40) into a training and holdout sample. Multilevel linear mixed-effects models, with maximum-likelihood estimation, were used to examine change across sessions for each item within the training sample. Data were detrended within each split, removing trend effects in means and variances (standardised per variable, per time-point). Whilst not an assumption of the modelling procedure, the aim was to improve model fit. This way, within-person and between person relationships between the variables of interest could be investigated after taking growth processes into account.

A lag-1 panel-GVAR using full-information maximum likelihood (FIML) estimation was fitted using the psychonetrics package (Epskamp, 2020). As we modelled observed variables (i.e. no latent factors), the model is similar to a cross lagged panel model with random intercept with the covariance structure for the first time point implied by the temporal structure. By separating within from between person variance, the lagged relationships equal within-person variance (Hamaker et al., 2015). Using maximum likelihood estimation, all edges were included in the temporal, contemporaneous, and between-subject networks. Residual variances were estimated using a Cholesky decomposition. Missingness was handled using FIML which adjusts the likelihood function so that each case contributes information on the variables that are observed. Multiple imputation and FIML will come to similar results when data are missing at random (Collins et al., 2001).

Confirmatory testing involved fitting a model in the holdout sample, specifying the adjacency matrix. Parameter invariance between samples was tested by estimating a model where we introduced equality constraints. Finally, we estimated a non-detrended model for comparison, where models are comparable (detrended and nondetrended). This suggests that detrending has not biased results, supporting causal inference (Falkenström et al., 2017).

Model fit was assessed using a series of fit statistics. To assess models, we used relative fit indices (Normed Fit Index (NFI), Tucker Lewis index (TLI), Incremental Fit Index (IFI), Parsimony-Adjusted Measures Index (PNFI) and Relative Fit Index (RFI))

which compare a chi-square for the model to one from a baseline model and non-centrality based indices (Comparative Fit Index (CFI) and Root Mean Square Error of Approximation (RMSEA) with 95% Confidence Intervals (CI). Absolute fit indices, Chi-square (χ^2) was reported but not interpreted given it's sensitive to sample size. Of these indices, PNFI values above approximately .75 and RMSEA values <.05 indicate good fit; for the others, values ≥.90-.95 and are variably accepted as cut-offs for good fit (Sivo et al., 2006).

The panel data model from the training dataset, along with separate temporal (within-persons temporal patterns); contemporaneous (within-person fluctuations predicting other within-person fluctuations in the same time-window, after controlling for temporal effects); and between-persons (associations between stable averages) network models, were used for visualisation and interpretation of parameters. Within the graphical model, the conditional dependence relations between symptoms are estimated, where the line between nodes, ("edges"), represent shared unique variance that may be an indication of a causal pathway, or a common external (unmeasured) cause. The centrality metric, Expected Influence (EI), was estimated within each network. EI is sum of edge weights, either to, "In EI", or from, "Out EI", a symptom, reflect the centrality of the symptom within the network.

We estimated unregularised Graphical Gaussian models (GGM) at each timepoint, using undetrended data, to assess the network structure across sessions. At each timepoint we assessed for topological overlap using the goldbricker function.(Jones, 2018) Estimations were based on the Spearman covariance matrices and following an iterative modelling procedure using the Extended Bayesian Information Criterion (EBIC). Selecting unregularised GGMs according to EBIC has been shown to converge to the true model (Foygel & Drton, 2010; Williams et al., 2020). The ggmModselect algorithm runs 100 graphical lasso models (estimating sparse inverse covariance matrices using a lasso (L1) penalty), refits all models without regularisation, adding and removing edges until EBIC no longer improved (Blanken et al., 2022). The best performing model (EBIC parameter) was selected to provide a conservative GGM (high specificity).

Results

Sample Characteristics

The characteristics of the training and holdout samples are shown in Table 2. In total, combined they included 113,608 patients who attended at least three sessions. Ages ranged from 17 to 94 years old. Proportionally, there were more females (67%); and more patients from White ethnicity groups (63%). Ethnicity was reflective of the population estimates for London(Office for National Statistics, 2017). Most patients received High Intensity Cognitive Behavioural Therapy (CBT), and the next most frequently delivered was Low Intensity CBT, with 11% receiving a different mode of therapy (i.e., Counselling, Behavioural Couples Therapy, Dynamic Interpersonal Therapy, Eye Movement Desensitization and Reprocessing (EMDR), Mindfulness-Based Cognitive Therapy (MBCT), or Interpersonal Psychotherapy (IPT)).

There was a broad range of presenting problems (also referred to as a 'problem descriptor' in IAPT) which are diagnoses based on ICD-10 and represent the focus of treatment agreed between a patient and clinician. Figure 1 shows the mean symptoms scores across the six time points. All symptoms are shown to change over time (all $p<0.001$) and the slope of the trajectory was similar across items. Mean PHQ-9 total reduced from 14.13 (SD=6.26) at timepoint one to 10.7 (SD=6.59) at timepoint six, and GAD-7 total from 12.98 (SD=5.19) to 9.88 (SD=5.71).

Panel graphical VAR modelling

The panel graphical VAR was estimated in the training sample. Confidence interval (CI) plots for the model are available at https://osf.io/gp6dw/. Figure 2 shows the temporal, contemporaneous, and between-person networks. The training model (n=68,165) contained 16 items and six timepoints, resulting in 544 estimated parameters. The fit statistics for all models are displayed in Table 3. The root-mean-square error of approximation (RMSEA) of the training model was 0.014 (95%CI: 0.014;0.015), and incremental fit indices were excellent. The confirmatory model in the holdout sample (n=45,443) showed excellent fit. This was further supported by the equality constrained model which also showed excellent fit. Finally, the non-detrended model showed good fit, with the high to near perfect spearman correlations between

	Training Set n = 67048		Hold out set n = 44645	
PHQ-9 Total: Mean (SD)	14.13 (6.26)		14.15 (6.25)	
GAD-7 Total: Mean (SD)	12.98 (5.19)		12.98 (5.19)	
Number of sessions: Mean (SD)	8.07 (4.84)		8.05 (4.85)	
Age: Mean (SD)	37.76 (13.44)		37.78 (13.48)	
Gender				
Male	21396	31.91 %	14466	32.40 %
Female	45357	67.65 %	29983	67.16 %
Missing / not disclosed	295	0.44%	196	0.44%
Ethnicity (ONS)				
Asian	7024	10.48 %	4681	10.48 %
Black	7331	10.93 %	5030	11.27 %
Chinese	471	0.70%	316	0.71%
Mixed	3890	5.80%	2661	5.96%
Other	2641	3.94%	1725	3.86%
White	42438	63.29 %	28210	63.19 %
Missing	3,253	4.85%	2,022	4.53%
Intervention type				
LI CBT	25819	38.51 %	17223	38.58 %
LI Other	3815	5.69%	2502	5.60%
HI CBT	28332	42.26 %	18909	42.35 %
HI Other*	7401	11.04 %	4916	11.01 %
Missing	1681	2.51%	1095	2.45%

	Training Set n = 67048		Hold out set n = 44645	
Presenting Problem (primary diagnosis)				
Adjustment disorder	518	0.77%	333	0.75%
Agoraphobia	322	0.48%	234	0.52%
Alcohol related disorder	30	0.04%	19	0.04%
Bereavement	333	0.50%	213	0.48%
Bipolar affective disorder	39	0.06%	29	0.06%
Body Dysmorphic Disorder	11	0.02%	9	0.02%
Depressive episode	23555	35.13 %	15450	34.61 %
Eating disorder	156	0.23%	98	0.22%
GAD	11041	16.47 %	7232	16.20 %
Hypochondriacal disorder	440	0.66%	304	0.68%
Insomnia	144	0.21%	69	0.15%
Mixed anxiety & depression	4323	6.45%	3001	6.72%
OCD	1342	2.00%	900	2.02%
Panic disorder	2402	3.58%	1647	3.69%
Personality Disorders	7	0.01%	2	0.00%
PTSD	2159	3.22%	1365	3.06%
Recurrent depression	4377	6.53%	2960	6.63%
Social phobia	1994	2.97%	1410	3.16%
Somatoform disorder	335	0.50%	232	0.52%
Specific phobia	667	0.99%	427	0.96%
Unspecified Anxiety Disorder	548	0.82%	366	0.82%
Missing (not specified)	13313	19.85 %	8345	18.69 %

*Table 2. Sample characteristics. *(Counselling, IPT, Psychodynamic, MBCT, EMDR)*

detrended and non-detrended adjacency matrices (temporal r = .82; contemporaneous r = .99; between r =0.93).

Temporal network

The saturated temporal network model was dense, with mostly small but significant parameters at the adjusted p-value ($p < 0.0001$), mean association: r=0.03 (median=0.02). The network displayed moderate to large autocorrelations, with suicidal ideation as the strongest (r=0.27).

The most prominent bidirectional associations, following the autocorrelations, were between depressed mood and anhedonia; excessive worry and difficulty controlling

worry; difficulty controlling worry and feeling nervous/anxious; psychomotor retardation/agitation and restlessness (all |r| >0.05). The most prominent unidirectional associations (|r| >0.05) were between depressed mood to feeling like a failure; apprehensive expectation to difficulty controlling worry; apprehensive expectation to excessive worry; apprehensive expectation to feeling nervous/anxious and suicidal ideation to feeling like a failure. While these associations are the most prominent, the cut-off of 0.05 was arbitrary and 34 associations had CIs in the range of 0.05.

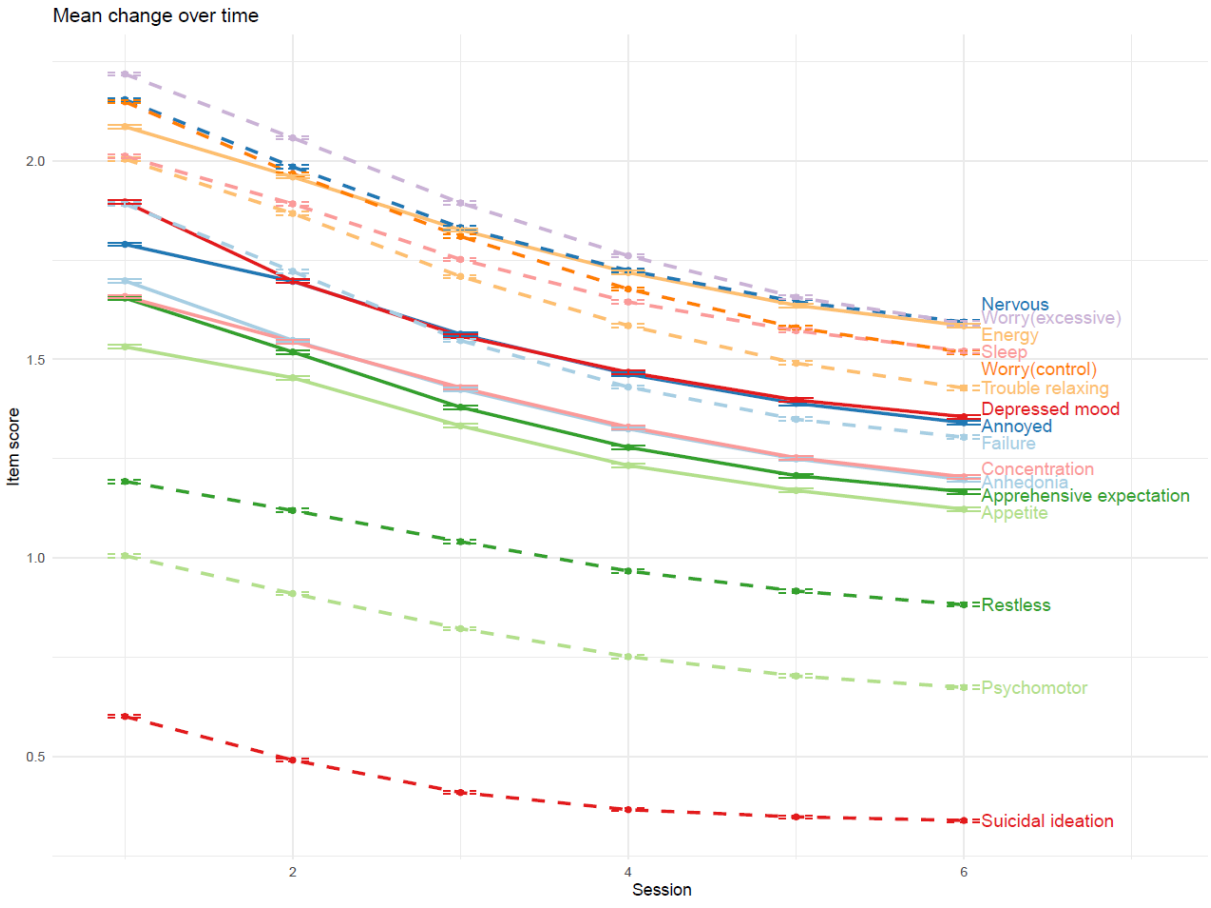

Figure 1. Mean symptoms scores (and standard error) across the six time points. Dashed lines are PHQ-9 items and solid lines are GAD-7 items.

Considering the centrality of the items, depressed mood (z=2.37), anhedonia (z=1.74), feeling nervous (z=0.96) and apprehensive expectation (z=0.94) had the strongest In-Expected Influence (all z>.9). Excessive worry (z=1.32), difficulty controlling worry (z=1.22) and trouble relaxing (z=1.10>1), has the strongest Out-Expected Influence.

Contemporaneous and between person models

The within-person contemporaneous network was also dense with most associations highly significant (p<0.0001). Contemporaneous within/between networks were highly correlated (r=0.79), suggesting a high degree of homogeneity of effects – i.e., low between-person differences. The strongest associations within-persons (|r| >0.2) were excessive worry and difficulty controlling worry; depressed mood and anhedonia; difficulty controlling worry and feeling nervous; energy and sleep; restlessness and trouble relaxing; and feeling like a failure and depressed mood. At the within-persons level, the most central items were difficulty controlling worry, depressed mood, trouble relaxing and excessive worry (z >1). The strongest associations between-persons (|r| >0.3) were excessive worry and difficulty controlling worry; depressed mood and anhedonia; psychomotor agitation/retardation and restlessness; anhedonia and depressed mood; depressed mood and feeling like a failure; and restlessness and trouble relaxing. In the between-persons network, depressed mood, and difficulty controlling worry were most central (z >1). Centrality of items between the within and between networks was correlated r=0.72.

Unregularised, cross-sectional networks using the Gaussian graphical stepwise model selection ("ggModSelect") algorithm at each time point (see https://osf.io/gp6dw/), could not be distinguished from unity (r=0.99), indicating near perfect replication of network structures across all six timepoints. The mean density of networks (the sum of all edges within each network) was 7.27 (sd=0.09, range: 7.12 to 7.34), incrementally increasing over time.

	Training model	Hold out model	Confirmatory model	Equality constrained model	Training model (nondetrended)
df	4208	4208	4464	8672	4208
Chisq	63960	48365	25525	108247	119256
NFI	0.984	0.982	0.982	0.984	0.970
PNFI	0.908	0.906	0.906	0.935	0.895
TLI	0.984	0.982	0.984	0.984	0.969
RFI	0.983	0.980	0.980	0.983	0.968
IFI	0.985	0.983	0.985	0.985	0.971
CFI	0.985	0.983	0.985	0.985	0.971
RMSEA	0.014	0.015	0.017	0.014	0.020
RMSEA 95% CIs	0.014:0.015	0.015:0.015	0.017:0.017	0.014:0.014	0.020:0.020

Table 3. Fit statistics across panel graphical VAR models.

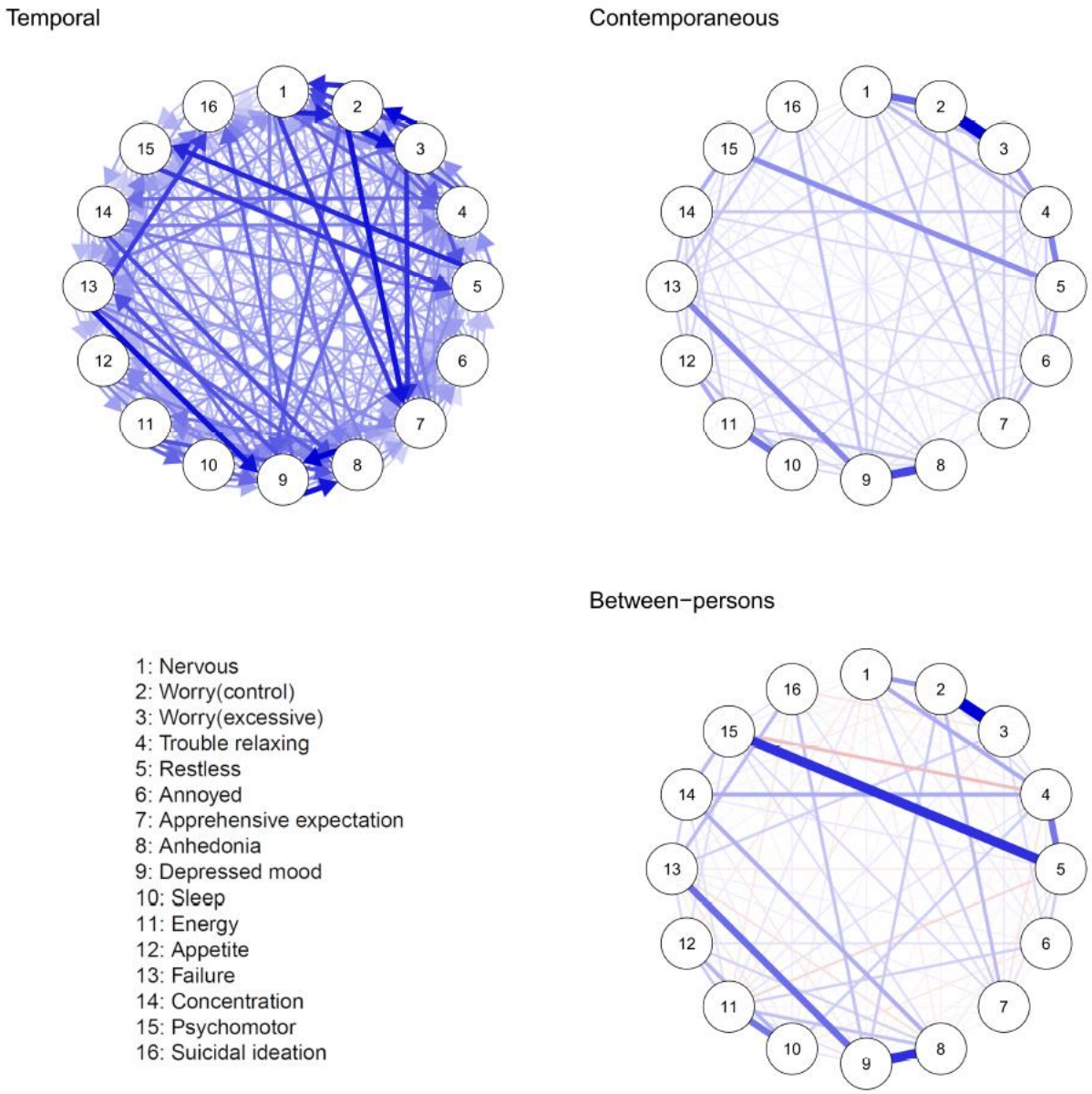

Figure 2: Panel graphical VAR *model. Circles represent symptoms, and connections (undirected drawn as lines or directed drawn as an arrow) indicate predictive relationships. Blue lines indicate positive relationships, red lines indicate negative relationships. The width and saturation of a line indicates the strength of the relationship. In the temporal network (left), directed lines indicate where a symptom predicts another symptom at the next session after controlling for all other variables. Within the contemporaneous (middle) lines represent partial correlations between symptoms at the same timepoint, after controlling for all other variables and temporal effects. The between-persons network (right) indicating partial correlations between stable averages. We only plot significant edges, and* the *visualisation of autocorrelations in the temporal network has been omitted to improve visualisation; a figure including autocorrelations can be found in supplementary materials.*

Discussion

This study explored dynamics of symptom change during psychotherapy. Using sessional symptom data from a large sample receiving treatment for common mental disorders, the results show a large co-occurrence of symptom change over time. Symptoms decreased across the board, and there was a strong temporal dependence between various symptoms. The network structure of associations, however, remained the same. Mean changes were somewhat different for different symptoms, but they tended to change together. The results of these analyses are statistically reliable; generalise to a holdout sample; and provide insights in the temporal effects and whether these associations covary at the trait (between person), or state level (within person). While we do not know whether findings generalize to a non-psychotherapy (e.g. waitlist control) condition, we assume that some of the observed patterns in the data are due to psychotherapy, e.g. the overall symptom reduction over time. In the rest of the discussion, we consider interpretation, implications, specific findings, strengths and limitations.

Interpretation of the dynamics can be viewed in several ways. These findings highlight a syntactical equivalence (Markus, 2004), with the results supporting both common cause and systems theory which are often considered to be diametrically opposed. A dynamic systems theory view is that a broad range of symptoms were active and that these in turn influenced other symptoms over time. From a common cause perspective, the density of the network would suggest a common latent variable (i.e. symptoms reflect an unobserved construct). We might infer causal (temporal) associations between symptoms from the temporal network model, supporting a systems interpretation, as a common cause model assumes no direct causal relations between observations. It is also likely that both are true simultaneously; a hybrid model where the common cause reflects onset and the dynamic system, maintenance (Fried & Cramer, 2017). These theories are under determined given the data, requiring experimental intervention to differentiate these theories (Fried, 2020). From a systems perspective, one might have expected a sparser model with bridging symptoms identified between clusters of similar symptoms to explain the development of co-morbidity(Jones et al., 2019). The sparsity usually revealed in network studies may be related to a combination of using underpowered small datasets and regularization.

Therefore, in this large sample, the density of significant associations may be more representative of the actual complexity of the psychopathological system (i.e. closer to the true model (Mcgrath, 2005)) and as such the sparsity assumption may be invalid.

This brings us to the clinical implications. The models using detrended and undetrended data were comparable which strengthens the ability to make inferences around processes of change (Falkenström et al., 2017). Change mechanisms or causal effects were also most likely to be identified within the contemporaneous network where confounding by stable variables was mitigated (Falkenström et al., 2020). There is heterogeneity in the sample, with variation in individual factors, diagnoses, and types of therapy received. On the one hand, if there is a common process underlying all psychotherapeutic approaches (e.g. exposure), certain symptoms may respond similarly (regardless of sample heterogeneity), where symptoms are interchangeable indicators of a process (e.g. avoidance). Change in one symptom should result in changes throughout the network leading to a change in overall symptom severity. Such an interpretation rests on assumptions that: there are no other external effects; that we have modelled all relevant variables; and that we have the accurate time-steps by which variables evolve. On the other hand, certain symptoms were more dominant, by which we mean they had stronger and more numerous edges, within the network structures. If such symptoms exhibited the highest causal force, which is one possible interpretation of the data, then these symptoms may have triggered changes that rippled through the network. If this were the case, worry (excessiveness and controllability), along with trouble relaxing, appeared to hold the strongest influence on other symptoms. The influence of these symptoms and depressed mood were also highlighted at the contemporaneous level. Feeling nervous, depressed mood and anhedonia were most influenced by other symptoms. This may suggest that during psychotherapy, on average, strategies targeting worry and trouble relaxing may bring about changes throughout the network, either directly or through pathways to the most influenced symptoms.

Some specific findings are worth discussing in some detail. The association between depressed mood and anhedonia was consistent with other findings (Hebbrecht et al., 2020), representing core symptoms of depression (Levis et al., 2020), and excessive and uncontrollable worry as a transdiagnostic process (i.e. repetitive negative thinking) (Ehring & Watkins, 2008; McEvoy et al., 2013). Worry symptoms

(excessiveness/controllability) covaried, as did depressed mood and anhedonia. The controllability of worry covaried with feeling nervous; energy with sleep; restlessness with trouble relaxing; and feelings of failure with depressed mood. Suicidal ideation at one session, predicted by itself at an earlier session, was the strongest association in the temporal network, with suicidal ideation predicting a sense of failure and depressed mood at the next session. To a lesser degree, depressed mood also influenced suicidal ideation at the next timepoint. This is notable given that suicidal ideation is generally a peripheral symptom in many network studies (Beard et al., 2016) and whilst considered clinically important, it is rarely targeted with direct interventions in the same way as depressed mood or worry. The emergence of this association may be due to the use of a considerably larger and naturalistically treated patient sample compared to most prior studies which may have encountered floor effects on measures of suicidal ideation given their smaller and often non-clinical samples.

According to dynamic systems theory, differences between states can reflect attempts for correction and, depending on the mechanism of change, can lead to a re-organisation in the system – shift in state (e.g. from 'disordered' to 'healthy'). Within this panel model, the structure of the network does not change over time, across the time-period measured (six sessions). A critical tipping point may not have been reached (i.e. on average, the 'disordered' state is maintained). On average, the most change occurred within this timeframe, but changes to the stability and density of the networks may have altered were further sessions included. Such shifts may be revealed in separate dynamic networks of those whose symptoms remit versus those whose symptoms persist, or more notably at the idiographic level, where identifying these state transitions could have a deterministic effect on treatment outcome.

The study captured between session changes and appeared, to a degree, to have also captured changes that occurred at shorter intervals (the contemporaneous network displayed symptom dynamics which unfolded faster than the timeframe of measurement). The measurement approach may not have allowed for sufficient granularity of symptomatic change processes during psychotherapy. These may be better captured by more frequent measurement, including approaches less reliant on retrospective recall, such as the use of ecological momentary assessments (EMA). The implementation of EMA during therapy might allow for idiographic modelling of

change processes which could directly inform the therapeutic process as it unfolds (Fisher & Boswell, 2016).

A clear strength of this study lies in using routine clinical data from a large sample in a naturalistic setting and not constraining analyses to any diagnostic category or specific therapy type. Findings may therefore be generalizable to a broad population of adults seeking psychotherapies for common mental disorders. There are limits to the generalizability as only services in the London area were included and all participants received healthcare free at the point of use, so replication in other settings and locations may be required. The study captures provisional diagnosis; these are not formal diagnosis and there was no assessment of co-morbidity.

There are limitations to deriving true causal relationships between symptoms in this study. This requires consideration the assumptions of the statistical model. First, while we can identify temporal precedence, and the approach allows for conditional inferences across levels (Adolf & Fried, 2019), the modelling approach captured group level processes. Second, the model does not capture measurement error, and cannot account for the absence of unmeasured external variables (other core psychopathological symptoms) or time-varying confounders. Third, some of these associations may be due to topological overlap (although we tested for this and it was not present across the cross-sectional networks). Fourth, ergodicity, while not a required assumption for causal statements, is implausible in in such a heterogeneous sample, although the average group model was highly similar to the average individual model over time. Finally, the model does not reveal likely subgroups with different trajectories of change. Indeed, in a similar sample, four trajectories of change based on the PHQ-9 and GAD-7 sum scores were identified (Saunders, Buckman, et al., 2020b). As such, the findings from this study can only be taken as potential causal associations and inferences about intra-individual processes of change during psychotherapy in this sample relate to a hypothetical average person. Identification of subgroups combined with latent growth network modelling (Deserno et al., 2021) may offer additional insights into the change mechanisms during psychotherapy, help us understand how different subgroups respond to therapy, and what specific factors may contribute to better outcomes.

This study mapped the symptom dynamics during psychotherapy but there is still a question about what is influencing this change. It is uncertain as to whether these changes occur due to: in-session process such as exposure, as a transdiagnostic procedure (Carey, 2011); features of the therapeutic alliance such as the development of epistemic trust (Fonagy & Allison, 2014); therapeutic procedures such as developing strategies to address repetitive negative thinking (Spinhoven et al., 2018); between session behaviour change (Mausbach et al., 2010); or regression to the mean (Hengartner, 2020). Such features of psychotherapy, where measurable could be integrated into moderated network models where the network is conditioned on the mechanism of change (Haslbeck et al., 2019). Such advances will help us to further understand how psychotherapy works.

The focus on symptoms feeds into a biomedical understanding of mental health difficulties and omits many important variables (e.g. experiential and quality of life related constructs). A more comprehensive biopsychosocial model would require including markers generally associated with prognoses regardless of the type of treatment received including markers of the severity of the mental health condition, and also social support, life events, sociodemographics and socioeconomic factors (Buckman, Saunders, Arundell, et al., 2022; Buckman, Saunders, O'Driscoll, et al., 2021; Buckman, Saunders, Stott, et al., 2022, 2021). While this introduces complexity at the modelling and data collection levels, developments across both these areas will further develop our understanding of change during therapy. Nonetheless, this study may help elucidate the biobehavioural understanding of change during psychotherapy.

Much of the research to date has focused on change at the mechanistic level or sum-score changes, with little focus on change at the level of specific symptoms and even less on their temporal associations. The relationship between symptoms can help to predict outcomes and potentially inform the development of more targeted treatments (Kendler & Campbell, 2009; O'Driscoll et al., 2021). It may also help inform an understanding of phenomena such as early sudden gains (Tang & DeRubeis, 1999). This study provides a significant contribution to the network literature: informing network methodology; addressing concerns about network replicability (Forbes et al., 2021); and overcoming barriers present in previous research limited by sample size and cross-sectional design.

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CHAPTER 4
Symptom-Specific Effects of Counselling for Depression compared to Cognitive Behavioural Therapy

Abstract

Introduction: Cognitive Behavioural Therapy (CBT) and Counselling for depression (CfD) are recommended first-line treatments for depression. They have different approaches to bring about symptomatic change, yet there is little understanding of the impact those approaches have on change during treatment. This study aimed to identify whether CBT and CfD target different symptoms and explore the implications of modelling choices when quantifying change during treatment.

Methods: The study included a retrospective cohort of individuals with a diagnosis of depression, who had received five or more sessions of CBT or CfD, from primary/community care psychological therapy (IAPT) services in England. Symptom specific effects of treatment were identified using moderated network modelling including all items from the PHQ-9 and GAD-7. Change was modelled several ways within the whole sample and a propensity score matched sample (n=3446).

Results: The whole sample (N=12,756) were predominantly female (68.5%), the mean age was 39.1 (13.3). CBT for depression directly affected excessive worry, trouble relaxing, and apprehensive expectation. CfD directly affected thoughts of being a failure. CBT had a stronger influence on changes between suicidal ideation and concentration, whereas CfD had a stronger influence on the associated change between being easily annoyed and apprehensive expectation. There were inconsistencies when modelling change using the first and second appointments as the baseline. Residual score models produced more conservative findings than models using difference scores.

Conclusions: CfD and CBT for depression have differential effects on symptoms demonstrating specific mechanisms of change. CBT was uniquely associated with changes in symptoms associated with anxiety so may be better suited to those with anxiety symptoms comorbid to their depression. When assessing change the baseline should be the first therapy session not the pre-treatment assessment with residual scores preferred over difference score methods.

Introduction

There is a strong preference among patients for psychological therapies over antidepressant medications (McHugh et al., 2013). Cognitive Behavioural Therapy (CBT) and Counselling for Depression (CfD) are among the most used psychological therapies for depression, both are efficacious and recommended as first-line treatments for depression(National Institute for Clinical Excellence, 2022). They are equally effective on average, but many patients do not experience symptomatic improvement with these treatments (Cuijpers et al., 2008). There is some evidence that outcomes can be improved by identifying for whom each type of treatment is most likely to be beneficial (Cohen & DeRubeis, 2018). However, precision mental health care is hampered by a lack of understanding of how the individual treatments bring about symptomatic improvements (Hayes & Hofmann, 2021), and issues of measurement that effect the accuracy and utility of precision models (Fried & Cramer, 2017).

The symptom experiences of people with depression are heterogeneous (Fried et al., 2022) with evidence of differential treatment effects on specific symptoms (Bekhuis et al., 2018; Boschloo et al., 2019). During psychotherapy, change in one symptom is highly dependent on other symptoms (O'Driscoll, Epskamp, et al., 2022) and effects of a treatment when controlling for the influence of all other symptoms are likely to be small. Modelling the direct influence of treatments on symptom change may elucidate unique differences between treatments, informing how treatments work, and thus the potential suitability of a given treatment for an individual based on their pre-treatment characteristics.

CfD aims to engender change by exploring the emotional meaning associated with experiences and developing alternative ways of understanding these experiences to inform a new self-concept (Roth et al., 2009). CBT for depression on the other hand aims to bring about change through cognitive processes (e.g. challenging negative automatic thoughts) and behavioural processes (e.g. reduced avoidance, balancing activities) (Beck et al., 1979). A recent clinical trial demonstrated the non-inferiority of CfD at 6 months but inferiority to CBT at 12 months (Barkham et al., 2021). While analyses of routine clinical data suggests that at the aggregate level outcomes are comparable (Pybis et al., 2017). Two studies have highlighted the potential for pre-treatment data to be used to stratify patients into groups that are more likely to benefit

from one of these types of treatment than from the other (Delgadillo & Salas Duhne, 2020; Saunders, Buckman, et al., 2020). One was an exploratory study, and the other had only a small sample receiving CfD. Those studies were not able to investigate the differential effects of the treatments on symptoms so could not elucidate mechanisms, used outcomes based on pre-post treatment change which can introduce a high degree of bias, (Vickers & Altman, 2001) and were only able to use data at two time points, the first of which was a pre-treatment assessment occurring some time before treatment started and may not be an appropriate baseline.

Capturing the nuance in symptom profiles and determining how best to overcome the issues of bias in modelling change during treatment for depression could inform how these therapies affect symptomatic change and hold potential to better inform shared treatment decision making. There are several numerical methods to measure change, and comparisons of approaches are not new (Lord, 1967). Four approaches in the literature are common, difference (or gain) scores, percentage (or proportional) change, post-score only, and residual change. There's a general consensus that calculating residual change where the final score is the outcome while adjusting for the baseline score is the most efficient approach (Bland & Altman, 2011; Senn, 2006; Vickers, 2001). However, in both research and clinical practice, differences scores are most used due to ease of calculation and simple, if misleading, interpretation. These different approaches can lead to different results (eg, Lord's paradox) (Lord, 1967). The difference score does not adjust for baseline imbalance, and indeed these may be reversed (Vickers & Altman, 2001) – patients with high scores at baseline generally improve more than those with low scores: (where higher scores indicate greater severity). Although difference scores appear intuitively interpretable, where the measure is ordinal (as in most psychological measures), the difference score will no longer be ordinal (Harrell, 2018). Measuring within-person change will also be affected by regression to the mean and measurement error. In addition, in comparison to RCTs, within clinical practice, allocation to an intervention will be informed by patient preference as well as clinical decision making, which in turn and the person's preference, the decision making will partly be informed by symptomatology. This introduces a selection bias, where future measurements will be closer to the person's true mean (Barnett et al., 2005). A preferred method is to use the final score as the outcome and baseline as covariate, although this method is not impervious to bias,

particularly when there are pretreatment differences (Senn, 2006). An alternative approach is to incorporate the change score as the outcome and baseline score as covariate, the benefit of which is purported to assess whether change occurred in each group (Laird, 1983). How change is calculated can lead to inaccurate estimation of association, and are unlikely to lead to the same result (Nickerson & Brown, 2019). While comparisons have been studied (O'Connell et al., 2017) this has not been investigated within the network literature.

The aims of this study were to a) identify the direct influence of CBT compared to CfD on symptom change and b) explore the implications of modelling using either the first appointment in the services (assessment) or the second appointment (first treatment session) as the baseline timepoint, and of quantifying symptom change during treatment in a variety of ways: using final scores, difference scores, proportional change, and residual scores.

Method

Participants

Routine clinical data were gathered from eight Improving Access to Psychological Therapies (IAPT) services. All were part of the North Central and East London IAPT Service Improvement and Research Network (NCEL IAPT SIRN) (Buckman, Saunders, Cape, et al., 2021; Saunders, Cape, et al., 2020). IAPT services operate as part of a nationwide program operated by the National Health Service (NHS), to provide evidence-based psychological treatment for depression and anxiety disorders (Clark, 2018). Participants were those that underwent either CBT or CfD treatment for depression (determined by the 'problem descriptor' of the treatment episode, based on ICD-10 diagnostic codes) and had item level data available. To identify changes due to treatment, only patients who attended five or more treatment sessions were included (see eFigure 1 in Supplement for participant flow).

Intervention conditions

CfD and CBT were delivered by clinicians with doctoral qualifications in clinical or counselling psychology, or with post-graduate diplomas in CBT. Sessions lasted 50-60 minutes and typically 8-16 sessions were offered. Prior to treatment patients completed an initial assessment (session 1), those offered CfD or CBT were placed

on a waiting list to start treatment. As such, session 2 represents the first treatment session, typically occurring 4-12 weeks after the assessment session.

CfD is a manualized form of psychological therapy derived from the humanistic competence framework (Roth et al., 2009) using therapy manuals from randomised controlled trials. The specific area of humanistic practice on which the CfD competences are based is termed person-centred/experiential therapy (Elliott et al., 2004; Mearns & Thorne, 2007) and also integrates aspects of emotion-focused therapy (Greenberg & Watson, 1998). This modality targets the emotional problems underlying depression along with intrapersonal processes (such as excessive self-criticism) that often maintain depressed mood. The therapy aims to help patients contact underlying feelings, make sense of them, and reflect on the new meanings which emerge.

High Intensity CBT involves structured, protocol-driven, disorder-specific interventions in line with set competencies (Roth & Pilling, 2008). Psychotherapists are trained based on a national curriculum (Department of Health, 2011). Second wave CBT approaches to depression combine behavioural and cognitive approaches to modify biases in information processing and avoidance behaviours (Beck et al., 1976).

Outcome measures

IAPT services are mandated to collect sessional outcome data with all patients as well as numerous socio-demographic and treatment related variables (Buckman, Stott, et al., 2021), this includes the Patient Health Questionnaire 9-item version (PHQ-9) (Kroenke et al., 2001), a measure of depressive symptoms; and the Generalized Anxiety Disorder Scale 7-item version (GAD-7) (Spitzer et al., 2006), a measure of generalized anxiety disorder symptoms. The items of both measures are used to assess symptom change across treatment. The scores from session 1 (assessment) and session 2 (first treatment session) are used as baseline scores, and the scores in the final treatment session were used as the post-treatment score.

Statistical Analysis

Total score and symptom change

The change was modelled between the two interventions on PHQ-9 and GAD-7 using linear regressions with the final score as the outcome and baseline score as a covariate. This indicates whether the final session score has changed more or less

than expected based on the baseline score and the regression equations. This was conducted separately for sessions 1 and 2 as baselines. We also estimated change across each of the sixteen individual symptoms (using session 2 as baseline) with false discovery rate (FDR) corrected p-values within both the whole and propensity score matched samples.

Covariates – Propensity Score Matching

Estimation of the residual models were conducted using the whole sample and a propensity score matched sample. Propensity score matching was used to control for confounding as intervention type was not randomly assigned. Matching variables included session 1 item scores (PHQ-9 and GAD-7), gender (Male/Female), employment status (employed/unemployed), taking psychotropic medication (yes/no), age (continuous), ethnicity (based on UK Census categories: White, Mixed, Asian, Black, Chinese, Other), and baseline functional impairment as measured using the Work and Social Adjustment Scale (Mundt, Marks et al., 2002) total score. Propensity score matching was performed using MatchIt package (Ho et al., 2011). Mahalanobis distance matching within the propensity score caliper method (0.25) was used for matching analysis.

Network Intervention Analysis

Changes scores were estimated for all 16 symptoms of the PHQ-9 and GAD-7. We estimated the residual and difference scores with both session 1 and session 2 as baselines, to account for regression to the mean. Scores were calculated as follows: Difference Score (DS) = postscore – prescore; Final Score (FS) = post score; Proportional change (PC) = 100*DS/prescore; Residual Score (RP) = postscore ~ prescore; Residual Change Score (RC) = DS ~ prescore.

Moderated Network Models (Haslbeck et al., 2019) were estimated using elastic net regularization with parameters selected via 10-fold cross-validation, then combining neighbourhood estimates using the AND-rule and estimating the linear moderation effects of the interventions. To determine the stability of the estimates (edges and moderating effects) the residual models were refitted using 1000 bootstraps producing bootstrapped sampling distributions of all parameters. Within the network, the associations are conditional on all other variables in the model and the direct effects from the treatment node to the symptoms is the mean change difference in those

	CfD (N=1868)	CBT (N=10888)	P	d / V
PHQ-9 Total Session 1:				
Mean (SD)	13.1 (8.15)	14.7 (7.66)	<0.001	-0.21
Median [Min, Max]	14.0 [0, 27.0]	16.0 [0, 27.0]		
GAD-7 Total Session 1:				
Mean (SD)	10.7 (6.96)	12.3 (6.54)	<0.001	-0.23
Median [Min, Max]	12.0 [0, 21.0]	14.0 [0, 21.0]		
PHQ-9 Total Session 2:				
Mean (SD)	14.4 (6.37)	15.3 (6.07)	<0.001	-0.15
Median [Min, Max]	14.0 [0, 27.0]	16.0 [0, 27.0]		
GAD-7 Total Session 2:				
Mean (SD)	12.2 (5.57)	13.2 (5.26)	<0.001	-0.18
Median [Min, Max]	12.0 [0, 21.0]	14.0 [0, 21.0]		
PHQ-9 Total Final Session:				
Mean (SD)	9.23 (6.94)	9.54 (6.80)	0.079	-0.04
Median [Min, Max]	8.00 [0, 27.0]	8.00 [0, 27.0]		
GAD-7 Total Final Session:				
Mean (SD)	8.33 (6.12)	8.26 (5.87)	0.66	0.01
Number of sessions: Mean (SD)	10.4 (3.9)	10.9 (4.6)	<0.001	0.12
Age: Mean (SD)	38.5 (13.10)	42.5 (13.5)	<0.001	0.30
Gender			<0.001	0.06
Male	468 (25.1%)	3515 (32.3%)		
Female	1396 (74.7%)	7336 (67.4%)		
Missing/not disclosed	4 (0.2%)	37 (0.3%)		
Ethnicity			<0.001	0.07
Asian	171 (9.2%)	1677 (15.4%)		
Black	232 (12.4%)	1301 (11.9%)		
Chinese	10 (0.5%)	63 (0.6%)		
Mixed	111 (5.9%)	710 (6.5%)		
Other	86 (4.6%)	398 (3.7%)		
White	1210 (64.8%)	6393 (58.7%)		
Missing	48 (2.6%)	346 (3.2%)		

Table 1: Sample characteristics and group differences. P-values and effect sizes reported (Cohen's d or Cramer's V).

symptoms between the interventions. We also inspected the three-way interactions (moderation effects) to see how treatment affects the pairwise interactions between the other symptoms.

Results

Group Characteristics

Total scores on PHQ-9 and GAD-7 were higher at sessions 1 and 2 for the CBT group, and age, ethnicity, and gender differed between the groups (see Table 1). There was no evidence of differences between groups on the symptom measures at the final session. Propensity score matching resulted in matching equal numbers of CBT patients to patients in the CfD group (N=3446, 1723 per treatment).

Total score and symptom change

Within the whole sample there was a greater degree of change in anxiety but not depression during CBT than CfD. This effect was larger for the final GAD-7 score when controlling for session 2 scores: $F(1,12753)=22.985$, $p<0.001$, estimated marginal means ± standard error (CBT:9.47(0.06), CfD:9.62 (0.15)) than when controlling for session 1 scores: $F(1,12753)=11.832$, $p<0.001$, (CBT: 8.18(0.05), CfD 8.8(0.12)). There was no evidence of a difference between groups for the final PHQ-9 total score when controlling for session 1 PHQ-9 scores $F(1,12753)=0.881$, $p=0.348$, (CBT: 9.47(0.06), CfD: 9.62(0.15) or session 2 scores, $F(1,12753)=3.178$, $p=0.075$, (CBT: 9.46(0.06), CfD: 9.71(0.13)). Within the propensity score matched sample, there was a greater degree of change in both anxiety and depression during CBT than CfD when controlling for the session 2 score, PHQ total score: $F(1,3443) = 6.945$, $p<0.009$ (CBT:8.92(0.14), CfD:9.43(0.14); and GAD-7 total score $F(1,3443)= 19.59$, $p<0.001$ (CBT: 7.72(0.12),CfD:8.49(0.12)).

Symptom change is plotted in Figure 1. After correcting for FDR there was evidence that all GAD-7 symptoms and psychomotor disturbance were lower at end point for CBT than CfD (eTable 1 in Supplement). Within the propensity score matched samples, anhedonia, depressed mood, and all the GAD-7 symptoms except feeling nervous were lower at end point for CBT than CfD.

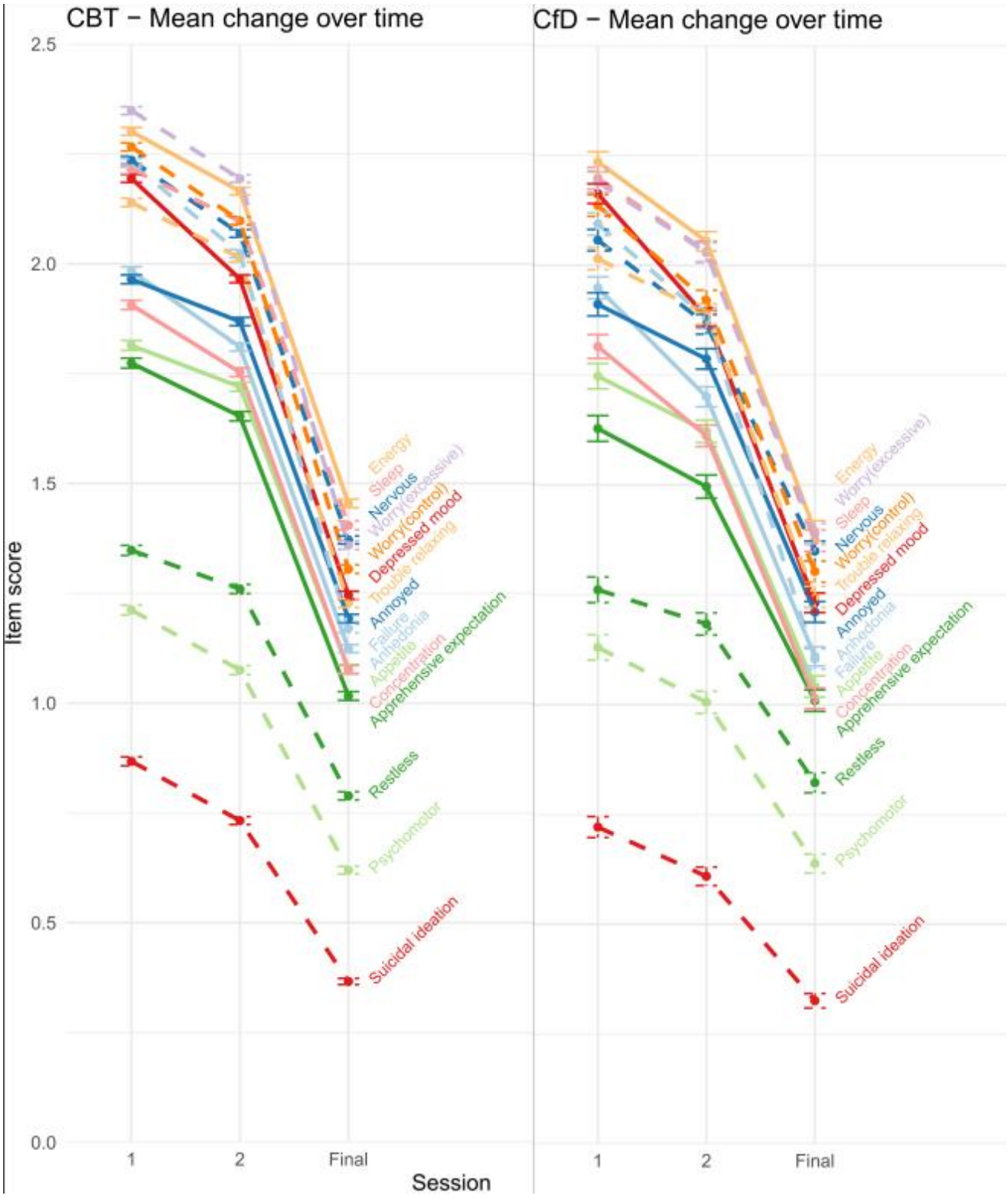

Figure 1: mean change and standard error for each symptom at session 1 and 2 (baseline measures) and the final session of treatment.

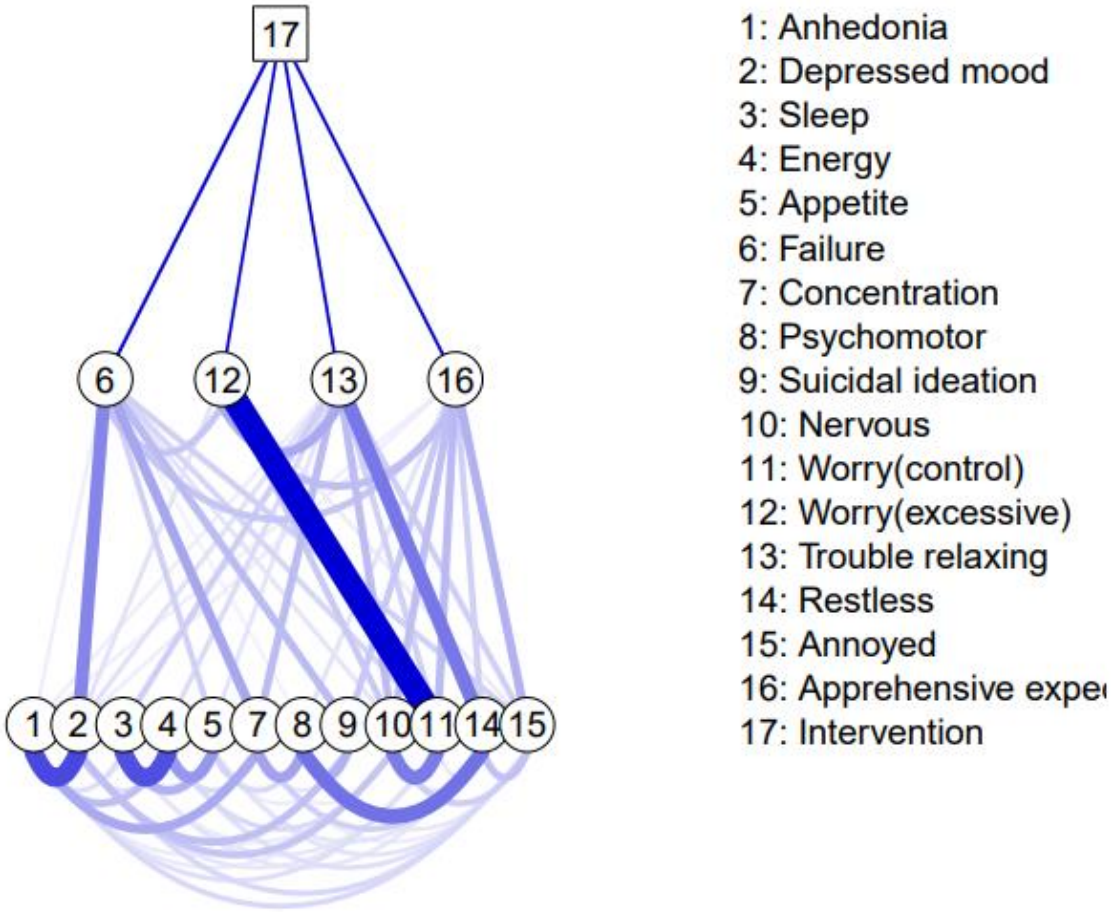

Figure 2: Network plot (RCX2). This represents the propensity matched models which were virtually identical. The network includes intervention (CBT or CfD) as a square node and items from the PHQ-9 and GAD-7. The thickness and saturation of the edges between symptoms is proportional to the strength of the association. Within the MGM, the inclusion of the intervention node allows us to explore moderation effects, identifying symptoms that are uniquely influenced by the intervention type, thereby demarcating intervention-specific effects with the network. Edges between intervention and a symptom indicates a larger direct item-specific effect for one of the interventions, but direct effects that are shared by both interventions will not be included into the network model. This direct effect may account for the spread throughout the network and indicate likely pathways through which an intervention may influence symptoms. The edges between the intervention node and symptoms are direct associations – the heatmap below indicates the strength and direction of these associations.

Network Intervention Analysis

The propensity score model is plotted in Figure 2 (all models are plotted in Figure 2 in Supplement), and the direct associations specified in Figure 3. Most edges were reliably estimated, included in all or nearly all, of the 1000 bootstrapped samples (Figure 2 and 3 in Supplementary Material).

Results using the difference score with session 1 as the baseline were different than other change models (e.g. correlation between matrices DS and RC1, r>0.48), with

the direct associations negatively correlated will all other estimates, including modelling the difference score with session 2 as the baseline, r = -0.60. Direct associations found with residual score models using the session 1 baseline were different to those found using session 2 data. The associations found when using session 2 as the baseline were consistent whether using the final score or residual score outcome, (r>.98).

The whole sample residual models using the session 2 baseline were similar (r >0.99), and similar to the propensity score matched models (r > 0.98). Fewer direct associations were identified in the propensity score matched sample using the residual change score outcomes. In these models, using the session 2 baseline, there was consistency across four items identified as having direct associations, three with CBT and one with CfD. Across the propensity score matched models, there was a larger effect on thoughts of being a failure with CfD (RCX2: 0.03) and a larger effect on excessive worry (RCX2: 0.02), troubling relaxing (RCX2: 0.02) and apprehensive expectation (RCX2: 0.02) with CBT.

When looking at the influence of treatment on symptom-to-symptom interactions (Figure 4), there was less consistency between models. While there was consistency between residual models within samples, there was very little between samples (whole and propensity score matched).

Within the whole sample there was evidence of stronger related change between anhedonia and appetite during CBT, than CfD (CBT: 0.05, CfD: 0.03). Further, the CBT group showed an associated change between suicidal ideation and restlessness (0.03), suicidal ideation and being easily annoyed/irritated (0.04) and between depressed mood and psychomotor disturbance (0.01); these were absent for the CfD group.

Between the propensity score matched models only two effects were identified in both models: the CfD group showed a stronger related change between feeling annoyed and apprehensive expectation (CBT: 0.09, CfD: 0.13). There was also a difference between groups on the associated change between suicidal ideation and concentration (CBT: 0.06, CfD: 0.04), with the CBT group displaying stronger associated change than the CfD group. Within the discussion, only interactions observed across both propensity score models are interpreted.

Figure 3: Heat map of direct associations for each model. The heatmap displays the direct associations between symptoms and intervention type obtained using the different methods of calculating change and against different baseline timepoints. Colour scale: darker = stronger, with blue reflecting direct associations with CBT and red reflecting direct association with CfD. In the headings, the number refers to the baseline used (i.e. session 1 or 2), DS: Difference Score, FS: Final Score only, PC: proportional change, RP: Residual score (post score ~ baseline), RC: Residual score (change score ~ baseline), X: propensity score matched samples.

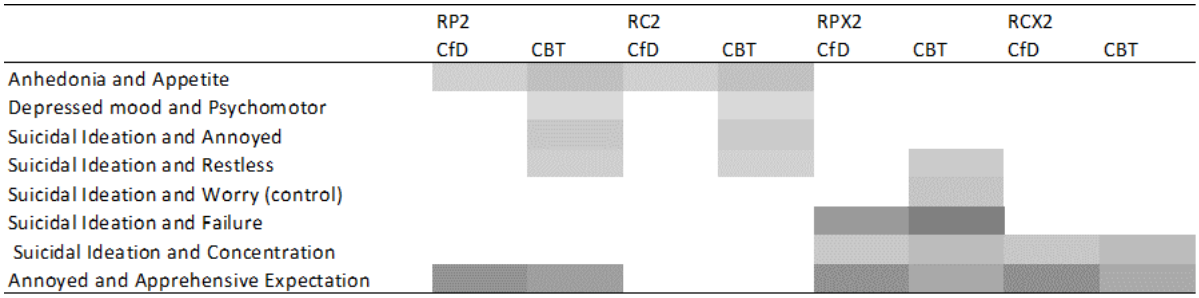

Figure 4: The influence of the type of intervention on symptom-to-symptom interactions. The values represent the presence and strength of the influence for the associations that differentiate the interventions. Colour scale: darker = stronger.

Discussion

This study investigated differences in symptom-specific effects of CBT and CfD, and the impact of modelling symptom change in a variety of commonly used ways for adults with depression treated in primary/community care psychological therapy services. We found that CBT for depression may work by directly affecting excessive worry, trouble relaxing and apprehensive expectation, while CfD may work by affecting thoughts of being a failure. These effects were specific to the type of treatment, i.e., they were not shared effects or indirect effects of changes in other symptoms influenced by the treatments. There were also treatment specific effects on symptom-

to-symptom interactions. CfD had a stronger influence on the associated change between feeling annoyed and apprehensive expectation than CBT. While the associated change between suicidal ideation and concentration was greater for CBT than CfD.

We found variability in the results obtained from different ways of measuring change. There was little consistency in the results between using session 1 and session 2 as a baseline. This is important because many observational studies and clinicians use pre-post change in a symptom measure score as their primary outcome. Further, within treatment settings there can be a period (weeks to months) between initial assessment (session 1) and commencing treatment (session 2). Hence, session 2 appears to be a more appropriate baseline for measuring treatment related symptom change. Differences between the whole and propensity score matched samples would suggest that there is an influence of covariates but it is less evident when estimating direct associations, although propensity score matching cannot fully redress selection biases or confounding given the potential influence of unmeasured variables (Steiner et al., 2010). The difference score and proportional change models produced inconsistent results however the final score model (a simple method) and residual score approaches were consistent. This echoes the established but rarely adhered to methodology of regressing the second baseline measurement (baseline) on the post-score or difference score where a residual score for each participant can be modelled within the network.(O'Connell et al., 2017) Although established for clinical trials, this also appears to fit for observational data in naturalistic settings.

The results provide evidence to elucidate how these therapies may work. For example, compared to CBT, CfD was directly associated with a change in the thoughts of being a failure. CfD also demonstrated a greater associated change between feeling annoyed and apprehensive expectation (feeling afraid that something bad will happen) than CBT. This fits with the theoretical underpinnings of CfD targeting the development of self-concept and conditions of worth and their link to emotional processes (Murphy, 2019). CBT encompasses a number of approaches to tackling depression most of which also target beliefs about the self, however it appears that this effect may not be as direct as it was in CfD. It might be that in the CBT delivery there was a greater focus on altering ruminative thinking processes than the content of negative thoughts and self-beliefs themselves (Veale, 2008). For both treatments self-beliefs may represent

an important target as we found an indirect effect of treatments on depressed mood via thoughts of being a failure.

CBT for depression was uniquely associated with changes in symptoms associated with anxiety. Some of the observed symptom effects could be considered mechanistic (reflecting an underlying physiological, neurobiological or functional mechanism) others more descriptive (Mansell et al., 2009). The changes in excessive worry and apprehensive expectation were both uniquely associated with CBT and, as another form of repetitive negative thinking (like rumination), has been identified as a transdiagnostic mechanism and treatment target (Spinhoven et al., 2019). Excessive worry has a strong temporal influence on the change in other symptoms during psychotherapy (O'Driscoll, Epskamp, et al., 2022) and CBT has been found to have a moderate effect on repetitive negative thinking (Spinhoven et al., 2018). CBT was also directly associated with trouble relaxing. Trouble relaxing has been identified as a central symptom within remission networks following CBT (Lorimer et al., 2020) and as a bridge between symptoms of anxiety and depression (Bard et al., 2022). There is some evidence that these symptoms are associated with experiential avoidance so CBT might be bringing about symptom change by tackling this process (Hsu, Mullarkey, Dobias, Beevers, & Björgvinsson, 2019).

There was a stronger associated change between suicidal ideation and concentration for CBT than CfD. Within this sample, we cannot identify temporal precedence. However, in a dynamic network model of change during psychotherapy, temporal influence was stronger for concentration on suicidal ideation than the other way around. (O'Driscoll, Epskamp, et al., 2022) Concentration has been identified as a central symptom in a relapse network (Lorimer et al., 2020) and may be reflective of poor meta-cognitive capacity to regulate impulsive tendencies to harm oneself (O'Driscoll, Nolte, et al., 2022). Although not evidenced in both models there was an indication that CBT may be associated with change between suicidal ideation and several symptoms (restlessness, feelings of failure and controllability of worry) suggesting indirect pathways through which CBT may reduce suicidal ideation.

Limitations

We attempted to balance groups on observed covariates, but they may have differed on important, unmeasured confounders such as those related to aspects of severity,

(Buckman, Saunders, Cohen, et al., 2021; Lorenzo-Luaces et al., 2020) to socio-demographics or socio-economic factors (Buckman et al., 2022; Delgadillo & Salas Duhne, 2020), and as such the differences observed may be due to external factors. There are other selection variables and mechanisms of interest to measure when comparing these treatment approaches. For example, previous experiences of treatment, where those who received CfD may have previously had CBT, adherence to treatment (fidelity and engagement), or therapeutic alliance which has been shown to influence change (Falkenström et al., 2016). The PHQ-9 and GAD-7 cover core symptoms, however, there are many other symptoms of depression and anxiety (Fried et al., 2022) that are relevant to understanding the mechanisms of change within these treatments. Secondly, the study measures change between two time points, dynamic processes of change are more complex (O'Driscoll, Epskamp, et al., 2022) and the temporal relationship in respect of each treatment is unknown. Third, while the analysis represents the largest network comparison of psychological treatments to-date, the directional associations were small and similar to a smaller study (Boschloo et al., 2019). This is not unexpected when comparing clinically equivalent treatments and controlling for the influence of symptoms on one another. Though this does suggest that knowledge of individual symptoms alone is unlikely to be sufficient to inform clinical decisions, it may not lead to better prognostic estimates or make it easier to select between generally similar treatment types (Buckman, Cohen, et al., 2021). Finally, this study provides a methodological illustration of the different results that emerge from modelling decisions rather than a statistical comparison of models and these might inform the determination of treatment outcomes in routine clinical care and future observational studies alike.

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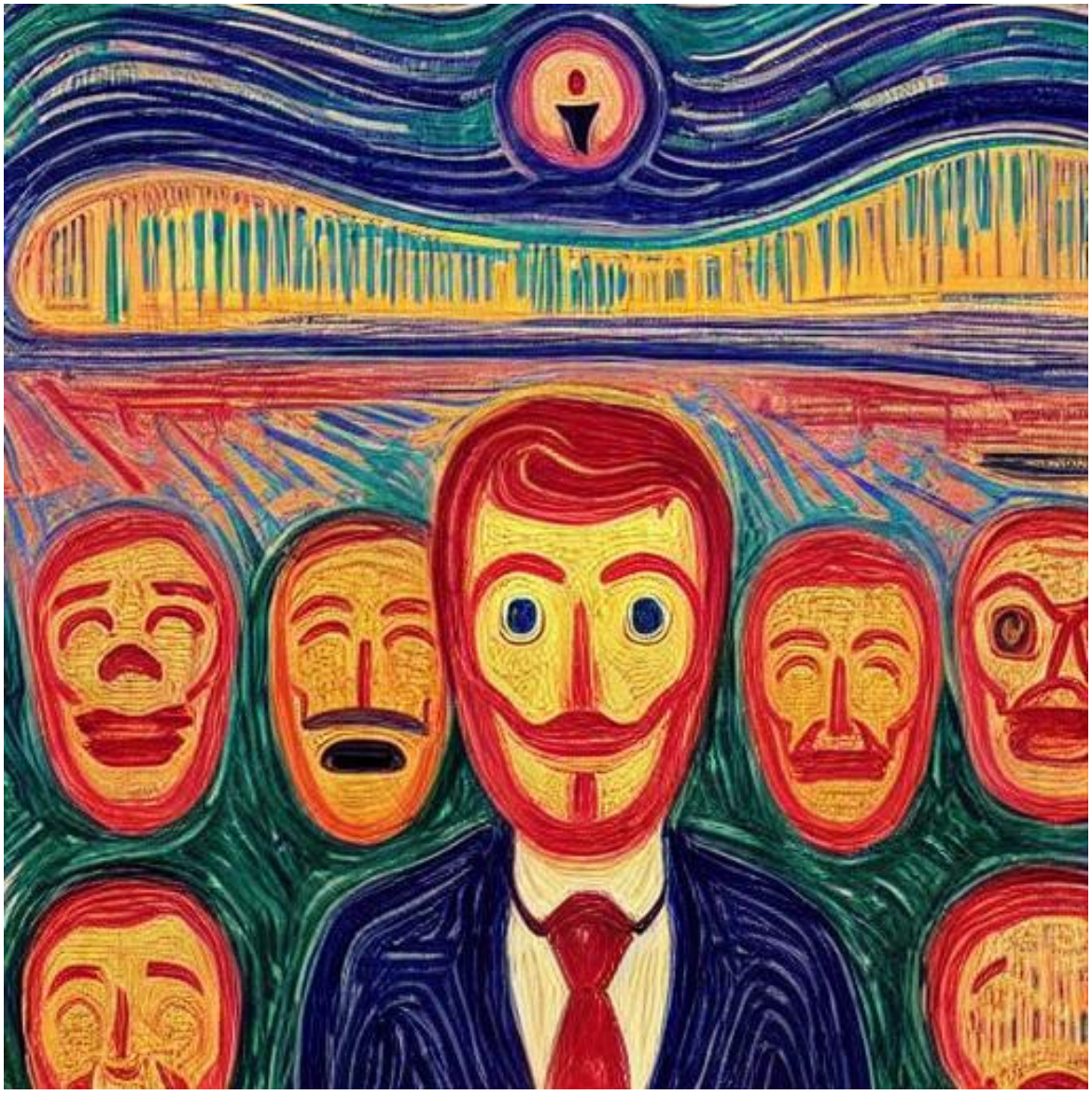
CHAPTER 5
The Effects of Diagnostic Group on the Association Between Personality and Psychopathological Symptoms: A Moderated Network Analysis



Abstract

Background: Personality functioning and psychopathology are interrelated, yet clinically they are demarcated. Diagnostically, we can distinguish between affective disorders and personality disorders, but there is overlap between features, and the interrelationship between these features may be important in the consideration of treatment approaches. Taking an integrative perspective, the present study aimed to determine whether the associations between processes implicated in the development of personality problems/disorders (e.g., mentalization, attachment, and emotion regulation) and psychopathological symptoms differed between diagnostic groups.

Methods: Cross sectional group differences were examined by estimating the moderation effects of diagnostic groups (borderline personality disorder, affective disorders, and community controls: N = 1386) on the relationship between features within a graphical network model. The resulting model displayed two-way interactions (linear regressions) between variables and three-way interactions (moderation effects of the group).

Results: The network model evidenced 11 direct associations between variables and the diagnostic group when controlling for all other variables. The influence of the group on pairwise interactions (the strength of dependencies between groups) indicated nine effects. The results indicate differential associations between personality factors and psychopathology between diagnostic groups notably affective instability and facets of mentalization and emotion regulation. Notably, identity problems and symptoms of PTSD did not differentiate clinical groups.

Conclusion: Conditional dependence between features provides additional information (above mean severity) to discriminate between, and identify putative causal relations within, diagnostic groups.

Introduction

Personality and psychopathology are not distinct. Historically a distinction has been drawn between psychopathology (mood) and personality disorders (PD) (Wright & Hopwood, 2022) with recent advances such as Hierarchical Taxonomy of Psychopathology (Kotov et al., 2017) and Research Domain Criteria (Insel et al., 2010) moving towards increased integration. Indeed, research suggests that personality traits show stronger relationships to clinical disorders (Kotov et al., 2010) than personality disorders (Samuel & Widiger, 2008). The question is not just about the unique features of PD but also how the common elements with mood disorder function differently in generating the clinical features that we use to recognise the disorder.

From a developmental perspective, the theory suggests that early formative experiences result in adaptive responses to the environment. Early adversity may interrupt the development of 'ideal' relations between a child and caregiver, i.e. epistemic trust (Luyten et al., 2020) leading to the development of, at least, initially adaptive responses (attachment style) optimising adjustment and enabling the regulation of emotions. Experiencing multiple or persistent trauma or adverse events, at any stage, has been associated with a disturbance in an individual's ability to regulate their emotions and their ability to form and maintain relationships (Gerber et al., 2018; Poole et al., 2018). These responses can influence the development of other cognitive processes (e.g., effective mentalizing). Responses may alter in response to changes in the environment, but, where they do not, they may become less adaptive, potentially leading to the development of psychopathology (Luyten & Fonagy, 2022). The emergence and severity of psychopathology throughout the developmental trajectory will, in turn, influence the development of personality features (Hilsenroth et al., 2018). Where co-morbidity is common, in the case of BPD the prevalence of having a co-morbid mood disorder has been estimated at 29% (Grant 2008), it is important to consider mutually reinforcing interactions both within and between disorder specific criteria (e.g., Rifkin-Zybutz et al., 2021 for mentalizing capacities).

Contemporaneously, the pattern of behaviour will be informed by the developmental trajectories, with personality and psychopathology reciprocally relaying between behaviour and consequence. A person experiences distress, psychopathological symptoms may arise, and unhelpful behaviours develop in response to their

experience. For example, someone with borderline personality disorder may engage in self-harming behaviours in response to feeling rejected, while someone with a mood disorder may withdraw from social life in response to the same experience. These thoughts, feelings and behaviours make it more difficult for the person to maintain or develop their functioning. While borderline personality disorder is characterized by interpersonal difficulties, and mood disorders by affective symptoms, it is self-evident that as a consequence of experiencing a mood disorder one's interpersonal functioning is likely to be affected, and consequences of interpersonal difficulties will likely affect one's mood.

Within a network theory approach to mental disorders (Borsboom, 2017) these bi-directional interactions between features of an experience operate within a system. While a state may be triggered by an event, if it crosses a threshold, a 'disordered' state, this can become self-sustaining, where symptoms influence other symptoms in the absence of the triggering event and are difficult to shift out of without intervention (Hayes & Andrews, 2020). According to this theory, it would be expected that disorder systems or networks should be different, with different features driving the maintenance of the disorder.

Network analysis allows us to model these processes, identify cooccurrence and inter-dependence of symptoms, and inform us about commonalities and differences between groups and can help to explain the comorbidity that exists between disorders. To date, the network literature has focused on the central features of BPD rather than the distinguishing features. Network analysis in BPD supports the view that affective instability plays a central role within BPD (Peters et al., 2022; Richetin et al., 2017; Southward & Cheavens, 2018; von Klipstein et al., 2021). Where associations have been explored with personality and psychopathology, facets of emotional regulation have been prominent (Southward & Cheavens, 2018) as well as chronic emptiness (Köhne & Isvoranu, 2021; Southward & Cheavens, 2018). This study aimed to overcome methodological shortcomings in these studies, specifically the use of non-clinical samples and small sample sizes, that affect the ability to robustly estimate and compare networks. In addition, this study is the first to compare BPD to a mood disorder and control group. With this, we acknowledge that given the heterogeneity of

the diagnostic groups, it is likely that this characterization will obscure important differences.

The aim of this study was to determine whether the demarcation between personality and psychopathology was warranted. In order to identify what is unique to each group and what is shared we compared the diagnostic groups in terms of both severity and the interrelation between symptoms and traits. Although the study was exploratory, we expected there to be differences between groups with the relationships between symptoms and traits generally stronger for BPD than for mood disorder and, stronger for mood disorder than for nonclinical controls. This hypothesis is consistent with studies demonstrating increased comorbidity between symptoms and traits in BPD compared to mood disorder and non-clinical controls (Oldham, 2011).

Method

Design

The study used a cross sectional between groups design. Key variables capture social functioning (personality and attachment), emotional and cognitive regulation (emotional regulation and mentalization), and symptoms of psychiatric disorders (borderline personality traits, paranoia, depression, hostility, anxiety, and posttraumatic stress).

Participants

Data collected as part of the 'Probing Social Exchanges' project, which employs computational neuroscience to better understand mood disorders as well as Borderline and Antisocial Personality Disorder. Ethical approval for the BPD/ASPD/ HC study was acquired from the Research Ethics Committee (REC) of Wales (REC number: 12/WA/0283) and for the reduced sub-study from the London Queen Square REC (REC number: 16/LO/0077). Participants with borderline personality disorder were recruited from clinical services in London specialising in the treatment of PD, a sample of individuals with primary diagnosis of affective disorder including major depression (MD) were recruited from local NHS psychological treatment services (IAPT); and non-clinical controls from the community (CR) were recruited following their responding to advertisement material distributed through various media. Findings from separate analyses of subsamples from this research program have been

published (Euler et al., 2021; Huang et al., 2020; Michael et al., 2021; Rifkin-Zybutz et al., 2021; Stagaki et al., 2022).

The participants were between 18 and 65 years old, fluent in spoken and written English. Individuals with recent psychotic episodes, severe learning disabilities, or current or past neurological disorders or traumas were excluded.

Diagnoses were based on the Structured Clinical Interview for DSM-IV axis II personality disorders (American Psychiatric Association, 2000).

Measures

Social/interpersonal functioning

Inventory of Interpersonal Problems-32 (IIP-32, Barkham, Hardy, & Startup, 1996) a 32-item measure span a range of social behaviours that people find challenging to engage in (e.g., hard to make friends) or use too much (e.g., argue with other people too much). The IIP subscales demonstrated good internal consistency in this study (Cronbach's α = 0.80 to 0.88). Two circumplex scores for individual dimensions, affiliation -sociability (affiliation) and control - dominance (dominance), were computed from the eight standardized scale scores to index the degree of warmth and dominance in the profile of problems (Acton & Revelle, 2004).

Experiences in Close Relationships Revised (ECR-R; (Sibley et al., 2005) consists of 36 items with 18 items for each subscale capturing Attachment Avoidance (anxiety over abandonment) and Attachment Anxiety (avoidance of intimacy). Subscale internal consistency in this study were α = 0.91 and 0.90 for avoidance and anxiety respectively.

Emotional and cognitive regulation

Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) a 36-item questionnaire assessing problems in multiple domains of emotion regulation, including Lack of Emotional Awareness (Awareness), Nonacceptance of Emotional Responses (Nonacceptance), Difficulties Engaging in Goal-Directed Behavior (Goals), Lack of Clarity of Emotional Responses (Clarity), Limited Impulse Control Difficulties (Impulse), and Access to Emotion Regulation Strategies (Strategies). The internal consistency of DERS subscales in this study were: α = 0.81 (Awareness), 0.93 (Nonacceptance), 0.86 (Goals), 0.87 (Clarity), 0.92 (Impulse), and 0.91 (Strategies).

Reflective Functioning Questionnaire (RFQ; Fonagy et al., 2016), a 54-item measure of reflective functioning, the operationalized form of mentalizing. The RFQ assesses the mentalization capacity of oneself and others. The first subscale is certainty about mental states (Mentalization - certain); high scores on this scale reflect excessive certainly about mental states. The second subscale refers to a lack of knowledge about mental states (Mentalization - uncertain); this scale reflects a lack of knowledge about mental states. Subscale internal consistency in this study were α = 0.91 and 0.90 for uncertain and certain respectively.

Symptoms of psychiatric disorders

Personality Assessment Inventory – Borderline sub-section (PAI-BOR; Morey, 2004) was used to assess borderline personality traits, with subscales for affective instability, identity problems, negative relationships, and self-harm. Internal consistency for subscales in this study: identity problems α = 0.82, affective instability α = 0.88, negative relationships α = 0.74, and self-harm α = 0.87.

Green Paranoid Thought Scale (GPTS; Green et al., 2008), is a 16 item measure assessing persecutory ideation, with two scales, thoughts of social reference and thoughts of persecution. Internal consistency for the subscales in this study: α = 0.95 and 0.97 for thoughts of social reference and thoughts of persecution, respectively.

Brief Symptom Inventory (BSI; Derogatis & Melisaratos, 1983), a 53-item scale assessing psychological symptomatology. In this study we used the depression, hostility and anxiety subscales, with respective internal consistencies (α = 0.93,0.92 and 0.87).

Posttraumatic Stress Checklist Scale (PCL; Weathers, Litz, Herman, Huska, & Keane, 1993) measures the 17 PTSD symptoms described in the DSM-V. The three subscales are re-experiencing, avoidance and arousal, with respective internal consistencies in this study of α =0.92, 0.90, and 0.90.

Statistical Analysis

Missing data were handled using the multivariate imputation by chained equation (MICE) package (Zhang, 2016). Data were transformed to relax the normality assumption (nonparanormal transformation: (Zhao et al., 2012). Unique Variable Analysis (UVA) and Exploratory Graph Analysis (EGA) were applied using the *EGAnet*

package (Christensen & Golino, 2021) and Mixed Graphical Model (MGM), implemented in the R-package mgm (Haslbeck et al., 2020) in R (R Core Team, 2021).

Unique Variable Analysis (UVA) was used to identify and reduce the influence of redundant variables in this multivariate data set (Christensen et al., 2020). There are two reasons to reduce redundancy in data. First, as redundant variables can create minor factors or correlated residuals which lead to the overestimation of the number of factors in the data (Christensen et al., 2020). Second, redundant variables can influence the accurate and valid estimation of network measures (Hallquist et al., 2019). Specifically, redundant nodes in a network are likely to have higher node strength values (absolute sum of a node's connections) due to redundancy rather than actual increased connectivity to other nodes.

UVA begins by first computing a pairwise association measure. In this study, the weighted topological overlap was calculated. Weighted topological overlap is a network measure that determines the extent to which nodes in a network “overlap” by quantifying the similarity between a pair of variables' shared connections (e.g., weights, signs, quantity; see Christensen et al., 2020 for more details). Next, using only the nonzero (absolute) weighted topological overlap values, an empirical distribution is estimated to obtain the p-values (with significance $p < 0.05$). Significant values suggest that a pair of variables is redundant. Because there are many non-zero values (leading to multiple comparisons), an adjustment to the p-value is necessary. We applied the default method that uses an ‘adaptive’ alpha (Pérez & Pericchi, 2014), which adjusts the alpha based on sample size (here, the number of nonzero values). After, UVA passes the redundancies onto us and we made the definitive decisions on whether variables were redundant based on the shared connections, and our theoretical knowledge about the topological overlap between the variables, where uncertain redundancies were ignored. The redundant variables were then combined into a latent variable.

We then used exploratory graph analysis (EGA) to estimate the number of dimensions in multivariate data using undirected network models (Golino et al., 2020; Golino & Epskamp, 2017)). EGA first applies a network estimation method followed by a community detection algorithm (Louvain) for weighted networks. The algorithm begins

by randomly sorting nodes into communities with their neighbours and then uses modularity (Newman, 2006) to iteratively optimize its community partitions by exchanging nodes between communities and evaluating the change in modularity until it no longer improves.

We then estimated a Mixed Graphical Model (MGM, in which we included all subscales as continuous, and diagnosis as categorical. In estimating the networks, an elastic net regularization was applied to reduce the inclusion of spurious edges, resulting in networks that are sparser and have higher specificity (Epskamp et al., 2018). The moderation approach proposed here uses a nodewise estimation approach with a single L1-regularization term that includes both main effects and interactions (which are interactions and moderation effects, respectively, from a graph-perspective). Models select the regularization parameter with 10-fold cross-validation and specified that estimates across neighbourhood regressions should be combined (AND rule). As the regression on the moderator variable includes many terms, this renders the AND-rule very conservative (Haslbeck & Waldorp, 2015). In estimating the MGM, all linear moderation effects of diagnosis are estimated. Direct associations between group and nodes are reported as odds ratios. In order to estimate the stability of the estimated edges and moderation effects, the model was refit using 1000 bootstrap samples to provide the bootstrapped sampling distribution of all parameters. When interpreting edges, those between variables can be interpreted as partial correlations, whereas relations between the diagnostic group and variables can be interpreted in terms of (averaged) regression coefficients.

Within the MGM, the inclusion of diagnosis allows us to explore moderation effects, identifying constructs that are uniquely influenced by diagnosis, thereby demarcating diagnosis-specific effects with the network. While focusing on links between the diagnosis node, we are also interested in differences in network structure among the constructs, as these may also reflect group differences. Identifying moderation effects (group differences) between networks requires significant power; as such, smaller and less stable moderation effects are expected (Haslbeck et al., 2019).

Within the network model, the edges between diagnosis and a construct indicate a larger direct construct-specific effect for one of the groups. In the interpretation of

these edges, it is important to note that direct effects that are shared by all groups will not be included into the network model. This direct effect may account for the spread throughout the network and indicate likely pathways through which a disorder may be maintained. Within the network the main effects from the diagnosis node to the other variables gives you the mean differences in those variables across the moderator group variable. Edges connecting to diagnosis are explored to identify the specific effect and reported as odds ratio. We also directly inspect the three-way interactions (moderation effects) to see how the moderator affects the pairwise interactions between the other variables.

Open data and transparency

Raw data will be available on request. Covariance matrices and r code to reproduce the analysis and the supplementary material are available in an open repository: https://osf.io/948qj/.

Results

Participant characteristics

The study sample consisted of 1386 adults, aged 16 to 65 years. There was no significant difference between groups on age, $F(2, 1383) = 1.44$, $p = 0.24$. There were more women (n = 997) than men (n= 379) in the sample, X^2 (8, 1386) = 40.58, $p < 0.001$. Groups did not differ by ethnicity, X^2 (8, 1386) = 13.58, $p = 0.94$, however participants were primarily white. Groups differed by employment status, X^2 (8, 1386) = 206.11, $p < 0.001$. Individuals with a diagnosis of BPD were more likely to be unemployed (BPD: 53.5%, CR: 15.6%, MD: 23.0%).

	BPD (n=398)	CR (n=675)	MD (n=313)
Gender			
Male	71 (17.8%)	228 (33.8%)	80 (25.6%)
Female	322 (80.9%)	445 (65.9%)	230 (73.5%)
Transgender /	2 (0.5%)	1 (0.1%)	3 (1.0%)
Other	2 (0.5%)	1 (0.1%)	0 (0%)
Missing	1 (0.3%)	0 (0%)	0 (0%)
Age			
Mean (SD)	30.7 (9.66)	31.8 (11.2)	31.1 (10.4)
Median [Min, Max]	29.0 [17.0, 58.0]	29.0 [16.0,	28.0 [18.0,
Missing	4 (1.0%)	0 (0%)	0 (0%)
Employment status			
Employed	120 (30.2%)	413 (61.2%)	186 (59.4%)
Unemployed	213 (53.5%)	105 (15.6%)	72 (23.0%)
Student	54 (13.6%)	151 (22.4%)	50 (16.0%)
Retired	4 (1%)	6 (0.9%)	2 (0.6%)
Missing	7 (1.8%)	0 (0%)	3 (1.0%)
Ethnicity			
White	292 (73.4%)	492 (72.9%)	207 (66.13%)
Black/Black British	31 (7.8%)	44 (6.5%)	28 (9.0%)
Mixed	36 (9.0%)	52 (7.7%)	26 (8.3%)
Asian/British Asian	25 (6.3%)	70 (10.3%)	39 (12.4%)
Not stated	14 (3.5%)	17 (2.5%)	13 (4.2%)

Table 1. Descriptive data on sample.

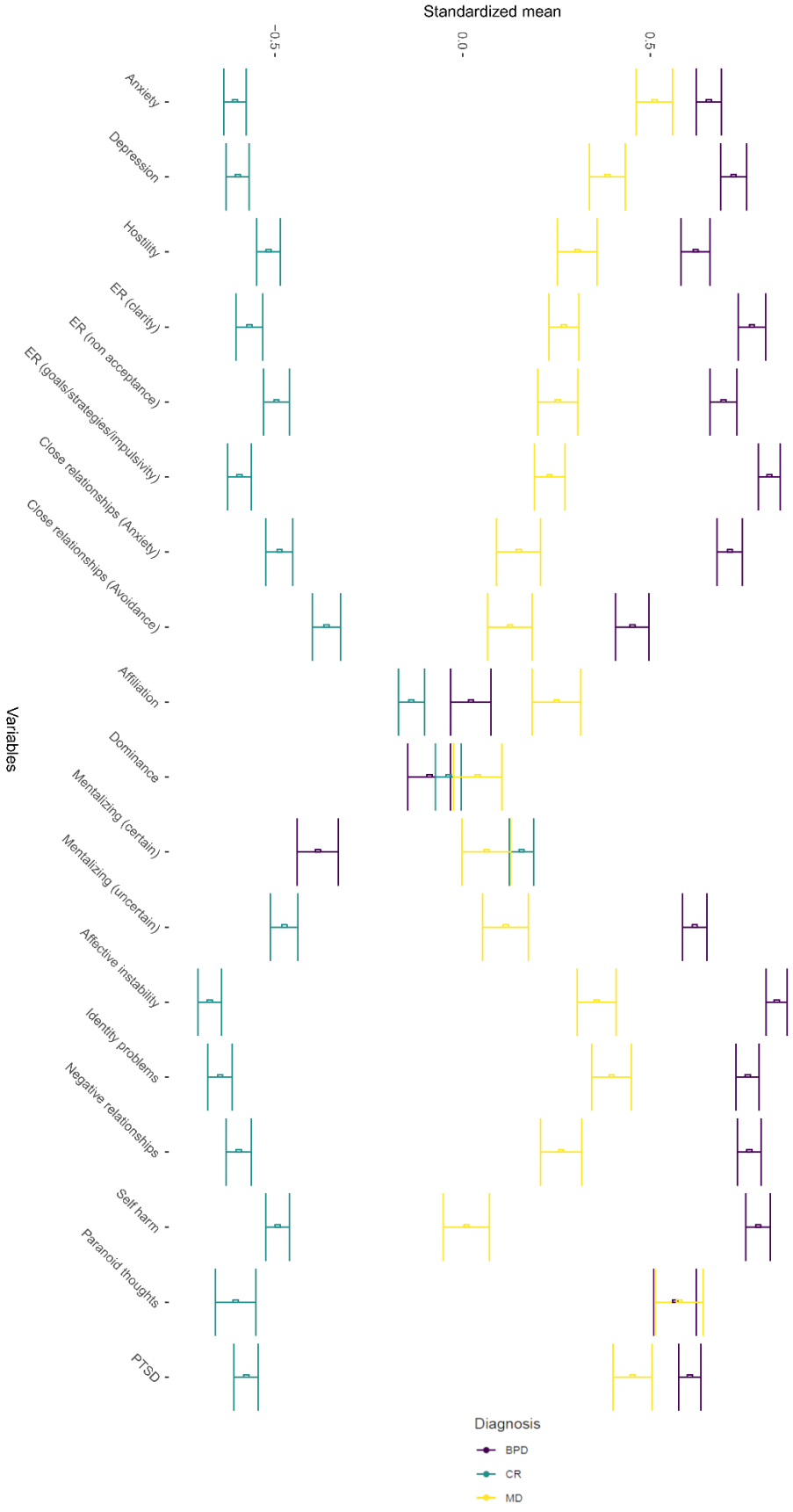


Figure 1: Standardised mean and error of all variables for each group included in the network model.

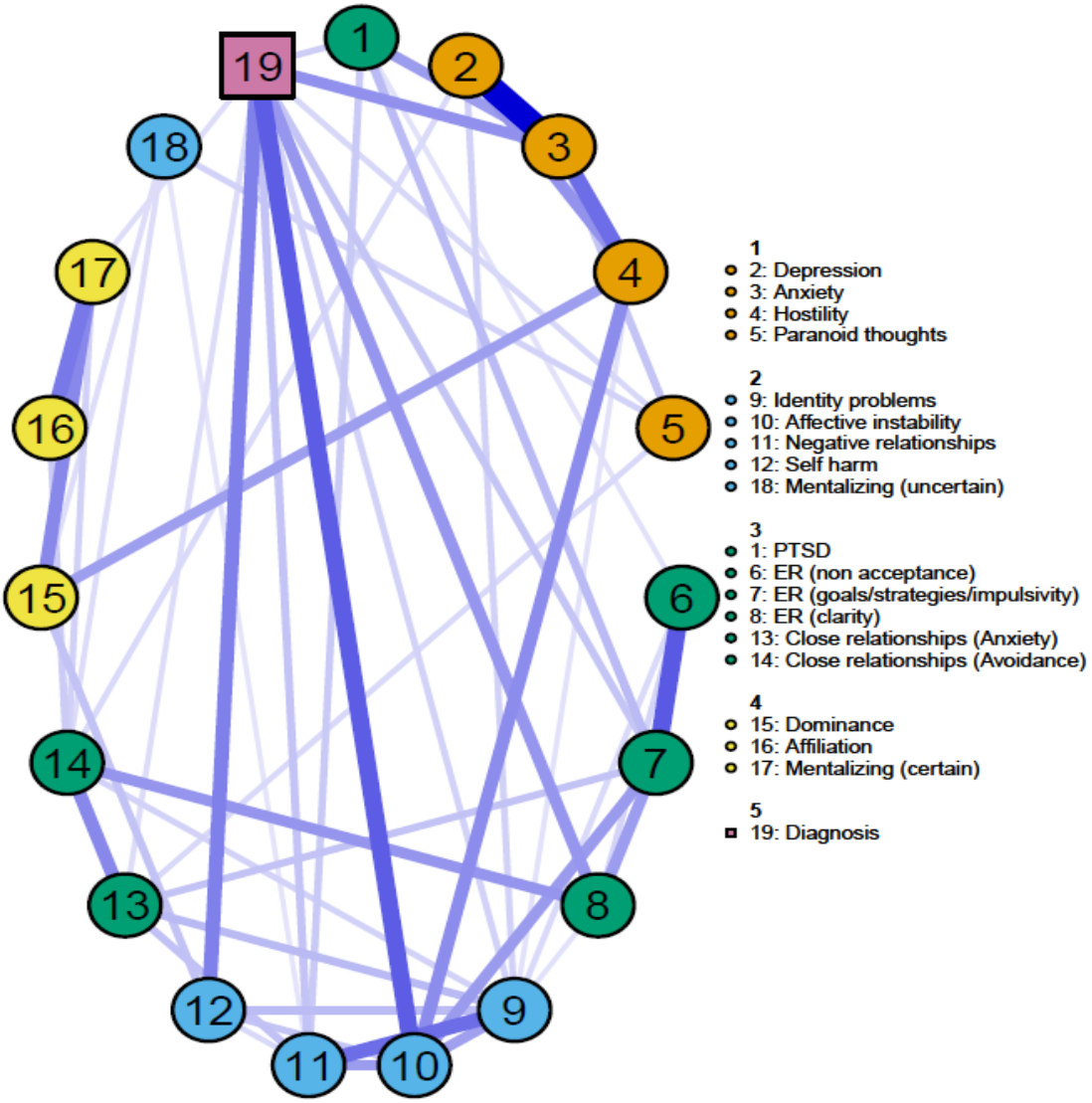


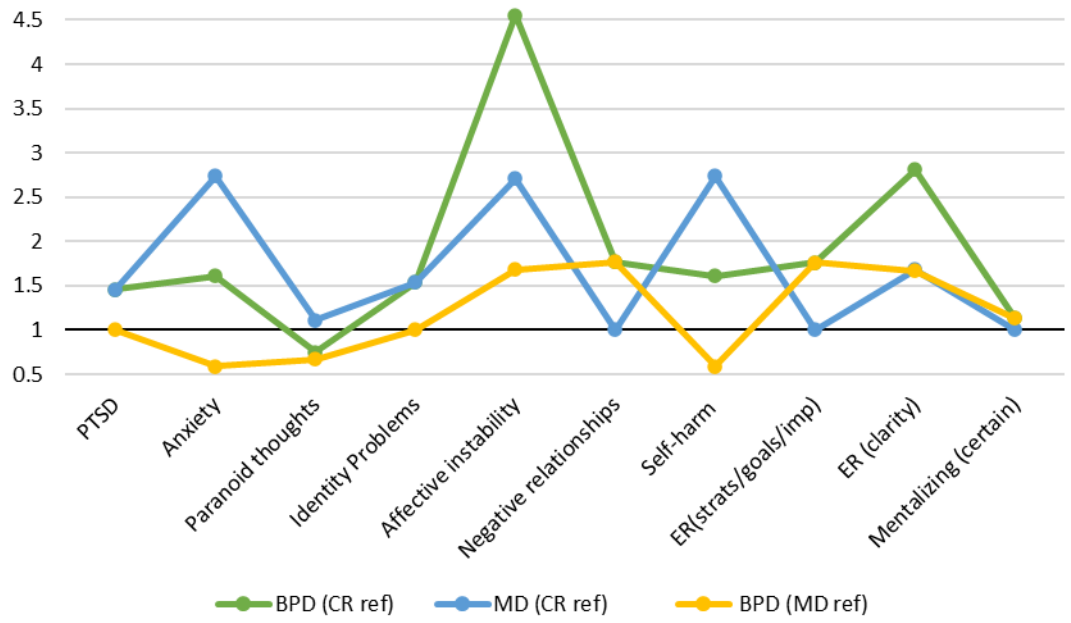
Figure 2. Moderated Network. The network includes subscales from the DERS, RFQ, PAI, PCL, BSI, IIP-32, ECR and the diagnosis. The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Blue edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. Colour of node represents the community the variable falls under.

Network modelling

UVA analysis suggested redundancy for 8 associations. PCL subscales were combined into a PTSD node, GPTS subscales were combined into a paranoid thoughts node and DERS strategies, goals, impulsivity were combined into an

emotional regulation (ER goals, strategies, impulsivity) node. Other suggestions were rejected due to lack of clear content overlap. The standardized means and errors for the included variables are shown in Figure 1. Descriptives for all items are included in supplementary materials. The mean difference was significant between groups, except for paranoia (BPD and MD were not significantly different), mentalizing (certainty), (MD and CR were not significantly different) and dominance (no significant difference between groups).

Exploratory graph analysis identified four communities. The first community included depression, anxiety, hostility, and paranoid thoughts, all related to psychopathology. The second community included identity problems, affective instability, negative relationships, self-harm and mentalizing (uncertain). This community was characterised by borderline personality traits. The third community included PTSD, the three ER variables and the two close relationship variables. The fourth community included mentalizing (certain) with dominance and affiliation. The network model evidenced 11 direct associations between variables and the diagnosis group when controlling for all other variables (Table 2 and Figure 3). Most edges were reliably estimated, included in all or nearly all, of the 1000 bootstrapped samples (see supplementary figure 1). The ORs are conditional on all other variables in the model. The model has been estimated with ℓ1-regularized regression, in which the regularization parameters have been selected with 10-fold cross-validation with the goal that the parameter estimates generalize to new samples. As such, the reported parameters are all significant, and it is not necessary to perform any hypothesis test on the ORs or the underlying variables. ER (strategies/goals/impulsivity), ER (clarity), affective instability, negative relationships, close relationships (anxiety) and mentalizing (certain) were associated with increased odds of having BPD compared to both other groups. PTSD and identity problems were associated with increased odds of having BPD or MD compared to CR but not compared to each other. Anxiety, paranoid thoughts, and self-harm were associated with increased odds of having MD compared to BPD and CR.



	BPD (CR ref)	MD (CR ref)	BPD (MD ref)
Symptoms of psychiatric disorders			
PTSD	1.46	1.46	1
Anxiety	1.61	2.74	0.59
Paranoid thoughts	0.75	1.11	0.67
Identity problems	1.54	1.54	1
Affective instability	4.55	2.71	1.68
Negative relationships	1.77	1	1.77
Self-harm	1.61	2.74	0.59
Emotional and cognitive regulation			
ER (strategies/goals/impulsivity)	1.76	1	1.76
ER (clarity)	2.81	1.68	1.67
Mentalizing (certain)	1.13	1	1.13
Social/interpersonal functioning			
Close Relationships (Anxiety)	1.24	0.88	1.4

Table 2 and Figure 3: Odds ratios (OR) for direct associations between group and variables as identified within the network model. Note that the ORs are conditional on all other variables in the model.

After conditioning on diagnostic group, the individual networks showed similar structures (r = 0.91 to 0.96). The influence of the group on pairwise interactions (i.e., the strength of dependencies between groups) indicated 9 effects (Table 2). For instance, the linear dependency between node 8, ER (clarity) and node 18, Mentalizing (uncertain) was strongest for BPD (0.24), less so for CR (0.13) and absent in MD. Conversely, the linear dependency between node 13, close relationships

(Anxiety) and node 14, close relationships (Avoidance) was strongest for MD (0.52), slightly lower for CR (0.44) and absent in BPD.

		BPD	MD	CR	%
ER (goals/strategies /impulsivity)	ER (clarity)	0.18	0.08	0.21	59
ER (goals/strategies /impulsivity)	Depression	0.07	0	0	77
Mentalizing (uncertain)	Self-harm	0	0.16	0	87
Mentalising (uncertain)	ER (clarity)	0.24	0	0.13	97
Mentalizing (certain)	ER (clarity)	0	0	0.2	94
Mentalizing (certain)	Hostility	0	0.2	0	89
Negative relationships	Hostility	0.07	0	0	71
Close relationships (Anxiety)	Close relationships (Avoidance)	0.22	0.52	0.44	57
Identity problems	Affective instability	0.18	0.41	0.21	78

Table 2. Influence of the moderator on pairwise interactions. The weights between variables are not partial correlation coefficients (but have the same interpretation). % = the proportion of all 1000 bootstrap estimations where diagnosis would influence the pairwise association.

Discussion

This study reveals differences in the personality and symptom networks between BPD, mood disorder and control groups. While the general topology of the networks was similar between groups, there were differences in terms of the direct influence of diagnostic group on node, and the associations between nodes. This suggests that when comparing BPD and mood disorder, personality and psychopathology are less distinct than previously thought. The most notable were the roles of emotional and cognitive regulation. The findings support established diagnostic criteria, while also raising new insights. In the remainder of the discussion, we interpret the findings and consider the difference between our findings and previous work, highlight some limiting conditions, and raise clinical implications.

In the area of social/interpersonal functioning, close relationships (anxiety) differed between groups, where they were more pronounced for BPD, and less associated with MD than with CR. In contrast, the pairwise association between both close relationship scales, anxiety and avoidance, was strongest for MD, then CR, and less for BPD. This may relate to a level of coherence that is only there for organized attachment, secure or insecure, while BPD may more closely associated with a disorganized attachment style (Luyten et al., 2020). The attachment style findings highlight the potential role of

switching between attachment strategies in interpersonal contexts in BPD where unstable relationships and attachment are strong predictors of BPD severity (Conway et al., 2012; Feske et al., 2007) and the incoherence may contribute to ER (Gunderson, 1996)

There were clear emotional and cognitive regulation differentiators with ER (clarity and goals/strategies/impulsivity), and mentalizing (certain) differentiating BPD from both other groups. The pairwise association between mentalizing (uncertain) and ER (clarity) was strong for BPD, less so for CR and absent in MD, while an association between mentalizing (certain) and ER (clarity) was only present for CR. These results are in line with a previous study highlighting these aspects of ER in relation to PAI and IIP items (Southward & Cheavens, 2018). Where there were no associations between mentalization and ER (clarity) in MD, this may suggest that poor mentalization in MD may be a consequence of depression and not its cause. The importance of ER in BPD has previously been highlighted and suggested to more strongly associate with BPD features than interpersonal difficulties and psychopathology (Cheavens et al., 2012; Glenn & Klonsky, 2009). Metacognitive problems may affect the ability of individuals with BPD a to set goals, use strategies, and control impulsive behaviours, as well as their ability to think clearly about their emotions (Vega et al., 2020).

As expected, affective instability strongly differentiates BPD from the other groups, in line with prior network analysis (Richetin et al., 2017; Southward & Cheavens, 2018). However, identity problems were associated with higher odds of having BPD or MD compared to CR but not each other – a finding not reported before, although the severity of BPD was greater than that of MD. Further, the strength of association between identity problems and affective stability was strongest for MD, then CR and BPD. Items assessing identity problems overlap with features of depression (e.g., emptiness, abandonment, lack of purpose) and while qualitative differences may exist (Elsner et al., 2018), the distinction may not be captured by the PAI-BOR. However, the analysis does control for symptoms of depression and anxiety suggesting that this may still reflect an elevated trait. While defining, these features are not specific to BPD, with other studies supporting a dimensional association (Distel et al., 2016; Peckham et al., 2020; Skodol et al., 2011) which is also in line with HiTop conceptualizations.

Negative relationships also differentiated BPD from the other groups, and an association between negative relationships and hostility was only present for BPD. Hostility for individuals with BPD may be experienced as more intense, and expressed more frequently, compromising the quality of the relationships (Critchfield et al., 2008; Zanarini et al., 2007). This relationship is supported by momentary assessment research (Hepp et al., 2017), where the bidirectional relationships between hostility and rejection and disagreement were stronger in a BPD group compared to a depression group. An association between psychiatric symptoms and mentalization was only present in the MD group. Within MD, mentalizing (certain) was associated with hostility and mentalizing (uncertain) was related to self-harm. This may indicate that different modes of emotional expression are associated with different modes of mentalizing. It may also be the case that this may differentiate subtypes of mood disorder (Blatt & Zuroff, 1992). Given the absence of impact of hostility on relationships in MD, hostility may be directed against the self in MD, where hostility may be indicative of shame and self-criticism. Symptoms of PTSD were also associated with an increased odds of having BPD or MD compared to CR but not with each other. This finding is interesting given the argument around complex trauma and calls to rename BPD, complex PTSD (Ford, 2019; Kulkarni, 2017). The findings here suggest that trauma is related more broadly to psychopathology and not specific to BPD, in line with recent findings regarding the p-factor (Caspi & Moffitt, 2018; Schaefer et al., 2018). MD was more associated with anxiety, paranoia, and self-harm than the two other groups. While self-harm (severity) was more pronounced for BPD, within the network self-harm was associated with increased odds of having MD compared to BPD and CR. This suggests that a feature prominently associated with BPD may be more pervasive. Regarding the self-harm subscale, it is important to note that these items measure impulsive tendencies that may lead to self-harm; they do not specifically ask about the frequency of suicidal or self-harming behaviours which may be a more suitable differentiator (Nelson et al., 2022).

Our theoretical structure did not directly map onto the network community structure. Mentalizing (certain) and mentalizing (uncertain) fell into different communities. Mentalizing (uncertain) was in a community with the borderline personality traits while mentalizing (certain) grouped with both close relationship variables and dominance and affiliation. This would suggest that these modes of mentalization are not only

separable and conceptually distinct but are associated with different aspects of personality functioning, where uncertainty may be more indicative of impaired mentalizing (Morosan et al., 2020). From a measurement perspective, mentalizing (certain) may be a psychic equivalence parameter reflecting non-mentalizing mode (equating internal states with reality) (Luyten et al., 2020) and may serve as an amplifier of inner experience (appraisals and affect) not only in BPD but also depression (Luyten & Fonagy, 2018). PTSD (a latent variable comprising re-experiencing, avoidance, and arousal subscales) was in a community with ER strategies indicating a close relationship between PTSD symptoms and emotional regulation in this sample.

The present findings have implications for enhancing the understanding of integrating personality functioning and psychopathology. Specifically, that processes viewed as being specific to a disorder can be prominent in other disorders, for instance, the relevance of identity problems and affective instability in the mood disorders group. With development in clinical research of empirically support personalised treatment selection approaches (Cohen et al., 2020; Keefe et al., 2021) assessment of personality features may have transdiagnostic relevance. From this study, identity problems, emotion regulation, and mentalizing may be of particular interest as testable candidates for such approaches. Clinically, mean level severity coupled with information derived from idiographic networks can inform assessment and treatment, where intervention selection (or components thereof) focuses on targeting the relationship between nodes rather than the node specifically or disorders more broadly.

There are limiting conditions of this study that limit the ability to derive inferences in relations to the association between groups. As a cross-sectional study, we are limited in our ability to identify causality. Temporal analysis, for instance, through panel modelling (Epskamp, 2020) would improve the ability to establish Granger causality. While cross-sectional networks reflect the between person associations, there is evidence in the BPD network literature that baseline networks are strongly predictive of relationships between change trajectories in BPD (von Klipstein et al., 2021) providing some support for inference. It also fails to recognize the heterogeneity of the diagnostic groups and can miss important differences between groups at the within-person level. The variables in the model were chosen by the researchers from a large

battery of assessments as best reflecting the constructs of interest. There are invariably unmeasured variables that may confound the results. For instance, within the analysis it was assumed that group moderated the associations however it is possible that that relations between features may be consequent to the presence of an unmeasured construct.

Conclusion

The study highlights the importance of taking an integrative approach to personality and the psychopathology. and findings suggest some practical recommendations. Considering the difference between groups, and considering the associations within groups, we must not only integrate psychopathology into personality, but personality into psychopathology.

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CHAPTER 6

Development and optimisation of an ecological momentary intervention to support dynamic goal pursuit.

Abstract

Background: Individuals experience difficulties pursuing goals within their environment where they will need to navigate numerous goal priorities. Effective goal dynamics require flexible and generalisable pursuit skills. This study aimed to develop and piloting a personalised approach to implementing goal pursuit invention in daily life.

Methods: The study involved three iterations to test and gradually improve all features of the intervention. Within the pilot, 73 participants completed a week of ecological momentary assessments before completing an intervention training session, after which participants continues to complete EMA while also receiving just-in-time intervention prompts for 3 weeks. We evaluated the feasibility and acceptability, efficacy and individual change processes by combining intensive (single case experimental design) and extensive (group level) methods.

Results: The results suggest that the digital intervention was feasible and acceptable to participants. Participants endorsed high acceptability ratings relating to both the study procedures and the intervention. Participants demonstrated significant improvements in goal pursuit.

Conclusions: A pilot just in time adaptive intervention using self-monitoring of behaviour, COM-B and mental contrasting and implementation intentions strategies to improve dynamic goal pursuit delivered via an EMI procedure was shown to be feasible and acceptable amongst a non-clinical adult sample. Future research should consider the utility of this approach as an additional component within psychological interventions to improve goal pursuit. Sustaining goal pursuit throughout interventions is central to their effectiveness and warrants further evaluation

Introduction

We can all experience difficulties in developing, pursuing and achieving our goals. This can be influenced by our internal state (e.g., mood and motivation), environmental factors (e.g. competing goals or demands) and resources (e.g. skills and opportunity). In this study we aim to improve day-to-day goal pursuit by assessing the influences on goal pursuit in the moment using ecological momentary assessment, as well as providing strategy training and prompts through ecological momentary intervention to promote strategy use

According to social cognitive theory, in the context of pursuing different goals throughout the day, individuals will navigate their goals by considering their personal goals, environmental factors, and behavioural factors and make decisions based on these factors (Bandura, 1991). This theory has been extended using control system principles to articulate the 'fluid' dynamics between processes with relevance to time varying behavioural interventions These factors will change over time, interact and dynamically influence one another. A person may have a goal to complete a work project, feeling overwhelmed they may decide to pursue a different goal, for instance, going for a walk, following which they may more able to return to the project but now need pursue another goal, child care. Individuals will compare their current state to desired goal state, and based on discrepancy be motivated to pursue their goals while balancing multiple concurrent and sometime competing demands. The application of this theory to intervention suggests a need for a "perpetually adapting" intervention (Martín et al., 2020).

We require the ability to prioritise goal pursuit in a dynamic environment, determining how much effort to allocate, and deciding when to shift our attention to other goals (Ballard et al., 2021). Managing this is a dynamic, within-person process that varies over time based on how much progress a person has made towards their goals. These goals or tasks related to goals, vary in how demanding they are, and our ability to pursue those goals will be influenced by capacity. Pursuing goals requires effort, both physical and mental, not just due to the difficulty of the task (Hendy et al., 1997) but also in maintaining a mental representation of the goal (Botvinick & Braver, 2015) and

we need to make decisions around the allocation of resources to the task (e.g. breaking down a task or abandoning it) affecting successful pursuit. Effort can be considered synonymous with motivation where measured objectively (Halahakoon et al., 2020) with motivation influenced by expectancy or certainty and value attributed to the outcome with people exerting more effort if the outcome is perceived to be more likely, important and rewarding (Neal et al., 2017). In addition, mood, particularly anhedonia, has been associated with behavioural reward processing deficits (Halahakoon et al., 2020).

Successful goal pursuit requires a number of steps: option generation, cost-benefit decision leading to option selection, initiation and pursuit (Husain & Roiser, 2017). Failure at any point can reduce the likelihood of pursuit, and there is a need to anticipate obstacles (Hofmann et al., 2012). By considering obstacles, the individual is better able to anticipate and plan for challenges that may arise as they work towards their goal (Kappes & Oettingen, 2014). The individual requires the ability to employ metacognitive strategies such as planning, self-monitoring and flexibility to overcome challenges and individuals may benefit from prompts and support to facilitate these strategies (Chen et al., 2020).

People's intentions do not always translate into action: medium-to-large changes in intentions may only lead to small-to-medium changes in behaviour (Webb & Sheeran, 2006). Most interventions focus on altering specific behaviours within specific contexts, the results are not conclusive: personalized feedback, goal setting, and self-monitoring appear promising, but are not consistently effective across behaviours and contexts (Hennessy et al., 2020). It is also not clear whether these skills generalise to other behaviours and contexts. Simple strategies or micro-interventions can provide easy access and low effort solutions to increase or maintain engagement in behaviour change (Baumel et al., 2020). These strategies may be simple but may be difficult to sustain without practice.

Ecological momentary assessment (EMA) and Ecological momentary intervention (EMI) both to the use of real-time data collection and intervention techniques to study or modify behaviour. While EMA involves collecting data from participants in their natural environment or in real-time, EMI involves providing feedback or intervention to participants in real-time, based on the data collected from EMA. These methods may

enhance ecological validity, for instance through reducing retrospective recall biases, and also afford the ability to model the temporal relationships between cognitive, affective, and behavioural processes (Shiffman et al., 2008). Interventions can be personalised, based on the momentary assessments, and delivered in anticipation of a change in the target behaviour – just in time adaptive interventions (Nahum-Shani et al., 2015). Such a method can benefit the generalisation of skill acquisition, where the just in time intervention prompts the individual allocate increased resources toward skill acquisition.

We propose an intervention described in the Methods which aims to bolster skill acquisition (i.e. effective goal pursuit) through the combination of evidence-based strategies and EMI implementation. These strategies include frequent self-monitoring, shown to improve goal attainment (Hennessy et al., 2020); mental contrasting with implementation intentions ((MCII) Oettingen, 2012), shown to produce a moderate effect on health behaviours (Cross & Sheffield, 2019) and the COM-B model (Michie et al., 2011) as a framework for goal setting.

Smart phones are an assistive technology with the capability to enable us to overcome obstacles in our daily lives. Their ubiquitous use in our daily lives and the ability for participants to use their own device makes them a useful tool for research and delivering in the moment interventions. Applications employing EMA/EMI on the user's own phone, affords researchers and clinicians the ability to personalise assessment and intervention to the individual, analyse data in real time and use question logic to respond to participants context (van Berkel et al., 2017) providing opportunities for dynamic adaptation of assessment to previous responses. There are potential drawbacks, such as the burden of completing frequent measurements during the day which may also be disruptive to participants' daily activities (Gouveia & Karapanos, 2013), which in turn can affect retention rates, and the need for additional software on the participants phone in order to collect the data. None the less, the deployment of interventions via mobile devices provides the opportunity to deliver intervention on scale as either stand alone or an adjunct intervention. EMA alone can act as a form of self-monitoring facilitating an awareness of thoughts, emotions and behaviour. From a clinical perspective the information provided via EMA can also support ecological

valid assessment and screening, experiential learning and within the context of an intervention shed light on the mechanisms of change (Kazdin, 2007).

Randomised control trials are regarded as the 'gold standard' when assessing digital interventions. An n-of-1 study design using intensive measurements can allow for more accurate and time sensitive analysis of effects at the within-person level (Deaton & Cartwright, 2018). This can complement the evaluation of efficacy and safety of individualised interventions (Kravitz et al., 2018), where it is possible to estimate intervention effects at the group and individual level. In addition, the intensive measurement of relevant goal pursuit processes can be used to model the dynamics in daily life (Epskamp et al., 2018). With the intention of developing an intervention for implementation within clinical sample, we optimised design following a research model for developing digital health interventions through iterations (Wilson et al., 2018).

The aim of this study was to develop, evaluate and implement a just-in-time adaptive intervention to improve goal pursuit. The intervention would provide training in a goal pursuit strategy, that could easily be incorporated into participants' daily lives in terms of time and effort, with the aim that in future research this intervention could be used as an adjunct to behavioural interventions (psychological or health related).

The aim was addressed by (1) developing a personalised approach to implementing a goal pursuit intervention in daily life, (2) identifying barriers and facilitators, and monitoring the implementation process of the intervention through several iterations (3) piloting the intervention to evaluate its feasibility and acceptability, efficacy and individual change processes by combining intensive (single case experimental design (SCED)) and extensive methods (see Figure 1).

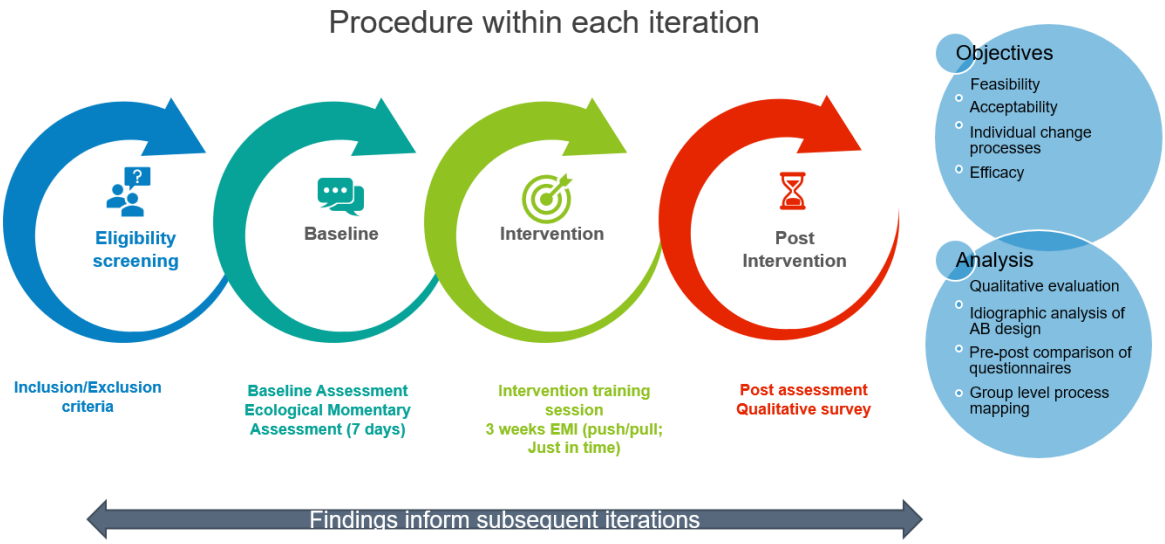

Figure 1. Procedure for optimising and piloting the ecological momentary intervention.

Methods

Study Design.

The study involved three iterations to test and gradually improve all features of the intervention (see Figure 1), to ultimately inform an RCT evaluation of the intervention (EMI vs TAU). Two iterations focused on optimisation and the third iteration was an uncontrolled pilot study. After each iteration, feedback was used to improve the design and intervention to increase the feasibility and acceptability. Questionnaires and strategy training were delivered via Qualtrics and EMA/EMI using m-path (Mestdagh et al., 2022).

Participants

Individuals were eligible if over the age of 18; able to read and understand English; were based in the UK; and had a personal mobile phone with Android or IOS operating software. Exclusion criteria: current mental health difficulties: anyone scoring above 15 on the PHQ-9 (or >1 on the suicidal ideation item) and 12 on the GAD-7, or undertaking psychotherapy at the time the study was conducted. The study was approved by the UCL Ethics Review Committee. A flowchart of the study is shown in Figure 2.

Developing the intervention

Developing the intervention relied on adapting existing evidence-based strategies for goal pursuit. The aim was to develop an intervention adaptable to an individual's goals

(whatever they might be) and generalisable to accommodate shifts and changes in goal focus during an individual's daily life. A self-guided training session was developed and supplemented with abbreviated prompts that could be delivered throughout the intervention period.

During the training period the COM-B model for behaviour change (COM-B: Michie et al., 2011) and Mental Contrasting Implementation Intentions strategy (Oettingen, 2012) were used to facilitate goal setting through identifying an important and feasible goal, and assessing barriers relating to capability, opportunity, and motivation. The person then imagines a desired future outcome and mentally contrasts it with where they are at in the present, and identifies obstacles in the present that prevent goal attainment. The person then uses the implementation intentions strategy (contingency or 'if-then' planning) to problem solve overcoming barriers. The combination aims to create a link between the obstacle and the instrumental behaviour to overcome it, and when critical situations arise, goal-directed behaviour is immediate, automatic, and effective (Oettingen, 2012).

Participants, follow an online guide (see Chapter 6 Supplementary materials) and write down their responses to every step of the exercise. First, participants identify a goal they wanted to fulfil the most in the next four weeks. To ensure adequate motivation, participants rate their motivation from one to ten and those with a motivation lower than seven are prompted to reconsider their goals. Second, participants are guided to vividly imagine the best outcome associated with fulfilling their goals. Third, obstacles that may impede their goal progress are considered and participants are instructed to think about their obstacles in terms of whether they have the knowledge and skills required (i.e., capacity) and whether the current environment was suitable for their goal pursuit (i.e., opportunity). Following that, they imagine one main obstacle and identify an action to overcome the obstacle to inform an if-then plan using the format "If … (obstacle) … then I will ... (action or thought to overcome the obstacle)". It was stressed that goals change throughout the day and they could change their goals freely during the intervention, prompting them to use MCII as a daily mental strategy for general goal pursuits. Finally, the participants review the steps and reconsider any step requiring further elaboration.

Feasibility

Within each iteration, we collected information relating to the experience of participating in the study, specifically undertaking EMA and the intervention. This included Likert scale questions assessing ease, helpfulness and intrusiveness of the EMI, perceived effectiveness and utility of undertaking the intervention, and helpfulness of the strategy training guide. Participants could also provide qualitative feedback on their goal progress and experience. Feasibility was assessed through data relating flow of participant recruitment and retention throughout the intervention. Acceptability was assessed post intervention. This feedback took the form of a questionnaire assessing how feasible and acceptable the EMA schedule was for them, whether it was easy, helpful, enjoyable, or whether it was intrusive and impeded optimal goal-pursuit (see Chapter 6 Supplementary material).

Assessment of outcomes

Primary Outcome

To test the preliminary efficacy of our intervention, goal pursuit was used as the primary outcome. This was measured using EMA and participants were also asked about goal attainment post intervention.

Secondary measures

To test whether the intervention focused on goal pursuit related processes, we assessed participants' pre-post changes on six goal-pursuit related measures.

Action Orientation: Action Control Scale (ACS-90; Diefendorff et al., 2000), the scale is divided into three subscales: Hesitation (8 items), the ability to initiate a task; Preoccupation (8 items), the ability to actively work on the task; and Volatility (6 items), the ability to stay action-oriented till completion.

Defeatist Performance Beliefs: 15 item Defeatist Performance Beliefs scale (DPB; (Cane et al., 1986) measuring overgeneralized negative thoughts in goal-striving.

Prospective Imagery: Prospective Imagery Test (PIT; Holmes et al., 2008) measuring the ability to vividly imagine positive and negative future orientated scenarios.

Intertemporal choice: 27-item Money Choice Questionnaire (MCQ; Kirby et al., 1999)to measure preferences between small immediate rewards and large delayed rewards. A general delay discounting parameter (“k”) is estimated, such that greater k values represent steeper delay discounting.

Difficulties in Emotion Regulation: 18-item Difficulties in Emotion Regulation Scale (DERS; Victor & Klonsky, 2016)) measuring participants’ emotion regulation abilities.

Reimbursement

EMA studies require commitment from participants over a long period of time (up to 6 times a day for 28 days), therefore drop-out rates can be high. Appropriate incentives can encourage compliance. Therefore, we created a two-fold incentive. All participants (including those who chose to withdraw part way through) were entered into a prize draw to win a £50 voucher. They received £20 if they reached 70% completion of EMA. Participants also received a personalised report outlining their results if they reached 70% completion at the end of the study. Participants were also incentivised through in app functions such as earning badges and data visualisation.

Ecological Momentary Assessment

Participants completed a series of questions, a number of times a day over the course of 28 days. The number changed across iteration. The questions aimed to (i) track mood and motivation, (ii) assess goal characteristics such as reward, meaning and importance, and (iii) estimate the extent to which people are acting towards a goal, can visualize it and feel self-efficacious.

Goal pursuit, *“I am acting towards a goal”*, was the primary outcome. Other questions measured mood *“How do you feel right now”* (smiley visual analogue scale), anhedonia, *“I’m enjoying what I am doing”*; motivation, *“I feel motivated”*; expectation, *“I feel hopeful”*; energy, “*I feel energised”*; and questions related to their goal, domain, *“ What I am doing is related to [recreation/relaxation, education, relationships, work or health]”;* difficulty, *“What I am doing is difficult”;* importance, *“What I am doing is important”*; reward, “*What I am doing is rewarding”*; meaning, *“What I am doing is meaningful”*; implementation, *“I know how I am going to reach this goal”*; and representation, *“I can picture myself achieving this goal”*.

Ecological Momentary Intervention

Design was guided by Risk of Bias in N-of-1 Trials (RoBiNT) Scale, to ensure the methodological quality of intervention studies using single-case methodology (see Chapter 6 Supplementary Material).

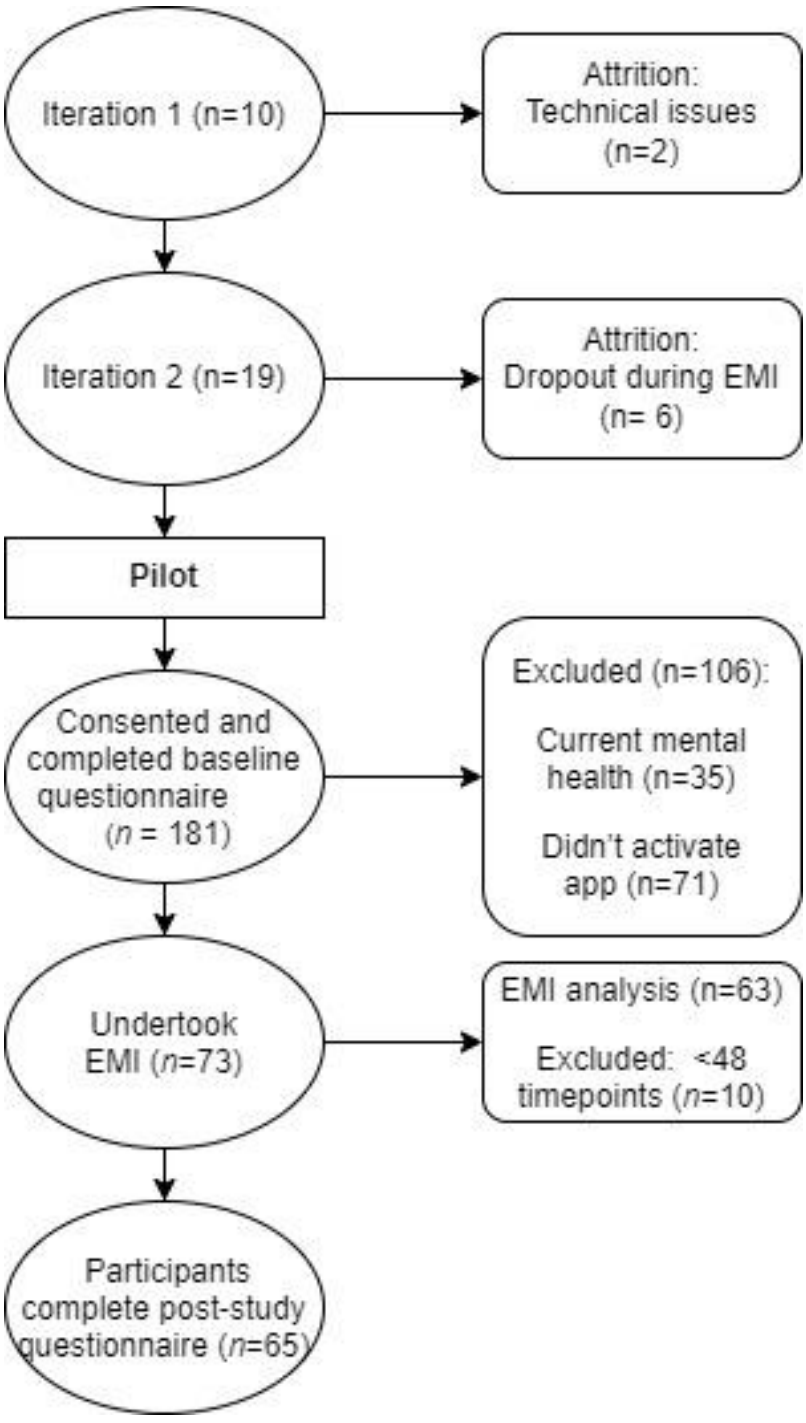

Figure 2. Flowchart of design and participant flow

Iteration 1. Push/Pull (n=10)

Following the completion of baseline measures, participants completed the self-guided COM-B/MCII training online (see Chapter 6 Supplementary material). Over the next 28 days participants answered EMA questions, at 6 time points during the day. Questionnaire times were customized for each participant, based on their waking/sleep times, and were set at regular intervals. Participants were given 60 minutes to complete the questionnaire before it expired.

The EMI component was push/pull, participants were sent a prompt notification with a summary of the MCII strategy every morning, they could also access the guide on the home screen of the app at any time. Participants could also track their responses on the EMAs and review their total numbers of responses given, their daily average response rate, and the number of EMAs completed that day on M-path.

Following the intervention, participants completed post questionnaires and a survey on the acceptability of the procedure and intervention.

All ten participants completed the study however technical issues were experienced by two participants affecting EMA response rates (63%: 73% when removing those experiencing technical issues). Overall, the participants found the experiment acceptable.

Iteration 2. Personalised prompts (n=19)

Iteration 2 followed the same protocol as Iteration 1, but we added a baseline phase with the followed adaptations. Following the completion of baseline measures, participants completed a 7-day EMA monitoring period during which they complete 6 EMA surveys per day, occurring at semi-random intervals within an individualised 12-hour waking period.

The data from the 7-day monitoring was then analysed, for purposes of identifying optimal delivery of intervention prompts. Analysis of the initial 7-day EMA data include within-person summary statistics and exploratory multiple regressions, allowing

identification of items predicting goal pursuit. The strongest predictor was then set as a target for triggering prompts to engage with MCII.

Following the completion of 7-day monitoring, participants completed the self-guided COM-B/MCII training online. For the following 21 days participants continue to complete EMA, and were sent EMI prompts via the smartphone app when a prompt had been triggered - if on an EMA their score on the target variable fell below a certain threshold (1SD below their rolling average).

In comparison to iteration 1, engagement was poor during this iteration (20%) with only 12/19 completing the study. Some participants reported that they found the number of EMAs intrusive and negatively affected their goal pursuit. Participants found the intervention prompts helpful and wished the experiment was more focused on the intervention.

From an experimenter perspective the identification of personalised targets was hampered by poor engagement (i.e. unreliable estimates).

Iteration 3 (Pilot).

Iteration 3 followed the same protocol as iteration 2, with the following adaptations: EMA surveys were reduced from 6 to 4. The initial 7 days was used for baseline measurement only (not for identifying targets). During the intervention period (the subsequent 21 days) all participants received a prompt at the start of each day, as previous respondents requested more focus on the intervention component, following which, the goal pursuit variable alone was used to trigger prompts (falling 1SD below their rolling average). If the individual indicated low goal pursuit they were not asked subsequent questions relating to the goal (domain, difficulty, importance, reward, meaning, implementation, representation), as this was considered aversive in previous iterations. The poor engagement (20%) also highlighted the need for more collaborative relationship between researcher and participant which was addressed by researchers providing feedback on compliance and helping with any issues (up to two times where dropping below 80% compliance) and built in app rewards (badges) for active participation

Data Analysis

Acceptability

To evaluate the acceptability of study procedures, participants' experiences were assessed in the post-intervention questionnaire and analysed descriptively.

EMA Analysis

Pre-processing

Participants with less than 48 timepoints were removed from EMA analysis. In addition, participants were excluded where there was a baseline trend (OLS standardized beta coefficient > +/-0.3) on the basis that differences between phases can be difficult to interpret if improvement trends are observed in phase A (i.e. due to natural improvement unrelated to the intervention).

SCED Meta- Analysis

The data obtained from the single-case experimental phase design used in this study have a hierarchical two-level structure with observations (level 1) nested within individuals (level 2). This nested structure induces dependency within the data: observations vary not only due to random sampling within a participant, but also between participants. We estimated a design-comparable, between base standardized mean differences (BC-SMD) using restricted maximum likelihood (REML) methods (Pustejovsky et al., 2014). This is a two-step process. The first step is to estimate a hierarchical linear model for the data, treating the measurements as nested within cases. The second step calculates an effect size estimate by first substituting restricted maximum likelihood estimates in place of the corresponding parameters, then applying a small-sample correction (similar to Hedges' g). We modelled baselines including both fixed and random effects for level. The treatment phase was modelled with linear trends with both fixed and random effects at level and slope. Assumptions were set around session level error structure (Autoregressive (AR1) with variance differing by phase).

In addition, we estimated the differences in scores between the two phases using Ruscio's A (Ruscio, 2008). This metric reflects the probability that a randomly selected timepoint in phase B is larger than a randomly selected timepoint in phase A

(calculated via Monte-Carlo simulation: 10000 runs: Hussey, 2019). We also estimated the unstandardised difference in scores between the median values in the two phases.

Pre-post change

Differences between baseline and post intervention assessment measures were estimated using paired-sample t-test.

Network modelling

In order to explore the theoretical conceptualisation of goal pursuit dynamics we estimated a temporal network analysis. We generated two models, the first with mood related variables (Mood, Motivation, Energy, Hope, Interest) and Goal Pursuit (as these were captured at each timepoint), and a separate model with goal specific variables (Difficulty, Meaning, Reward, Importance, Implementation and Representation) and Goal Pursuit. These were assessed separately, as participants only rated the goal specific variables if their goal pursuit was >1SD of their rolling average.

We estimated multilevel vector auto-regresssion networks using mlVAR (Epskamp et al., 2019), using the method lmer (sequential univariate multilevel estimation) with orthogonal estimation and visualized them with the package qgraph (Epskamp et al., 2012).

Both a temporal network: how the variable is predicted by all other variables (after controlling for all other temporal effects) at the previous timepoint; and a contemporaneous network: how variables are associated at the same timepoint (controlling for the influence of all other variables and temporal effects) were used within the results. The model assumes stationarity and as such, all items were detrended before including them in the network.

Results

As the purpose of the initial two iterations was to inform the optimisation of the EMI, only data from iteration 3, the pilot, are reported in this section.

Participant characteristics.

Sample characteristics are presented in Table 1. The total sample size was 73 participants (participants undertaking the EMI) with 65 completing post intervention measures. There were more female than male participants. While there was variation

in ethnicity, there were no Black participants, and the majority of the sample were students. This was a healthy sample with low to no symptom of depression, PHQ-9: M=3.71 (SD=3.73), [range: 0 -15] and anxiety, GAD-7: M=3.45 (SD=3.65), [range: 0 - 12].

		Frequency	Percent
Gender	Female	46	63.01
	Male	26	35.62
	Not defined	1	1.27
Age	M (SD) [Range]	25.05 (7.49)	[18 - 54]
Ethnicity	Asian	27	36.99
	Chinese	15	20.55
	Mixed	1	1.37
	Other	4	5.48
	White	26	35.62
Employment	Employed	25	34.25
	Student	46	63.01
	Unemployed/ Unable to work	2	2.74

Table 1. Baseline sample characteristics

Acceptability

Post intervention, the participants completed a survey on the acceptability of the intervention (see Table 2). Twenty-two (34.9%) respondents stated they achieved the goal “a little better than expected”, sixteen (25.3%) “much better than expected”, while only 2 people reported not achieving the goal or experiencing a decline in their ability to reach a desired objective. When asked to assess the general ability to effectively pursue goals, fourteen (22.2%) subjects said it became much better and thirty-three (52.3%) reported a slight improvement. Two people indicated that their overall competence in accomplishing goals has deteriorated (one participant’s goal was to get a promotion, and they didn’t get it; it wasn’t clear why the other participant thought their competence had deteriorated).

Open feedback on user-experience was largely positive. In general, participants endorsed the simplicity and interactivity of using the app and having a visualisation to help track their responses. They suggested decreasing the number of notifications during the day and making a more varied list of EMAs to avoid respondent fatigue.

Individuals stated the MCII strategy was helpful, and engaging with the app helped them become more aware of their own goal-related behaviours.

"… helped to keep reminding myself what I needed to accomplish and keep it in the forefront of my mind".

"Whenever I see a reminder from the app, I seem to be persuaded to do something to change the current situation, even though I might have answered the questions with a negative emotion."

Question	M(SD) [range]
Did you achieve the goal?	4.5(1.6) [1-7]
How would you rate the improvement in your ability to purse goals?	4.9(1.2) [1-7]
Overall, did you enjoy the experiment?	5.6(1.1) [3-7]
Did the online guide explain the strategy clearly enough?	5.7(1.2) [3-7]
Did the strategy make you more aware of your own behaviour?	5.5(1.3) [1-7]
Was the online guide sufficient for you to fully understand the strategy?	5.5(1.2) [2-7]
Was the online guide useful to help you elaborate you goals and obstacles?	5.1(1.2) [2-7]
Did answering the questions take you too much time every day?	2.4(1.5) [1-7]
Did receiving/answering the questions disrupt your goal pursuit?	2.6(1.4) [1-5]
How intrusive did you find the messages?	3.6(1.6) [1-7]
Was it easy to respond to the questions through the day?	5.3(1.6) [1-7]
Were the strategy reminders useful to help you pursue your goals?	5.1(1.6) [1-7]
Will you continue to use this strategy?	Yes: 48 (76%)
Would you recommend this strategy to a friend?	Yes: 54 (86%)

Table 2. Acceptability questions and ratings.

	Baseline		Intervention	
	Mean (SD)	Median (MAD)	Mean (SD)	Median (MAD)
Mood	6.73(0.93)	6.71(0.77)	6.73(0.94)	6.82(0.62)
Motivation	5.81(1.49)	5.82(1.64)	5.84(1.73)	6.07(1.38)
Energy	5.82(1.35)	5.78(0.97)	5.79(1.67)	5.96(1.77)
Energy	3.63(1.1)	3.76(0.91)	3.63(1.2)	3.50(1.45)
Pursuit	6.13(1.41)	5.93(1.27)	6.48(1.33)	6.55(1.35)
Expectancy	3.75(1.22)	4.04(1.16)	3.89(1.6)	3.65(1.36)

Table 3. EMA descriptives. SD= standard deviation; MAD = median absolute deviation

Primary outcome: Goal Pursuit SCED meta-analysis

We assessed change in goal pursuit between the baseline and intervention phase for 73 participants (Table 3). Throughout the experiment, participants goal pursuit domains were recreation/relaxation (28.64%), education (24.22%), relationships (16.61%), work (16.17%), and health (14.35%). There was a small effect size (BC-SMD) 0.15, 95% CIs [0.03 to 0.27]. The intervention had an immediate significant effect, increasing participants' goal pursuit by 0.495 (0.152) ($p<0.001$) but no significant additional improvement during the intervention period (intervention trend: 0.002 (0.002)). The probability of superiority (Ruscio's A) was 0.59 [0.54, 0.63]. There was a large amount of heterogeneity (I^2 =78.2%; H^2=4.6) with twenty participants demonstrating CI's > 0.5, three below (suggesting poorer performance during intervention phase) and the rest unclear (CIs crossing 0.5). The median difference between phases was 0.41 (1.29).

Secondary outcomes

Sixty-five participants completed the post intervention measures. No significant pre post change was noted on DPB t(64)=0.36, p=0.72; PIT t(64)=0.47, p=0.64; DERS t(64) = 0.47, p=0.64; MCQ t(25)=1.36, p=0.19; PHQ-9 t(61)=1.65, p=0.10; and GAD-7 t(64)=-0.24, p=0.81. GAD-7 and PHQ-9 were affected by floor effects. On the ACS subscales, Hesitation was significant t(64)=2.1121, p=0.04 but not Volatility t(61)=-0.76017, p=0.45 or Preoccupation t(61)=1.0326, p=0.31. There was no significant change between baseline and intervention phases for the other EMA variables: mood (BC-SMD 0.03, 95%CIs [-0.07 to 0.13]), motivation (BC-SMD 0.03, 95%CIs [-0.08 to 0.14]), energy (BC-SMD -0.01, 95%CIs [-0.13 to 0.11]), anhedonia (BC-SMD -0.01, 95%CIs [-0.12 to 0.10]) and expectancy (BC-SMD 0.06, 95%CIs [-0.07 to 0.19]).

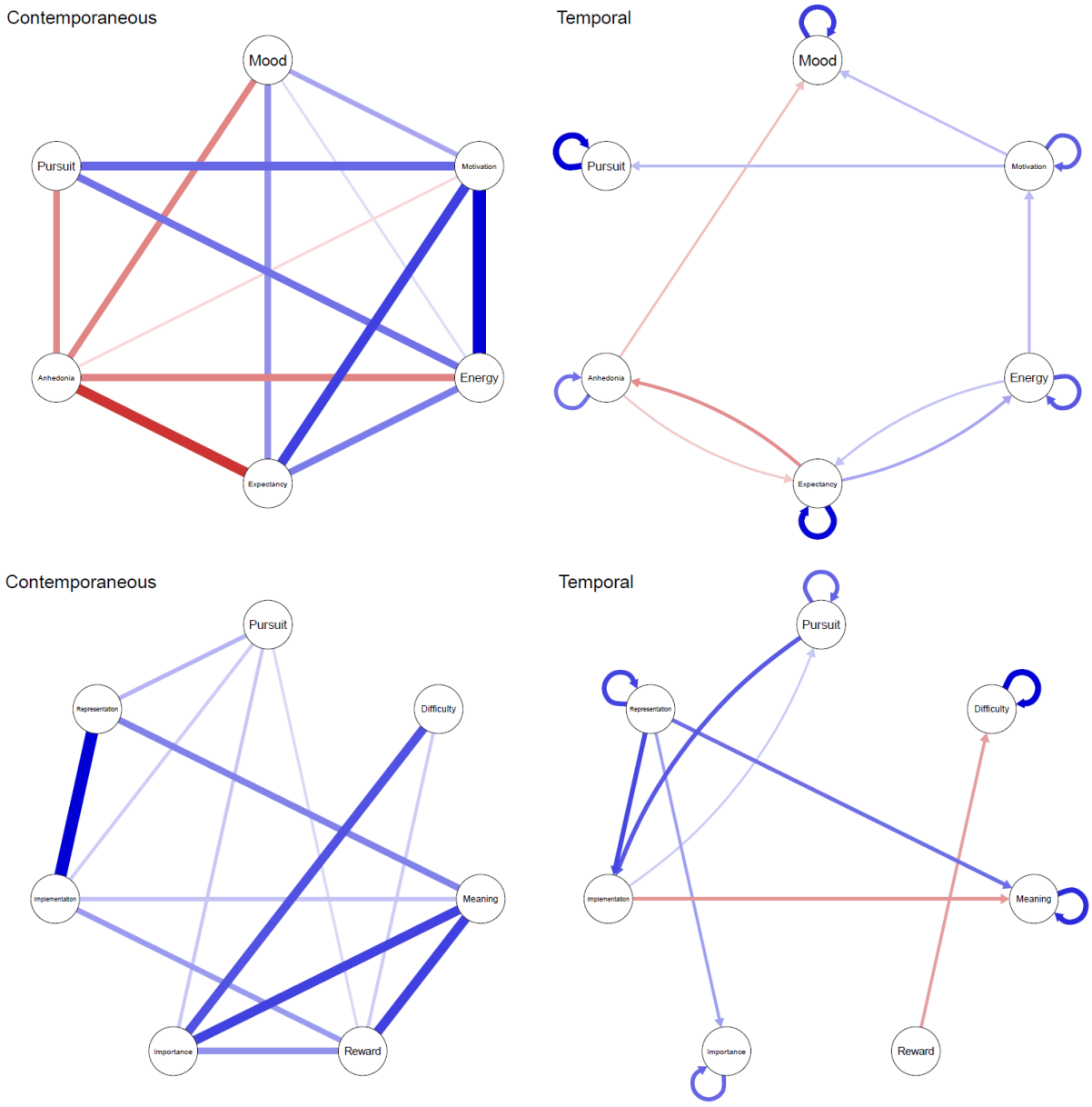

Figure 3. Network plots of the primary (top) and secondary (bottom) variables.

Contemporaneous networks

In order to elucidate dynamic processes during goal pursuit we also estimated the network of associations between variables (Figure 3). The contemporaneous network visualises the partial correlations between variables at the same timepoint (controlling for the influence of all other variable's and temporal effects). Within the primary network, mood related variables were associated as expected (mood, motivation, energy, expectation) and anhedonia, motivation and energy directly associated with goal pursuit (explained variance for goal pursuit: R^2= 0.24). While in the secondary network, goal specific variables were strongly associated, with representation,

implementation, importance and reward directly associated with goal pursuit (explained variance for goal pursuit: R^2= 0.07).

Temporal networks

The temporal network demonstrates how the variables predict each other from one timepoint to the next. Within the primary temporal network, all variables demonstrated strong autocorrelations, only motivation predicted pursuit at the next time point, with motivation predicated by energy. There was a bidirectional relationship between expectation and anhedonia, with anhedonia negatively predicting mood. Expectation and mood both influenced each other at the next timepoint.

Within the secondary network, there were strong autocorrelations for all variables except implementation and reward. Pursuit was predicted by Implementation but had a stronger influence on Implementation. Representation also predicted implementation at the next time point and also importance and meaning. While implementation negatively predicted meaning at the next timepoint. Reward negatively predicted difficulty and difficulty only predicted itself.

Discussion

The present study aimed to develop, evaluate and implement a just-in-time adaptive intervention to improve goal pursuit. Overall, the results suggest that the digital intervention was feasible and acceptable to participants. Our results show that participants endorsed high acceptability ratings relating to both the study procedures and the intervention. While there was a high level of attrition between baseline measures and those setting up the app, there was a high level of retention and completion for those who did begin the EMI. There was a significant improvement in goal pursuit (between baseline and intervention) with the majority of participants achieving their primary goal, and reporting that they would continue using the strategy, supporting its potential effectiveness in promoting positive behaviour change. There was no improvement on pre-post measures measuring processes associated with goal pursuit. The following discussion will provide a more detailed analysis of these findings, including the strengths and limitations of the study, implications for future research, and practical implications for the use of digital interventions in a clinical sample.

This study focuses on the dynamics of goal pursuit including the reality that people will switch between multiple goals. There is little in the intervention literature on dynamic within-person processes that helps individuals pursue goals over time. Similar digital intervention studies have looked at the use of employing within person dynamic data to inform prompts. Korinek et al. (2018) used dynamical systems modelling within their adaptive intervention to increasing walking behaviour in overweight adults to set an "ambitious but doable" goal for the participants. While Fallon et al. (2021) used a micro randomised control design to randomise participants to an intervention option (providing goal or social feedback relating to a physical activity goal) based on the individuals specific state. Notably, their results suggested that the effectiveness of the intervention depended on the stage of their goal pursuit (how close they were to attainment). This study contributes to the literature by using the within person variation on goal pursuit to prompt the intervention leading to improved goal pursuit over time.

The only change in associated goal pursuit measures, was on hesitation: the ability to initiate intended actions. This construct would appear to align with implementation intentions, looking to improve the ability to translate specific intentions into behaviour. This construct has been suggested to be particularly important for goal striving across a number of domains (Diefendorff et al., 1998). Given the emphasis on mental representation within the strategy, it was surprising that there was no improvement in representation. This may be due to the sensitive of the measures, where similar measures have not been associated with task performance (Clark & Maguire, 2020). The measures did not capture the vividness or intensity of imagery, which would be important phenomena underpinning scene construct (Hassabis & Maguire, 2007), we might expect to be targeted. While we assessed processes related to goal pursuit, we did not assess mechanisms of change related to all strategies. Self-monitoring, for instance, is thought to improve mental health and wellbeing by increasing emotional self-awareness (ESA) (Bakker & Rickard, 2018; Kauer et al., 2012). Future studies should endeavour to identify measures related to the mechanisms of change.

The network analysis can inform our understanding of dynamic goal pursuit highlighting a complex cyclical process involving both interdependence, influence, and self-sustaining processes. There were no changes in in associated goal pursuit measures, either on pre-post measures or EMA items. Contemporaneously,

motivation and reward were directly associated with goal pursuit while anhedonia was negatively associated. While in terms of goal specific constructs, representation, implementation, importance and reward were directly associated with goal pursuit. Given the emphasis on mental representation within the strategy, it was surprising that there was no improvement in representation, and being able to visualise the goal appeared to predict goal pursuit indirectly through implementation. Only motivation and implementation (knowing how they would achieve the goal), predicted goal pursuit at the next timepoint, with goal pursuit itself the strongest predictor of goal pursuit. This would seem to suggest that the intervention directly targets goal pursuit, rather than indirectly through an associated process (e.g. motivation). Indeed, within the sample, motivational levels were high. Pursuit also predicted implementation, suggesting that when goal pursuit is self-sustaining and boosts confidence in knowing how to achieve the goal. This is in line with GOAL (goal-oriented action linking) architecture where motivation arises from the individual's perception that their actions can impact the likelihood of achieving a goal (Ballard et al., 2021). Self-monitoring behaviour and the implementation of the strategy may aid goal reprioritisation where goal pursuit itself is a driver of further goal pursuit (within or between goals) as noted by the bidirectional relationship between pursuit and implementation.

The study had a number of strengths and also limitations. The development of the study procedure over multiple iterations facilitated adjustments including short momentary assessments, efficient reporting process, low attrition and high compliance. In addition to the app, the researchers provided consistent support through the intervention period, with reminder emails in particular appeared useful in improving compliance. For EMA technology to be successful in gathering accurate data and sustaining user interest over time, it is essential to engage users effectively. This is especially important when considering the translational application to mental health where it can facilitate individuals taking a more active role in their recovery (Wichers et al., 2011).

While there is an indication of effect on goal pursuit, through the single case design we can see that it while it may bring about change for some, it was unclear for most, and not at all for others. In addition, the trend over the intervention didn't indicate an incremental benefit, however it may have been sustaining pursuit, and without prompts we may have seen a decline. Without a follow-up it's also unclear whether changes

are maintained over time without prompts. Self-report requires self-awareness and indeed we viewed the EMA as an active component enhancing awareness, but this could affect the measurement (either through meaning associated with items or change consequential to EMA) and this reactivity can interfere with causal claims (Doherty et al., 2020).

The study aimed to personalise the just in time adaptive intervention. Within the second iteration we aimed to personalise the approach by identifying predictors of goal pursuit within the baseline period. However, this approach was hampered by poor compliance. In the pilot we adopted a more conservative approach focusing solely on variation in goal pursuit, further studies may be able to improve the design by reinstating this approach. Finally, in relation to strategy training, the results from the initial iteration indicated that online self-facilitated guide was considered optimal over video, there is evidence that the mode of learning may affect the size of the effect, where facilitator led is stronger than self-facilitated (Wang et al., 2021).

Behavioural interventions that can be delivered via an app can address barriers that typically hamper engagement in interventions, and may aid in study retention. Strategies for user engagement are a key aspect of EMI design. Within the study, reducing the burden was an important consideration, through the iterations we reduced the number of assessments and also introduced branching of responses when not pursuing a goal. The number of assessments still presented an issue for some and this reduction comes at cost to the availability and validity of data, for instance non-random missing data (we had far fewer responses to model the secondary network). Passive monitoring offers a great reduction of burden but will rely on proxy measures of goal pursuit and associated psychological process and may not be as relevant for some goals as others (Trifan et al., 2019).

Further research will need to consider piloting this EMI within a clinical sample before proceeding to a larger trial. The design has been optimised so that it could easily be incorporated into an individual’s daily life in terms of time and effort with the aim that in future research this could be used as an adjunct to behavioural interventions (psychological or health related). Further considerations will need to be given to whether this should be tested as a standalone or an adjunct within an established intervention, for instance facilitating behavioural activation for depression, or with

cognitive behavioural therapy targeting the negative symptoms of psychosis. Within this study the individuals were required to possess adequate motivation to pursue the goal. There is a question whether this would be appropriate for those who lacked motivation, as experienced in depression or psychosis? It's also unclear what aspects of design may need to vary, where it's been suggested that while compliance is related to fewer prompts in non-clinical samples, within studies with clinical samples more frequent prompts led to higher compliance (Doherty et al., 2020). Factoring in severity, the intensity of the intervention may need to be modified. Equally it is uncertain whether this intervention would produce change in a clinical sample. On the one hand within this sample the presence of a ceiling effect likely reduces the sensitivity of the measure to detect differences given the participants baselines. Therefore, individuals with poorer goal pursuit have more room for improvement and may benefit more from the intervention. One the other hand, the mechanism of change within a non-clinical sample may be different to that of a clinical sample, and between different clinical samples (Barch et al., 2016). Therefore, further research will need to carefully consider the design, intensity, and appropriateness of this EMI intervention for use within different clinical samples, while also accounting for differences in the mechanism of change between non-clinical and clinical samples.

Conclusion

A pilot just in time adaptive intervention using self-monitoring of behaviour, COM-B and MCII strategies to improve dynamic goal pursuit delivered via an EMI procedure was shown to be feasible and acceptable amongst a non-clinical adult sample. Given potential feasibility, these results provide a foundation from which future research may implement more rigorous methodology to assess efficacy within clinical populations who experience goal pursuit deficits. The effect on goal pursuit was explored and showed preliminary evidence of an effect; however, this should be tested in a fully powered trial prior to drawing conclusions. Future research should consider the utility of this approach as an additional component within psychological interventions to improve goal pursuit. Sustaining goal pursuit throughout interventions is central to their effectiveness and warrants further evaluation.

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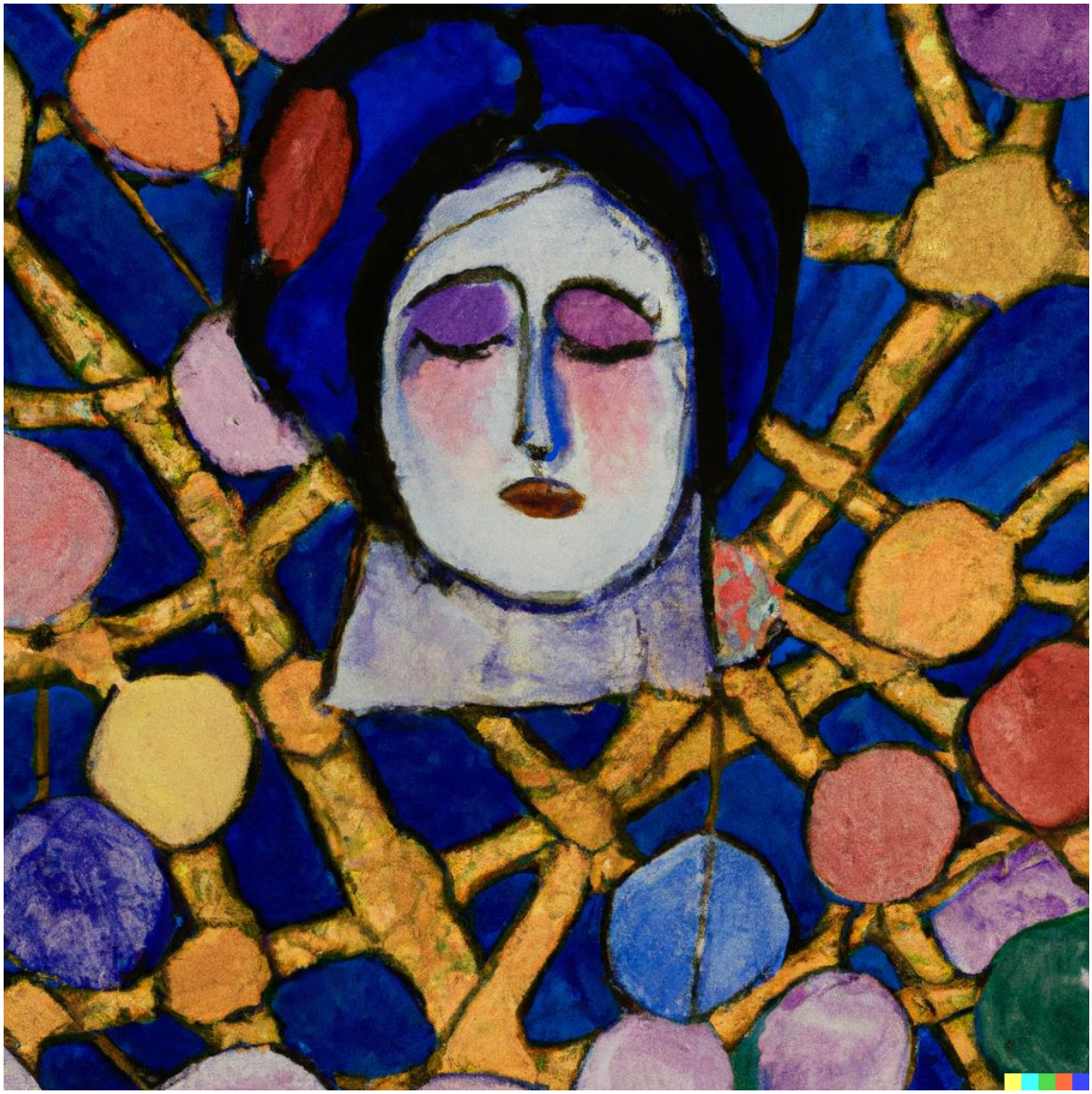
CHAPTER 7



Discussion

Preface

In this thesis, I explored the importance of considering the heterogeneity of symptoms and comorbidities in mental health conditions. Each chapter illuminates different aspects of complexity in mental health, ranging from symptom networks and comorbidities, to mechanisms of change during psychotherapy, to the impact of treatment approaches on specific symptoms. The studies suggest that transdiagnostic assessment and formulation of symptoms can inform clinical management and prognosis. They can also provide insight into the dynamic process of symptom change during psychotherapy, and the need for causal hypotheses relating to structure, mechanism, and process. Furthermore, the differential effects of CBT and CfD on symptoms demonstrate the importance of understanding specific mechanisms of change. The study on personality processes and psychopathological symptoms suggests that there are differential associations between symptoms across diagnostic groups, and conditional dependence between features can provide additional information to discriminate between and identify putative causal relations within these groups. Finally, the study on digital behavioural health interventions shows promise in improving goal pursuit and could be a valuable adjunct to traditional behavioural interventions. Overall, the studies share a common goal of better understanding the multifaceted nature of mental health, with the aim of improving diagnosis, treatment, and care for individuals experiencing mental health conditions.

In this final Chapter, I will place our findings in the perspective of other recent scientific advances within the complexity research. First, I will summarize the main findings that originated from this thesis. Next, I will postulate the main lessons learned regarding the clinical utility of the findings. Finally, I will discuss methodological challenges and recommend focus points for future research. I will end with some concluding remarks.

Summary of main findings

Chapter 2

Within the second chapter I explored the differential impact of individual symptoms on prognosis and assessing whether individual symptoms offer predictive value above sum scores in adults seeking treatment for depression in primary care. The findings of the study suggest that item-level analysis is crucial in informing the content of assessments and there may be value in considering individual items over scale scores when predicting prognosis. Although sum scores were associated with outcomes at three to four and six to eight months, item level models of outcomes post-treatment and the sum score models explained considerably more variance at nine to twelve months. Pessimism was identified as the most important predictor of future outcomes, independent of its mean, and an important bridge symptom.

The study's findings extend our understanding of the prognostic value of individual symptoms in depression treatment. Where there is strong support for pre-treatment symptom severity (as is sum score) as a prognostic marker (Bower et al., 2013; Driessen et al., 2010; Fournier et al., 2009; Weitz et al., 2015), this analysis shows that “the whole is greater than the sum of its parts", where we consider symptoms each interacting with one another as different or greater than the conceptualisation of symptoms as interchangeable and acting in isolation from one another. While specific symptoms may be a useful prognostic marker in depression, they are only part of the picture and should be considered in conjunction with other factors such as social support and life events Buckman et al., 2021; Buckman, Saunders, O’Driscoll, et al., 2021) and duration of anxiety and depression has also been shown to be an important prognostics factor (Buckman, Saunders, Cohen, et al., 2021).

Additionally, the study employed network analysis to explore the functional relations among comorbid symptoms of depression and anxiety disorders. The symptom network comprised three communities clustering into anxiety items, depressive cognitions, and depressive physical symptoms. The primary bridge symptoms between communities were sadness, pessimism, and indecision. The most central symptoms across both centrality metrics were sadness and failure/worthless. These results provide evidence that bridging symptoms may be important in the emergence

of comorbidity between anxiety disorders and depression. Notably pessimism was highlighted as a strong predictor of outcome, and acts as a bridge symptom between different clusters of symptoms. Pessimism has been identified as a key symptom that may aid clinical understanding and treatment of depression (Fatima et al., 2021; Maltby et al., 1998; McKenzie et al., 2010). While the analysis highlights the importance of symptom interactions rather than individual symptoms, it can give rise to hypothesis, for instance whether a discrete intervention targeting pessimism would alter the network structure and lead to improved outcome? This finding informed the development of the ecological momentary intervention in Chapter 6. Central symptoms as targets for intervention is largely theoretical (Borsboom & Cramer, 2013) where change in a central symptom should lead to changes in associated symptoms – a propelling effect. Central symptoms have been shown to be predictive of outcome (Rodebaugh et al., 2018), and have been used to identify possible targets (Fried et al., 2018; Spiller et al., 2020). Other papers have questioned the use of centrality metrics altogether (Bringmann et al., 2019; Dablander & Hinne, 2019). It is possible to simulate the effect of intervening on a specific symptom in the network, the results of which suggest a propelling effect – although this is limited to the Ising model (only assessing the presence of a symptom rather than severity) (Lunansky et al., 2022). If we are to use central symptoms as targets this approach does involve generating idiographic networks, and only a couple of small studies have investigated this through personalised interventions for mood disorder (Fisher et al., 2019) and eating disorder (Levinson et al., 2023) suggesting some promise for this avenue of treatment development.

The study's findings contribute to our understanding of the prognostic value of individual symptoms and the bidirectional relationship between symptoms of depression and anxiety disorders in adults seeking treatment for depression in primary care. The study's results emphasize the need for treatments to assess and address comorbidity adequately and consider the bidirectional relationship between symptoms and associations that may be mediated by another symptom. The study's findings have important clinical implications and highlight the significance of assessing individual symptoms beyond sum scores in predicting prognosis.

Chapter 3

Chapter 3 aimed to understand the mechanisms of action and processes of change during psychotherapy. This was explored through the dynamics of symptom change during psychotherapy using sessional symptom data from a large sample receiving treatment for common mental disorders. Overall, the results showed a large co-occurrence of symptom change over time, with symptoms decreasing across the board, and a strong temporal dependence between various symptoms. The network structure of associations remained the same, but mean changes were somewhat different for different symptoms, although they tended to change together. The results of these analyses were statistically reliable, generalizable to a holdout sample, and provided insights into the temporal effects and whether these associations covary at the trait or state level.

For example, the network structure of associations between symptoms remained the same, which is consistent with previous studies that have identified stable network structures across different mental health disorders (Fried et al., 2018). The finding that symptoms tended to change together is also consistent with previous research that has shown that symptoms of mental health disorders are highly interconnected and that interventions targeting one symptom may have a propelling effect on other symptoms (Lunansky et al., 2022).

The study also highlighted the importance of certain symptoms in influencing other symptoms within the network. Specifically, worry (excessiveness and controllability), along with trouble relaxing, appeared to hold the strongest influence on other symptoms, while feeling nervous, depressed mood, and anhedonia were most influenced by other symptoms. These findings are consistent with previous research that has identified worry as a transdiagnostic process and core symptom of many mental health disorders, and depressed mood and anhedonia as core symptoms of depression. The study also identified a strong association between suicidal ideation and other symptoms, which is notable given that suicidal ideation is often considered a peripheral symptom in many network studies. These findings suggest that interventions targeting symptoms such as worry and trouble relaxing may have a direct or indirect effect on suicidal ideation, which could inform treatment strategies for individuals at risk of suicide.

The study's findings were based on routine clinical data from a large sample in a naturalistic setting and not constrained to any diagnostic category or specific therapy type. While this aimed to identify common process of change, it likely overshadows differences that will exist within therapies. This was explored further in Chapter 3. The study captured between-session changes and appeared to have also captured changes that occurred at shorter intervals, which adds to the understanding of the intra-individual processes of change during psychotherapy. The use of a large and naturalistically treated patient sample compared to most prior studies may have also contributed to the emergence of certain associations, such as the strong association between suicidal ideation and other symptoms.

Overall, the study's findings contribute to the growing body of literature on the dynamics of symptom change during psychotherapy, and provide insights into the temporal effects and whether these associations covary at the trait or state level. These findings have implications for the development of more targeted treatments that consider the interconnectivity of symptoms within the network. Further research is needed to examine the mechanisms underlying these associations and to explore the potential of using ecological momentary assessments to capture more granular symptomatic change processes during psychotherapy.

Chapter 4

Chapter 4 explored whether Cognitive Behavioural Therapy (CBT) and Counselling for depression (CfD) target different symptoms and the implications for modelling choices when quantifying change during treatment. The study found that CBT and CfD for depression have differential effects on symptoms demonstrating specific mechanisms of change. CBT was uniquely associated with changes in symptoms associated with anxiety and may be better suited to those with anxiety symptoms comorbid to their depression. The study also found that when assessing change, the baseline should be the first therapy session, not the pre-treatment assessment with residual change scores preferred over difference score methods.

The results of this study provide novel insights into how CBT and CfD may work in the treatment of the symptoms of depression and anxiety. Specifically, the study found that CBT may work by directly affecting excessive worry, trouble relaxing, and apprehensive expectation, while CfD may work by affecting thoughts of being a failure.

These findings are consistent with the theoretical underpinnings of these therapies and highlight the importance of targeting specific symptoms in the treatment of depression. The study also found differences in the impact of the two therapies on symptom-to-symptom interactions. CfD had a stronger influence on the associated change between feeling annoyed and apprehensive expectation than CBT, while CBT was uniquely associated with changes in symptoms associated with anxiety and suicidal ideation. These findings suggest that the two therapies may have distinct mechanisms of action and may be better suited to addressing different types of symptoms or symptom constellations. It would be worth testing if these findings replicate in a non-IAPT sample.

The study also highlights methodological considerations in assessing change in psychological therapies. Specifically, the study found that using the first therapy session as a baseline may introduce bias and that residual change scores should be preferred over difference score methods. These findings have important implications for the design and interpretation of observational studies and clinical trials in psychological therapy.

Overall, the results of this study are consistent with previously published knowledge about the mechanisms of action of CBT and CfD in the treatment of depression. The study provides novel insights into how these therapies may work and highlights important methodological considerations in assessing change in psychological therapies. These findings have important implications for the development and refinement of psychological therapies and for improving the outcomes of patients being treated for depression.

Chapter 5

Chapter 5 investigated whether different diagnostic groups exhibit different associations between personality processes and psychopathological symptoms. The study found that there are differential associations between personality factors and psychopathology between diagnostic groups, and conditional dependence between features provides additional information to discriminate between, and identify putative causal relations within, diagnostic groups.

The results of this study are consistent with the expectations of the study and add to the existing literature on the relationship between personality and psychopathology in

BPD, mood disorder, and control groups. The study found that while the general topology of the networks was similar between groups, there were differences in the direct influence of diagnostic group on node and the associations between nodes. These differences suggest that personality and psychopathology are less distinct between BPD and mood disorder than previously thought, with emotional and cognitive regulation playing important roles in differentiating these groups. This is important because it highlights the heterogeneity of psychopathology and the need for a personalized approach to diagnosis and treatment. Understanding the unique associations between personality factors and symptoms within specific diagnostic groups can inform the development of targeted interventions that address the underlying psychological processes contributing to the symptoms. Additionally, identifying conditional dependencies between features can help clarify the causal mechanisms underlying psychopathology and guide the development of more effective treatments. Overall, this research can help improve the accuracy and effectiveness of diagnosis and treatment for individuals with mental health disorders.

These findings are consistent with previous studies that have highlighted the importance of emotional regulation in BPD, as well as the fact that this feature is more strongly associated with BPD features than interpersonal difficulties and psychopathology (Cheavens et al., 2012; Glenn & Klonsky, 2009). The study also found that mentalizing (certain) differentiated BPD from both other groups and was associated with close relationships, dominance, and affiliation. These findings add to the growing literature on the importance of mentalizing in BPD and depression(Luyten & Fonagy, 2022), suggesting that this process may be a potentially useful target for personalized treatment approaches.

The study also found that identity problems were associated with higher odds of having BPD or mood disorder compared to controls, but not each other. This finding adds to the evidence that identity problems are a key feature of BPD, but may also be relevant to other forms of psychopathology. Moreover, the study found that negative relationships differentiated BPD from other groups, with an association between negative relationships and hostility only present for BPD. Hostility may be experienced more intensely in BPD, resulting in compromised relationship quality, which is supported by momentary assessment research (Hepp et al., 2017). The findings add to the existing literature on the importance of emotional regulation and mentalizing in

BPD and mood disorder, and the relevance of identity problems and negative relationships to psychopathology more broadly.

These results contribute to the argument for transdiagnostic assessment and personalized treatment approaches that incorporate personality features may be useful in the management of individuals with BPD and mood disorders. However, it is important to recognize the study's limitations, including the cross-sectional design and the potential for unmeasured confounding variables.

Chapter 6

Chapter 6 aimed to determine whether a digital behavioural health intervention could improve goal pursuit in individuals. A pilot just in time adaptive intervention using self-monitoring of behaviour, COM-B and MCII strategies to improve dynamic goal pursuit delivered via an EMI procedure was both feasible and acceptable. The digital intervention was shown to be effective in improving goal pursuit, with the majority of participants achieving their primary goal and reporting that they would continue using the strategy. This suggests that incorporating such interventions as an adjunct to behavioural interventions (psychological or health-related) could be a promising approach in future research.

The study indicated preliminary effectiveness in relation to goal pursuit (both through A/B analysis and self-reported goal attainment). These findings are consistent with previous studies on the use of digital interventions to improve goal pursuit (Fallon et al., 2021; Korinek et al., 2018) which also found that using within-person dynamic data to inform prompts can be effective in promoting positive behaviour change. However, the study did not find any improvement on pre-post measures measuring processes associated with goal pursuit, which was surprising given the emphasis on mental representation within the strategy. This suggests that further investigation may be needed to understand the mechanisms underlying the effectiveness of the intervention. Nevertheless, the study's strength lies in its use of a single-case design, which allowed for a detailed analysis of the within-person dynamics of goal pursuit and provided a foundation for future research to implement more rigorous methodology to assess efficacy within clinical populations.

The network analysis in this study provided insight into the complex cyclical process of goal pursuit, highlighting the interdependence, influence, and self-sustaining

processes involved. Additionally, the analysis showed that the intervention directly targets goal pursuit, rather than indirectly through associated processes, such as motivation. This finding aligns with the GOAL architecture (Ballard et al., 2021), which suggests that motivation arises from an individual's perception that their actions can impact the likelihood of achieving their goal.

Overall, the findings of this study support the use of digital interventions to improve goal pursuit and provide a foundation for future research to explore the utility of this approach as an additional intervention element within psychological interventions to improve goal pursuit. The study also highlights the importance of user engagement and reducing burden in the design of digital interventions. Further research is needed to understand the mechanisms underlying the effectiveness of the intervention and to investigate the appropriateness of this approach within different clinical populations.

Clinical Implications

These chapters are united by their focus on investigating mental health conditions from a multidimensional perspective, recognizing that diagnoses and labels do not fully capture the complexity of these conditions. Network approaches hold promise to inform personalized approaches to psychological therapy. The network approach conceptualizes mental disorders as dynamic systems consisting of symptoms that are in direct causal relationships with each other and may offer possibilities to guide and evaluate therapeutic interventions. Symptom networks can be used to develop personalized interventions through a thorough investigation of the causal mechanisms of individual-level symptom networks, which is likely to inform the generation of population-level interventions by clustering individuals with similar causal mechanisms.

The findings hold important clinical implications for the treatment of common mental health problems. They highlight the importance of assessing symptoms trans-diagnostically and further suggest the need for clinicians to consider the interrelations between individual symptoms to gain information about prognosis. Clinicians would benefit from paying more attention item-level information, for instance, Chapter 2 highlighting pessimism a critical predictor of future outcomes. Network analysis

provides insights into the functional relations among comorbid symptoms emphasizing the need for treatments to address comorbidity adequately.

Within practice, psychological formulation can be informed by clinical expertise and data driven evidence. This evidence may be nomothetic and idiographic. Psychological formulation and network approaches, share similarities in their focus on the interconnectedness of symptoms and the underlying causes of mental health issues. In psychological formulation, the clinician seeks to understand the client's history, personality, and current life circumstances to develop a comprehensive understanding of their symptoms. Similarly, symptom networks use statistical techniques to identify patterns of symptom co-occurrence. Both approaches emphasize the importance of individualized and holistic assessments to develop effective treatment plans. They are complementary approaches that aim to uncover the complex and multifaceted nature of mental health disorders. Idiographic approaches provide the individual but it is more difficult to generalise. At the same time, evidence from group-based studies do not provide information about what is generally true of people but only what is true on average (Lamiell, 1998). While people will differ in both their symptomatology and causal pathways, evidence from group-based studies can and do serve as a starting point for individualised formulation. As clinicians, we interpret client data informed by nomothetic theories and empirical evidence alongside our clinical experience (Page et al., 2008). We hold a bias, and will be trying to fit the individual within a framework. Network models, which are statistical models, are agnostic, and can provide science-informed models that we can use to test and enhance clinical formulations in our practice. For example, through assess relationships within functional analysis (Scholten et al., 2022) and integrate clinical formulation with data-driven information (Burger et al., 2022). These approaches will require a shift in clinical practice and will need to demonstrate clear utility through clear actionable insights if they are to be adopted (Fried, 2020).

The Ecological momentary intervention study highlights the opportunities for clinicians to augment interventions with EMI. The technology holds benefit to improve the effectiveness of interventions. The goal pursuit Emi would allow clinicians to track patient progress over time, while patient’s receive immediate feedback and support, maintaining progress between sessions. In order to maximize the effectiveness of EMI, clinicians must first ensure that the technology is an appropriate fit for the patient’s

needs and goals. Clinicians must also consider the patient's comfort level with using the technology, and the resources available for developing and implementing an EMI. Once the patient has agreed to use the technology, the clinician should review the patient's goals and develop a plan to address these goals with the EMI. This plan should include the frequency of prompts and measurements, as well as the type of information to be collected. It is important for clinicians to be aware of the potential benefits and risks associated with EMIs. While EMIs can be used to help achieve goals and improve patient outcomes, they can also be used to collect sensitive data that may be misused or misinterpreted. Clinicians should ensure that patient's privacy and confidentiality are maintained, and that data collected is used appropriately.

Methodological considerations

Within this thesis I am proposing the utility of network psychometry as a tool to explore the complexity of mental health presentations. This involved using a number of network approaches, the gaussian graphical model to analyse cross sectional data and 'fusing' multiple datasets to control for between study differences (Epskamp et al., 2018), a mixed graphical model to analyse different types of data cross sectionally (Haslbeck & Waldorp, 2015), community detection using exploratory graph analysis (Golino & Epskamp, 2017), unique variable analysis to identify redundant nodes within networks (Christensen et al., 2020), panel graphical vector-autoregressive model to analyse sessional data (Epskamp, 2020) extend by using confirmatory network procedures, and a multi-level vector autoregressive network model (Epskamp et al., 2019) to analyze multivariate time series data.

The findings from Chapter 2 provide some novel methodological insights. The panel gvar approach had not been undertaken in such a large sample and challenges some of the assumptions around network modelling, namely, the assumption of sparsity, while also providing evidence for both the common cause and network approach (depending on your interpretation) suggesting syntactical equivalence (Markus, 2004). This may be taken as support for criticism of the network approach which suggests they can be identical to latent variable models, but because of the large number of parameters and reliance on single items, overfit, lack parsimony and result in poorer model fit than comparative models (Krueger et al., 2010). However, the related

assumption of local independence is imposed in latent variable models. The assumption is that correlations between two variables can be suppressed if they are both caused by a third variable. This is because the third variable is the "common cause" of both variables, and its effect on both variables will mask any direct causal relationship between the two variables. Theoretically and clinically we ‘know’ this assumption is violated within psychological disorders where we can clearly establish causal chains and we can observe symptoms as dependant or related to each other in a non-linear fashion. However, we cannot fully model these processes and at this stage, network modelling does not provide the solution to modelling these complex causal relations.

Despite the myriad of approaches, the quality of data is of most importance. The studies have varied in the quantity and quality, from RCT data from six trials, to IAPT sessional data which had a vast number of participants but more restricted in measurement of symptoms (breath and scale) to a dataset with a large number of measures but a small sample, and finally an intensive measurement on a discrete number of items.

Critical Reflections

In critically reflecting on network theory in light of the findings presented in the thesis, several key considerations emerge. These aspects include the comparison of network theory with latent variable theory, the replicability of findings and the validation processes utilized in the research.

Comparison of network theory with latent variable theory. There is a question as to whether the empirical findings can be evaluated for their support of network theory over latent theory? The answer is, probably not. Caution needs to be taken when attempting to draw inferences from statistical models, when multiple equivalent models exist with the same fit to the data (Fried, 2020). A well-fitting factor model does not prove the existence of psychological constructs (Vaidyanathan et al., 2015). Similarly, a network model with good fit may not identify the optimal intervention point within a causal system, as the data could be generated under an alternative causal model like the common cause model. Network theory proposes that mental disorders arise from direct interactions between symptoms, as opposed to latent variable theory, which

postulates that symptoms are indicators of an underlying, often unobserved, latent variable, such as a mental disorder. If the empirical findings indicate that symptoms are more accurately conceptualized as interacting with one another in a complex, dynamic system rather than emanating from a single latent entity, this would bolster support for network theory. Key indicators of support for network theory would include evidence of specific, non-arbitrary interactions between symptoms, the centrality of certain symptoms within these networks, and the ability to identify symptom clusters that bridge to other mental health issues without a common underlying factor. However, this can be inferentially problematic, where, for instance, the most central symptom in a network, may also correspond to an item with highest loading in a factor model. All inferences require strong causal assumptions to be met.

Within the debate between network and latent approaches there is a need for transparency in the selection of statistical models based on research goals - whether it is to test theories or to explore data for hypothesis generation. Within the chapters of this thesis, the aim has been hypothesis generation and not to test theories, as such there are limits to the extent that the chapters can contribute to a theoretical debate. If theory exploration was the aim, this would have involved comparing and contrasting different theoretical frameworks, such as network theory and latent theory, to assess their applicability and explanatory power in explaining phenomena observed in data.

Replicability of findings across empirical chapters. The replicability of findings across the empirical chapters (Chapters 2-5) are crucial for confirming the robustness of network models. Replicability here refers to the extent to which similar empirical findings can be observed across different samples, measures, and times. Convergence across chapters would suggest that the network structures and symptom connections are not artifacts of particular samples or methods but are indicative of generalizable patterns. Methods to increase replicability such as large sample size, reliability of measures, and adequacy of statistical analysis (Asendorpf et al., 2013) were planned within each chapter. All studies use measures with high reliability, however using single items lead to measurement error. Measurement error may impair the ability to detect the true network but that this impairment is mitigated when the sample is large or when combining multiple-indicators per variable (De Ron et al., 2022). In Chapter 2, data from six RCTs is pooled, with differences between studies

factored into the analysis, with internal cross-fold validation offering an additional layer of robustness supporting the final model estimates. Chapter 3, employed routine clinical data from a large sample in a naturalistic setting and not constraining analyses to any diagnostic category or specific therapy type. The statistical model selected a conservative GGM (high specificity) and was replicated in the confirmatory holdout sample. Chapter 4, also employs a large sample, with sensitivity analyses to reduce biases in interpretation. However, a simulation study would be required to assess the robustness of a given model in various scenarios, and replication in an independent sample would be required. In chapter 5, the analysis uses a large sample size, nodes are composite scores from reliable measures, and the use of the regularization parameter with 10-fold cross-validation and specifying that estimates across neighbourhood regressions should be combined led to conservative estimation increasing the stability of the estimates. Overall, robust methods were employed to ensure the replicability of findings.

Validation processes in analysis: In addition to replication the validation processes are paramount in ensuring the credibility of the thesis' findings. Validation included pre-registration of studies, which enhances transparency and reduces bias by specifying the research plan in advance. While early chapters were more exploratory, only chapters 5 and 6 were pre-registered, given their more hypothesis driven nature. These earlier chapters could have been pre-registered with clear guidelines available for the pre-registration of secondary data. Code checking (verification of statistical scripts for accuracy) ensures that the analyses are correctly executed. Within all studies a second researcher would review the code for accuracy. While I engaged in preliminary data analysis to understand and detect potential issues with data quality, this was not verified by a second researcher. Open code, where codes for statistical analysis are made publicly available, fosters reproducibility and transparency in research. For the secondary studies, raw data were not publicly available due to licencing arrangements. Otherwise materials (e.g. code) were made publicly available via the Open Science Framework. Where raw data could not be shared, data [matrices to reproduce the models] that support the findings of each study were made available.

Generalisability to underrepresented groups: In considering the generalisability of network theory and the findings presented in the thesis to groups historically under-represented in research literature, we must acknowledge the limitations inherent in much of psychological research. Generalizability, or the extent to which the results of a study can be applied to other settings, populations, and times, is a cornerstone of robust psychological theory and practice. When it comes to groups that have been under-represented in research, the issue of generalizability takes on an additional ethical dimension, pertaining to inclusivity and the fair distribution of the benefits of research.

Network theory, offers a potentially powerful framework for understanding mental health disorders and other psychological outcomes as they manifest across various populations. The generalizability of this theory is contingent upon the diversity of the samples on which the network models are based. While the samples used aimed to represent the general population, and I clearly state the demographic composition and context of the sample in all chapters to enhance transparency regarding the generalizability of the findings, the finding will obscure results pertinent to specific subgroups who may demonstrate different network profiles. Key sociocultural, economic, and environmental factors that are unique to under-represented groups, and consideration of other variables such neurodevelopmental symptoms, could lead to different patterns of connectivity within psychological networks, and these factors may also influence the nature and strength of associations presented, as well as shedding light on the role of these factors in the processes explored.

The genesis of this thesis moving from nomothetic to idiographic measurement, moves in the direction of being able to represent these differences, but such subgroup or individual level analysis was beyond the remit of the thesis. As such, the resulting theory and models may not accurately reflect the psychosocial dynamics of under-represented groups.

To enhance generalizability, several considerations and changes are suggested: While the data from the IAPT, will reflect a wide range of patients from diverse backgrounds accessing psychological therapy, future analysis could investigate the network profiles of specific subgroups. Currently, I am exploring cultural heritage

variations in mental health symptom networks, and this could be extended to look at specific groups such as individuals with autism or long-term conditions.

In regards the methodology, some of the approaches I undertook were unable to factor in categorical data, however, it is possible through the use of mixed graphical modelling (Haslbeck & Waldorp, 2015) as used in Chapters 4 and 5. This method, would have afforded me the ability, within cross sectional analysis, to account for contextual factors that are relevant to under-represented groups. From this I would have been able to identify difference. More importantly though, is the need to build and test theories with specific populations. This iterative process could help ensure that conclusions drawn are either more universally applicable, or specific to the population of interest.

Finally, involving members of the under-represented groups, at different stages of the research process, would ensure that the research is relevant and respectful to their experiences. By addressing these areas, researchers can work towards ensuring that network theory and the corresponding findings are applicable to a wider array of populations, thereby supporting the development of a more inclusive and representative body of psychological research.

Patient and public involvement and engagement

Patient and public involvement and engagement (PPIE) refer to actively involving patients, caregivers, and members of the public in the research process to ensure that their insights and experiences are incorporated into research design, conduct, and dissemination. While my doctoral research has focused on mental health assessment, diagnosis, and interventions using secondary data and complex analysis, I have not included PPIE in my studies. In this discussion, I will elaborate on the importance of PPIE, the limitations of not incorporating it into my research, how it could have been included, and the challenges that prevented its incorporation.

Incorporating PPIE into research is crucial for ensuring that research is relevant, ethical, and useful for the end-users, such as patients, families, and communities. By

involving individuals with lived experiences of mental health issues in the research process, researchers can gain a deeper understanding of the real-world impact of their work, identify research priorities that are meaningful to stakeholders, and improve the quality and applicability of research findings.

For instance, it would have been useful to have an advisory group of people with common mental health problems, who have accessed psychological services, serving as a source of valuable advice and accountability. I could have hosted workshops and online discussions for collaborative input on our project's process. This could have further included co-researcher opportunities for individuals from the advisory panel in the latter stages of the study.

At the project design stage, the advisory group could have reviewed and provided input on the scope and design of the studies, especially advising on measurement, and end user priorities. For the intervention study it would have been useful to have their input on data collection, designing and reviewing data collection methods and tools, ensuring they are acceptable and minimize drop-outs. Most importantly, across all the studies, PPIE feedback on the analysis phase would have been extremely helpful. The PPIE group could have helped me to contextualize preliminary findings, thus enhancing the interpretation of results, particularly when considering the clinical application of the findings.

In the final reporting and dissemination phase, these individuals could have actively contributed to co-authoring publications, ensuring sensitivity and accessibility of language and terminology. I produced a blog on some of the research (O’Driscoll, 2023), and this group could also have co-developed this output.

One of the limitations of not including PPIE in my doctoral research is the potential lack of relevance and applicability of my findings to the target population. Without the input of individuals with lived experiences of mental health issues, there is a risk that the research questions, methods, and outcomes may not align with the needs and priorities of those directly affected by mental health conditions. As a result, the effectiveness and real-world impact of the research may be limited.

There were several challenges that prevented me incorporating PPIE into my doctoral research. Primarily, the limited resources such as time and funding to effectively engage with patients and the public, but also a lack of training on how to

effectively incorporate PPIE into my research practices. This is something I endeavour to address in future projects.

Future Research Directions

Each chapter aimed to build on the previous and address areas of limitation. However, there are still a range of future research directions.

Future research could examine the central structures within the network, formulate hypotheses and test them on an independent sample. For instance, whether bridge edges belonging to pessimism, sadness and indecisiveness re-emerge in an independent sample or whether a discrete intervention targeting pessimism would alter the network structure and lead to improved outcomes. Exploring the prognostic value of networks on deterioration of symptoms which would extend utility of network analysis, although the benefits of such an approach currently appear limited (Buckman et al., 2020). Finally, improved symptom measurement, broader coverage and scale, may improve prediction of changes over time. Research could use more frequent measurement approaches, such as ecological momentary assessments (EMA), to capture changes in symptom dynamics during psychotherapy at shorter intervals. Separate dynamic networks of those whose symptoms remit versus those whose symptoms persist and at the idiographic level to identify state transitions that could have a deterministic effect on treatment outcome.

Within all the studies there may be unmeasured variables that confound results. Identification of nodes should be theory based, but the inclusion of important time variant and time invariant variables could lend network analytics at the population level to stratification approaches to treatment. If these methods aim to elucidate causal patterns this will require modelling a combination of factors, including genetic predisposition, environmental factors, and life experiences. Multilayer networks (network of networks) integrating neural, behavioural, and symptomatic systems would allow us to consider these dynamics across systems (Blanken et al., 2021; Simpson-Kent et al., 2021).

Dynamic processes of change are complex and the temporal relationship in respect of each treatment is unknown and would be worth exploring in future research. This may include replication or investigation of symptom dynamics under various scenarios

which may support the robustness of the findings or shed light on differential dynamics under different condition.

The EMI study requires additional piloting in a clinical sample to determine its effectiveness as a potential adjunct to existing psychological or health-related interventions. The study's design has been optimized for easy incorporation into an individual's daily routine, but it is unclear whether this intervention would be appropriate for those who lack motivation, as often seen in depression or psychosis. Further consideration needs to be given to whether this intervention should be tested as a standalone or as an adjunct to an established intervention, such as behavioural activation for depression or cognitive behavioural therapy for targeting negative symptoms of psychosis. It's important to factor in the severity of the clinical sample, as the intensity of the intervention may need to be modified accordingly. Compliance with the intervention may also differ between clinical and non-clinical samples, with studies suggesting that more frequent prompts may lead to higher compliance in clinical samples.

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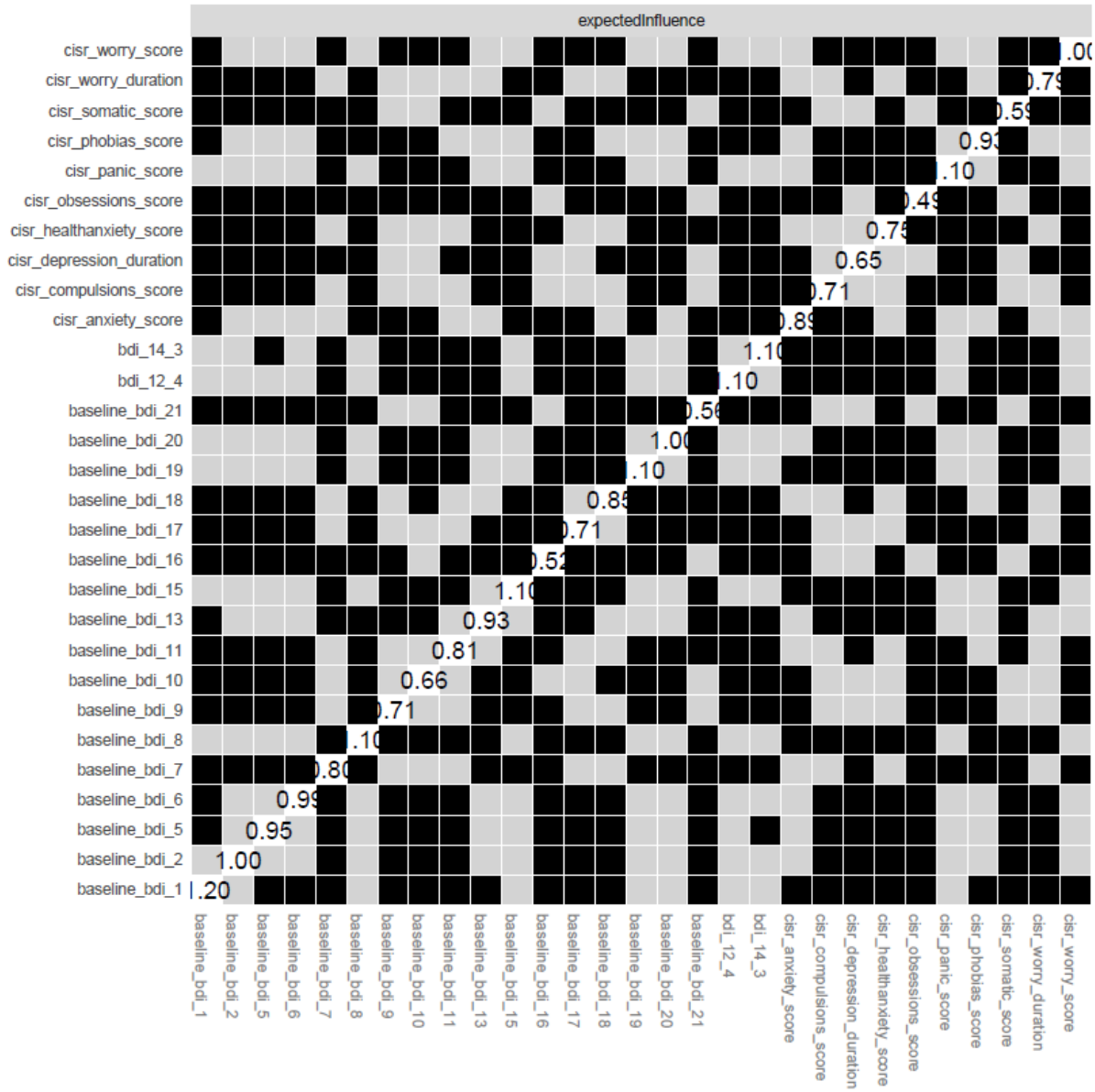
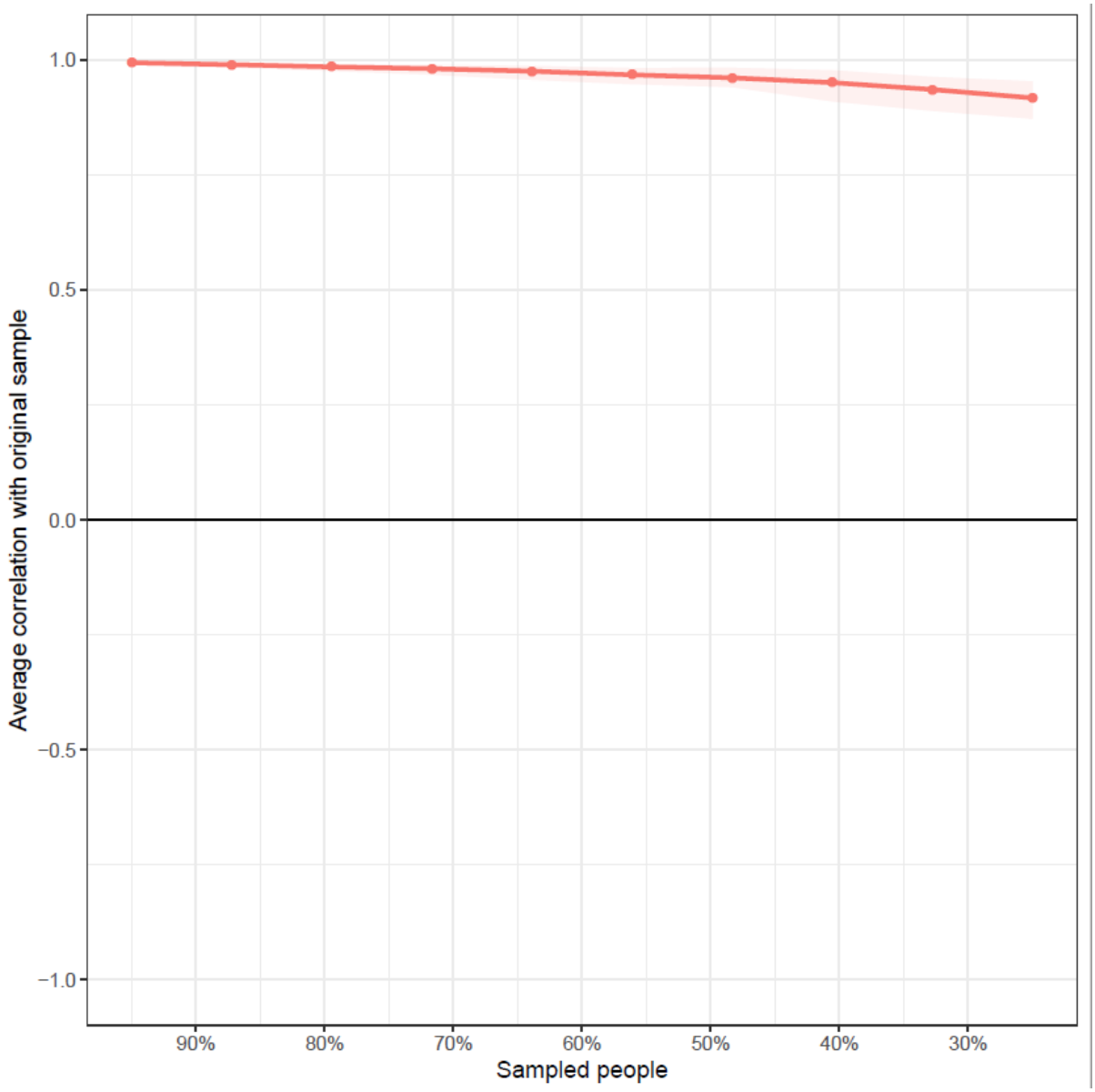
CHAPTER 2 Supplementary Materials

No	Variable	Stats / Values	Freqs (% of Valid)	Graph
1	Sadness..BDI. [integer]	Mean (sd) : 1.3 (0.8) min < med < max: 0 < 1 < 3 IQR (CV) : 1 (0.6)	0: 271 (9.5%) 1: 1865 (65.3%) 2: 427 (14.9%) 3: 295 (10.3%)	
2	Pessimism..BDI. [integer]	Mean (sd) : 1.5 (0.9) min < med < max: 0 < 1 < 3 IQR (CV) : 1 (0.6)	0: 266 (9.3%) 1: 1231 (43.1%) 2: 888 (31.1%) 3: 473 (16.6%)	
3	Guilt..BDI. [integer]	Mean (sd) : 1.3 (0.9) min < med < max: 0 < 1 < 3 IQR (CV) : 1 (0.7)	0: 440 (15.4%) 1: 1354 (47.4%) 2: 733 (25.7%) 3: 331 (11.6%)	
4	Punishment..BDI. [integer]	Mean (sd) : 1.1 (1.2) min < med < max: 0 < 1 < 3 IQR (CV) : 2 (1)	0: 1204 (42.1%) 1: 710 (24.8%) 2: 343 (12.0%) 3: 601 (21.0%)	
5	Self.dislike..BDI. [integer]	Mean (sd) : 1.7 (0.9) min < med < max: 0 < 2 < 3 IQR (CV) : 1 (0.5)	0: 197 (6.9%) 1: 1185 (41.5%) 2: 855 (29.9%) 3: 621 (21.7%)	
6	Self.critism..BDI. [integer]	Mean (sd) : 1.6 (0.9) min < med < max: 0 < 2 < 3 IQR (CV) : 1 (0.6)	0: 312 (10.9%) 1: 1003 (35.1%) 2: 969 (33.9%) 3: 574 (20.1%)	
7	Suicidal.thoughts..BDI. [integer]	Mean (sd) : 0.7 (0.7) min < med < max: 0 < 1 < 3 IQR (CV) : 1 (1.1)	0: 1312 (45.9%) 1: 1279 (44.8%) 2: 169 (5.9%) 3: 98 (3.4%)	
8	Crying..BDI. [integer]	Mean (sd) : 1.5 (1) min < med < max: 0 < 1 < 3 IQR (CV) : 1 (0.7)	0: 470 (16.4%) 1: 1031 (36.1%) 2: 743 (26.0%) 3: 614 (21.5%)	
9	Agitation..BDI. [integer]	Mean (sd) : 1.2 (0.8) min < med < max: 0 < 1 < 3 IQR (CV) : 1 (0.7)	0: 503 (17.6%) 1: 1550 (54.2%) 2: 536 (18.8%) 3: 269 (9.4%)	
10	Indecisiveness..BDI. [integer]	Mean (sd) : 1.6 (1) min < med < max: 0 < 2 < 3 IQR (CV) : 1 (0.6)	0: 387 (13.5%) 1: 1027 (35.9%) 2: 880 (30.8%) 3: 564 (19.7%)	
11	Loss.of.energy..BDI. [integer]	Mean (sd) : 1.6 (0.8) min < med < max: 0 < 2 < 3 IQR (CV) : 1 (0.5)	0: 90 (3.1%) 1: 1222 (42.8%) 2: 1156 (40.5%) 3: 390 (13.6%)	
12	Sleep.pattern..BDI. [integer]	Mean (sd) : 1.7 (0.9) min < med < max: 0 < 2 < 3 IQR (CV) : 1 (0.5)	0: 265 (9.3%) 1: 891 (31.2%) 2: 1015 (35.5%) 3: 687 (24.0%)	
13	Irritability..BDI. [integer]	Mean (sd) : 1.3 (0.9) min < med < max: 0 < 1 < 3 IQR (CV) : 1 (0.7)	0: 586 (20.5%) 1: 1174 (41.1%) 2: 781 (27.3%) 3: 317 (11.1%)	
14	Appetite..BDI. [integer]	Mean (sd) : 1.4 (1) min < med < max: 0 < 1 < 3 IQR (CV) : 1 (0.7)	0: 627 (21.9%) 1: 1058 (37.0%) 2: 691 (24.2%) 3: 482 (16.9%)	
15	Concentration..BDI. [integer]	Mean (sd) : 1.5 (0.7) min < med < max: 0 < 2 < 3 IQR (CV) : 1 (0.5)	0: 194 (6.8%) 1: 1165 (40.8%) 2: 1294 (45.3%) 3: 205 (7.2%)	
16	Fatigue..BDI. [integer]	Mean (sd) : 1.6 (0.8) min < med < max: 0 < 2 < 3 IQR (CV) : 1 (0.5)	0: 160 (5.6%) 1: 1250 (43.7%) 2: 1011 (35.4%) 3: 437 (15.3%)	
17	Libido...BDI. [integer]	Mean (sd) : 1.5 (1.1) min < med < max: -1 < 2 < 3 IQR (CV) : 3 (0.7)	-1: 1 (0.0%) 0: 718 (25.1%) 1: 671 (23.5%) 2: 673 (23.5%) 3: 795 (27.8%)	
18	Generalised.Anxiety..cisr. [integer]	Mean (sd) : 2.2 (1.5) min < med < max: 0 < 2 < 4 IQR (CV) : 3 (0.7)	0: 577 (20.2%) 1: 406 (14.2%) 2: 470 (16.4%) 3: 602 (21.1%) 4: 803 (28.1%)	
19	Compulsions..cisr. [integer]	Mean (sd) : 0.8 (1.2) min < med < max: 0 < 0 < 4 IQR (CV) : 2 (1.6)	0: 1868 (65.4%) 1: 241 (8.4%) 2: 387 (13.5%) 3: 220 (7.7%) 4: 142 (5.0%)	
20	Health.anxiety..cisr. [integer]	Mean (sd) : 1.1 (1.2) min < med < max: 0 < 1 < 4 IQR (CV) : 2 (1.2)	0: 1394 (48.8%) 1: 506 (17.7%) 2: 476 (16.7%) 3: 359 (12.6%) 4: 123 (4.3%)	
21	Obsessions..cisr. [integer]	Mean (sd) : 1.4 (1.6) min < med < max: 0 < 0 < 4 IQR (CV) : 3 (1.2)	0: 1590 (55.6%) 1: 76 (2.7%) 2: 232 (8.1%) 3: 493 (17.2%) 4: 467 (16.3%)	
22	Panic..cisr. [integer]	Mean (sd) : 0.7 (1.3) min < med < max: 0 < 0 < 4 IQR (CV) : 1 (1.7)	0: 1994 (69.8%) 1: 158 (5.5%) 2: 293 (10.2%) 3: 260 (9.1%) 4: 153 (5.3%)	
23	Phobia..cisr. [integer]	Mean (sd) : 1.3 (1.3) min < med < max: 0 < 1 < 4 IQR (CV) : 2 (1)	0: 1164 (40.7%) 1: 479 (16.8%) 2: 707 (24.7%) 3: 318 (11.1%) 4: 190 (6.6%)	
24	Somatic..cisr. [integer]	Mean (sd) : 1.5 (1.4) min < med < max: 0 < 1 < 4 IQR (CV) : 3 (0.9)	0: 1071 (37.5%) 1: 438 (15.3%) 2: 504 (17.6%) 3: 532 (18.6%) 4: 313 (10.9%)	
25	Worry..cisr. [integer]	Mean (sd) : 2.5 (1.3) min < med < max: 0 < 3 < 5 IQR (CV) : 2 (0.5)	0: 289 (10.1%) 1: 387 (13.5%) 2: 522 (18.3%) 3: 872 (30.5%) 4: 787 (27.5%) 5: 1 (0.0%)	
26	Loss.of.pleasure...Interest..BDI. [integer]	Mean (sd) : 1.6 (0.7) min < med < max: 0 < 2 < 3 IQR (CV) : 1 (0.5)	0: 121 (4.2%) 1: 1285 (45.0%) 2: 1167 (40.8%) 3: 285 (10.0%)	
27	Failure...Worthlessness..BDI. [integer]	Mean (sd) : 1.6 (0.8) min < med < max: 0 < 2 < 3 IQR (CV) : 1 (0.5)	0: 286 (10.0%) 1: 975 (34.1%) 2: 1205 (42.2%) 3: 392 (13.7%)	

Item level descriptive data.

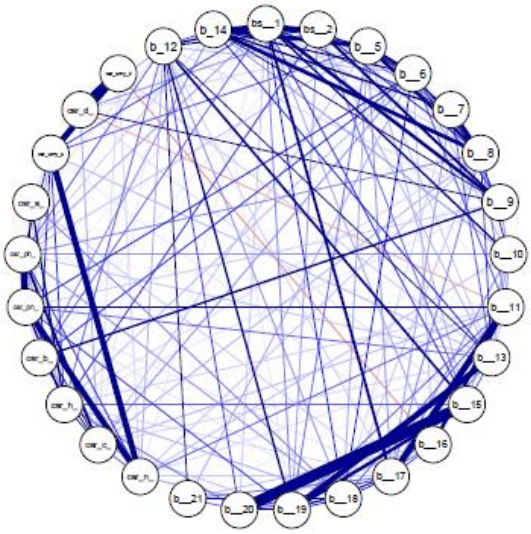


Expected influence: significant difference.

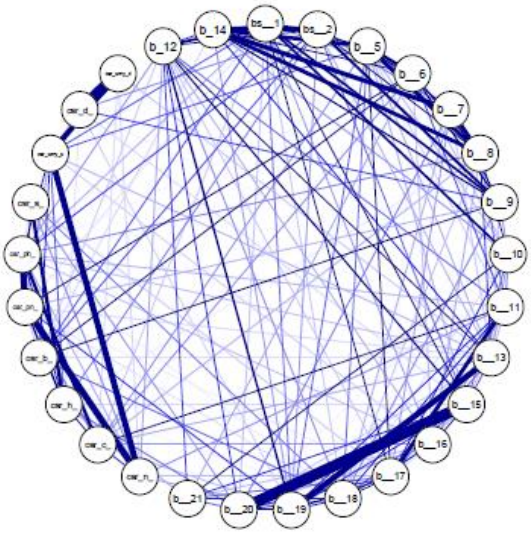


Expected influence stability.

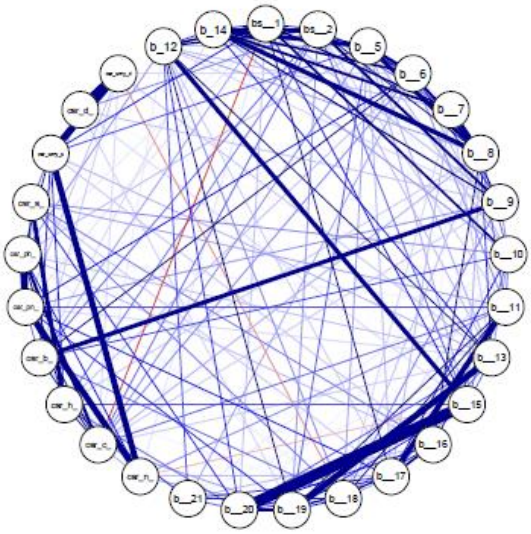
COBALT



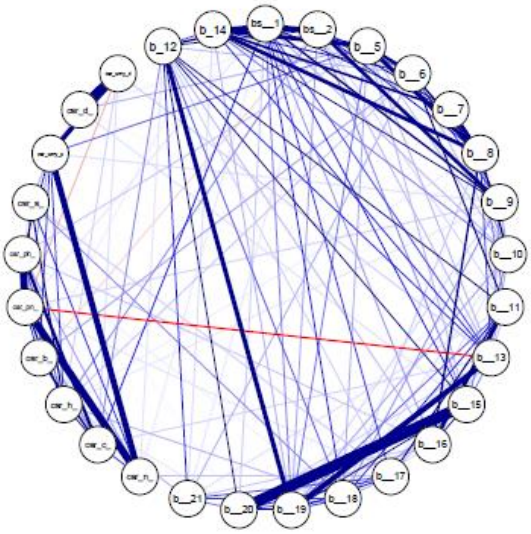
GENPOD



MIR



TREAD



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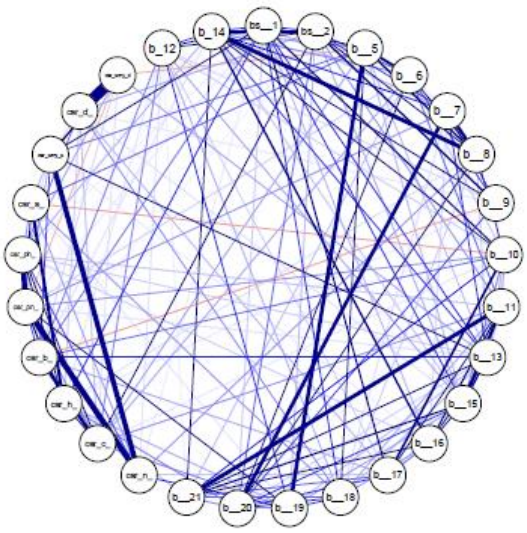
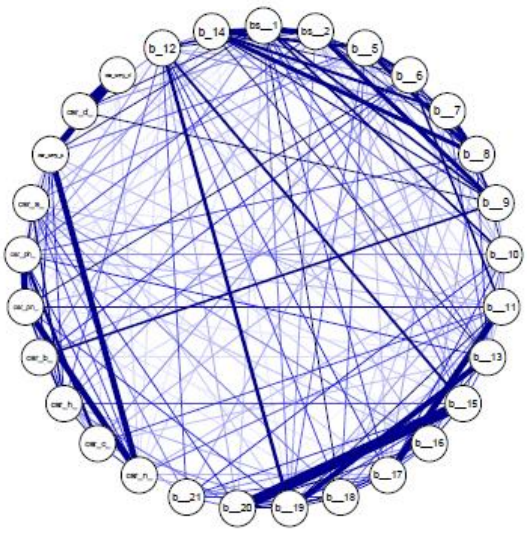
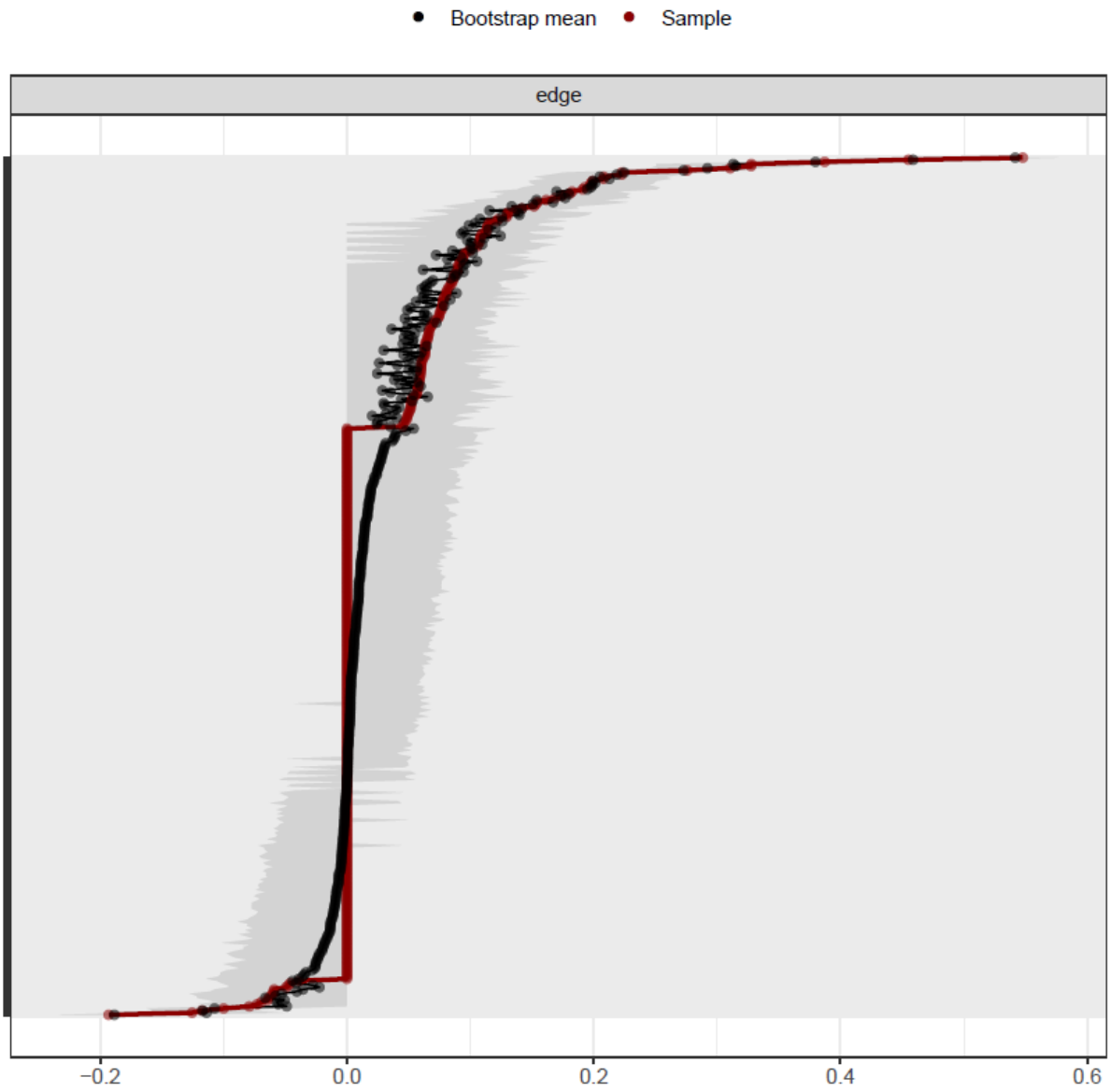


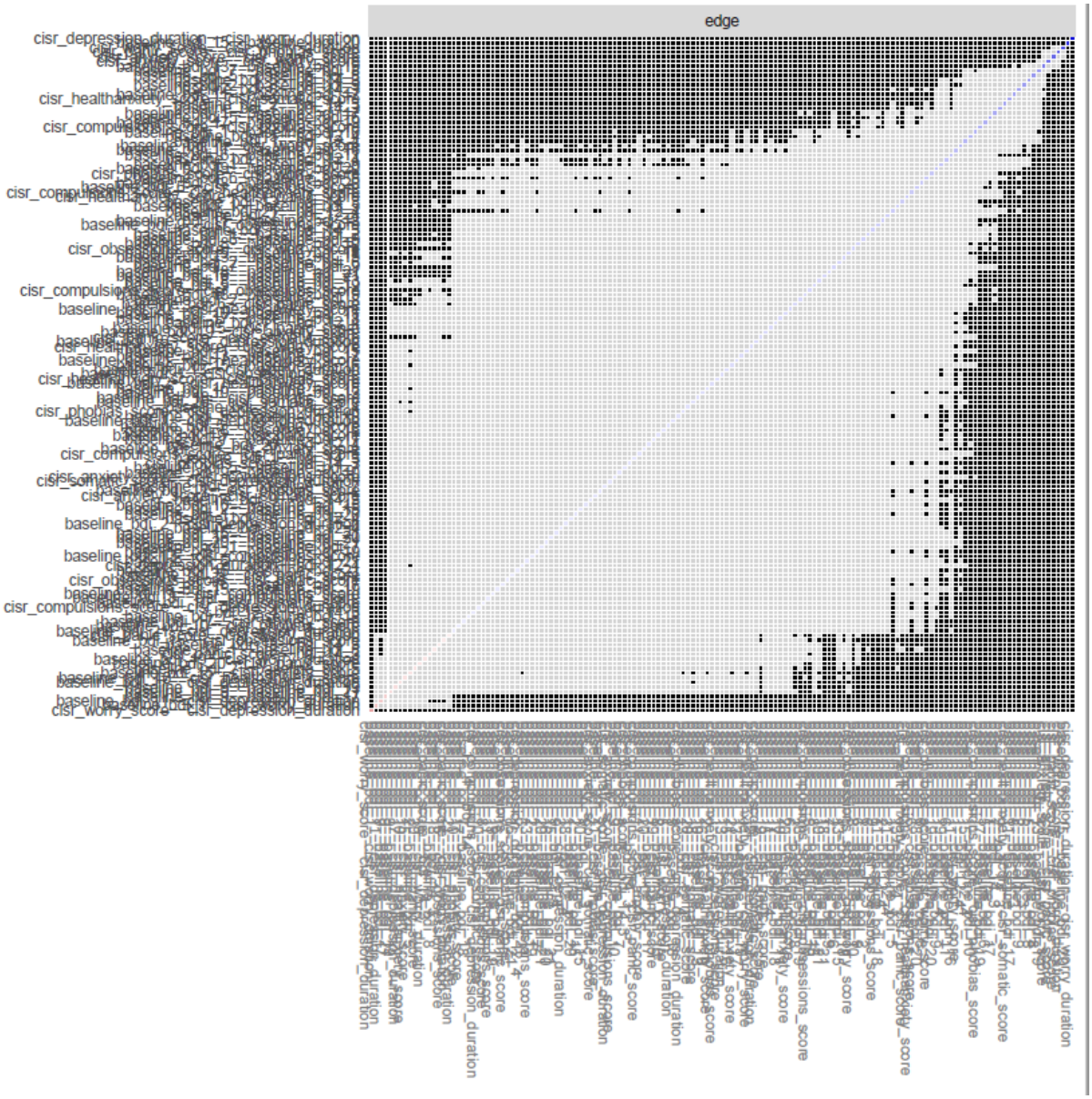
PANDA



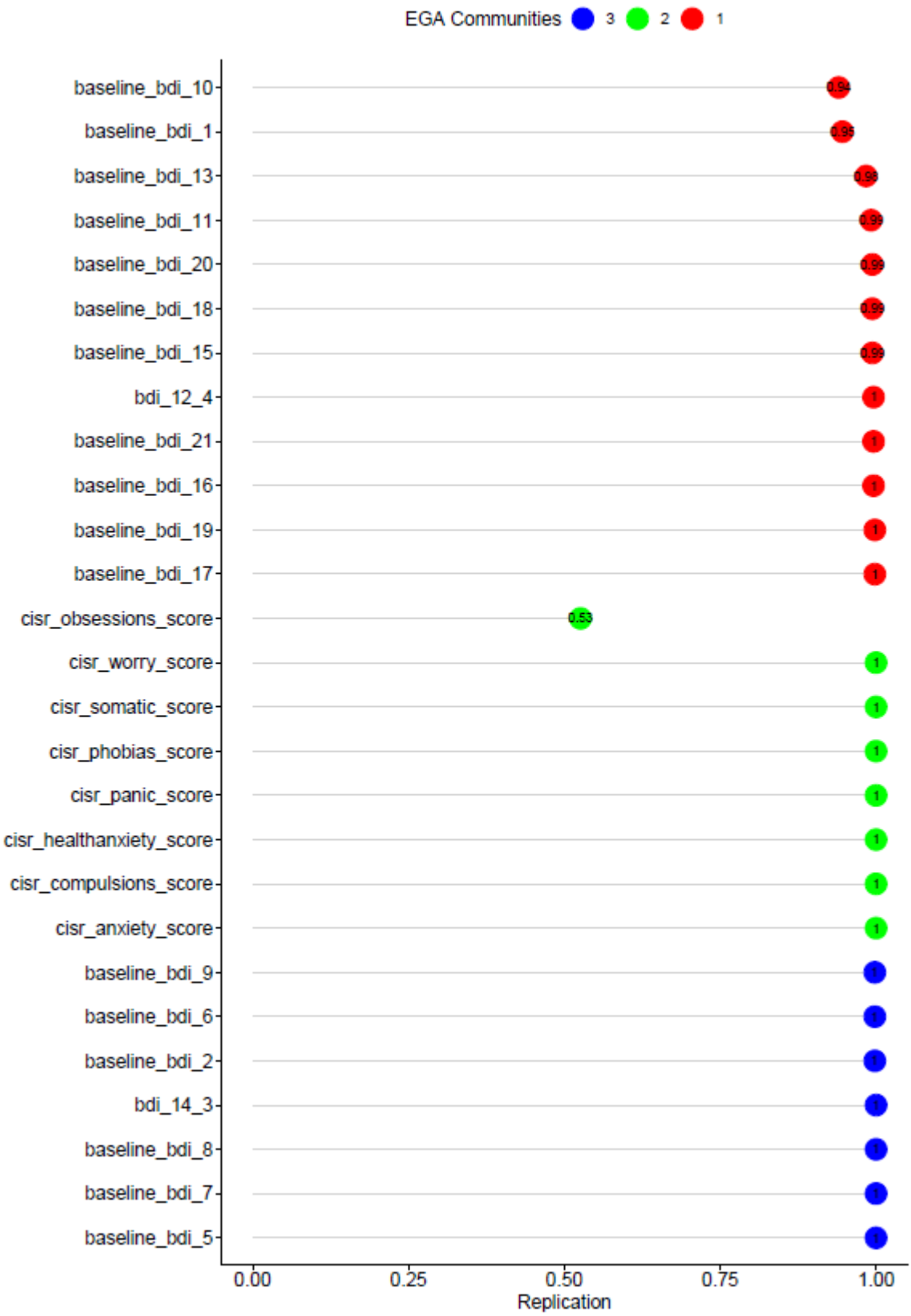
Study level networks with FGL penalty.



Edge weight confidence intervals.



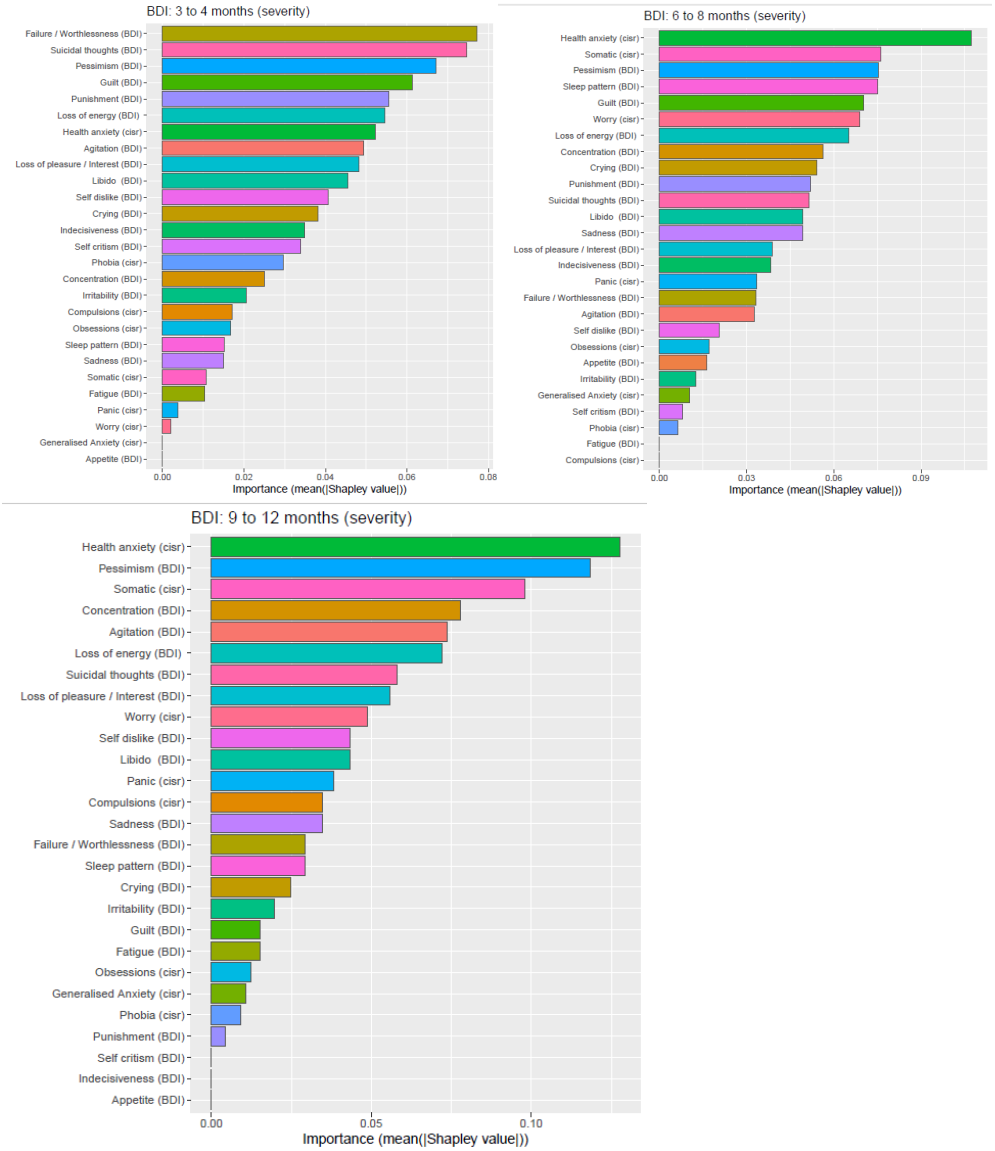
Edge weights difference test



Bootstrapped communities.

		BDI-II Score		
		RMSE	R^2	MAE
3 to 4 months N=2171	Items	0.901	0.190	0.721
	Sum score	0.899	0.191	0.718
6 to 8 months N=1286	Items	0.894	0.204	0.719
	Sum score	0.892	0.204	0.721
9 to 12 months N=1102	Items	0.898	0.198	0.731
	Sum score	0.908	0.176	0.741

Prediction modelling against BDI-II at outcome



Shapley values for variable importance are plotted: (showing the difference contribution of items to predictions) for BDI-II as outcome

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Plots may be viewed at https://osf.io/gp6dw/

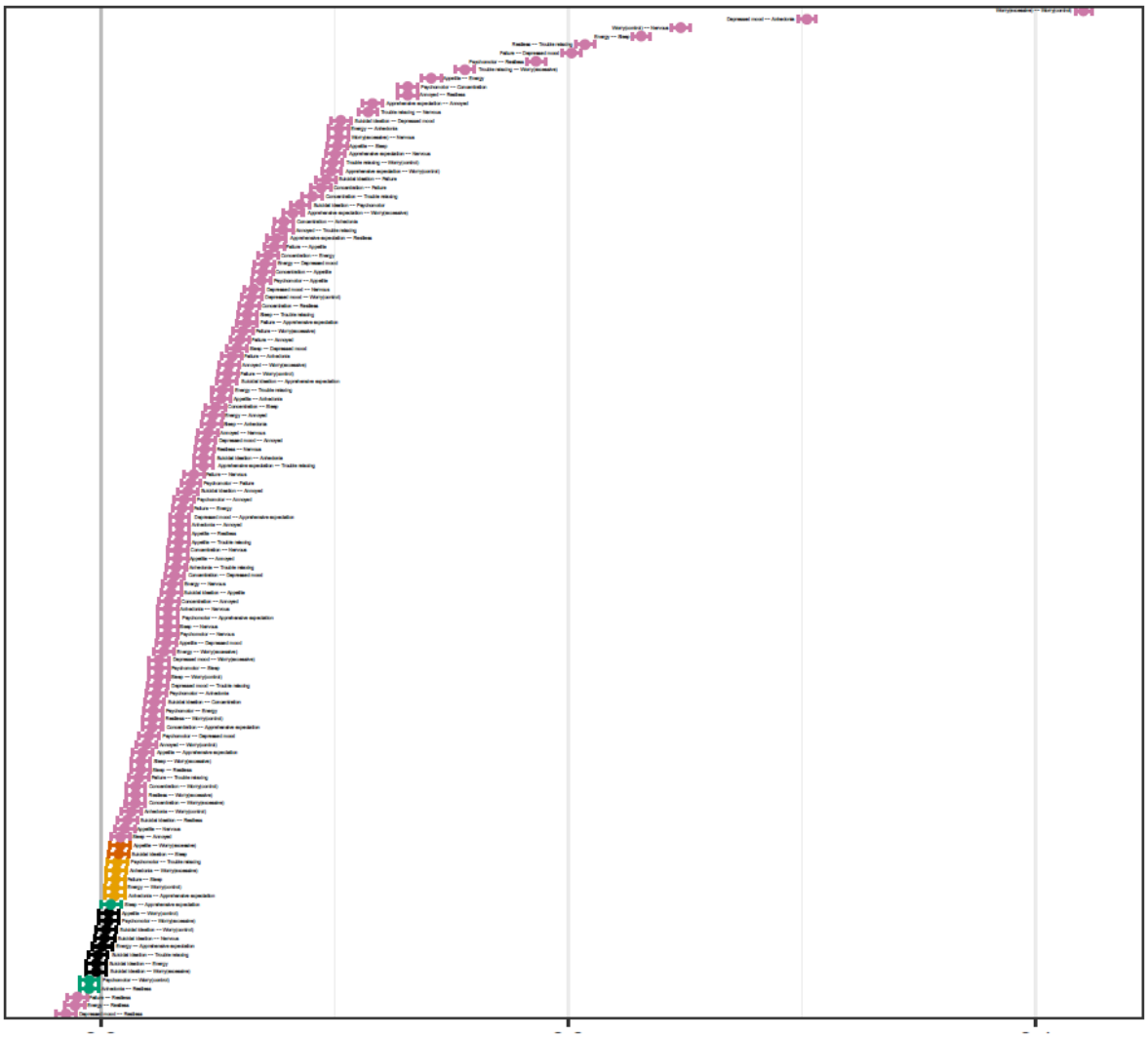

Figure 1: Confidence Intervals for contemporaneous network

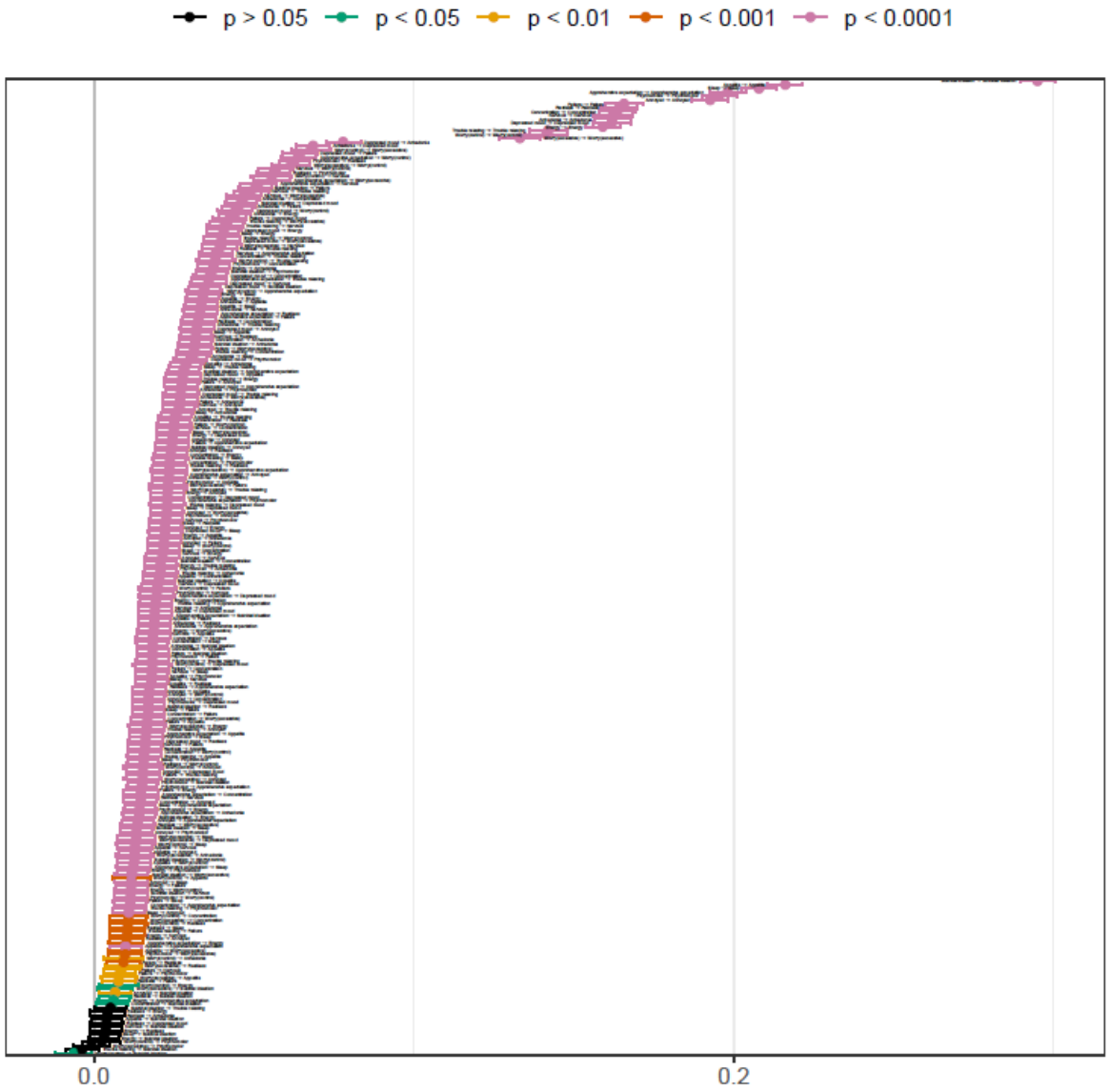

Figure 2. Confidence Intervals of estimates within temporal network.

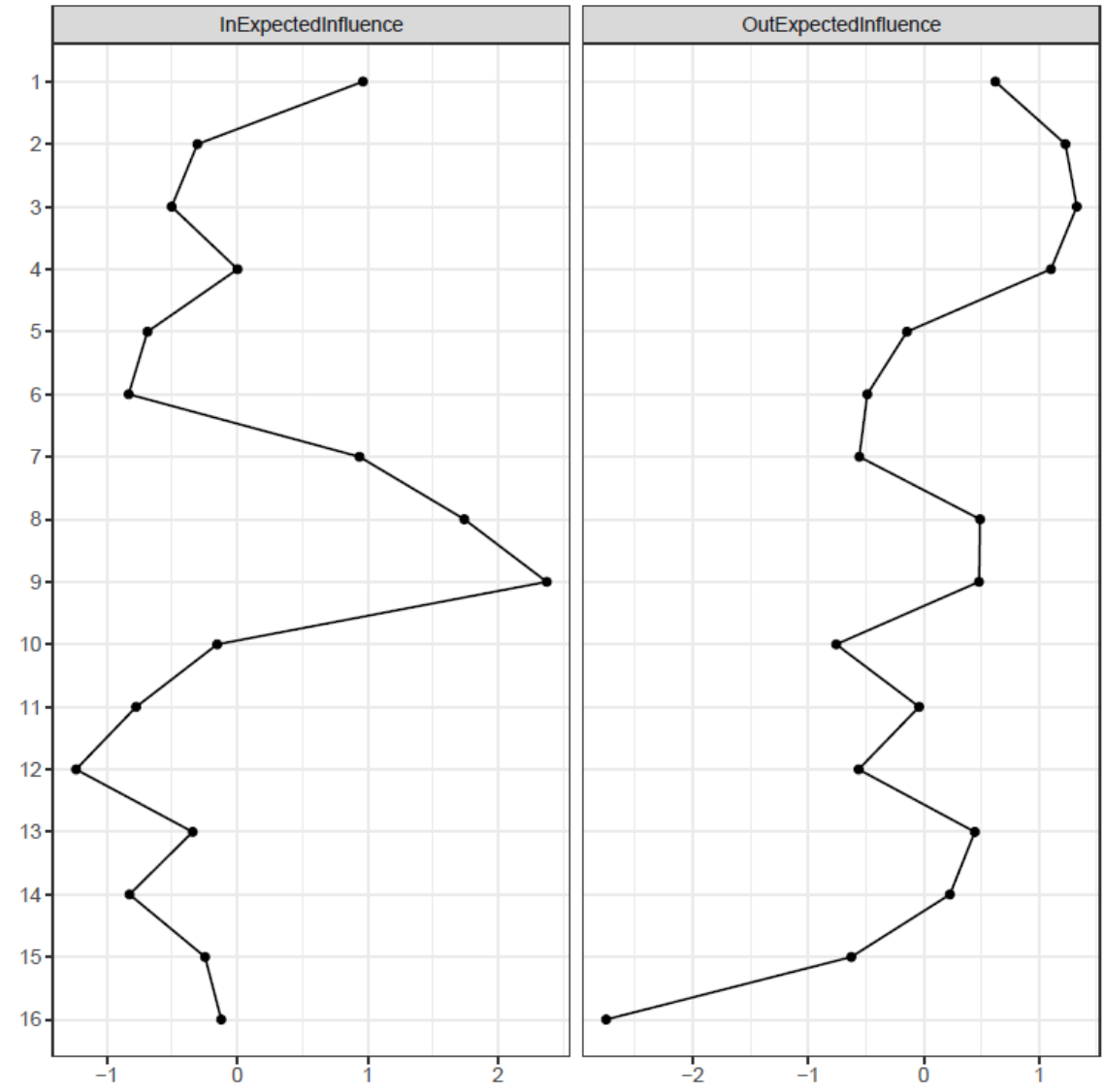

Figure 3: Centrality Estimates for temporal network

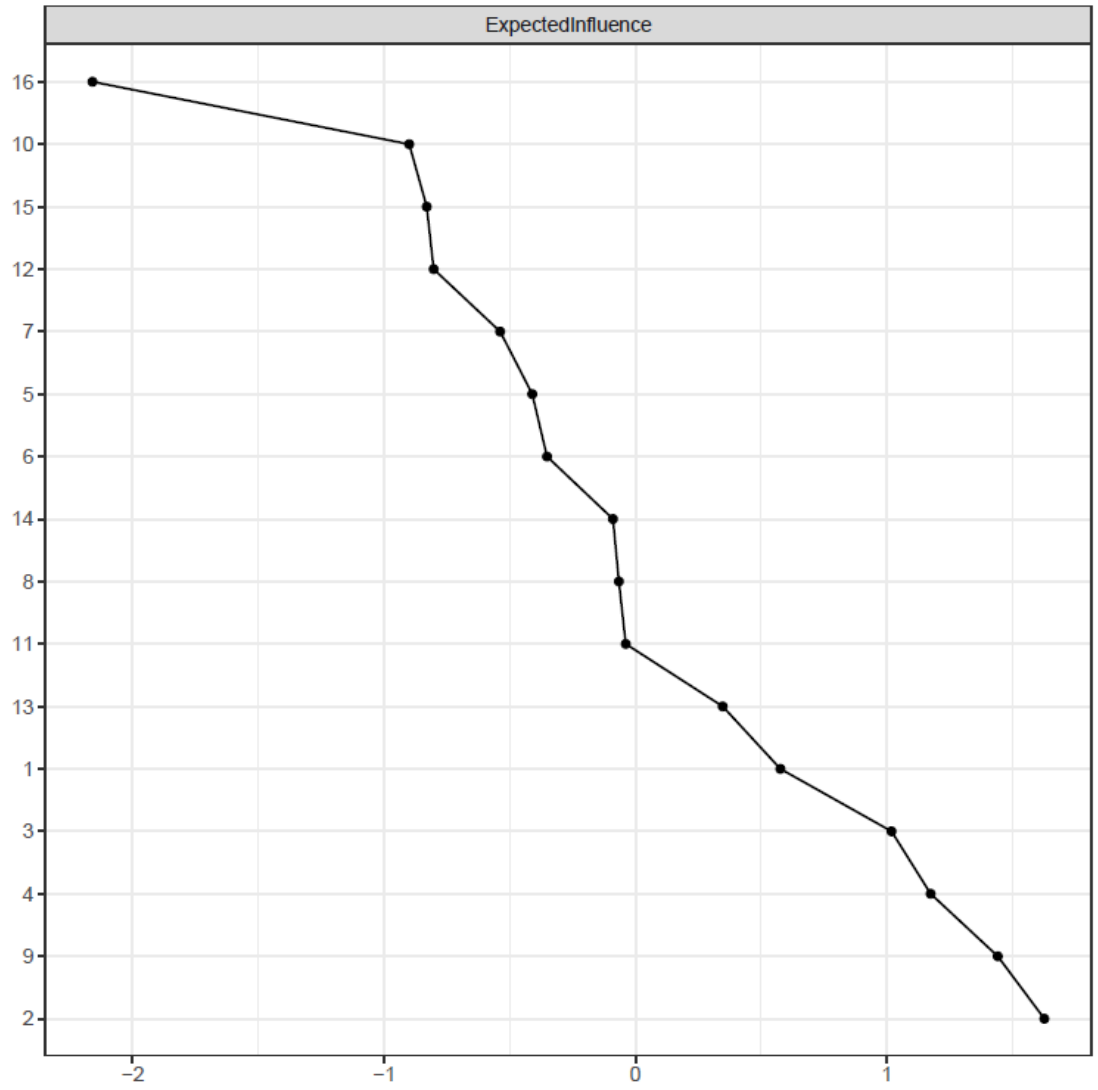

Figure 4: Centrality Estimates for contemporaneous network

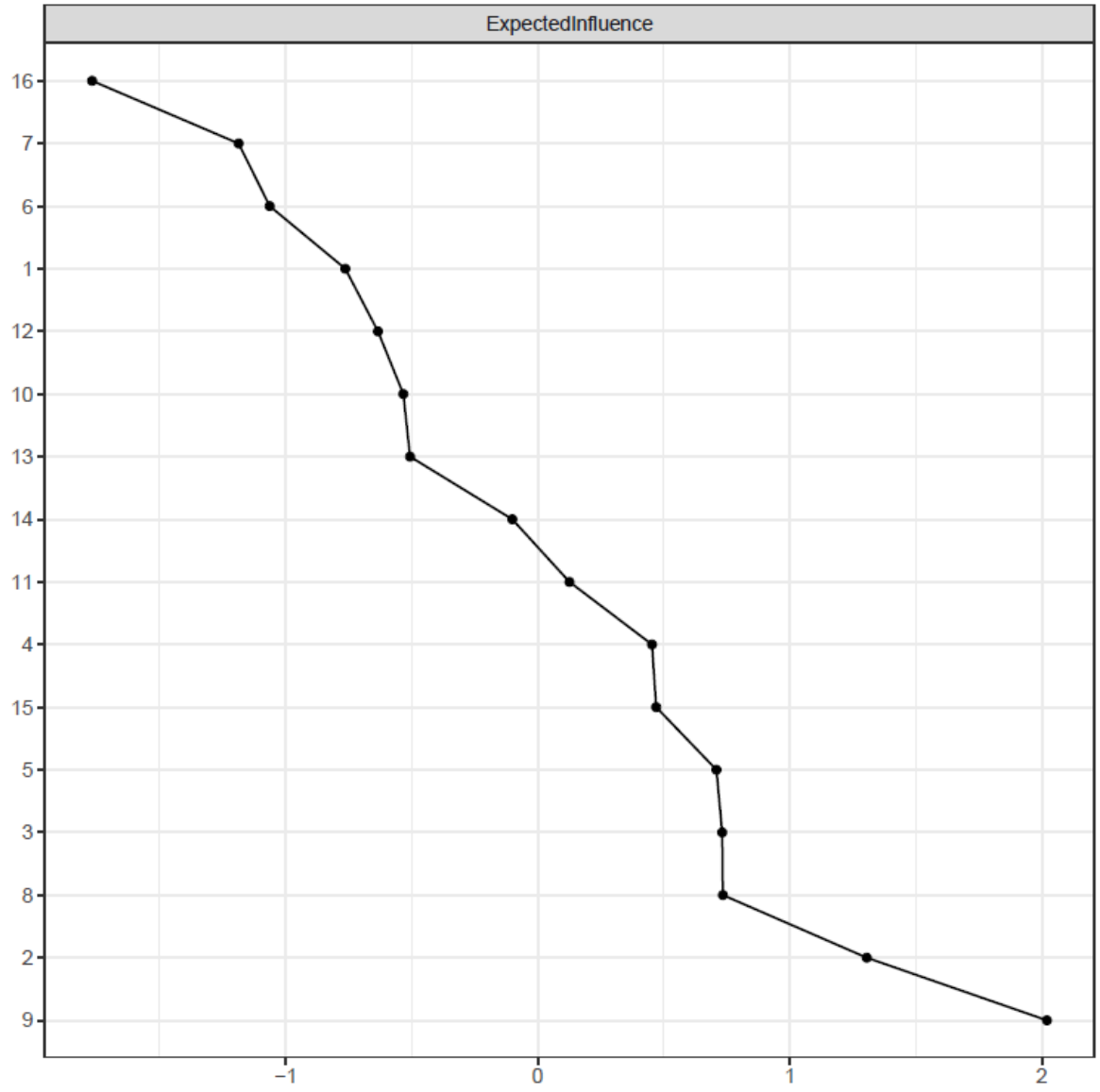

Figure 5: Centrality Estimates for between subject network

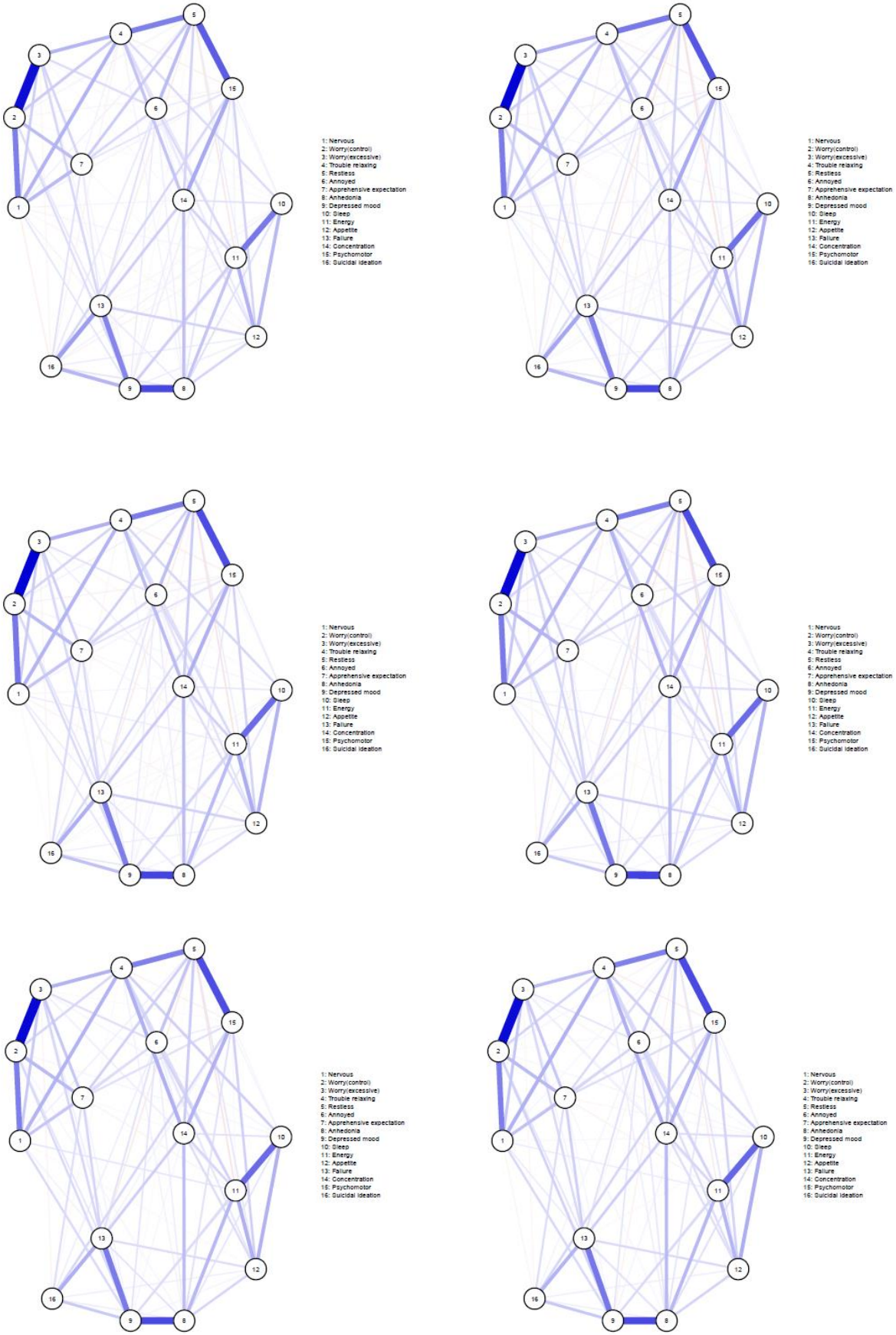

Figure 6: cross sectional networks for each time point (1 to 6).

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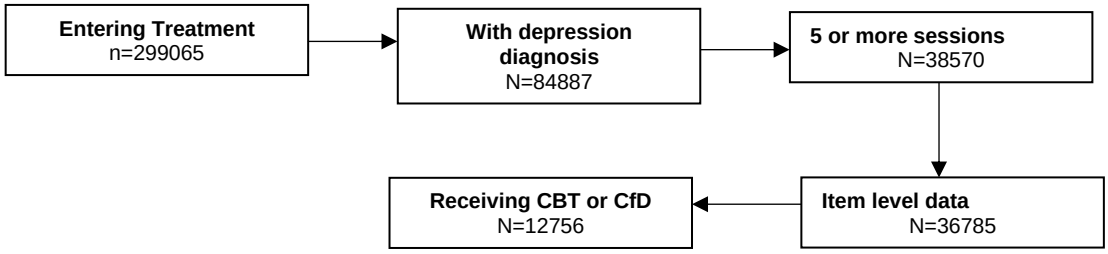

Figure 1. Participant Flow with Reasons for Inclusion

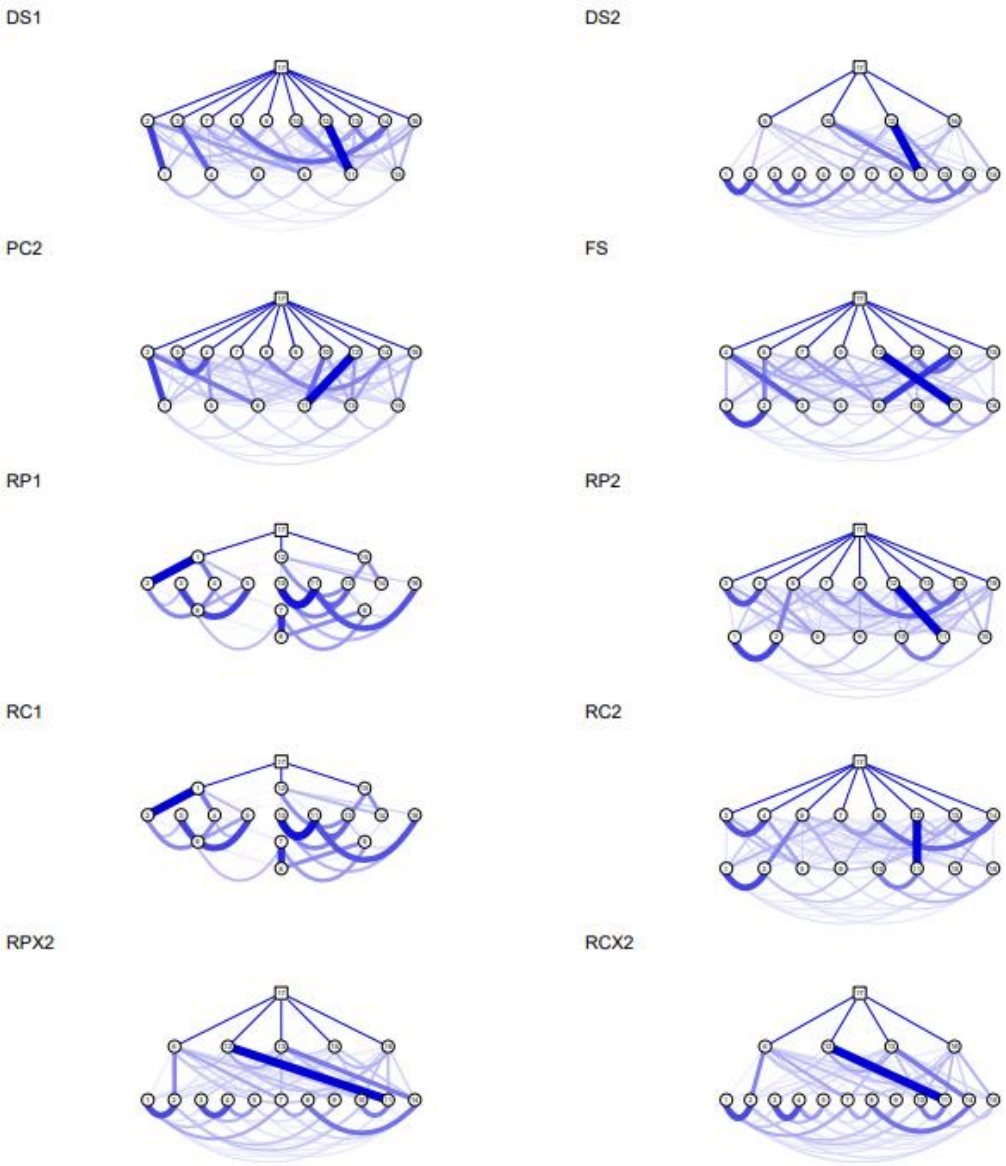

Figure 2: The networks correspond to the different approaches to measuring change. The networks include intervention (CBT or CfD) as a square node and items from the PHQ-9 and GAD-7. The thickness and saturation of the edges between symptoms is proportional to the strength of the association. The edges between the intervention node and symptoms are direct associations – the heatmap below indicates the strength and direction of these associations.

Symptom	Statistic	EMM (SE) CBT, CfD		
Anhedonia	F(1,12753) = 1.394, p=0.343	-	F(1,3443) = 5.651, p<0.04*	1.06(0.02), 1.12(0.02)
Depressed mood	F(1,12753) = 0.872, p=0.560	-	F(1,3443) = 6.23, p<0.03*	1.17(0.02),1.25(0.02)
Sleep	F(1,12753) = 0.046, p=0.910	-	F(1,3443) = 0.599, p<0.468	
Energy	F(1,12753) = 0.298, p=0.843	-	F(1,3443) = 0.857, p<0.406	
Appetite	F(1,12753) = 0.013, p=0.910	-	F(1,3443) =2.285 , p<0.174	
Failure	F(1,12753) = 0.201, p=0.843	-	F(1,3443) = 0.072, p<0.789	
Concentration	F(1,12753) = 0.017, p=0.910	-	F(1,3443) = 1.249, p<0.325	
Psychomotor	F(1,12753) = 5.38, p=0.046*	0.62(0.01), 0.66(0.02)	F(1,3443) = 2.520, p<0.163	
Suicidal ideation	F(1,12753) = 0.165, p=0.843		F(1,3443) = 2.999, p<0.132	
Nervous	F(1,12753) = 6.724, p=0.027*	1.36(0.01), 1.42(0.01)	F(1,3443) = 5.075, p<0.133	
Worry(control)	F(1,12753) = 10.066, p=0.011*	1.29(0.01), 1.37(0.02)	F(1,3443) = 8.689, p<0.043*	1.22(0.02),1.32(0.02)
Worry(excessive)	F(1,12753) = 17.083, p<0.001*	1.35(0.01), 1.45(0.02)	F(1,3443) = 13.951, p<0.008*	1.35(0.02), 1.38(0.02)
Trouble relaxing	F(1,12753) = 8.839, p=0.012*	1.22(0.01), 1.29(0.02)	F(1,3443) = 13.882, p<0.002*	1.38(0.02), 1.41(0.02)

Restless	F(1,12753) = 9.407, p=0.011*	0.78 (0.01), 0.85 (0.02)	F(1,3443) = 8.72, p<0.008*	1.01(0.02),1.06(0.02)
Annoyed	F(1,12753) = 5.143, p=0.046*	1.19(0.01), 1.24(0.02)	F(1,3443) = 9.045, p<0.008*	1.11(0.02),1.12(0.02)
Apprehensive expectation	F(1,12753) = 7.128, p=0.027*	1.01(0.01), 1.07(0.02)	F(1,3443) = 13.113, p<0.002*	1.01(0.02), 1.04(0.02)

Table 1: Raw symptom change statistics. P-values corrected for FDR. EMM= Estimated Marginal Means

Figure 2: Bootstrapped stability plots. RCX2

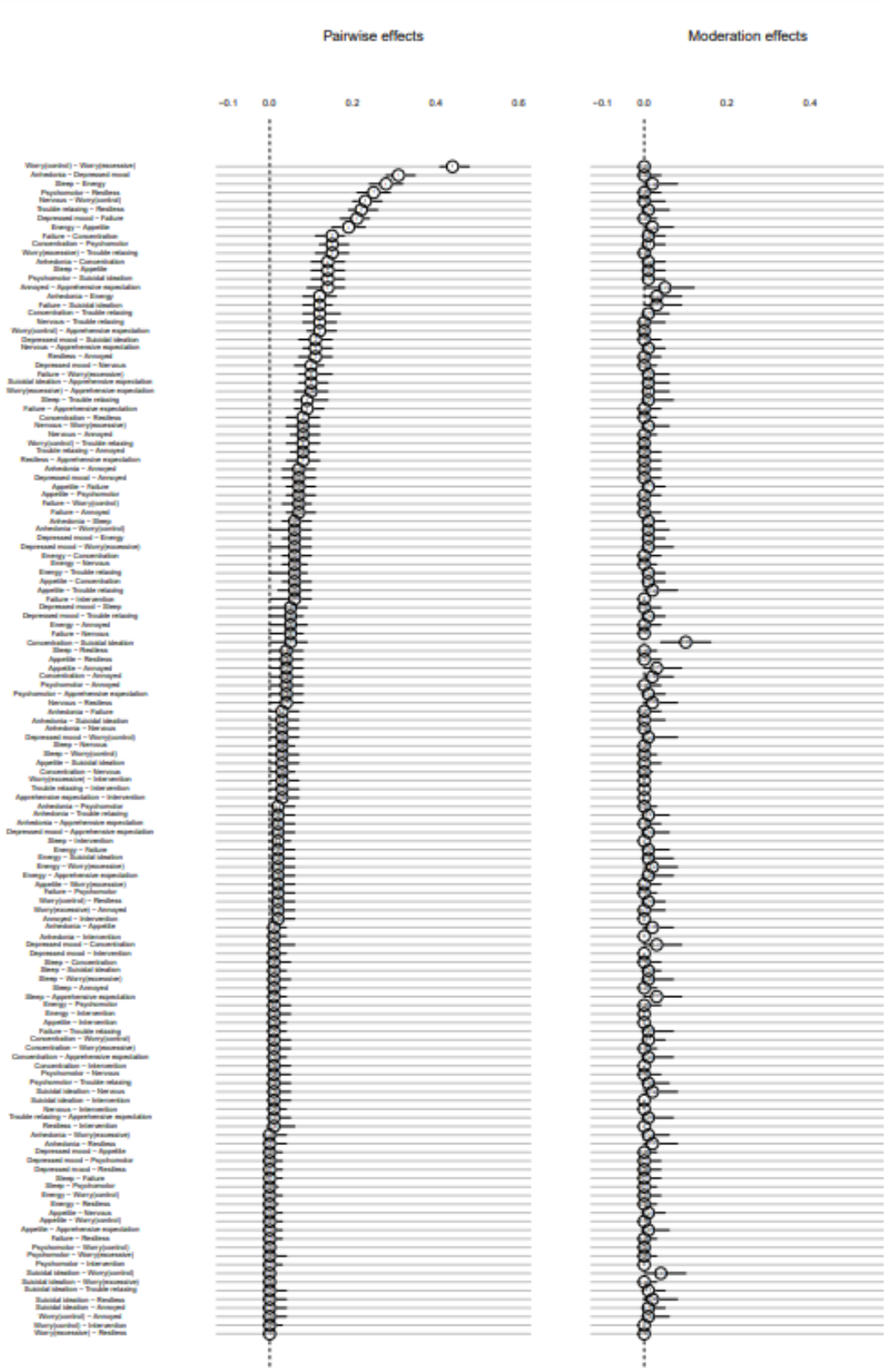

Figure 3: Bootstrapped stability plots. RPX2

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	BPD (n=398)	HC (n=675)	MDD (n=313)
PCL (re-experiencing)			
Mean (SD)	18.0 (5.25)	9.93 (4.90)	16.0 (5.60)
Median [Min, Max]	19.0 [5.00, 25.0]	8.00 [5.00, 25.0]	16.0 [5.00, 25.0]
Missing	18 (4.5%)	20 (3.0%)	36 (11.5%)
PCL (avoidance)			
Mean (SD)	25.0 (6.57)	13.2 (6.33)	21.2 (7.19)
Median [Min, Max]	26.0 [7.00, 35.0]	11.0 [7.00, 35.0]	22.0 [7.00, 35.0]
Missing	17 (4.3%)	19 (2.8%)	36 (11.5%)
PCL (arousal)			
Mean (SD)	18.7 (4.77)	9.67 (4.80)	15.8 (5.43)
Median [Min, Max]	19.0 [5.00, 25.0]	8.00 [5.00, 25.0]	16.0 [5.00, 25.0]
Missing	18 (4.5%)	20 (3.0%)	36 (11.5%)
BSI (Depression)			
Mean (SD)	2.58 (1.08)	0.67 (0.78)	1.90 (1.03)
Median [Min, Max]	2.83 [0, 4.00]	0.50 [0, 3.67]	2.00 [0, 4.00]
Missing	36 (9.0%)	17 (2.5%)	21 (6.7%)
BSI (Anxiety)			
Mean (SD)	2.08 (1.02)	0.46 (0.61)	1.77 (1.08)
Median [Min, Max]	2.17 [0, 4.00]	0.17 [0, 3.83]	1.67 [0, 4.00]
Missing	36 (9.0%)	17 (2.5%)	21 (6.7%)
BSI (Hostility)			
Mean (SD)	1.69 (1.08)	0.46 (0.57)	1.14 (0.860)
Median [Min, Max]	1.60 [0, 4.00]	0.20 [0, 3.60]	1.00 [0, 3.80]
Missing	34 (8.5%)	17 (2.5%)	21 (6.7%)
GPTS (Reference)			
Mean (SD)	43.2 (16.6)	24.0 (10.6)	36.3 (15.1)
Median [Min, Max]	42.5 [16.0, 80.0]	20.0 [16.0, 72.0]	34.0 [16.0, 80.0]
Missing	42 (10.6%)	22 (3.3%)	32 (10.2%)
GPTS (Persecution)			
Mean (SD)	38.9 (19.6)	20.7 (9.65)	30.6 (17.9)
Median [Min, Max]	35.0 [16.0, 80.0]	16.0 [16.0, 78.0]	22.0 [16.0, 80.0]
Missing	42 (10.6%)	20 (3.0%)	31 (9.9%)
DERS (nonacceptance)			
Mean (SD)	23.0 (6.13)	12.9 (5.88)	18.7 (6.75)
Median [Min, Max]	24.0 [6.00, 30.0]	12.0 [6.00, 30.0]	19.0 [6.00, 30.0]
Missing	22 (5.5%)	17 (2.5%)	16 (5.1%)
DERS (goals)			

	BPD (n=398)	HC (n=675)	MDD (n=313)
Mean (SD)	21.2 (3.80)	14.3 (4.84)	17.6 (3.46)
Median [Min, Max]	22.0 [7.00, 25.0]	14.0 [5.00, 25.0]	18.0 [8.00, 25.0]
Missing	26 (6.5%)	15 (2.2%)	16 (5.1%)
DERS (impulse)			
Mean (SD)	22.9 (5.71)	11.1 (4.82)	16.4 (5.00)
Median [Min, Max]	24.0 [7.00, 30.0]	10.0 [6.00, 30.0]	15.0 [7.00, 30.0]
Missing	25 (6.3%)	16 (2.4%)	16 (5.1%)
DERS (strategies)			
Mean (SD)	32.2 (6.09)	17.0 (6.97)	25.3 (6.55)
Median [Min, Max]	34.0 [10.0, 40.0]	15.0 [8.00, 40.0]	26.0 [11.0, 40.0]
Missing	23 (5.8%)	16 (2.4%)	16 (5.1%)
DERS (clarity)			
Mean (SD)	17.7 (4.36)	10.4 (3.84)	14.1 (2.70)
Median [Min, Max]	18.0 [5.00, 25.0]	10.0 [5.00, 25.0]	14.0 [5.00, 24.0]
Missing	26 (6.5%)	15 (2.2%)	16 (5.1%)
PAIS (Identity problems)			
Mean (SD)	14.3 (3.14)	6.52 (3.65)	11.5 (3.84)
Median [Min, Max]	15.0 [3.00, 18.0]	6.00 [0, 17.0]	12.0 [0, 18.0]
Missing	14 (3.5%)	13 (1.9%)	28 (8.9%)
PAIS (Affective instability)			
Mean (SD)	14.8 (2.94)	5.94 (3.56)	10.9 (3.99)
Median [Min, Max]	16.0 [3.00, 18.0]	5.00 [0, 18.0]	11.0 [1.00, 18.0]
Missing	15 (3.8%)	11 (1.6%)	28 (8.9%)
PAIS (Negative relationships)			
Mean (SD)	13.5 (3.26)	6.47 (3.62)	9.90 (3.70)
Median [Min, Max]	14.0 [2.00, 18.0]	6.00 [0, 18.0]	10.0 [0, 18.0]
Missing	19 (4.8%)	13 (1.9%)	28 (8.9%)
PAIS (Self-harm)			
Mean (SD)	11.7 (4.62)	4.02 (3.31)	5.57 (4.11)
Median [Min, Max]	12.0 [1.00, 18.0]	3.00 [0, 17.0]	5.00 [0, 18.0]
Missing	16 (4.0%)	11 (1.6%)	28 (8.9%)
ECR (Anxiety)			
Mean (SD)	5.15 (1.16)	3.11 (1.28)	3.92 (1.36)
Median [Min, Max]	5.33 [1.72, 6.94]	3.06 [1.00, 6.56]	4.00 [1.00, 6.94]
Missing	40 (10.1%)	20 (3.0%)	29 (9.3%)
ECR (Avoidance)			
Mean (SD)	4.05 (1.39)	2.84 (1.18)	3.35 (1.27)
Median [Min, Max]	4.00 [1.06, 7.00]	2.67 [1.00, 6.28]	3.22 [1.00, 6.94]
Missing	35 (8.8%)	21 (3.1%)	27 (8.6%)

	BPD (n=398)	HC (n=675)	MDD (n=313)
IIP (Dominance)			
Mean (SD)	-9.82 (11.7)	-8.45 (9.04)	-10.1 (9.23)
Median [Min, Max]	-9.39 [-35.5, 19.6]	-7.41 [-38.6, 18.9]	-9.95 [-38.6, 13.1]
Missing	34 (8.5%)	19 (2.8%)	35 (11.2%)
IIP (affiliation)			
Mean (SD)	3.76 (11.0)	2.76 (8.70)	4.86 (9.88)
Median [Min, Max]	4.18 [-32.4, 30.8]	2.71 [-30.3, 25.8]	4.62 [-22.0, 27.8]
Missing	34 (8.5%)	19 (2.8%)	35 (11.2%)
RFQ (too certain)			
Mean (SD)	13.2 (11.0)	23.8 (14.1)	19.4 (13.9)
Median [Min, Max]	10.0 [0, 59.0]	21.0 [0, 72.0]	16.0 [0, 71.0]
Missing	47 (11.8%)	24 (3.6%)	34 (10.9%)
RFQ (too uncertain)			
Mean (SD)	29.3 (14.6)	11.9 (10.2)	17.5 (12.6)
Median [Min, Max]	27.0 [3.00, 73.0]	9.00 [0, 55.0]	15.0 [0, 55.0]
Missing	47 (11.8%)	24 (3.6%)	34 (10.9%)
Gender			
Male	71 (17.8%)	228 (33.8%)	80 (25.6%)
Female	322 (80.9%)	445 (65.9%)	230 (73.5%)
Transgender / Transsexual	2 (0.5%)	1 (0.1%)	3 (1.0%)
Other	2 (0.5%)	1 (0.1%)	0 (0%)
Missing	1 (0.3%)	0 (0%)	0 (0%)
Age			
Mean (SD)	30.7 (9.66)	31.8 (11.2)	31.1 (10.4)
Median [Min, Max]	29.0 [17.0, 58.0]	29.0 [16.0, 62.0]	28.0 [18.0, 69.0]
Missing	4 (1.0%)	0 (0%)	0 (0%)
Employment status			
Full time	50 (12.6%)	226 (33.5%)	115 (36.7%)
Part time	47 (11.8%)	81 (12.0%)	35 (11.2%)
Casual work	5 (1.3%)	21 (3.1%)	3 (1.0%)
Self Employed	16 (4.0%)	68 (10.1%)	20 (6.4%)
Internship/apprenticeship	1 (0.3%)	7 (1.0%)	7 (2.2%)
Student	54 (13.6%)	151 (22.4%)	50 (16.0%)
Retired	4 (1.0%)	6 (0.9%)	2 (0.6%)
Carer	1 (0.3%)	10 (1.5%)	6 (1.9%)
Unemployed	213 (53.5%)	105 (15.6%)	72 (23.0%)
Missing	7 (1.8%)	0 (0%)	3 (1.0%)
Ethnicity			
White-British	261 (65.6%)	385 (57.0%)	146 (46.6%)

	BPD (n=398)	HC (n=675)	MDD (n=313)
White-Irish	9 (2.3%)	4 (0.6%)	8 (2.6%)
White-Other	22 (5.5%)	103 (15.3%)	53 (16.9%)
Black/Black British-Caribbean	22 (5.5%)	14 (2.1%)	11 (3.5%)
Black/Black British-African	5 (1.3%)	27 (4.0%)	14 (4.5%)
Black/Black British-Other	4 (1.0%)	3 (0.4%)	3 (1.0%)
Mixed-White and Black Caribbean	8 (2.0%)	11 (1.6%)	7 (2.2%)
Mixed-White and Black African	2 (0.5%)	10 (1.5%)	4 (1.3%)
Mixed-White and Asian	11 (2.8%)	15 (2.2%)	3 (1.0%)
Other mixed	15 (3.8%)	16 (2.4%)	12 (3.8%)
Asian/British Asian-Indian	6 (1.5%)	22 (3.3%)	12 (3.8%)
Asian/British Asian-Pakistani	11 (2.8%)	11 (1.6%)	10 (3.2%)
Asian/British Asian-Bangladeshi	5 (1.3%)	11 (1.6%)	8 (2.6%)
Asian/British Asian-Other	2 (0.5%)	17 (2.5%)	8 (2.6%)
Chinese	1 (0.3%)	9 (1.3%)	1 (0.3%)
Not stated	14 (3.6%)	17 (2.5%)	13 (4.2%)

Table 1. (to go into supplementary material) Descriptive data on sample and subscales used.

	1 (N=398)	2 (N=675)	3 (N=313)	Overall (N=1386)
PTSD				
Mean (SD)	0.606 (0.592)	-0.577 (0.838)	0.453 (0.924)	-0.00487 (0.974)
Median [Min, Max]	0.647 [-1.73, 1.86]	-0.682 [-1.73, 3.38]	0.342 [-1.73, 2.84]	0.0206 [-1.73, 3.38]
BSI_Depression				
Mean (SD)	0.722 (0.687)	-0.600 (0.811)	0.386 (0.854)	0.00227 (0.989)
Median [Min, Max]	0.810 [-1.60, 2.00]	-0.555 [-1.60, 2.24]	0.329 [-1.60, 3.31]	0.0116 [-1.60, 3.31]
BSI_Anxiety				
Mean (SD)	0.656 (0.669)	-0.607 (0.779)	0.511 (0.854)	0.00821 (0.975)
Median [Min, Max]	0.698 [-1.43, 2.00]	-0.553 [-1.43, 2.24]	0.455 [-1.43, 3.31]	0.0214 [-1.43, 3.31]
BSI_Hostility				
Mean (SD)	0.621 (0.762)	-0.518 (0.830)	0.306 (0.936)	-0.00480 (0.980)
Median [Min, Max]	0.726 [-1.55, 2.00]	-0.784 [-1.55, 2.24]	0.263 [-1.55, 3.31]	-0.0992 [-1.55, 3.31]
Paranoia				
Mean (SD)	0.566 (1.13)	-0.605 (1.41)	0.577 (1.13)	-0.00194 (1.40)
Median [Min, Max]	0.695 [-4.99, 3.92]	-0.722 [-4.05, 4.52]	0.562 [-2.42, 3.91]	0.0844 [-4.99, 4.52]
DERS_nona				
Mean (SD)	0.696 (0.718)	-0.497 (0.903)	0.254 (0.938)	0.0151 (1.01)
Median [Min, Max]	0.697 [-1.90, 2.06]	-0.529 [-1.90, 3.31]	0.204 [-1.90, 2.88]	0.0116 [-1.90, 3.31]
DERseile				
Mean (SD)	0.818 (0.580)	-0.595 (0.834)	0.232 (0.727)	-0.00274 (0.965)
Median [Min, Max]	0.853 [-1.46, 2.08]	-0.642 [-2.27, 3.33]	0.145 [-1.11, 2.89]	-0.0127 [-2.27, 3.33]
DERS_cl				
Mean (SD)	0.771 (0.727)	-0.569 (0.921)	0.270 (0.714)	0.00526 (1.01)
Median [Min, Max]	0.864 [-2.10, 2.09]	-0.630 [-2.10, 3.31]	0.148 [-2.10, 2.88]	-0.0562 [-2.10, 3.31]
PAIS_BOI				
Mean (SD)	0.760 (0.616)	-0.647 (0.832)	0.397 (0.928)	-0.00740 (1.02)
Median [Min, Max]	0.798 [-1.38, 1.97]	-0.668 [-2.55, 3.31]	0.253 [-2.55, 3.10]	-0.0544 [-2.55, 3.31]
PAIS_BOA				
Mean (SD)	0.837 (0.558)	-0.674 (0.806)	0.357 (0.914)	-0.00737 (1.02)
Median [Min, Max]	0.930 [-1.28, 1.99]	-0.554 [-2.48, 2.13]	0.297 [-2.00, 3.31]	0.0384 [-2.48, 3.31]
PAIS_BON				

	1 (N=398)	2 (N=675)	3 (N=313)	Overall (N=1386)
Mean (SD)	0.764 (0.639)	-0.597 (0.870)	0.262 (0.965)	-0.0122 (1.03)
Median [Min, Max]	0.746 [-1.77, 1.97]	-0.608 [-2.80, 2.13]	0.245 [-2.80, 3.31]	-0.0750 [-2.80, 3.31]
PAIS_BOS				
Mean (SD)	0.788 (0.662)	-0.493 (0.813)	0.00986 (1.09)	-0.0119 (1.01)
Median [Min, Max]	0.857 [-1.18, 1.99]	-0.607 [-1.81, 2.13]	-0.163 [-1.81, 3.31]	0.0277 [-1.81, 3.31]
ECRRANX				
Mean (SD)	0.712 (0.671)	-0.489 (0.931)	0.149 (1.03)	0.000206 (1.03)
Median [Min, Max]	0.810 [-1.40, 1.89]	-0.475 [-2.66, 3.31]	0.108 [-2.66, 2.88]	0.00535 [-2.66, 3.31]
ECRRAVOI				
Mean (SD)	0.452 (0.882)	-0.363 (0.971)	0.126 (1.06)	-0.0186 (1.03)
Median [Min, Max]	0.553 [-2.18, 1.89]	-0.344 [-2.57, 3.31]	0.0473 [-2.57, 2.88]	-0.0170 [-2.57, 3.31]
IIP_dom32				
Mean (SD)	-0.0888 (1.14)	-0.0378 (0.894)	0.0402 (1.15)	-0.0349 (1.03)
Median [Min, Max]	-0.0965 [-2.97, 1.84]	0.0107 [-3.19, 3.31]	-0.135 [-3.19, 2.97]	-0.0348 [-3.19, 3.31]
IIP_aff32				
Mean (SD)	0.0220 (1.07)	-0.137 (0.906)	0.250 (1.14)	-0.00384 (1.02)
Median [Min, Max]	0.161 [-3.31, 1.84]	-0.138 [-3.03, 3.31]	0.208 [-2.42, 2.97]	-0.000892 [-3.31, 3.31]
LRFc				
Mean (SD)	-0.386 (1.09)	0.157 (0.850)	0.0631 (1.15)	-0.0203 (1.02)
Median [Min, Max]	-0.498 [-2.57, 1.81]	0.172 [-2.57, 3.31]	-0.0152 [-2.57, 2.88]	-0.0152 [-2.57, 3.31]
LRFu				
Mean (SD)	0.618 (0.654)	-0.476 (0.951)	0.115 (1.08)	-0.0282 (1.02)
Median [Min, Max]	0.675 [-1.40, 1.81]	-0.543 [-2.44, 3.31]	-0.0259 [-2.44, 2.88]	-0.0259 [-2.44, 3.31]
df$Referral_Diagnosis				
Mean (SD)	1.00 (0)	2.00 (0)	3.00 (0)	1.94 (0.714)
Median [Min, Max]	1.00 [1.00, 1.00]	2.00 [2.00, 2.00]	3.00 [3.00, 3.00]	2.00 [1.00, 3.00]

Table 2: descriptives of items included in network

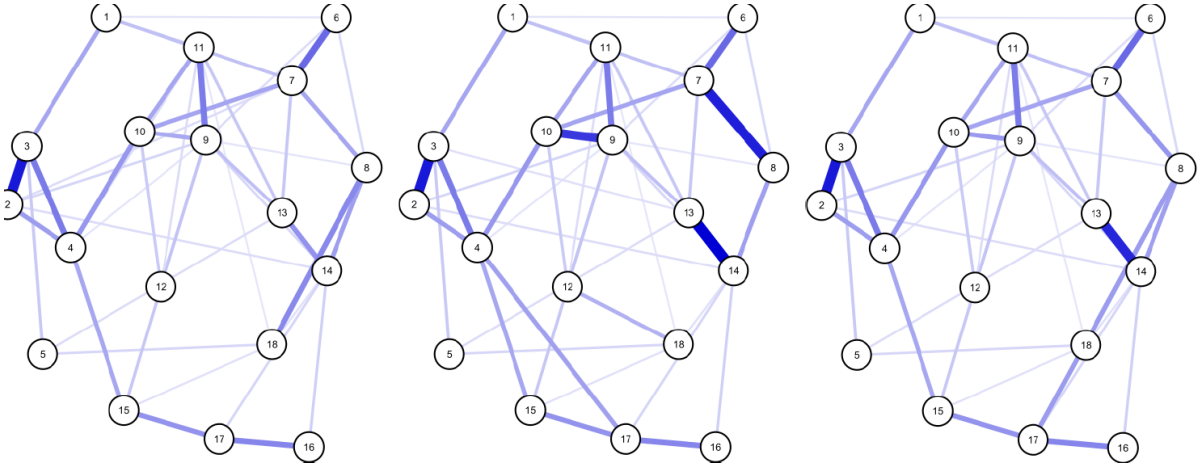

Figure 1: Individual network plots.

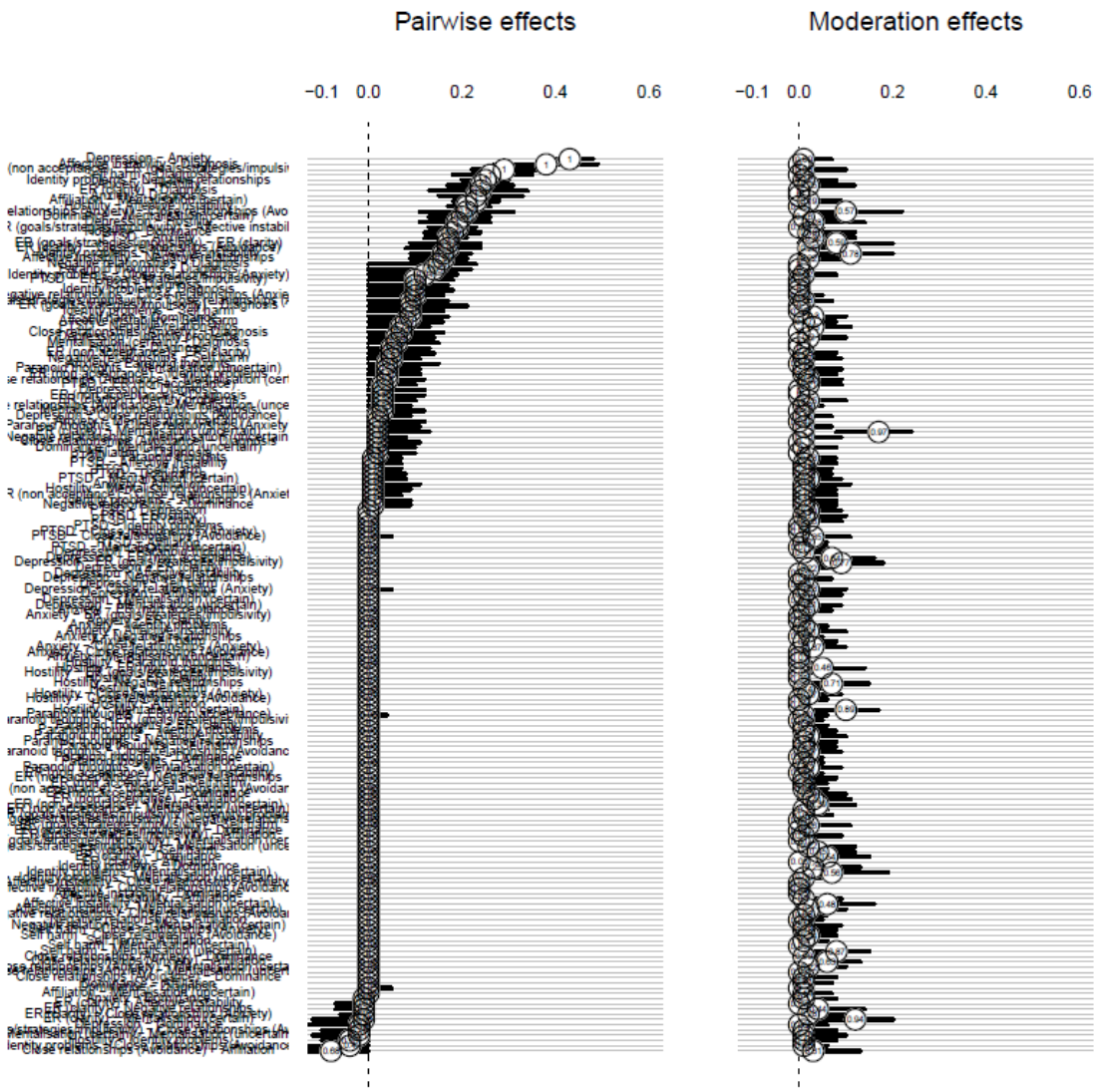

Figure 2: Stability Plots

CHAPTER 6 Supplementary Materials

Methodological SCED approach based on the RoBiNT Scale

Item	RoBiNT Scale	SCED details, per optimisation iteration (anticipated points)
Internal validity subscale		
1	Design	A *replicated AB-design* with 40×A-B (total of 80 phases), providing the opportunity to observe the experimental effect 40 times. (*2 points*)
2	Randomisation	The baseline phase lasted 7 days (up to 28 timepoints) (1 *points*)
3	Sampling behaviour during all phases	The baseline phase lasted 7 days, with at least four times a day sampling, resulting in 28 *data points* (*phase A*) (assuming 100% compliance to diary). The intervention phase ran over 3 weeks, with four times a day sampling, resulting in *84 data points* (*phase B*) (assuming 100% compliance to diary). Even if the compliance rate should be lower, the amount of data points will lie >5 data points. (*2 points*)
4	Blinding of participants and HCP delivering the treatment	*Blinding* of the participant and practitioner is *not feasible*. The behavioural treatment is delivered through a web-platform independently of the researcher; however, the HCP provides technical support and encouragment. Neither the participant nor the HCP is blinded. (*0 points*)
5	Blinding (masking) of assessors	Participants complete self report assessments and receive intervention prompts and are *not blinded* to treatment phase, therefore, not independent of the therapy process. (*0 point*)
6	Inter-rater agreement	The measure of the target behaviour is a *subject ve measure* relying on *self-reports* from the digital diaries. (*0 points*)
7	Treatment adherence	The treatment is delivered through a *web-platform* following a standardised approach. Adherence to treatment (%) is calculated using *digital log-in data*. (*2 points*)
External validity and interpretation subscale		
8	Baseline characteristics	Baseline characteritics were assessed. Furthermore, prompts in the internvetion phase were informed by data collected duiring the baseline phase. (*2 points*)
9	Setting	The participant will engage with the online treatment in their everyday life, and therefore, it will not be possible to include details about the specific environment. (*1 point*)
10	Dependent variable (target behaviour)	**Table 2** provides an overview of all diary items, which are scores on a 10-point Likert-Scale. (*2 points*)
11	Independent variable (treatment)	A detailed description of the intervention is provided, including the *intervention content*, and frequency of intervention. (*2 points*)
12	Raw data record	*All cases* are recorded. Raw data will be presented with a data point for each diary entry. (*2 points*)
13	Data analysis	Data will be analysed and reported for each participant individually. Structured visual analysis, effect size measures and multilevel models will be applied. (2 points)
14	Replication	The study will be conducted across iterations allowing for replication of results. Across all iterations, data from n=92 participants will be available. (2 points)
15	Generalisation	Patients will be heterogeneous in their characteristics. Furthermore, retrospective self-reports will be completed by each participant *pre–post treatment* (for details, see **table 3**). (*1 point*)

Table 1: **Methodological SCED approach based on the RoBiNT Scale**

Did you achieve the goal?	(1= much better than expected - 6 = worse
In relation to your ability to effectively pursue goals more generally, how would you rate your ability?	1= much better, 6 - much worse)
Overall, did you enjoy the experiment?	1 = not at all 7 = very much
Did the online guide explain the strategy clearly enough?	1 = not at all 7 = very much
Did the strategy make you more aware of your own behaviour?	1 = not at all 7 = very much
Was the online guide sufficient for you to fully understand the strategy?	1 = not at all 7 = very much
Was the online guide useful to help you elaborate you goals and obstacles?	1 = not at all 7 = very much
Did answering the questions take you too much time every day?	1 = not at all 7 = very much
Did receiving/answering the questions disrupt your goal pursuit?	1 = not at all 7 = very much
How intrusive did you find the messages?	1 = not at all 7 = very much
Was it easy to respond to the questions through the day?	1 = not at all 7 = very much
Were the strategy reminders useful to help you pursue your goals?	1 = not at all 7 = very much
Will you continue to use this strategy?	Yes/No
Would you recommend this strategy to a friend?	Yes/No

Table 2. Acceptability Questionnaire.

Strategy training guide.

https://uclpsych.eu.qualtrics.com/jfe/form/SV_2gg5x8q3Pd2qyjk

Thank you for completing the first week of EMA. We will use this data to personalise prompts to help you improve your goal pursuit. Part of this will be to learn and use our goal-pursuit strategy.

Before you start with the exercise, please be aware that it involves thoughts and images rather than rational or effortful thinking. It involves going slow, creating time and space for thinking and imagining. It is critical that no interruptions occur during the exercise. Start the session when you feel calm and comfortable. This is your time now. Everything else has to wait. Clear your mind and create space to imagine.

Goal

Think about the next four weeks *(you can also use another timeframe (e.g., 24 hours, 12 months or no timeframe)*, what is your one dearest goal that you would like to fulfil and that you also think you could fulfil during this time frame? Fulfilling your goal should be challenging for you, but you should feel that it is possible for you.

Motivation

0 1 2 3 4 5 6 7 8 9 10

How likely is it you will pursue this goal

If it's less than 7, you should consider if this goal is important enough to you right now.

Is it worth spending effort to change?

Yes

No

Do you believe it's possible to achieve this goal?

Yes

No

If you have several goals, for this exercise select the one that is most important to you. You can then practice this strategy for your other goals. The goal can be about your relationships, your health, a job, school, or anything else that is important to you.

Find this one specific goal, summarize it in 3 to 6 words, and keep it in the front of your mind.

Outcome

Now, what is the best thing, the best outcome that you associate with fulfilling your goal? How would fulfilling your goal make you feel? What would be the best thing about achieving your goal?

Find the best outcome, summarize it in 3 to 6 words. Keep it in the front of your mind.

Now, imagine this best outcome as vividly as possible. Give your thoughts and images free reign. Let your mind go. You can close your eyes if you would like. Imagine and feel it as fully as you can.

-- Slowly come back, and we will continue.

Obstacles

Firstly, consider the practical obstacles holding you back. These may require you to reconsider your goal or break your goal down into smaller parts so that you can successfully reach those goals in order to achieve the main goal.

Capacity

Do I know what I need to do to achieve this goal?

Do I have the knowledge, skills, and/or physical ability?

Are there skills that need to be developed in order to progress to more challenging goals?

Please write down what you may need

Opportunity

Will my circumstances / environment make it difficult to achieve my goal?

Are there practical barriers?

Sometimes there is a conflict between demands in our lives e.g relationships/family and work. Is this a time management obstacle or prioritizing what goal is most important right now?

Please write down any barriers

Now, go a little further and look inside. What is it in you that stands in the way of you making your goal come true? What behaviour of yours or what emotion could hinder you from fulfilling your goal? Dig deeper, what is in you that stops you from realizing your goal? What is your one main inner obstacle?

Find it, summarize it in 3 to 6 words, and keep it in the front of your mind.

And again, imagine your one main inner obstacle occurring as vividly as possible. Imagine it playing out and stopping you from achieving your goal. What would that look like? Give your thoughts and images free reign. Let your mind go. You can close your eyes if you would like. Imagine this and feel it as fully as you can.

-- Slowly come back, and we will continue.

Plan

What can you do to overcome your obstacle? Identify one action you can take or one thought you can think to overcome your obstacle. What can you do? Identify one action or one thought.

Find it, summarize it in 3 to 6 words. Keep it in the front of your mind.

Overcome	Prevention	Opportunity
What can I do to overcome the obstacle? In which situation?	What can I do to prevent the obstacle? In which situation?	What opportunities can I seize in order to approach solving my concern in an effective way? In which situation?
If a certain situation (the obstacle) arises, then I will act in a certain way to OVERCOME the obstacle.	If a certain situation (to prevent the obstacle) arises, then I will act in a certain way to PREVENT the obstacle from occurring.	If a certain situation (an opportunity to effectively solve my concern) arises, then I will act in a certain way to APPROACH solving my concern.
EXAMPLE I want to overcome my obstacle of eating sweets by eating a piece of fruit instead: If I feel a craving for sweers after dinner (situation), then I will eat a piece of fruit instead (action).	EXAMPLE I want to prevent my obstacle of eating sweets by buying fruit (instead of sweets): If I go shopping this afternoon (situation), then I will buy fruit (action).	EXAMPLE I want follow a more healthy diet by eating more vegetables: If I meet my friend on Monday night for dinner (situation), then I order my favorite vegetarian meal (action).

Sometimes the best contingencies are to act the opposite of how we feel e.g. If I feel sad then I want to withdraw, however being around others is more likely to help our mood, so my plan may be: *if I feel sad then I will reach out to someone*.

If my goal is to complete my dissertation, and I identify scrolling through social media on my phone as a barrier I might set the contingency: I*f I sit down to study then I will set a Pomodoro on my phone*
Equally, we need to listen to our bodies, if I feel tired maybe it's counterproductive to keep pushing myself to study so I might set the additional contingency: *if I feel tired then I will go for a 20-minute walk*.

Now make your if-then plan:
Take your obstacle and place it after the word "if."
Similarly, place the behaviour to overcome your obstacle after the word "then":

If … (obstacle) … then I will ... (action or thought to overcome your obstacle).

Summarize your plan below:

Excellent work.

This was the four-step exercise. It always works the same:

1. You first name a goal that is challenging, but feasible.
2. Then you find the very best outcome and imagine this outcome.
3. Then you find your main obstacle and imagine this obstacle.
4. Finally, you make a plan, an if-then plan of how to overcome the obstacle.

As you go through the four weeks your goals will change day to day
(maybe even hour to hour) as other goals take priority. For instance, at any point in the day rest may be your goal, but consider are you pursing it effectively?

Your overall goal may also change in this time.
Allow yourself the flexibility to shift or change course or pick up on a goal you had to pause.
The aim here is to increase your ability to pursue goals throughout your life.

Use this strategy for all goals that arise.

- You can use this for long-term as well as for short-term goals.
- You can use this for small as well as for big goals.
- Use it when you are stressed or when you feel uneasy.
- It helps you to sort things out.
- **This strategy can be a companion to guide you through everyday life and long-term development.**

You may have some difficulties at the beginning. Be patient, the more often you practice, the better you will become in using it and the more you will get engaged in life.

Practice as often as you can – play with it!

REVIEW

Goal: What is your goal?

	Yes	No
Is this goal dear to you?	○	○
Do you think you can achieve it?	○	○
Is it challenging for you?	○	○
Did you summarize it in 3-6 words?	○	○

Outcome: What is the best outcome?

	Yes	No
Is it a truly fulfilling outcome?	○	○
Did you summarize it in 3-6 words?	○	○
Did you take enough time to imagine this best outcome?	○	○

If not, close your eyes and imagine the best outcome. Imagine it fully.

Obstacle: What is your main inner obstacle?

	Yes	No
Is your obstacle an inner obstacle?	○	○
Is it a true inner obstacle? Think about it more deeply!	○	○
Did you summarize it in 3-6 words?	○	○
Did you take enough time to imagine your main obstacle?	○	○

If not, close your eyes and imagine your main obstacle. Imagine it fully.

Plan: What is your if-then plan?

	Yes	No
Did you find an effective action to overcome your obstacle?	○	○
Did you summarize it in 3-6 words?	○	○
Check if the plan has the following structure: "If [obstacle], then I will [action]."	○	○

If not, create the if-then plan again.

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RESEARCH ARTICLE Open Access

The importance of transdiagnostic symptom level assessment to understanding prognosis for depressed adults: analysis of data from six randomised control trials

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Abstract

Background: Depression is commonly perceived as a single underlying disease with a number of potential treatment options. However, patients with major depression differ dramatically in their symptom presentation and comorbidities, e.g. with anxiety disorders. There are also large variations in treatment outcomes and associations of some anxiety comorbidities with poorer prognoses, but limited understanding as to why, and little information to inform the clinical management of depression. There is a need to improve our understanding of depression, incorporating anxiety comorbidity, and consider the association of a wide range of symptoms with treatment outcomes.

Method: Individual patient data from six RCTs of depressed patients (total $n = 2858$) were used to estimate the differential impact symptoms have on outcomes at three post intervention time points using individual items and sum scores. Symptom networks (graphical Gaussian model) were estimated to explore the functional relations among symptoms of depression and anxiety and compare networks for treatment remitters and those with persistent symptoms to identify potential prognostic indicators.

Results: Item-level prediction performed similarly to sum scores when predicting outcomes at 3 to 4 months and 6 to 8 months, but outperformed sum scores for 9 to 12 months. Pessimism emerged as the most important predictive symptom (relative to all other symptoms), across these time points. In the network structure at study entry, symptoms clustered into physical symptoms, cognitive symptoms, and anxiety symptoms. Sadness, pessimism, and indecision acted as bridges between communities, with sadness and failure/worthlessness being the most central (i.e. interconnected) symptoms. Connectivity of networks at study entry did not differ for future remitters vs. those with persistent symptoms.

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(Continued from previous page)
Conclusion: The relative importance of specific symptoms in association with outcomes and the interactions within the network highlight the value of transdiagnostic assessment and formulation of symptoms to both treatment and prognosis. We discuss the potential for complementary statistical approaches to improve our understanding of psychopathology.

Keywords: Item level analysis, Network modelling, Comorbidity, Depression, Anxiety

Background

Psychological therapies and medication are effective treatments for depression (e.g. [1, 2]). However, effect sizes have been modest and gains in treatment outcomes have plateaued [3]. Interventions for depression target a broad range of symptoms, and knowledge of 'what' is being intervened upon is not necessary to the delivery of most treatments, and poses problems for causal inference [4]. To improve interventions, we may need to improve our knowledge of the structure of depression [5].

Depression is heterogeneous in terms of aetiology and symptom profile [6–8]. Mood disorders are highly comorbid with anxiety disorders and may share psychological and biological vulnerabilities [9, 10]. The risk of one disorder can increase the risk of another [11], and the same end state may be achieved via many different paths (equifinality) [12, 13]. These disorders are not discrete entities and, as such, neglecting the symptomatic heterogeneity discards potential insights [14].

There is strong evidence that different symptoms are not equivalent or interchangeable [15] and studies of individual symptoms in the last decade have brought important understanding. For example, individual symptoms may differ in response to treatment [16, 17] and have been shown to have a differential impact on functioning [18–20]. Depression is a recurrent disorder with the probability of relapse strongly associated with the presence of residual depressive symptoms at the end of treatment [21, 22]. Comorbid anxiety disorders are related both to worse treatment outcomes [23] and to an increased risk of relapse [21]. An assumed unidimensional view of depression, characterised by sum score (sum of symptom severity scores) measurement and prediction models, conceals the variability within depression [24]. Understanding the relative importance of comorbid symptoms may offer more information than severity of disorder alone and provide additional treatment and prognostic information [25]. Large-scale, multisite clinical trial data, coupled with innovative statistical methods, can provide categorisation and treatment optimisation to provide immediate benefits by informing clinical decisions [26–28].

There is also value in studying the relations among these symptoms. Network theory posits that the relationships between common affective, cognitive, and somatic symptoms of these disorders may reflect potential causal pathways and elucidate maintenance mechanisms [29]. Depression and anxiety have been modelled as symptom networks using cross-sectional and longitudinal data, demonstrating the interrelation between the symptoms of each disorder, where comorbidity results from mutually reinforcing interrelation between symptoms of each disorder [30, 31]. Anhedonia, anxiety, worry, fatigue, and sadness are predominantly influential symptoms in these networks [5, 32, 33]. The relationship between symptoms/mechanisms can help to predict outcome and potentially inform treatment targets and the development of treatments targeting specific mechanisms [34].

There are inconsistencies in the network literature exploring depression and anxiety, due to design, sampling, and variability arising from differing measurement [15, 35]. When attempting to discriminate between groups for the purposes of identifying whom may benefit from treatment (prognosis at group level), there are varying results from network comparison studies, where it has been suggested that densely connected networks may be less likely to recover [36]. However, these differences are not always observed [37] and require large sample sizes to detect any effect. It is also unclear how these networks generalise to idiographic networks at the present stage. Past research has been conducted on small samples with low quality assessment of patients (or non-clinical samples) and lack of adequate consideration of comorbidity (missing out on the wider spectrum of anxiety disorders).

In this study we aim to:

1) Identify important symptoms for outcome by examining the (differential) impact of individual symptoms on prognosis for adults with depression that took part in randomised controlled trials after seeking treatment in primary care and assess whether individual symptoms offer predictive value above sum scores.
2) Discern the functional relations among symptoms and clarify the interplay between highly comorbid symptoms of depression and anxiety disorders.
3) Consider whether there are differences in the baseline symptom networks of patients that

remitted vs. those whose depression persisted, after treatment.

Method

Datasets

Data were drawn from a subset of the Dep-GP individual patient data (IPD) database [36]. The formation of the Dep-GP IPD dataset has been described elsewhere [36]. Bibliographic databases were searched up to 29 April 2020 for RCTs of unipolar depressed adults seeking treatment for depression or with depressive symptoms significant enough for them to seek treatment, recruited from primary care; had at least one active treatment arm; and used the CIS-R at baseline.

Studies were excluded if they were studies of patients with depression secondary to a diagnosis of personality disorder, psychotic conditions, or neurological conditions; bi-polar or psychotic depressions; children or adolescents; feasibility studies; or were studies of adults with either depression or an anxiety disorder, rather than a primary depression with or without comorbid anxiety. Additional inclusion criteria for the present study were the use of the Beck Depression Inventory (2nd Edition) (BDI-II) [37] at study entry. The inclusion criteria ensured uniformity in the measurement of depressive and anxiety symptoms, chronicity of problems, and determination of diagnoses including anxiety comorbidities.

Data on all individual patients from all six eligible RCTs were included in the current study, these were COBALT [38], GENPOD [39], PANDA [40], TREAD [41], MIR [42], and IPCRESS [43].

Measures

Individual items from the BDI-II [37], and individual symptom subscales of the CIS-R [44], including duration of depression and anxiety, which have been shown to be independently associated with prognosis for depressed adults [45].

Outcomes

The primary outcome was endpoint depressive symptoms at three to four months post-study entry. Five of the studies used the BDI-II at 3–4 months, and one used the PHQ-9. A continuous 'depression severity' score was developed by converting the responses on each measure to a latent trait depressive symptom severity score (PROMIS T-Score) [46], using the expected a posteriori parameter from a multidimensional item-response theory based score conversion tool [47]. Depressive symptoms (PROMIS T-Score) at 6–8 months post-study entry, and 9–12 months were secondary outcomes.

As a sensitivity analysis, the BDI-II scores were used as outcomes for the three time points (five studies at 3–4months; four studies at 6–8months, and three studies at 9–12 months).

Data analysis

All analyses were performed in R 3.6 [48] and Stata 16.0 [49]. Analysis code is available from https://osf.io/wck6b/. The data that support the findings of this study are available from the lead author of the Dep-GP (JB) subject to agreement from the chief investigators or data controllers of the individual RCTs. Restrictions apply to the availability of these data, which were used under licence for this study.

Pre-processing

Datasets were combined and pre-processed together. There was no missing data at study entry. All items were investigated to ensure they met assumptions for inclusion in the network models, including assessing for near zero variance, roughly equal variance of items, asymmetrical distributions, and topological overlap [50]. Items were removed if they violated assumptions across all studies. We aimed to address topological overlap using the 'goldbricker' function in R [51] with a threshold of 25% (correlations between items should have significantly different correlations with 25% of the other items), accepting minimal correlation of 0.5.The respective pair of items were combined into a single variable using principal component analysis (PCA) if reasonable to combine from a clinical perspective. Items were afterwards rescaled to their original Likert scale values to make variances comparable across items [52].

Association with outcomes

We aimed to examine the differential impact of individual symptoms on outcomes and assess whether individual symptoms offer predictive value above sum scores. Sum score totals were entered into a linear regression model, while the item severity scores were entered into an elastic net generalised linear model (ENR) [53]. ENR, a statistical method combining lasso and ridge regression approaches, minimises overfitting and the use of ten separate, tenfold repeated cross validation aids in assessing the effectiveness of the model. The item-level and sum-score models were compared using root mean squared error, mean absolute error, and R^2.

As the item-level predictors were assumed to be correlated and that we wished to assess the explanatory power of individual predictors, we estimated the contribution of each item to the outcome prediction using Shapley Additive exPlanations [54], following ENR model estimation. Five hundred Monte Carlo repetitions were used to estimate each Shapley value. This metric is more accurate than other variable importance metrics when predictors are dependent [55]. Items with large Shapley values

are 'important', indicating the relative contribution of an item to the model while accounting for correlated features in the data.

Network modelling

A graphical Gaussian model (GGM) aims to capture the direct effects (edges) between items while controlling for all other items in the network. A network was estimated by combining data from the six RCTs. The sample was then split into two networks (those with persistent symptoms vs. remitters: BDI-II score < 10 at 3–4 months); the networks were re-estimated and compared using the network comparison test with 1000 iterations [56].

We performed a number of analyses to test the robustness of the networks we estimated.

While lasso [57], regularised GGMs [58] are most frequently reported in the network literature, lasso specificity has recently been shown to be lower than expected in dense networks with many small edges, leading to an increase in false positives [59]. We also estimated an unregularized GGM using an iterative modelling procedure: the Extended Bayesian Information Criterion (EBIC). Selecting unregularized GGMs according to EBIC has been shown to converge to the true model [60]. The algorithm runs 100 glasso models, re-fits all models without regularisation,, and subsequently adds and removes edges until EBIC can no longer be improved. The best performing model (EBIC parameter) was selected to provide a conservative GGM estimation (high specificity).

Chronicity of disorders has been shown to interact with symptom severity [45, 61]. We corrected for the potential confounding effects of duration of depression and anxiety within the network models.

Combining data obtained from different studies holds the potential for between-study differences to influence estimation. A network estimation procedure (fused graphical lasso: FGL) [62] has been designed to manage this issue, however, this involves estimating networks individually and penalising between study differences. Where study size affects the estimation of edges, this can lead to penalization based on sample size rather than on true differences between the network structures [63]. As such, it was decided to estimate based on the combined sample and to compare this to the FGL network (joint estimation using a fused penalty, and 10-fold cross validation), to assess the potential influence of group level differences.

Finally, the network model was tested for the stability of expected influence centrality and the accuracy of interrelations using a nonparametric bootstrapping procedure (1000 iterations) [64]. For details of these, see the Supplementary material.

We obtained two types of information from the resulting network structures. First, symptoms can form clusters or communities with other symptoms to which they are connected reflecting commonalities between them. We estimated the community structure by using a bootstrapped walktrap algorithm [65], investigated for item stability before selecting communities. Second, the overall connectivity of a symptom, i.e. its connection to other symptoms, can be quantified in a number of ways and is referred to as centrality. Some scholars have argued that activation of a central symptom has the potential to activate associated symptoms in the network [66], where symptom centrality is then interpreted as symptom importance, given that identifying such symptoms may have the potential to elucidate the processes underlying comorbidity and implications for treatment. Within the context of communities specifically, symptoms which connected to more than one community are referred to as bridge symptoms. Within cross-sectional networks (as explored here), we refer to centrality as a statistical parameter, i.e. the strength of predictive associations between symptoms. Centrality does not automatically translate into clinical relevance [67] and cautious interpretation is warranted [63]. It requires consideration of how the symptoms activate within the network (flow or transfer), the conceptual similarity between symptoms, and whether there is missing information on the shared variance [68]. Symptom centrality was calculated using expected influence (EI: strength of the relationships a given node has with other node) and the geometric mean of the participation ratio (PR) and participation coefficient (PC), and normalised bridge expected influence centrality [69]. The PR quantifies the number and strength of edges, while the PC takes the community structure into account [70].

Results

Demographic details for the studies are presented in Table 1. Overall samples were comparable. The severity of depressive symptoms captured by BDI-II scores at baseline in the PANDA sample was lower than the other trials. Descriptive results are reported in the supplementary materials.

Association with outcomes

In order to assess the utility of item level models, we compared them to sum score models. For all item level models (Table 2), the optimal shrinkage parameters for the elastic net regression model were selected via minimum cross-validated error criterion (= 0.1 and λ = 0.05). While models performed similarly at 3–4 months and 6–8 months, the item level elastic net regression model outperformed linear regression with BDI-II and CIS-R (sum of anxiety items) totals at the 9–12-month

Table 1 Descriptive table of studies included in the dataset. Summary of included variables provided in supplementary materials. * International Baccalaureate equivalent ** High school diploma equivalent

	COBALT (*N* = 469)	GENPOD (*N* = 601)	IPCRESS (*N* = 295)	MIR (*N* = 480)	PANDA (*N* = 652)	TREAD (*N* = 361)	Overall (*N* = 2858)
Baseline BDI-II total							
Mean (SD)	31.8 (10.7)	33.7 (9.67)	33.2 (8.80)	31.1 (9.91)	23.9 (10.3)	32.1 (9.24)	30.4 (10.5)
Median [min, max]	30.0 [14.0, 60.0]	33.0 [15.0, 60.0]	33.0 [15.0, 58.0]	30.0 [14.0, 58.0]	23.0 [2.00, 54.0]	31.0 [14.0, 57.0]	30.0 [2.00, 60.0]
Gender							
Female	339 (72.3%)	408 (67.9%)	200 (67.8%)	332 (69.2%)	384 (58.9%)	239 (66.2%)	1902 (66.6%)
Male	130 (27.7%)	193 (32.1%)	95 (32.2%)	148 (30.8%)	268 (41.1%)	122 (33.8%)	956 (33.4%)
Age							
Mean (SD)	49.6 (11.7)	38.8 (12.4)	34.9 (11.6)	50.7 (13.2)	39.7 (15.0)	39.8 (12.6)	42.5 (14.1)
Median [min, max]	50.0 [18.0, 74.0]	38.0 [18.0, 74.0]	34.0 [18.8, 74.6]	51.0 [19.0, 84.0]	38.5 [18.0, 73.0]	39.0 [18.0, 69.0]	42.0 [18.0, 84.0]
Employment status							
Employed	206 (43.9%)	357 (59.4%)	178 (60.3%)	237 (49.4%)	433 (66.4%)	230 (63.7%)	1641 (57.4%)
Seeking employment	151 (32.2%)	123 (20.5%)	35 (11.9%)	102 (21.2%)	73 (11.2%)	48 (13.3%)	532 (18.6%)
Not seeking employment	112 (23.9%)	121 (20.1%)	82 (27.8%)	141 (29.4%)	146 (22.4%)	83 (23.0%)	685 (24.0%)
Education							
Degree or higher	95 (20.3%)	0 (0%)	102 (34.6%)	95 (19.8%)	230 (35.3%)	87 (24.1%)	609 (21.3%)
A-level or diplomas*	123 (26.2%)	0 (0%)	88 (29.8%)	135 (28.1%)	220 (33.7%)	104 (28.8%)	670 (23.4%)
GCSE**	131 (27.9%)	0 (0%)	62 (21.0%)	150 (31.2%)	145 (22.2%)	102 (28.3%)	590 (20.6%)
None or other	120 (25.6%)	0 (0%)	43 (14.6%)	100 (20.8%)	57 (8.7%)	68 (18.8%)	388 (13.6%)
Missing	0 (0%)	601 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	601 (21.0%)
Ethnicity							
White	459 (97.9%)	575 (95.7%)	281 (95.3%)	469 (97.7%)	579 (88.8%)	336 (93.1%)	2699 (94.4%)
Non-White	10 (2.1%)	26 (4.3%)	14 (4.7%)	11 (2.3%)	73 (11.2%)	25 (6.9%)	159 (5.6%)
Diagnoses							
Number of comorbid diagnoses	2.40 (1.09)	2.39 (0.92)	2.32 (0.99)	2.10 (0.97)	1.43 (1.18)	2.20 (1.17)	2.09 (1.12)
Generalised anxiety disorder	312 (66.52%)	410 (68.22%)	186 (63.05%)	219 (45.63%)	299 (45.86%)	238 (65.93%)	1664 (58.2%)
OCD	79 (16.84%)	114 (18.97%)	62 (21.02%)	62 (12.92%)	52 (7.98%)	50 (13.85%)	419 (14.7%)
Panic disorder	67 (14.29%)	51 (8.49%)	16 (5.42%)	45 (9.38%)	42 (6.44%)	14 (3.88%)	235 (8.2%)
Agoraphobia	61 (13.01%)	75 (12.48%)	28 (9.49%)	81 (16.88%)	42 (6.44%)	35 (9.70%)	322 (11.3%)
Social phobia	64 (13.65%)	64 (10.65%)	44 (14.92%)	58 (12.08%)	68 (10.43%)	52 (14.40%)	350 (12.2%)
Specific phobias	91 (19.40%)	127 (21.13%)	46 (15.59%)	62 (12.92%)	98 (15.03%)	61 (16.90%)	485 (17%)
Chronic fatigue syndrome	343 (73.13%)	476 (79.20%)	220 (74.58%)	311 (64.79%)	288 (44.17%)	257 (71.19%)	1895 (66.3%)

time point. The sensitivity analysis performed similarly. Due to the absence of two studies (IPCRESS and PANDA) at the 9–12-month endpoint, we reran the analyses for the earlier time points without these studies. This sensitivity analysis did not reveal any difference in the pattern of model performance.

Pessimism (Fig. 1) was consistently the most important item; health anxiety was in the upper quartile at each time point; and concentration, failure/worthlessness, also in the upper quartile at 3–4months; guilt and sleep at 6–8 months; and somatic symptoms at 9–12 months.

Network modelling

For the individual items in the network model, near zero variance (e.g. due to floor and ceiling effects) was not observed. However, we saw asymmetric distributions (skew) on a number of items. As such, a Spearman covariance matrix was estimated and used to estimate the network model. Multi-collinearity was identified for two pairs of items (loss of pleasure with loss of interest, failure with worthlessness). New items were constructed using PCA for each pair. The optimal model for the network analysis was an unregularized graphical Gaussian model using the EBIC.

A walktrap algorithm identified three, stable, symptom communities (median = 3, SD = 0.15, 95% CI [2.71, 3.29]). The three communities split into anxiety items, depressive cognitions and depressive physical symptoms. Bridging EI elucidated three bridging symptoms between the communities: sadness and indecisiveness (from the

Table 2 Performance of the regression models. Sum scores: BDI-II and CIS-R; RMSE root mean squared error; MAE mean absolute error; R^2 proportion of the variance explained

		PROMIS T-score		
		RMSE	R^2	MAE
3 to 4 months $N = 2646$	Items	0.925	0.146	0.73
	Sum scores	0.926	0.143	0.73
6 to 8 months $N = 1297$	Items	0.926	0.147	0.734
	Sum scores	0.924	0.146	0.735
9 to 12 months $N = 1110$	Items	0.919	0.161	0.744
	Sum scores	0.935	0.126	0.753

physical symptoms community) and pessimism (cognitive symptoms community).

Centrality estimates (i.e. measures of the strength of connection to other items) are reported in Fig. 2. The EI correlation stability coefficient was high (0.75), suggesting that the ordering of items based on centrality remained the same after re-estimating the network with fewer cases (the probability the correlation between original centrality indices and centrality of networks based on subsets was 0.7 or higher) and can be reliably interpreted.

The estimates from the different metrics (EI and PC/PR) were correlated ($r = 0.58$). The most central symptoms were sadness (PC/PR) and failure/worthlessness (EI). Failure/worthlessness had a significantly higher EI centrality than twenty-one other symptoms (see supplementary material). The next most central nodes (EI) were sadness, self-criticism, and loss of energy (all z-score > 1), followed by concentration, loss of pleasure/interest, and fatigue (z-score > 0.96), while the next most central nodes when using PC/PR were pessimism, failure/worthlessness, and punishment (all z-score > 1), then guilt, indecisiveness, and suicidal thoughts (all z-score > 0.80). Notably, while suicidal thoughts were highly central according the PC/PR metric (z-score = 0.80), it was much less central using EI (z-score = – 0.67). Loss of energy displayed the opposite relationship, more central for EI (z-score = 1.01) than PC/PR (z-score = – 2.03).

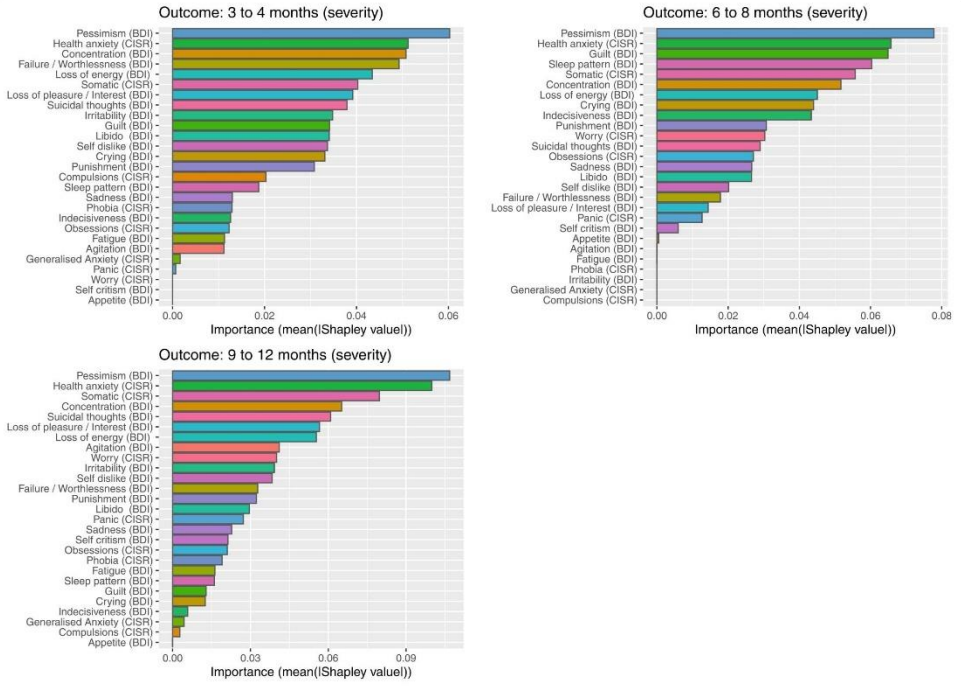

Fig. 1 Shapley values for variable importance are plotted: (showing the difference contribution of items to predictions)

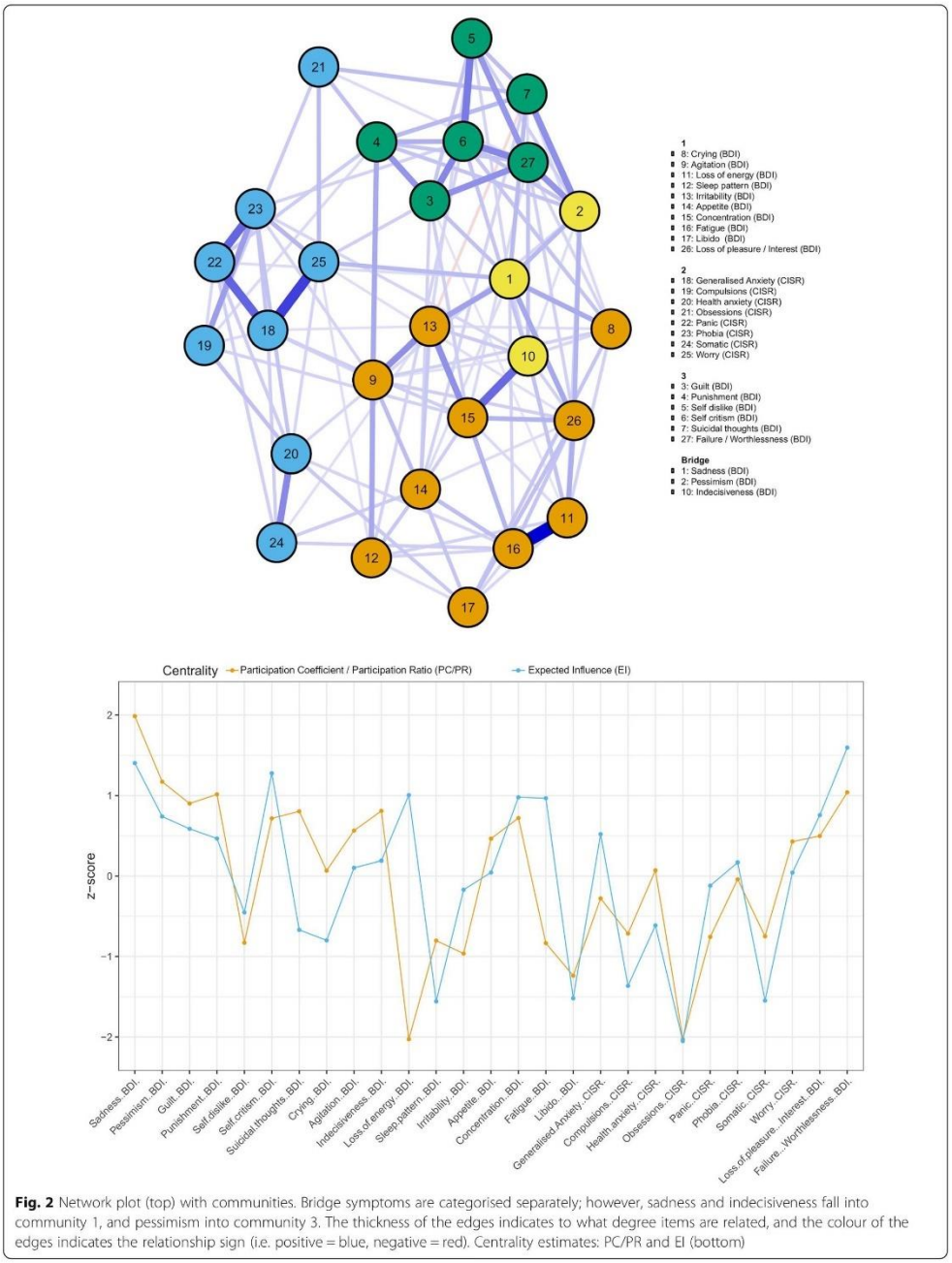

Fig. 2 Network plot (top) with communities. Bridge symptoms are categorised separately; however, sadness and indecisiveness fall into community 1, and pessimism into community 3. The thickness of the edges indicates to what degree items are related, and the colour of the edges indicates the relationship sign (i.e. positive = blue, negative = red). Centrality estimates: PC/PR and EI (bottom)

Loss of energy and obsessions were jointly the least central nodes using PC/PR, and obsessions was also the least central when using EI.

Robustness checks suggest the resulting graphical Gaussian model was stable and accurate. Stability and accuracy plots, individual networks (with the fused penalty) and the fused network model are supplied in the supplementary materials. Mean severity was not significantly correlated ($p < 0.05$) with EI ($r = 0.21$) or PC/PR ($r = -0.05$), while the standard deviation was significantly correlated for both EI ($r = -0.56$) and PC/PR ($r = -0.41$). Symptom severity was not associated with nodes being interconnected. Lower variability was associated with variability, which is the reverse of a more typical concern: differential variability driving the centrality of nodes [52].

The interrelation of the network and the FGL network were compared ($r = 0.72$), suggesting that between study differences had a small effect on network estimation. The network was corrected for the influence of duration of depression and anxiety; however, the overall influence on edge estimation was negligible (interrelation between the corrected network and a network estimated without duration variables: $r = 0.997$). Overall, the resulting network model can be considered robust.

Network comparison test

Networks (unregularized) were compared (1000 iterations) for those who were classified as in remission ($n = 956$) and those who were not ($n = 1466$). Mean severity differences at baseline were significant for all items ($p < 0.001$). The correlation between networks was high ($r = 0.67$). While there were significant difference between edges, the overall networks (see supplementary material) did not differ in connectivity (global strength invariance: $p < 0.08$) and post hoc tests were not warranted. There was only evidence of one difference in centrality between the networks: somatic symptoms were more connected in the remitter network than the persister network ($p < 0.001$).

Discussion

Individuals with depression also present with comorbidity, and this could present an issue for depression treatment. Understanding how symptoms influence one another across traditional diagnostic boundaries, and how they influence important outcomes, may provide insights relevant to the assessment and treatment of mood disorders. In this study, we initially examined the differential impact of individual symptoms on prognosis and assessed whether individual symptoms offer predictive value above sum scores. The item level models of outcomes post-treatment and the sum score models were similarly associated with outcomes at 3–4 and 6–8 months but explained considerably more variance at 9–12 months. Pessimism was consistently the most important predictor of future outcomes (independent of its mean), indicating that experiencing pessimism rather than severity of the symptom is responsible for this association. Secondly, we explored the functional relations among comorbid symptoms of depression and anxiety disorders using network analysis. The symptom network comprised of three communities clearly clustering into anxiety items, depressive cognitions, and depressive physical symptoms. The primary bridge symptoms between communities were sadness; pessimism; and indecision. The most central symptoms across both centrality metrics were sadness and failure/worthless. Finally, we analysed differences in the symptom networks at study entry for patients that remitted vs. those whose depression persisted, after treatment. Network comparison revealed no overall differences in connectivity. Together, the present findings suggest the utility of item-level analysis in informing the content of assessments and consideration of individual items over and above scale scores when predicting prognosis.

Findings in context

Exploring the associations with treatment outcomes revealed that item-level prediction methods performed similarly to sum scores and outperformed sum score models at the 9–12-month endpoint. It is not clear why there is a difference at this time point; while it was not due to attrition between endpoints, it could be due to random variation. It may also reflect the course of depression following intervention, or the cyclical nature of depression such that individual items are better at predicting the relapse or maintenance of symptoms after benefits of treatment have faded, or where an amelioration of symptoms occurred due to further treatment post randomisation. There is an ongoing debate in the field whether central items derived from network models offer predictive utility beyond other items [71–73]. Pessimism was not only the best predictor across outcomes; it was a central item (ranked 2nd on PC/PR and 6th on EI centrality) that acted as a bridge between communities and showed strong associations with sadness and failure/worthlessness. Sadness, comparatively, did not predict well across time points. It is worth noting that sadness falls within the physical symptom community and pessimism within the cognitive community. The amenability to act on an emotion (sadness) is understandably less than that of a cognition (pessimism), a target of cognitive therapy, while pessimism in association with a sense of failure/worthlessness may negatively impact treatment engagement (i.e. the motivation to sustain goal pursuit in the face of obstacles) [74]. Given the central role and prognostic value of

pessimism, we might speculate that it is associated with treatment factors, where pessimism hinders some people making progress and may not be directly addressed by some psychological treatments.

Symptoms of anxiety and depression clustered into separate communities with certain symptoms acting as bridges between communities. The bridge symptoms are statistically relevant and theoretically linked: indecision is a symptom in the classifications of both depression and generalised anxiety disorder, pessimism overlaps with worry [75] and the strong cross-community edge of sadness to worry was similar to findings in other studies [32, 76]. The results therefore provide evidence that these bridging symptoms may be important in the emergence of comorbidity between anxiety disorders and depression.

Planned comparisons of networks at study entry for those whose depression would persist versus those who would be in remission revealed no overall difference in connectivity, in contrast to Van Borkulo et al. [77], but similar to Schweren et al. [78].

Overall, we found no correlation between centrality metrics and Shapley values. This extends prior work on the association between centrality and the prognostic utility of items [71]. Failure/worthlessness was predictively important at 3–4 months, displayed high centrality and is suggested to be a key symptom in depression and anxiety [30]. The predictive utility of health anxiety and somatic concerns may be considered alongside the observation from the network comparison where there was a difference in centrality with somatic concerns more connected in the remitter network. Health anxiety was in the upper quintile of variable importance across time points, but relatively unimportant in terms of centrality. Not surprisingly, given the conceptual overlap, with health anxiety, the strongest edge was with somatic concerns. As such, the degree of concern for one's health, or attention to somatic symptoms, whilst not playing a significant role within the maintenance of depression, may act as a motivational spur to engage with treatment (in this way enabling rather than disabling the individual). The absence of this anxiety may reflect an apathy about one's health which is not captured by the motivational item in the BDI. While the predictive modelling did consider the influence of each item independent of the other items, modelling the predictive value of individual items may be improved by examining the association between the changes at symptom level and the overall network [79, 80].

The network derived in this study provides empirical phenomena that can be explained by principles of network theory. This requires interpreting the network as a causal system, even though we cannot infer temporal relationship between symptoms and there is an absence of causal mechanisms within the external field (e.g. environmental factors) [29]. These limitations apply to most of the findings in the network literature, although overinterpretation is common [81]. Holding this in mind, we can consider possible pathways and mediating role of symptoms through the network. For example, taking suicidal ideation as a clinically severe symptom, we can identify the shortest path from worry [82] passing through sadness (bridge), and from loss of pleasure/interest [83] to suicidal thoughts, passed through pessimism (bridge). It is possible that any causal effect between these connections may be part of a longer pathway within the network highlighting a need for greater attention to be given to symptom interactions.

The statistical model investigates a symptom level, transdiagnostic conceptualization of the symptom interactions for individuals diagnosed with depression participating in RCTs. These interventions are based on biological or psychological theories, most notably Beck's cognitive of theory of depression [84]. Clinically, pragmatism trumps theoretical completeness; simple interventions which achieve rapid change do not require a detailed appreciation of the potential underlying mechanisms. However, oversimplified theories may restrict the ability to identify causal patterns, and gaps emerge in practice where the model is suggested to not fit the patient [85]. More process-driven interventions targeting shared features of disorders have been developed [86, 87], yet there is no unifying theory. The findings presented may help bridge the gap between disorder-specific theories and more transdiagnostic theories. Considering how symptoms may interact can help clinicians and researchers to understand underlying processes and in turn to conceptualise their patients' difficulties in a way that supplements existing knowledge. A functional analysis which integrates the association between sadness and worry does not need to conceptualise the individual as having two disorders, but can consider how, for the individual, this interaction is being fuelled and may be contributing to their distress.

The journey to develop models that provide both explanatory and predictive utility will lead to greater understanding of psychopathology [88]. While the analysis presented is primarily exploratory, it sets up clear testable hypotheses. These can be derived by examining the central structures within the network, formulating hypotheses and testing on an independent sample [89]. For instance, whether the bridge edges belonging to pessimism, sadness, and indecisiveness re-emerge in an independent sample or whether a discrete intervention targeting pessimism would alter the network structure and lead to improved outcome. These statistical methods may help inform how identifying pathways and targets may lead to improved

treatments all dependent on better assessment of symptoms.

Strengths and limitations

This study has clear strengths, making use of a large sample of individuals participating in RCTs for depression in primary care. The use of same assessment measures at study entry removed the need to harmonise data across different measures for the network. While this is less true of outcomes where issues of measurement errors arise from the use of PROMIS T-Score, the sensitivity analyses provided confidence in the results.

The demographic balance across samples may affect generalisability; however, five of the six trials were pragmatic trials more closely representative of patient populations. Most cases of depression are treated in primary care, and the studies being set in primary care, improve the potential generalisability to patients seen in this setting [90].

This study was limited to the use of aggregate/group level findings to inform within person processes. However, the presence of an RCT outcome variable affords us the ability to detect changes from one state (e.g. depressed) to another (e.g. remitted), which is typically not the case with idiographic research studies that collect cross-sectional data. Exploring the prognostics value of networks on deterioration of symptoms would extend the utility of network analysis. This would however require generating idiographic networks, where reliable estimation necessitates many time points (low sensitivity at 100 time points [91].

The accuracy of the network is limited by the items included and those omitted. The network does not cover the breadth of comorbidity of symptoms across psychopathology and is missing other environmental variables. Social adversity is associated with worse treatment outcomes for some patients with depression; it can be important to assess for and address these issues in clinic, where possible, to mitigate the risks of poor prognoses [92]. There is also the possibility that the centrality of sadness particularly represents a strong association with a latent variable rather than a specific role within the network [93].

The network models adjusted for duration of depression and anxiety, and a sensitivity analysis assessed for the influence of between study variability, adding robustness to the findings. While RCTs are used in the analysis, treatment arms were not factored in and treated as equivalent when estimating outcome. This may make the findings generalizable where findings are applicable regardless of treatment offered especially as the treatments included reflect those commonly available in primary care. Controlling for treatment group within the outcome modelling and controlling for relevant covariates (e.g. age, gender and social economic status) would also have improved the robustness of the findings. Such adjustments would have been fitting where the emphasis was on developing the best predictive model, instead of comparing the predictive ability of symptoms vs. total scores. More comprehensive prediction modelling using the Dep-GP dataset has been conducted [94]. Additionally, our modelling did not include train/test split, as the whole sample was used in estimation of the network models. While a true out-of-sample 'holdout' dataset would have provided an unbiased evaluation of model fit, and is the preferred method for evaluating such models [95], the internal cross-fold validation employed in the symptom level model offers a layer of robustness supporting the final model estimates (where overfitting presents an issue). This study focussed on item-level analysis in comparison to sum-scores, future comparisons with models which may measure latent constructs in other ways, could be informative.

Single item symptom measurement will have unknown reliability and construct validity. Equally, the restricted range (e.g. a four-point scale) may not adequately capture the range of symptom variance occurring in the sample. Symptom measurement on a broader scale may improve the prediction of changes over time.

Conclusions

Our study used samples from high-quality randomised controlled trials, and the findings can be generalised to adults with depression being treated in primary care. This study has reiterated the importance of assessing for both depressive and anxious symptoms among adults seeking treatment for depression, and that valuable information about prognosis can be gained by understanding the interrelations between individual symptoms, information which is not available when considering sum scores or baseline symptom severity alone. This may be particularly important to longer term outcomes from treatment. Treatment selection and application is often hampered by comorbid symptoms and considered to introduce 'complexity' [96]. Considering the bidirectional relationship between symptoms and associations which may be mediated by another symptom (e.g. a bridge symptom) may help to consider comorbidity as normative.

While specific symptoms and associations have been highlighted, the aim is not to offer simple heuristics to inform clinical judgement and decision making. The relative importance of the highlighted associations should not be overweighed. The aim is not to identify individual items, but to consider the network of interactions. The critical role of individual symptoms and their interactions give rise to the activation of the network through pathways and anxiety and depressive cognitive

and physical symptoms may activate one another via these pathways. This network highlights how symptoms of depression and anxiety disorders influence one another. Clinically, there is a need for treatments to adequately assess and address comorbidity.

Abbreviations

BDI-II: Beck depression invention (2nd edition); CIS-R: Revised Clinical Interview Schedule; EBIC: Extended Bayesian information criterion; EI: Expected influence; ENR: Elastic net regression; FGL: Fused graphical lasso; GGM: Gaussian graphical model; IPD: Individual patient data; MAE: Mean absolute error; PC: Participation coefficient; PCA: Principal component analysis; PHQ-9: Patient Health Questionnaire 9; PR: Participation ratio; RMSE: Root mean squared error

Supplementary Information

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Additional file 1.

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Authors' contributions

Conceptualization (CO'D, JB, EF, RS), data curation (JB), statistical analysis (CO'D, JB), draft preparation (CO'D), review and editing (JB, EF, RS, ZC, GA, RD, SG, SH, TK, DK, GL, EW, NW, SP). All authors contributed to and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the authors of the individual trial studies. Restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

Not applicable

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Transdiagnostic symptom dynamics during psychotherapy

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Psychotherapy is an effective treatment for many common mental health problems, but the mechanisms of action and processes of change are unclear, perhaps driven by the focus on a single diagnosis which does not reflect the heterogeneous symptom experiences of many patients. The objective of this study was to better understand therapeutic change, by illustrating how symptoms evolve and interact during psychotherapy. Data from 113,608 patients from psychological therapy services who completed depression and anxiety symptom measures across three to six therapy sessions were analysed. A panel graphical vector-autoregression model was estimated in a model development sample (N = 68,165) and generalizability was tested in a confirmatory model, fitted to a separate (hold-out) sample of patients (N = 45,443). The model displayed an excellent fit and replicated in the confirmatory holdout sample. First, we found that nearly all symptoms were statistically related to each other (i.e. dense connectivity), indicating that no one symptom or association drives change. Second, the structure of symptom interrelations which emerged did not change across sessions. These findings provide a dynamic view of the process of symptom change during psychotherapy and give rise to several causal hypotheses relating to structure, mechanism, and process.

Psychotherapies are effective treatments for a broad range of common mental health problems, but do not work for a substantial proportion of patients[1]. It is still not clear how therapies work, or what the processes of change occur during psychotherapies[2]. This lack of knowledge is stifling the development of novel interventions that target the putative mechanisms maintaining the disorders, hence limiting the potential for improvements in patient outcomes. Dismantling studies and trials of individual treatment components can be informative, but have frequently been hampered by low-quality methodology[3]. It is widely believed that different psychotherapies share several common causal mechanisms and operate in ways that are more similar than they are different[4–7]. Common factors, such as therapeutic alliance, are unlikely to improve our understanding of change[2] and there is a need to focus on other mechanisms of change in psychotherapy[8,9].

The development of psychotherapy treatments has, for the most part, been tied to specific diagnoses, yet this does not reflect clinical reality where co-morbidity is the rule rather than the exception[10]. The evidence-base for the effectiveness of psychotherapies comes from randomised control trials (RCTs) which largely focus on specific diagnoses[11]. This assumes that treatments either target an underlying disease or target a specific set of symptoms commensurate with the diagnosis. In clinical practice, co-morbidity can present challenges for clinicians in selecting the most appropriate disorder-specific treatment, or the ordering of interventions to tackle the seemingly disparate presenting problems; this can lead to some comorbid presentations being labelled as 'complex'. The presence of comorbidity is likely an artefact of the classification of disorders[12,13] hence significant comorbidity exists within RCTs for depression[14] and is associated with treatment prognosis. While there are distinct features of diagnostic disorders, they are not discrete[15], with considerable symptom overlap across disorders[16,17]. Mapping symptoms across disorders reveals how this overlap can inform an understanding of the emergence of co-morbidity[18]. Symptom heterogeneity also occurs *within* disorders[19,20], with potential both for variability in diagnosis, or reaching the same diagnosis without any symptom overlap[21]. A transdiagnostic approach to

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psychopathology (i.e. aiming to identify overarching processes, by addressing causality and mechanism), might help overcome these obstacles and facilitate the identification of processes of change[22].

Modelling change (in symptoms for example) is a fundamental means by which we can better understand mental health problems and their treatment. Methodological approaches to understanding the processes of change during psychotherapies have largely considered symptomatic change as a shift in a latent construct (e.g. a difference in the sum score on a measure of depressive symptoms, as signalling a change in the latent construct of depression). This fits with the diagnostically congruent 'common cause' theoretical framework, which purports that symptoms are passive and interchangeable indicators of an underlying latent disease. Systems theory and network approaches[23] offer an alternative viewpoint, proposing that the disorder is an emergent property and that symptoms are autonomous causal agents[24,25]. According to systems theory, causal interactions between symptoms and relevant external factors can give rise to emergent states of psychopathology. An external event (e.g. loss of job) or internal event (e.g. brain trauma), can activate the system (psychological, social and biological processes), and the system will respond (e.g. symptoms activating neighbouring symptoms). While individuals may exist in states of equilibrium, crossing certain thresholds may shift the system into different self-sustaining (attractor) states, so the system may be maintained through causal loops despite the absence of the initial stressor[25,26]. If the psychotherapy activates change in an individual's distress, this change can be observed in transition between states. During a transition, the organization of the system and facilitators of change become apparent[27]. The system may reorganise and develop as the symptoms interact or may reach a critical point and transition into a different state (i.e. 'disordered' to 'healthy'). While change can be gradual or sudden, it requires significant disturbance to shift the system out of a pathological attractor state[28].

Investigations of the processes of change in large psychotherapy samples have typically focused on identifying profiles[29] of patients with differential outcomes and predictors of differential response trajectories[30]. Studies that have focused on symptoms have been hampered by the primary use of cross-sectional data where bidirectionality and statistical equivalence make inferences difficult[31]. Cross-sectional data limits interpretation because they cannot provide evidence for directed relationships (over time); and in cross-sectional data, statistical equivalence (i.e. having multiple models that can fit the data identically), is a larger concern than in temporal data[31]. Psychotherapy research has historically focused on between-person differences, either by comparing groups, or by studying correlations between individual characteristics[32]. Such relationships derived from group level analyses may not generalize to individuals[33]. To address these limitations, we will adopt a transdiagnostic, symptom level analysis, focusing on symptoms common across disorders, modelling change over time in a naturalistic setting of patients receiving psychotherapy. The modelling approach will also distinguish within-person variability (within a person over time and contexts), from between-person variability (stable traits and variations across persons)[34]. Within this analysis, the term within person does not refer to true within person observations (i.e. of an individual person), but of the within-person relationship of an average person (aggregated over people)[35].

This study will focus on the dynamics between common mental health symptoms during psychotherapy. We consider the modelled symptoms to represent an important part of a broader system and consider the interactive change and self-organisation of these signs and symptoms during the process of psychotherapy. The aim is to model transdiagnostic change, across therapies and across disorders, where the symptoms modelled reflect the core symptoms of depression and generalised anxiety in the DSM-5[36]. These are dimensionally normative symptoms (e.g. tiredness, nervousness) and are diagnostic features of many disorders (Table 1). Some of these symptoms may be descriptively transdiagnostic while others could be considered mechanistically transdiagnostic[37]. Through identifying dynamics of symptom change during psychotherapy, the results can inform theory on the structure of psychopathology and functional processes of change.

Results

Sample characteristics. The characteristics of the training and holdout samples are shown in Table 2. In total, combined they included 113,608 patients who attended at least three sessions. Ages ranged from 17 to 94 years old. Proportionally, there were more females (67%); and more patients from White ethnicity groups (63%). Ethnicity was reflective of the population estimates for London[38]. Most patients received High Intensity Cognitive Behavioural Therapy (CBT), and the next most frequently delivered was Low Intensity CBT, with 11% receiving a different mode of therapy [i.e., Counselling, Behavioural Couples Therapy, Dynamic Interpersonal Therapy, Eye Movement Desensitization and Reprocessing (EMDR), Mindfulness-Based Cognitive Therapy (MBCT), or Interpersonal Psychotherapy (IPT)].

There was a broad range of presenting problems (also referred to as a 'problem descriptor' in IAPT) which are diagnoses based on ICD-10 and represent the focus of treatment agreed between a patient and clinician. Figure 1 shows the mean symptoms scores across the six time points. All symptoms are shown to change over time (all $p < 0.001$) and the slope of the trajectory was similar across items. Mean PHQ-9 total reduced from 14.13 (SD = 6.26) at timepoint one to 10.7 (SD = 6.59) at timepoint six, and GAD-7 total from 12.98 (SD = 5.19) to 9.88 (SD = 5.71).

Panel graphical VAR modelling. The panel graphical VAR was estimated in the training sample. Confidence interval (CI) plots for the model are available at https://osf.io/gp6dw/. Figure 2 shows the temporal, contemporaneous, and between-person networks. The training model (n = 68,165) contained 16 items and six timepoints, resulting in 544 estimated parameters. The fit statistics for all models are displayed in Table 3. The root-mean-square error of approximation (RMSEA) of the training model was 0.014 (95% CI 0.014; 0.015), and incremental fit indices were excellent. The confirmatory model in the holdout sample (n = 45,443) showed excellent fit. This was further supported by the equality constrained model which also showed excellent fit. Finally, the

Symptoms	Generalised Anxiety	Depressive disorders	Schizophrenia	PSTD	Personality disorder borderline	Bipolar	Anorexia	OCD	Insomnia	Panic disorders	Specific phobia	Social Anxiety	
Feeling nervous, anxious or on edge	○		○	○	○	○	○	○		○	○	○	10
Not being able to stop or control worrying	○				○			○					3
Worrying too much about different things	○				○								2
Trouble relaxing	○		○	○		○				○			5
Restlessness	○	○	○	○		○							5
Becoming easily annoyed or irritable	○		○	○	○	○	○		○				7
Apprehensive expectation	○			○				○		○	○	○	6
Anhedonia		○	○	○				○					4
Feeling down, depressed, or hopeless		○	○		○		○		○				5
Sleep difficulties	○	○	○	○		○	○		○				7
Feeling tired or having little energy	○	○	○				○		○				5
Poor appetite or overeating		○	○				○						3
Feeling bad about yourself/ failure		○		○	○		○						4
Concentration	○	○	○	○		○			○				6
Psychomotor retardation/ agitation	○	○	○	○		○							5
Suicidal ideation		○	○	○	○	○	○	○					7
Total	11	10	12	11	7	7	7	4	4	3	2	2	

Table 1. Symptoms captured by the PHQ-9 and GAD-7 mapped onto features of DSM-5 disorders.

nondetrended model showed good fit, with the high to near perfect spearman correlations between detrended and nondetrended adjacency matrices (temporal $r = 0.82$; contemporaneous $r = 0.99$; between $r = 0.93$).

Temporal network. The saturated temporal network model was dense, with mostly small but significant parameters at the adjusted p-value ($p < 0.0001$), mean association: $r = 0.03$ (median $= 0.02$). The network displayed moderate to large autocorrelations, with suicidal ideation as the strongest ($r = 0.27$).

The most prominent bidirectional associations, following the autocorrelations, were between depressed mood and anhedonia; excessive worry and difficulty controlling worry; difficulty controlling worry and feeling nervous/anxious; psychomotor retardation/agitation and restlessness (all $|r| > 0.05$). The most prominent unidirectional associations ($|r| > 0.05$) were between depressed mood to feeling like a failure; apprehensive expectation to difficulty controlling worry; apprehensive expectation to excessive worry; apprehensive expectation to feeling nervous/anxious and suicidal ideation to feeling like a failure. While these associations are the most prominent, the cut-off of 0.05 was arbitrary and 34 associations had CIs in the range of 0.05.

Considering the centrality of the items, depressed mood ($z = 2.37$), anhedonia ($z = 1.74$), feeling nervous ($z = 0.96$) and apprehensive expectation ($z = 0.94$) had the strongest In-Expected Influence (all $z > 0.9$). Excessive worry ($z = 1.32$), difficulty controlling worry ($z = 1.22$) and trouble relaxing ($z = 1.10 > 1$), has the strongest Out-Expected Influence.

	Training set		Hold out set	
	n = 67,048		n = 44,645	
PHQ-9 total: mean (SD)	14.13 (6.26)		14.15 (6.25)	
GAD-7 total: mean (SD)	12.98 (5.19)		12.98 (5.19)	
Number of sessions: mean (SD)	8.07 (4.84)		8.05 (4.85)	
Age: mean (SD)	37.76 (13.44)		37.78 (13.48)	
Gender				
Male	21,396	31.91%	14,466	32.40%
Female	45,357	67.65%	29,983	67.16%
Missing/not disclosed	295	0.44%	196	0.44%
Ethnicity (ONS)				
Asian	7024	10.48%	4681	10.48%
Black	7331	10.93%	5030	11.27%
Chinese	471	0.70%	316	0.71%
Mixed	3890	5.80%	2661	5.96%
Other	2641	3.94%	1725	3.86%
White	42,438	63.29%	28,210	63.19%
Missing	3253	4.85%	2022	4.53%
Intervention type				
LI CBT	25,819	38.51%	17,223	38.58%
LI Other	3815	5.69%	2502	5.60%
HI CBT	28,332	42.26%	18,909	42.35%
HI Other*	7401	11.04%	4916	11.01%
Missing	1681	2.51%	1095	2.45%
Presenting problem (primary diagnosis)				
Adjustment disorder	518	0.77%	333	0.75%
Agoraphobia	322	0.48%	234	0.52%
Alcohol related disorder	30	0.04%	19	0.04%
Bereavement	333	0.50%	213	0.48%
Bipolar affective disorder	39	0.06%	29	0.06%
Body dysmorphic disorder	11	0.02%	9	0.02%
Depressive episode	23,555	35.13%	15,450	34.61%
Eating disorder	156	0.23%	98	0.22%
GAD	11,041	16.47%	7232	16.20%
Hypochondriacal disorder	440	0.66%	304	0.68%
Insomnia	144	0.21%	69	0.15%
Mixed anxiety and depression	4323	6.45%	3001	6.72%
OCD	1342	2.00%	900	2.02%
Panic disorder	2402	3.58%	1647	3.69%
Personality disorders	7	0.01%	2	0.00%
PTSD	2159	3.22%	1365	3.06%
Recurrent depression	4377	6.53%	2960	6.63%
Social phobia	1994	2.97%	1410	3.16%
Somatoform disorder	335	0.50%	232	0.52%
Specific phobia	667	0.99%	427	0.96%
Unspecified anxiety disorder	548	0.82%	366	0.82%
Missing (not specified)	13,313	19.85%	8345	18.69%

Table 2. Sample characteristics. *(Counselling, IPT, Psychodynamic, MBCT, EMDR).

Contemporaneous and between person models. The within-person contemporaneous network was also dense with most associations highly significant ($p < 0.0001$). Contemporaneous within/between networks were highly correlated ($r = 0.79$), suggesting a high degree of homogeneity of effects—i.e., low between-person differences. The strongest associations within-persons ($|r| > 0.2$) were excessive worry and difficulty controlling worry; depressed mood and anhedonia; difficulty controlling worry and feeling nervous; energy and sleep; restlessness and trouble relaxing; and feeling like a failure and depressed mood. At the within-persons level, the most central items were difficulty controlling worry, depressed mood, trouble relaxing and excessive worry ($z > 1$). The strongest associations between-persons ($|r| > 0.3$) were excessive worry and difficulty controlling worry;

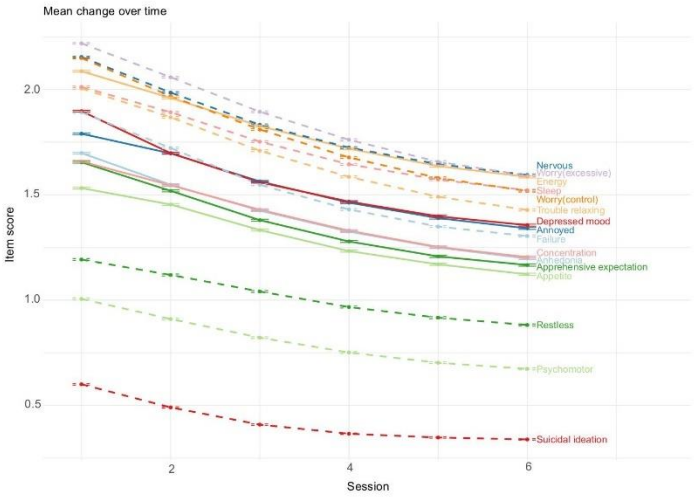

Figure 1. Mean symptoms scores (and standard error) across the six time points. Dashed lines are PHQ-9 items and solid lines are GAD-7 items.

depressed mood and anhedonia; psychomotor agitation/retardation and restlessness; anhedonia and depressed mood; depressed mood and feeling like a failure; and restlessness and trouble relaxing. In the between-persons network, depressed mood, and difficulty controlling worry were most central ($z > 1$). Centrality of items between the within and between networks was correlated $r = 0.72$.

Unregularised, cross-sectional networks using the Gaussian graphical stepwise model selection ("ggModSelect") algorithm[35] at each time point (see https://osf.io/gp6dw/), could not be distinguished from unity ($r = 0.99$), indicating near perfect replication of network structures across all six timepoints. The mean density of networks (the sum of all edges within each network) was 7.27 ($sd = 0.09$, range: 7.12 to 7.34), incrementally increasing over time.

Discussion

This study explored dynamics of symptom change during psychotherapy. Using sessional symptom data from a large sample receiving treatment for common mental disorders, the results show a large co-occurrence of symptom change over time. Symptoms decreased across the board, and there was a strong temporal dependence between various symptoms. The network structure of associations, however, remained the same. Mean changes were somewhat different for different symptoms, but they tended to change together. The results of these analyses are statistically reliable; generalise to a holdout sample; and provide insights in the temporal effects and whether these associations covary at the trait (between person), or state level (within person). While we do not know whether findings generalize to a non-psychotherapy (e.g. waitlist control) condition, we assume that some of the observed patterns in the data are due to psychotherapy, e.g. the overall symptom reduction over time. In the rest of the discussion, we consider interpretation, implications, specific findings, strengths and limitations.

Interpretation of the dynamics can be viewed in several ways. These findings highlight a syntactical equivalence[39], with the results supporting both common cause and systems theory which are often considered to be diametrically opposed. A dynamic systems theory view is that a broad range of symptoms were active and that these in turn influenced other symptoms over time. From a common cause perspective, the density of the network would suggest a common latent variable (i.e. symptoms reflect an unobserved construct). We might infer causal (temporal) associations between symptoms from the temporal network model, supporting a systems interpretation, as a common cause model assumes no direct causal relations between observations. It is also likely that both are true simultaneously; a hybrid model where the common cause reflects onset and the dynamic system, maintenance[40]. These theories are under determined given the data, requiring experimental intervention to differentiate these theories[31]. From a systems perspective, one might have expected a sparser model with bridging symptoms identified between clusters of similar symptoms to explain the development of co-morbidity[41]. The sparsity usually revealed in network studies may be related to a combination of using underpowered small datasets and regularization. Therefore, in this large sample, the density of significant associations may be more representative of the actual complexity of the psychopathological system (i.e. closer to the true model[42]) and as such the sparsity assumption may be invalid.

This brings us to the clinical implications. The models using detrended and undetrended data were comparable which strengthens the ability to make inferences around processes of change[43]. Change mechanisms or causal

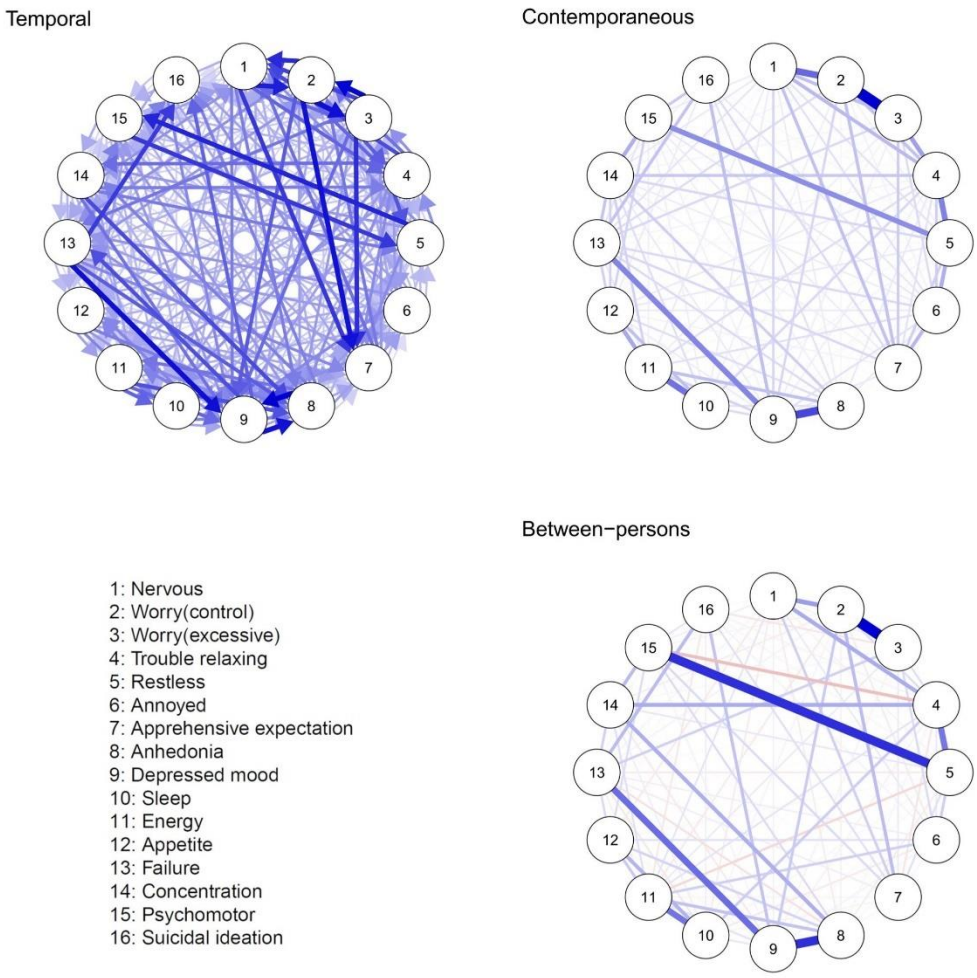

Figure 2. Panel graphical VAR model. Circles represent symptoms, and connections (undirected drawn as lines or directed drawn as an arrow) indicate predictive relationships. Blue lines indicate positive relationships, red lines indicate negative relationships. The width and saturation of a line indicates the strength of the relationship. In the temporal network (left), directed lines indicate where a symptom predicts another symptom at the next session after controlling for all other variables. Within the contemporaneous (middle) lines represent partial correlations between symptoms at the same timepoint, after controlling for all other variables and temporal effects. The between-persons network (right) indicating partial correlations between stable averages. We only plot significant edges, and the visualisation of autocorrelations in the temporal network has been omitted to improve visualisation; a figure including autocorrelations can be found in supplementary materials.

effects were also most likely to be identified within the contemporaneous network where confounding by stable variables was mitigated[44]. There is heterogeneity in the sample, with variation in individual factors, diagnoses, and types of therapy received. On the one hand, if there is a common process underlying all psychotherapeutic approaches (e.g. exposure[5]), certain symptoms may respond similarly (regardless of sample heterogeneity), where symptoms are interchangeable indicators of a process (e.g. avoidance). Change in one symptom should result in changes throughout the network leading to a change in overall symptom severity. Such an interpretation rests on assumptions that: there are no other external effects; that we have modelled all relevant variables; and that we have the accurate time-steps by which variables evolve. On the other hand, certain symptoms were more dominant, by which we mean they had stronger and more numerous edges, within the network structures. If such

	Training model	Hold out model	Confirmatory model	Equality constrained model	Training model (nondetrended)
df	4208	4208	4464	8672	4208
Chisq	63,960	48,365	25,525	108,247	119,256
NFI	0.984	0.982	0.982	0.984	0.970
PNFI	0.908	0.906	0.906	0.935	0.895
TLI	0.984	0.982	0.984	0.984	0.969
RFI	0.983	0.980	0.980	0.983	0.968
IFI	0.985	0.983	0.985	0.985	0.971
CFI	0.985	0.983	0.985	0.985	0.971
RMSEA	0.014	0.015	0.017	0.014	0.020
RMSEA 95% CIs	0.014:0.015	0.015:0.015	0.017:0.017	0.014:0.014	0.020:0.020

Table 3. Fit statistics across panel graphical VAR models.

symptoms exhibited the highest causal force, which is one possible interpretation of the data, then these symptoms may have triggered changes that rippled through the network. If this were the case, worry (excessiveness and controllability), along with trouble relaxing, appeared to hold the strongest influence on other symptoms. The influence of these symptoms and depressed mood were also highlighted at the contemporaneous level. Feeling nervous, depressed mood and anhedonia were most influenced by other symptoms. This may suggest that during psychotherapy, on average, strategies targeting worry and trouble relaxing may bring about changes throughout the network, either directly or through pathways to the most influenced symptoms.

Some specific findings are worth discussing in some detail. The association between depressed mood and anhedonia was consistent with other findings[45], representing core symptoms of depression[46], and excessive and uncontrollable worry as a transdiagnostic process (i.e. repetitive negative thinking)[47,48]. Worry symptoms (excessiveness/controllability) covaried, as did depressed mood and anhedonia. The controllability of worry covaried with feeling nervous; energy with sleep; restlessness with trouble relaxing; and feelings of failure with depressed mood. Suicidal ideation at one session, predicted by itself at an earlier session, was the strongest association in the temporal network, with suicidal ideation predicting a sense of failure and depressed mood at the next session. To a lesser degree, depressed mood also influenced suicidal ideation at the next timepoint. This is notable given that suicidal ideation is generally a peripheral symptom in many network studies[49] and whilst considered clinically important, it is rarely targeted with direct interventions in the same way as depressed mood or worry. The emergence of this association may be due to the use of a considerably larger and naturalistically treated patient sample compared to most prior studies which may have encountered floor effects on measures of suicidal ideation given their smaller and often non-clinical samples.

According to dynamic systems theory, differences between states can reflect attempts for correction and, depending on the mechanism of change, can lead to a re-organisation in the system—shift in state (e.g. from 'disordered' to 'healthy'). Within this panel model, the structure of the network does not change over time, across the time-period measured (six sessions). A critical tipping point may not have been reached (i.e. on average, the 'disordered' state is maintained). On average, the most change occurred within this timeframe, but changes to the stability and density of the networks may have altered were further sessions included. Such shifts may be revealed in separate dynamic networks of those whose symptoms remit versus those whose symptoms persist, or more notably at the idiographic level, where identifying these state transitions could have a deterministic effect on treatment outcome.

The study captured between session changes and appeared, to a degree, to have also captured changes that occurred at shorter intervals (the contemporaneous network displayed symptom dynamics which unfolded faster than the timeframe of measurement[40]). The measurement approach may not have allowed for sufficient granularity of symptomatic change processes during psychotherapy. These may be better captured by more frequent measurement, including approaches less reliant on retrospective recall, such as the use of ecological momentary assessments (EMA). The implementation of EMA during therapy might allow for idiographic modelling of change processes which could directly inform the therapeutic process as it unfolds[50].

A clear strength of this study lies in using routine clinical data from a large sample in a naturalistic setting and not constraining analyses to any diagnostic category or specific therapy type. Findings may therefore be generalizable to a broad population of adults seeking psychotherapies for common mental disorders. There are limits to the generalizability as only services in the London area were included and all participants received healthcare free at the point of use, so replication in other settings and locations may be required. The study captures provisional diagnosis; these are not formal diagnosis and there was no assessment of co-morbidity.

There are limitations to deriving true causal relationships between symptoms in this study. This requires consideration the assumptions of the statistical model. First, while we can identify temporal precedence, and the approach allows for conditional inferences across levels[51], the modelling approach captured group level processes. Second, the model does not capture measurement error, and cannot account for the absence of unmeasured external variables (other core psychopathological symptoms) or time-varying confounders. Third, some of these associations may be due to topological overlap (although we tested for this and it was not present across the cross-sectional networks). Fourth, ergodicity, while not a required assumption for causal statements, is implausible in in such a heterogeneous sample, although the average group model was highly similar to the average individual

model over time. Finally, the model does not reveal likely subgroups with different trajectories of change. Indeed, in a similar sample, four trajectories of change based on the PHQ-9 and GAD-7 sum scores were identified[29]. As such, the findings from this study can only be taken as potential causal associations and inferences about intra-individual processes of change during psychotherapy in this sample relate to a hypothetical average person. Identification of subgroups combined with latent growth network modelling[52] may offer additional insights into the change mechanisms during psychotherapy, help us understand how different subgroups respond to therapy, and what specific factors may contribute to better outcomes.

This study mapped the symptom dynamics during psychotherapy but there is still a question about what is influencing this change. It is uncertain as to whether these changes occur due to: in-session process such as exposure, as a transdiagnostic procedure[5]; features of the therapeutic alliance such as the development of epistemic trust[53]; therapeutic procedures such as developing strategies to address repetitive negative thinking[54]; between session behaviour change[55]; or regression to the mean[56]. Such features of psychotherapy, where measurable could be integrated into moderated network models where the network is conditioned on the mechanism of change[57]. Such advances will help us to further understand how psychotherapy works.

The focus on symptoms feeds into a biomedical understanding of mental health difficulties and omits many important variables (e.g. experiential and quality of life related constructs). A more comprehensive biopsychosocial model would require including markers generally associated with prognoses regardless of the type of treatment received including markers of the severity of the mental health condition, and also social support, life events, sociodemographics and socioeconomic factors[58–61]. While this introduces complexity at the modelling and data collection levels, developments across both these areas will further develop our understanding of change during therapy. Nonetheless, this study may help elucidate the biobehavioural understanding of change during psychotherapy.

Much of the research to date has focused on change at the mechanistic level or sum-score changes, with little focus on change at the level of specific symptoms and even less on their temporal associations. The relationship between symptoms can help to predict outcomes and potentially inform the development of more targeted treatments[11,62]. It may also help inform an understanding of phenomena such as early sudden gains[63]. This study provides a significant contribution to the network literature: informing network methodology; addressing concerns about network replicability[64]; and overcoming barriers present in previous research limited by sample size and cross-sectional design.

Methods

All methods were carried out in accordance with the Health Research Authority guidelines. NHS ethical approval was not required for this study (confirmed by the Health Research Authority July 2020, reference number 81/81). The data were provided by the IAPT services for evaluation as part of a wider service improvement project conducted in accordance with the procedures of the host institution and the NHS Trusts which operate the IAPT services (project reference: 00519-IAPT). At their initial contact with services all patients are informed that their data are sent to NHS Digital as part of national reporting, and may be used for research and service improvement by the services, and they are given the option to opt out of this if they wish. Only anonymised data from those patients that were considered to have opted-in for their data to flow in this way were included in the current project. No patient identifiable data were available to the research team.

Participants. We analyzed data from patients that received psychological therapy from eight Improving Access to Psychological Therapies (IAPT) services in the North and Central East London IAPT Service Improvement and Research Network (NCEL IAPT SIRN)[65] IAPT services provide evidence-based psychological treatments for common mental health disorders and are mandated to collect outcome measures at each session, which has resulted in over 98% pre-post treatment data availability[66]. In IAPT, high intensity therapy includes CBT, Behavioural Activation, Counselling, Interpersonal Psychotherapy, Short-term Psychodynamic Psychotherapy and EMDR, typically weekly for 10 to 16 session lasting 50 to 60 min, while low intensity therapy, tends to involve four to eight sessions of 30 min with practitioners guiding patients in the use of self-help material or computerized programmes based on CBT or Behavioural Activation[67].

For this study, patients were included if they received a minimum of three psychological therapy treatment sessions and if data were available on all the individual symptom items from the requisite symptom measures (detailed below). Only data from the first six treatment sessions were analysed regardless of the total number of sessions a patient received if beyond six.

Measures. Each session patients completed: the Patient Health Questionnaire 9-item version (PHQ-9[68]) a brief measure of depressive symptoms; and the Generalized Anxiety Disorder Scale 7-item version (GAD-7[69]), a measure of generalised anxiety disorder symptoms.

Plan of analysis. The analyses involved estimating a panel graphical vector-autoregressive model (panel GVAR) in the training data and confirmatory models to test generalizability by: (a) fitting the network model in the holdout sample; and (b) testing for parameter invariance between datasets by implementing equality constraints (i.e. edges constrained to be equal between the training and holdout set). Finally, cross sectional networks were estimated to visualise the network structure at each timepoint.

Treatment length differs across modalities, and substantial change typically occurs early in psychotherapy[63,70], with a previous analysis in a similar sample indicating that the trajectory of change could be identified by the third session for most patients, and by the sixth session for the remaining patients[29]. Temporal dynamics were modelled

across the first six sessions, chosen to capture these early causal dynamics during this period. The cap of six was also informed by the constraints of model complexity where convergence issues arise with each additional wave.

The dataset was randomly split (60:40) into a training and holdout sample. Multilevel linear mixed-effects models, with maximum-likelihood estimation, were used to examine change across sessions for each item within the training sample. Data were detrended within each split, removing trend effects in means and variances (standardised per variable, per time-point). Whilst not an assumption of the modelling procedure, the aim was to improve model fit. This way, within-person and between person relationships between the variables of interest could be investigated after taking growth processes into account.

A lag-1 panel-GVAR using full-information maximum likelihood (FIML) estimation was fitted using the psychonetrics package[71]. As we modelled observed variables (i.e. no latent factors), the model is similar to a cross lagged panel model with random intercept with the covariance structure for the first time point implied by the temporal structure. By separating within from between person variance, the lagged relationships equal within-person variance[72]. Using maximum likelihood estimation, all edges were included in the temporal, contemporaneous, and between-subject networks. Residual variances were estimated using a Cholesky decomposition. Missingness was handled using FIML which adjusts the likelihood function so that each case contributes information on the variables that are observed. Multiple imputation and FIML will come to similar results when data are missing at random[73].

Confirmatory testing involved fitting a model in the holdout sample, specifying the adjacency matrix. Parameter invariance between samples was tested by estimating a model where we introduced equality constraints. Finally, we estimated a non-detrended model for comparison, where models are comparable (detrended and nondetrended). This suggests that detrending has not biased results, supporting causal inference[43].

Model fit was assessed using a series of fit statistics. To assess models, we used relative fit indices (Normed Fit Index (NFI), Tucker Lewis index (TLI), Incremental Fit Index (IFI), Parsimony-Adjusted Measures Index (PNFI) and Relative Fit Index (RFI)) which compare a chi-square for the model to one from a baseline model and noncentrality based indices (Comparative Fit Index (CFI) and Root Mean Square Error of Approximation (RMSEA) with 95% Confidence Intervals (CI). Absolute fit indices, Chi-square (χ^2) was reported but not interpreted given it's sensitive to sample size. Of these indices, PNFI values above approximately 0.75 and RMSEA values < 0.05 indicate good fit; for the others, values ≥ 0.90–0.95 and are variably accepted as cut-offs for good fit[74].

The panel data model from the training dataset, along with separate temporal (within-persons temporal patterns); contemporaneous (within-person fluctuations predicting other within-person fluctuations in the same time-window, after controlling for temporal effects); and between-persons (associations between stable averages) network models, were used for visualisation and interpretation of parameters. Within the graphical model, the conditional dependence relations between symptoms are estimated, where the line between nodes, ("edges"), represent shared unique variance that may be an indication of a causal pathway, or a common external (unmeasured) cause. The centrality metric, Expected Influence (EI), was estimated within each network. EI is sum of edge weights, either to, "In EI", or from, "Out EI", a symptom, reflect the centrality of the symptom within the network.

We estimated unregularised Graphical Gaussian models (GGM) at each timepoint, using undetrended data, to assess the network structure across sessions. At each timepoint we assessed for topological overlap using the goldbricker function[75]. Estimations were based on the Spearman covariance matrices and following an iterative modelling procedure using the Extended Bayesian Information Criterion (EBIC). Selecting unregularised GGMs according to EBIC has been shown to converge to the true model[76,77]. The ggmModselect algorithm runs 100 graphical lasso models (estimating sparse inverse covariance matrices using a lasso (L1) penalty), refits all models without regularisation, adding and removing edges until EBIC no longer improved[78]. The best performing model (EBIC parameter) was selected to provide a conservative GGM (high specificity).

Data availability

All materials have been made publicly available via the Open Science Framework and can be accessed at https://osf.io/gp6dw/. Data [matrices to reproduce the models] that that support the findings of this study are also available there. The raw data are not publicly available due to them containing information that could compromise participant privacy/consent. The raw data that support the findings of this study are available on request from the corresponding author JEJB subject to appropriate permissions from the custodians of the data. restrictions apply to the availability of these data, which were used under license for the current study. The data were provided by the IAPT services for evaluation as part of a wider service improvement project conducted in accordance with the procedures of the host institution and the NHS Trusts which operate the IAPT services (project reference: 00519-IAPT).

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Author contributions
C.O'.D., S.E., E.I.F., R.S., and J.E.J.B. conceived of the original project. R.S., J.E.J.B., A.C. and S.P. were responsible for data collation and extraction, and C.O'.D. and R.S. for data cleaning. C.O'.D. conducted the data analyses with support from S.E., E.I.F., R.S. and consultation from all other authors. C.O'.D. wrote the original manuscript will support from S.E., E.I.F., R.S., A.C., J.S., J.E.J.B. and S.P. All authors contributed to consecutive drafts and approved the final manuscript.

Competing interests
The authors declare no competing interests.

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PSYCHOTHERAPIES

Symptom-specific effects of counselling for depression compared to cognitive–behavioural therapy

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ABSTRACT

Background Cognitive–behavioural therapy (CBT) and counselling for depression (CfD) are recommended first-line treatments for depression. While they approach change differently, there is little understanding of the impact those approaches have on change during treatment.

Objectives This study aimed to identify whether CBT and CfD target different symptoms and explore the implications of modelling choices when quantifying change during treatment.

Methods Symptom-specific effects of treatment were identified using moderated network modelling. This was a retrospective cohort study of 12 756 individuals who received CBT or CfD for depression in primary/community care psychological therapy services in England. Change was modelled several ways within the whole sample and a propensity score matched sample (n=3446).

Findings CBT for depression directly affected excessive worry, trouble relaxing and apprehensive expectation and had a stronger influence on changes between suicidal ideation and concentration. CfD had a stronger direct influence on thoughts of being a failure and on the associated change between being an easily annoyed and apprehensive of expectation. There were inconsistencies when modelling change using the first and second appointments as the baseline. Residual score models produced more conservative findings than models using difference scores.

Conclusions CfD and CBT for depression have differential effects on symptoms demonstrating specific mechanisms of change.

Clinical implications CBT was uniquely associated with changes in symptoms associated with anxiety and may be better suited to those with anxiety symptoms comorbid to their depression. When assessing change, the baseline should be the first therapy session, not the pretreatment assessment. Residual change scores should be preferred over difference score methods.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cognitive–behavioural therapy (CBT) and counselling for depression are recommended first-line treatments for depression and are considered equally effective on average. However, little is known about how change comes about.

WHAT THIS STUDY ADDS

⇒ This study investigates symptom-specific effects and identifies specific symptoms and symptom interactions associated with each intervention. In addition, it highlights methodological considerations when modelling change.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ CBT was uniquely associated with changes in symptoms associated with anxiety so may be better suited to those with anxiety symptoms comorbid to their depression.

BACKGROUND

There is a strong preference among patients for psychological therapies over antidepressant medications.[1] Cognitive–behavioural therapy (CBT) and counselling for depression (CfD) are among the most used psychological therapies for depression, both are efficacious and recommended as first-line treatments for depression.[2] They are equally effective on average, but many patients do not experience symptomatic improvement with these treatments.[3] There is some evidence that outcomes can be improved by identifying for whom each type of treatment is most likely to be beneficial.[4] However, precision mental healthcare is hampered by a lack of understanding of how the individual treatments bring about symptomatic improvements,[5] and issues of measurement that affect the accuracy and utility of precision models.[6]

The symptom experiences of people with depression are heterogeneous[7] with evidence of differential treatment effects on specific symptoms.[8 9] During psychotherapy, change in one symptom is highly dependent on other symptoms[10] and effects of a treatment when controlling for the influence of all other symptoms are likely to be small. Modelling the direct influence of treatments on symptom change may elucidate unique differences between treatments, informing how treatments work and thus the potential suitability of a given treatment for an individual based on their pretreatment characteristics.

CfD aims to engender change by exploring the emotional meaning associated with experiences and developing alternative ways of understanding

these experiences to inform a new self-concept.[11] CBT for depression, on the other hand, aims to bring about change through cognitive processes (eg, challenging negative automatic thoughts) and behavioural processes (eg, reduced avoidance and balancing activities).[12] A recent clinical trial demonstrated the non-inferiority of CfD at 6 months but inferiority to CBT at 12 months,[13] while analyses of routine clinical data suggest that at the aggregate level, outcomes are comparable.[14] Two studies have highlighted the potential for pretreatment data to be used to stratify patients into groups that are more likely to benefit from one of these types of treatment than from the other.[15 16] One was an exploratory study, and the other had only a small sample receiving CfD. Those studies were not able to investigate the differential effects of the treatments on symptoms so could not elucidate mechanisms. They also used outcomes based on pre–post treatment change which can introduce a high degree of bias,[17] the first of which was a pretreatment assessment occurring sometime before treatment started and may not be an appropriate baseline. The implications of different methods of calculating change within clinical trials have been investigated thoroughly (see online supplemental eMethod). Capturing the nuance in symptom profiles and illustrating how best to overcome the issues of bias in modelling change within real world data, during treatment for depression, could inform how these therapies affect symptomatic change and hold potential to better inform shared treatment decision-making.

OBJECTIVE

The aims of this study were to (1) identify the direct influence of CBT compared with CfD on symptom change using network intervention analysis[18] and (2) explore the implications of modelling using either the first appointment in the services (assessment) or the second appointment (first treatment session) as the baseline timepoint and of quantifying symptom change during treatment in a variety of ways: using final scores, difference scores, proportional change and residual scores.

METHODS

Participants

Routine clinical data were gathered from eight Improving Access to Psychological Therapies (IAPT) services. All were part of the North Central and East London IAPT Service Improvement and Research Network.[19 20] IAPT services operate as part of a nationwide programme operated by the National Health Service (NHS) to provide evidence-based psychological treatment for depression and anxiety disorders.[21]

Patients are assessed by a clinician to determine their needs and consider the most suitable intervention(s). Patients receive a diagnosis based on International Classification of Diseases, 10th Revision; this represents the focus of treatment agreed on a patient and a clinician. Patients are offered treatment(s) recommended by the National Institute for Health and Care Excellence (NICE) in guidance specific to the patient's diagnosis.[2] For less severe depression and anxiety disorders, NICE suggests a stepped-care approach to the delivery of psychological therapies. This means that low-intensity interventions are typically used first, before progressing to more intense treatments if required. For more severe depression, NICE recommends starting with high-intensity face-to-face psychological therapies (such as individual CBT or counselling) in combination with an antidepressant or as a monotherapy. The clinician will outline the interventions that are recommended to the patient and reach a shared decision on a treatment choice appropriate to the person's clinical needs, considering their preferences. Data from patients who underwent either CBT or CfD treatment for depression (high intensity) and had item-level data available were included in the study. To identify changes due to treatment, only patients who attended five or more treatment sessions were included (see online supplemental eFigure 1 for participant flow).

Intervention conditions

CfD and CBT were delivered by clinicians with doctoral qualifications in clinical or counselling psychology or with postgraduate diplomas in CBT. Sessions lasted 50–60 min and typically 8–16 sessions were offered. Prior to treatment, patients completed an initial assessment (session 1), and those offered CfD or CBT were placed on a waiting list to start treatment. As such, session 2 represents the first treatment session, typically occurring 4–12 weeks after the assessment session.

For details of the theory underlying these therapies and the competence frameworks, see online supplemental eMethods.

Outcome measures

IAPT services are mandated to collect sessional outcome data with all patients as well as numerous sociodemographic and treatment-related variables,[22] and this includes the Patient Health Questionnaire 9-item version (PHQ-9),[23] a measure of depressive symptoms; and the Generalized Anxiety Disorder Scale 7-item version (GAD-7),[24] a measure of generalised anxiety disorder symptoms. The items of both measures are used to assess symptom change across treatment. The scores from session 1 (assessment) and session 2 (first treatment session) are used as baseline scores, and the scores in the final treatment session were used as the post-treatment score.

Statistical analysis

Network intervention analysis

Changes scores were estimated for all 16 symptoms of the PHQ-9 and GAD-7. We estimated the residual and difference scores with both session 1 and session 2 as baselines, to account for regression to the mean. Scores were calculated as follows: Difference Score (DS)=postscore−prescore; Final Score (FS)=postscore; Proportional Change (PC)=100*DS/prescore; Residual Score (RP)=postscore−predict value (relationship of prescore–postscore); Residual Change Score (RC)=DS−predict value (relationship of prescore–DS).

Given the potential for topological overlap, we investigated multicollinearity cross-sectionally using the goldbricker function in the networktools package.[25] There were no node pairs where 75% of correlations were shared with other nodes at any of the timepoints.

Moderated Network Models[26] were estimated using elastic net regularisation with parameters selected via 10-fold cross-validation, then combining neighbourhood estimates using the AND rule and estimating the linear moderation effects of the interventions. To determine the stability of the estimates (edges and moderating effects), the residual models were refitted using 1000 bootstraps producing bootstrapped sampling distributions of all parameters. Within the network, the associations are conditional on all other variables in the model and the direct effects from the treatment node to the symptoms are the mean change difference in those symptoms between the interventions. The intervention node is binary,

where CBT is coded as 1 and CfD as 0. Direct associations are the associations between intervention and changes in individual symptoms, controlling for all other symptoms. We also inspected the three-way interactions (moderation effects) to see how treatment affects the pairwise interactions between the other symptoms.

Covariates: propensity score matching

Estimation of the residual models was conducted using the whole sample and a propensity score–matched sample. Propensity score matching was used to control for confounding as the intervention type was not randomly assigned. Matching variables included session 1 item scores (PHQ-9 and GAD-7), gender (male/female), employment status (employed/unemployed), taking psychotropic medication (yes/no), age (continuous), ethnicity (based on UK Census categories: White, Mixed, Asian, Black, Chinese, Other) and baseline functional impairment as measured using the Work and Social Adjustment Scale (Mundt, Marks *et al*, 2002) total score. Propensity score matching was performed using MatchIt package.[27] Mahalanobis distance matching within the propensity score calliper method (0.25) was used for matching analysis.

Total score and symptom change

For comparison purposes, change was modelled between the two interventions on PHQ-9 and GAD-7 sum scores using linear regressions with the final score as the outcome and baseline score as a covariate. This indicates whether the final session score has changed more or less than expected based on the baseline score and the regression equations. This was conducted separately for sessions 1 and 2 as baselines. We also estimated change across each of the 16 individual symptoms (using session 2 as baseline) with false discovery rate (FDR) co rrected p values within both the whole and propensity score–matched samples.

The study has followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines (see online supplemental eTable 1 for checklist). All materials have been made publicly available via the Open Science Framework and can be accessed at https://osf.io/ak4ev/.

FINDINGS

Group characteristics

Total scores on PHQ-9 and GAD-7 were higher at sessions 1 and 2 for the CBT group, and age, ethnicity, gender and number of days between session 1 and 2 (mean difference 6.5 days) differed between the groups (see table 1). There was no evidence of differences between groups on the symptom measures at the final session. Propensity score matching resulted in matching equal numbers of CBT patients to patients in the CfD group (n=3346, 1673 per treatment).

Network intervention analysis

The propensity score model is plotted in figure 1 (all models are plotted in online supplemental eFigure 2), and the direct associations are specified in figure 2. Most edges were reliably estimated and included in all or nearly all of the 1000 bootstrapped samples (online supplemental eFigures 2 and 3).

Results using the difference score with session 1 as the baseline were different than other change models (eg, correlation between matrices DS and RC1, r>0.48), with the direct associations negatively correlated will all other estimates, including modelling the difference score with session 2 as the baseline, r=−0.60. Direct associations found with residual score models using the session 1 baseline were different from those found using session 2 data. The associations found when using session 2 as the baseline were consistent whether using the final score or residual score outcome (r>0.98).

The whole sample residual models using the session 2 baseline were similar (r>0.99), and similar to the propensity score–matched models (r>0.98). Fewer direct associations were identified in the propensity score–matched sample using the residual change score outcomes. In these models, using the session 2 baseline, there was consistency across four items identified as having direct associations, three positively associated with CBT and one positively associated with CfD. Across the propensity score–matched models, there was a larger change of scores on thoughts of being a failure with CfD (RCX2: 0.03) and a larger effect on excessive worry (RCX2: 0.02), troubling relaxing (RCX2: 0.02) and apprehensive expectation (RCX2: 0.02) with CBT.

When looking at the influence of treatment on symptom-to-symptom interactions (figure 2), there was less consistency between models. While there was consistency between residual models within samples, there was very little between samples (whole and propensity score matched).

Within the whole sample, there was evidence of stronger related change between anhedonia and appetite during CBT than CfD (CBT: 0.05, CfD: 0.03). Further, the CBT group showed an associated change between suicidal ideation and restlessness (0.03), suicidal ideation and being easily annoyed/irritated (0.04) and between depressed mood and psychomotor disturbance (0.01); these were absent for the CfD group.

Between the propensity score–matched models, only two effects were identified in both models: the CfD group showed a stronger related change between feeling annoyed and apprehensive expectation (CBT: 0.09, CfD: 0.13). There was also a difference between groups on the associated change between suicidal ideation and concentration (CBT: 0.06, CfD: 0.04), with the CBT group displaying stronger associated change than the CfD group. Given the difference between interventions on the number of sessions attended, we controlled for the number of sessions within the RCX2 model. This did not alter any of the direct or indirect effects (see online supplemental eFigure 4). Within the discussion, only interactions observed across both propensity score models are interpreted.

Total score and symptom change

Within the whole sample, there was a greater degree of change in anxiety but not depression during CBT than CfD. This difference was larger for the final GAD-7 score when controlling for session 2 scores: $F(1,12753)=24.255$, $p<0.001$, $\omega_p^2=0.002$, estimated marginal means±SE (CBT: 8.28 (0.05), CfD: 8.98 (0.13)) than when controlling for session 1 scores: $F(1,12753)=17.94$, $p<0.001$, $\omega_p^2=0.002$ (CBT: 8.29 (0.06), CfD 8.9 (0.14)). There was no evidence of a difference between groups for the final PHQ-9 total score when controlling for session 1 PHQ-9 scores: $F(1,12753)=1.3$, $p=0.254$ (CBT: 9.58 (0.06), CfD: 9.77 (0.16) or session 2 scores: $F(1,12753)=4.385$, $p=0.036$ (CBT: 9.56 (0.06), CfD: 9.90 (0.15)). Within the propensity score–matched sample, there was a greater degree of change in both anxiety and depression during CBT than CfD when controlling for the session 2 score, PHQ total score: $F(1,3443)=6.836$, $p<0.009$ (CBT: 8.89 (0.14), CfD: 9.40 (0.14), and GAD-7 total score: $F(1,3443)=18.35$, $p<0.001$, $\omega_p^2=0.005$ (CBT: 7.72 (0.13), CfD:8.47 (0.12)).

Table 1 Sample characteristics and group differences

	CfD (n=1868)	CBT (n=10 888)	P value	d/V
PHQ-9 total session 1				
Mean (SD)	16.1 (5.81)	16.7 (5.75)	<0.001	−0.12
Median (min, max)	16.0 (0, 27.0)	17.0 (0, 27.0)		
GAD-7 total session 1				
Mean (SD)	13.2 (5.21)	14.1 (4.91)	<0.001	−0.17
Median (min, max)	14.0 (0, 21.0)	15.0 (0, 21.0)		
PHQ-9 total session 2				
Mean (SD)	14.4 (6.37)	15.3 (6.07)	<0.001	−0.15
Median (min, max)	14.0 (0, 27.0)	16.0 (0, 27.0)		
GAD-7 total session 2				
Mean (SD)	12.2 (5.57)	13.2 (5.26)	<0.001	−0.18
Median (min, max)	12.0 (0, 21.0)	14.0 (0, 21.0)		
PHQ-9 total final session				
Mean (SD)	9.23 (6.94)	9.54 (6.80)	0.079	−0.04
Median (min, max)	8.00 (0, 27.0)	8.00 (0, 27.0)		
GAD-7 total final session				
Mean (SD)	8.33 (6.12)	8.26 (5.87)	0.66	0.01
No of sessions: mean (SD)	10.4 (3.9)	10.9 (4.6)	<0.001	0.12
Days between session 1 and session 2	59.9 (49.7)	66.4 (48.9)	<0.001	0.13
Age: mean (SD)	38.5 (13.10)	42.5 (13.5)	<0.001	0.30
Gender			<0.001	0.06
Male	468 (25.1%)	3515 (32.3%)		
Female	1396 (74.7%)	7336 (67.4%)		
Missing/not disclosed	4 (0.2%)	37 (0.3%)		
Ethnicity			<0.001	0.07
Asian	171 (9.2%)	1677 (15.4%)		
Black	232 (12.4%)	1301 (11.9%)		
Chinese	10 (0.5%)	63 (0.6%)		
Mixed	111 (5.9%)	710 (6.5%)		
Other	86 (4.6%)	398 (3.7%)		
White	1210 (64.8%)	6393 (58.7%)		
Missing	48 (2.6%)	346 (3.2%)		

P values and effect sizes reported (Cohen's d or Cramer's V).
CBT, cognitive–behavioural therapy; CfD, counselling for depression; GAD-7, Generalized Anxiety Disorder Scale 7-item version; PHQ-9, Patient Health Questionnaire 9-item version.

Symptom change is plotted in figure 3. After correcting for FDR, there was evidence that all GAD-7 symptoms and psychomotor disturbance were lower at end point for CBT than CfD (online supplemental eTable 2). Within the propensity score–matched samples, anhedonia, depressed mood, suicidal ideation and all the GAD-7 symptoms were lower at end point for CBT than CfD.

CONCLUSIONS

This study investigated differences in symptom-specific effects of CBT and CfD, and the impact of modelling symptom changes in a variety of commonly used ways for adults with depression treated in primary/community care psychological therapy services. We found that CBT for depression may work by directly affecting excessive worry, trouble relaxing and apprehensive expectation, while CfD may work by affecting thoughts of being a failure. These effects were specific to the type of treatment, that is, they were not shared effects (where both interventions similarly affect symptoms this is not visualised) or indirect effects of changes in other symptoms influenced by the treatments. There were also treatment-specific effects on symptom-to-symptom interactions. CfD had a stronger influence on the associated change between feeling annoyed and apprehensive expectation than CBT. The associated change between suicidal ideation and concentration was greater for CBT than CfD.

We found variability in the results obtained from different ways of measuring change. There was little consistency in the results between using session 1 and session 2 as a baseline. This is important because many observational studies and clinicians use pre–post change in a symptom measure score as their primary outcome. Further, within treatment settings, there can be a period (weeks to months) between initial assessment (session 1) and commencing treatment (session 2). Hence, session 2 appears to be a more appropriate baseline for measuring treatment-related symptom change. Differences between the whole and propensity score–matched samples would suggest that there is an influence of covariates, but it is less evident when estimating direct associations, although propensity score matching cannot fully redress selection biases or confounding given the potential influence of unmeasured variables.[28] The difference score and proportional change models produced inconsistent results; however, the final score model (a simple method) and residual score approaches

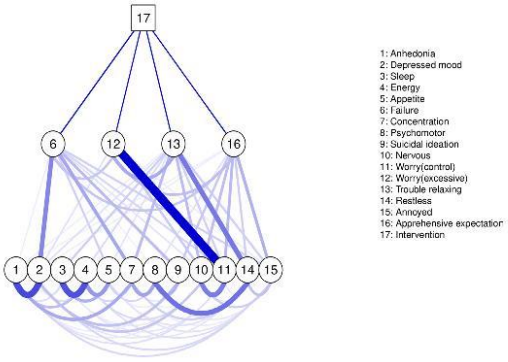

Figure 1 Network plot (RCX2). This represents the propensity-matched models which were virtually identical. The network includes intervention (CBT or CfD) as a square node and items from the PHQ-9 and GAD-7. The thickness and saturation of the edges between symptoms are proportional to the strength of the association. Within the mixed graphical model, the inclusion of the intervention node (CBT coded as 1 and CfD as 0) allows us to explore moderation effects, identifying symptoms that are uniquely influenced by the intervention type, thereby demarcating intervention-specific effects with the network. Edges between intervention and a symptom indicate a larger direct item-specific effect for one of the interventions, but direct effects that are shared by both interventions will not be included into the network model. This direct effect may account for the spread throughout the network and indicate likely pathways through which an intervention may influence symptoms. The edges between the intervention node and symptoms are direct associations—the heatmap below indicates the strength and direction of these associations. CBT, cognitive–behavioural therapy; CfD, counselling for depression; GAD-7, Generalized Anxiety Disorder Scale 7-item version; PHQ-9, Patient Health Questionnaire 9-item version; RC, Residual Score (change score–baseline); X, propensity score–matched samples.

were consistent. This echoes the established but rarely adhered to methodology of regressing the second baseline measurement (baseline) on the postscore or difference score where a residual score for each participant can be modelled within the network.[29] Although established for clinical trials, this also appears to fit for observational data in naturalistic settings.

The results provide evidence to elucidate how these therapies may work. For example, compared with CBT, CfD was directly associated with a change in the thoughts of being a failure. CfD also demonstrated a greater associated change between feeling annoyed and apprehensive expectation (feeling afraid that something bad will happen) than CBT. This fits with the theoretical underpinnings of CfD targeting the development of self-concept and conditions of worth and their link to emotional processes.[30] CBT encompasses a number of approaches to tackling depression as most of which also target beliefs about the self; however, it appears that this effect may not be as direct as it was in CfD. It might be that in the CBT delivery there was a greater focus on altering ruminative thinking processes than the content of negative thoughts and self-beliefs themselves.[31] For both treatments, self-beliefs may represent an important target as we found an indirect effect of treatments on depressed mood via thoughts of being a failure.

CBT for depression was uniquely associated with changes in symptoms associated with anxiety. Some of the observed symptom effects could be considered mechanistic (reflecting an underlying physiological, neurobiological or functional mechanism) others are more descriptive.[32] The changes in excessive worry and apprehensive expectation were both uniquely associated with CBT and, as another form of repetitive negative thinking (like rumination), have been identified as a transdiagnostic mechanism and treatment target.[33] Excessive worry has a strong temporal influence on the change in other symptoms during psychotherapy,[10] and CBT has been found to have a moderate effect on repetitive negative thinking.[34] CBT was also directly associated with trouble relaxing. Trouble relaxing has been identified as a central symptom within remission networks following CBT[35] and as a bridge between symptoms of anxiety and depression.[36] There is some evidence that these symptoms are associated with experiential avoidance so CBT might be bringing about symptom change by tackling this process.[37]

There was a stronger associated change between suicidal ideation and concentration for CBT than CfD. Within this sample, we cannot identify temporal precedence. However, in a dynamic network model of change during psychotherapy, temporal influence was stronger for concentration on suicidal ideation than the other way around.[10] Concentration has been identified as a central symptom in a relapse network[35] and maybe reflective of poor meta-cognitive capacity to regulate impulsive tendencies to harm oneself.[38] Although not evidenced in both models, there was an indication that CBT may be associated with a change between suicidal ideation and several symptoms (restlessness, feelings of failure and controllability of worry) suggesting indirect pathways through which CBT may reduce suicidal ideation.

Limitations

We attempted to balance groups on observed covariates, but they may have differed on important, unmeasured confounders such as those related to aspects of severity,[39 40] to sociodemographics or socioeconomic factors,[15 41] and as such the differences observed may be due to external factors. There are other selection variables and mechanisms of interest to measure when comparing these treatment approaches. For example, previous experiences of treatment, where those who received CfD may have previously had CBT, adherence to treatment (fidelity and engagement) or therapeutic alliance which has been shown to influence change.[42] The PHQ-9 and GAD-7 cover core symptoms; however, there are many other symptoms of depression and anxiety[7] that are relevant to understanding the mechanisms of change within these treatments. Second, the study measures change between two timepoints, dynamic processes of change are more complex[10] and the temporal relationship in respect of each treatment is unknown and would be worth exploring in future research. Third, the analysis represents the largest network comparison of psychological treatments to-date; however, at the individual level, knowledge of individual symptoms alone might not be sufficient to inform clinical decisions, and it may not lead to better prognostic predictions or make it easier to select between generally similar treatment types.[43] This is not to say the findings are not clinically meaningful, as they can be important when implementing decision-making at the population level (eg, around treatment selection and outcome measurement) potentially leading to improved recovery rates on a mass level. Finally, this study provides a methodological illustration of the different results that emerge from modelling decisions rather than a statistical comparison of models. While these findings illustrate issues with difference scores that have been well established within the

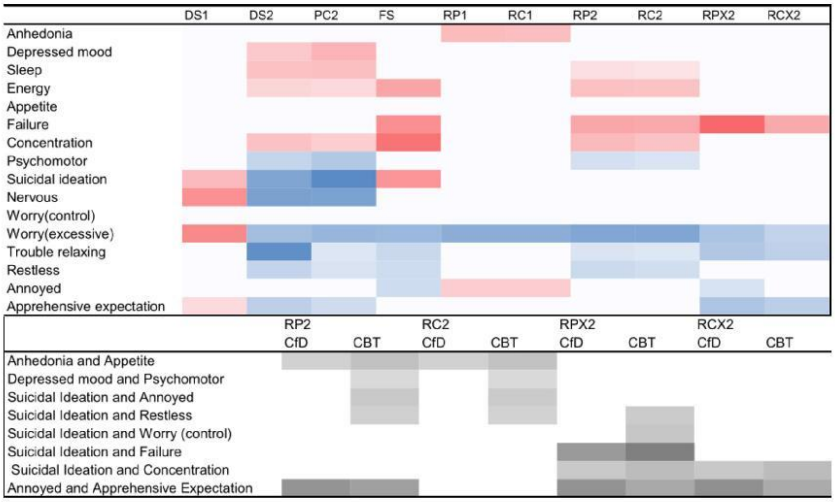

Figure 2 (Top) Heat map of direct associations for each model. The heatmap displays the direct associations between symptoms and intervention type obtained using the different methods of calculating change and against different baseline timepoints. Colour scale: darker=stronger, with blue reflecting direct associations with CBT and red reflecting direct association with CfD. In the headings, the number refers to the baseline used (ie, session 1 or 2), DS, Difference Score; FS, Final Score only; PC, Proportional Change; RP, Residual Score (post score–baseline); RC, Residual Score (change score–baseline); X, propensity score–matched samples. (bottom) The influence of the type of intervention on symptom-to-symptom interactions. The values represent the presence and strength of the influence for the associations that differentiate the interventions. Colour scale: darker=stronger. CBT, cognitive–behavioural therapy; CfD, counselling for depression.

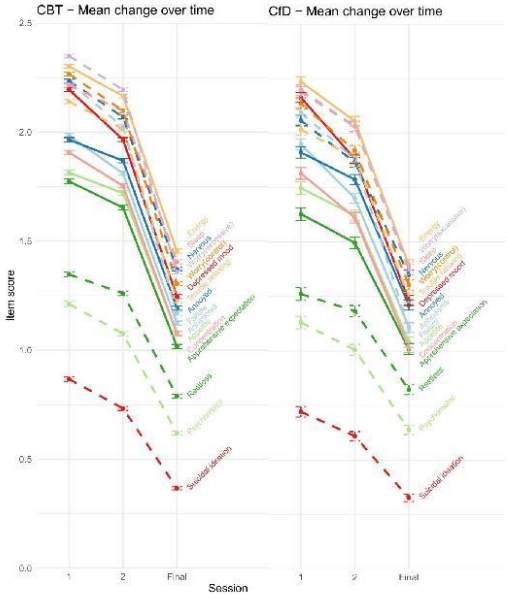

Figure 3 Mean change and SE for each symptom at session 1 and 2 (baseline measures) and the final session of treatment.

RCT literature (see online supplemental eMethod), a simulation study would be required to assess the robustness of a given model in various scenarios. Equally, while the study employs a large sample, increasing the accuracy of parameter estimates, replication in an independent sample would be required. These may inform the determination of treatment outcomes in routine clinical care and future observational studies alike.

CLINICAL IMPLICATIONS

It is important to understand how interventions work so that more effective and efficient treatments can be developed, and so that interventions can be more acceptable to patients. This study suggests that as CBT was uniquely associated with changes in symptoms associated with anxiety it may be better suited to those with anxiety symptoms comorbid to their depression.

The study also highlights methodological considerations. When assessing change, the baseline should be the first therapy session (or second session) not the pretreatment assessment. This will address potential sources of bias such as regression to the mean. When calculating change, residual change scores should be preferred over difference score methods.

Contributors CO'D conceived of the original project. RS, JEJB and SP were responsible for data collation and extraction, and CO'D and RS for data cleaning. CO'D conducted the data analyses with consultation from all other authors: JEJB, RS, SP, SE, SAN, SS and JW. CO'D is guarantor.

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