

Across boundaries

Transdiagnostic and network approaches
to psychopathology

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Transdiagnostic and network approaches to psychopathology

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General Introduction

Shortcomings of the Current Psychiatric Paradigm

Psychiatric diagnostic classification systems, such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and *International Classification of Diseases* (ICD), categorize and label psychopathology. Although these systems are meant to be atheoretical, they carry with them certain assumptions that have had considerable influence on how psychopathology is conceptualized, treated, and researched for many years now. In research, categorical diagnoses are used as the basis for the sample selection, theoretical framework, and methodology. While classification systems can have utility for clinical communication and as a guideline in clinical practice, the shortcomings of diagnostic classification systems have been a prevalent and ongoing point of discussion. Although these discussions are not by any means new or recent to psychiatry, these challenges have become more mainstream over the last decade¹. The current paradigm has therefore been undergoing critical questioning^{2,3}.

The concept that psychiatric diagnostics are not true representations of psychopathology and are instead pragmatic, man-made constructs is becoming more widely acknowledged. This reflects the *practical kinds* mindset of classification, in which there is a focus on utility and the pragmatic benefits of a diagnosis⁴. Psychopathology is complex and diagnoses are a way to make sense of it. Clinicians mostly use diagnostic classification systems for practical reasons, such as administration, teaching trainees, and sharing information with the patient and their family or caregivers and other clinicians, and making initial diagnoses, but find them less useful for treatment selection and prognosis^{5,6}. However, while it may not have been the intended purpose of the current diagnostic classification systems, certain assumptions have accompanied them that continue to impede progress in psychiatry⁷. As a research tool, the DSM has been unable to effectively facilitate categorization that accurately reflects clinical reality, which limits the relevance and usefulness of findings pertaining to *DSM* diagnostic categories.

One assumption underlying the current paradigm is that experiences of psychopathology can be neatly classified into discrete categories. Although the *DSM-IV* included a disclaimer that diagnostic categories are not meant to be considered discrete entities with hard boundaries⁸, this has generally been overlooked for the idea that boundaries between diagnostic categories are clear cut. However, these boundaries are often fuzzy, meaning that there is some overlap possible between categories. For instance, there has been considerable debate on the boundary between anxiety and depressive disorders⁹, and the high diagnostic flux between different eating disorders undermines the current categorical

diagnoses¹⁰. Many symptoms, behaviors, biomarkers, and so forth do not neatly adhere to diagnostic categories and can be present across multiple diagnoses, playing an important role in comorbidity¹¹. High rates of comorbidity is after all the rule rather than the exception in psychiatry^{12,13}. An over-emphasis on symptom checklist approaches (e.g., using the *DSM* as a laundry list of criteria) and lack of clinical and diagnostic training and expertise could play a role in this as well as excessive splitting of closely related conditions, which diminishes discriminatory power between diagnoses¹².

Additionally, categories impose often arbitrary boundaries between what is considered normal versus abnormal, healthy versus ill, and whether a disorder is present or absent. The dimensional approach to psychopathology, in which psychopathology is quantified on a continuum of severity rather than rated as present or absent, has gained traction and empirical support¹⁴⁻¹⁷. Consequently, the latest versions of the *DSM* and *ICD* attempted to include more dimensional approaches as, most likely, a combination of categorical and dimensional approaches is necessary¹⁸. However, categorical classifications that should have been treated as useful heuristics have become reified¹², and rather than being used to index disorders, many regard *DSM* criteria as constituting disorders^{19,20}.

Another assumption is that disorders are latent classes, as viewed through the disease model lens, in which symptoms are assumed to be caused by and co-occur due to a common cause- an underlying (latent) disorder^{4,21}. As such, one would experience anhedonia, depressed mood, and fatigue because they have a depressive disorder, and any relationship between these symptoms would be due to the underlying disorder. This would suggest that symptoms are “merely passive psychometric indicators of latent conditions”²². It would also imply that one would be able to experience a disorder without any symptoms. While one could certainly have a tumor without any symptoms, a psychiatric disorder without symptoms seems like a contradiction in terms. Clinicians may have and apply their own causal theories that deviate from the latent class or common cause perspective of psychopathology²³, but these perspectives have been the basis for many psychiatric studies²⁴.

Additionally, placement within these categories is based on polythetic classification, in which an individual needs to meet a certain number of criteria to be diagnosed with a particular disorder. This leads to a high degree of heterogeneity within categorical diagnoses, meaning that there are multiple ways to meet criteria. It is therefore possible for individuals with the same diagnosis to have numerous differing symptom profiles. For example, studies have found that there are hundreds of ways to meet criteria for major depressive disorder²⁵⁻²⁷ or post-traumatic stress disorder²⁸.

Heterogeneity within diagnoses could lead to less effective treatment by enforcing a “one size fits all” approach onto heterogeneous constructs. Consequently, focusing on diagnoses or sum-scores can lead to a loss of information on the nuance and differential impacts that individual symptoms can have²⁹⁻³¹.

Lastly, the symptom-reduction model that is derived from the prevailing diagnostic paradigm and currently dominates conventional care is limited. Recovery and remission are the primary goals of treatment, and that has often been measured as a reduction in symptom severity, partly as a result of reification and evaluations typically being based solely on *DSM* criteria³²⁻³⁴. Coupled with an overloaded mental healthcare system, this may mean that personal, existential, and social factors get ignored or are given limited attention. The symptom-reduction model can neglect the person while focusing on the disorder and symptomatology³⁵ and feed into the healthy versus ill categorization, such as with remission statuses, potentially taking away hope for recovery or a meaningful life while experiencing symptoms, especially if chronic. Patients with psychiatric disorders have indicated that while symptom reduction is an important treatment goal, other outcomes, such as improved well-being, psychosocial function, and more fulfilling lives, are as or more important to them³⁶⁻³⁸. For instance, some patients with moderately severe mood or anxiety symptoms can show full remission of symptoms only after improving current or entering new meaningful relationships. Furthermore, symptom reduction alone has been shown to not be enough as many continue to struggle with reduced psychosocial and cognitive functioning and well-being despite achieving remission from or reduction in symptoms³⁹⁻⁴¹.

Together, these flawed assumptions underlying the current diagnostic classification system could be reasons why research has had difficulty reaching consensus on the etiology, biological underpinnings, and structure of psychopathology. The nature of psychopathology is and has been an important question in psychiatry^{4,42}, and the validity of psychopathology being conceptualized as distinct categorical latent classes is scrutinized. Despite decades of research, it has not led to a substantially improved understanding of psychiatric disorders and symptoms, which has, in turn, deterred the development of better treatments. Although few clinicians and researchers unequivocally view psychiatric disorders as discreet categorical entities and many recognize the shortcomings of current diagnostic classification systems, many continue to adhere to the aforementioned assumptions about psychopathology for practical reasons. Nonetheless, the time has come to turn to other perspectives and approaches.

Paradigm Shift: Breaking Free of Boxes

Different approaches have been proposed to remedy the issues present in our current classification systems. Some consider these approaches to be alternatives to the current classification paradigm whereas others consider them to be supplementary. Either way, finding other ways to conceptualize, research, and treat psychopathology has been at the forefront of the current paradigm shifts.

One such approach is the transdiagnostic approach, which cuts across categorical diagnoses and potentially goes beyond them with the aim to improve how we "classify, formulate, treat, and prevent" psychopathology^{43,44}. It has also been proposed as a way to handle the heterogeneity of diagnostic categories and high rates of comorbidity as this approach forgoes categorical diagnoses as an organizing principle and instead focuses on dimensions of psychopathology. In this sense, the transdiagnostic approach can also easily incorporate the dimensional approach by spanning not only diagnoses but also the continuum of severity⁴⁵. The transdiagnostic approach in research could therefore be used to identify shared factors and biopsychosocial processes across diagnoses, such as is being done with the research initiatives the Hierarchical Taxonomy of Psychopathology (HiTOP)⁴⁶ and Research Domain Criteria (RDoc)⁴⁷.

There is growing evidence for transdiagnostic processes in psychopathology. For instance, emotion dysregulation, such as rumination⁴⁸, has consistently been shown to play a role across numerous disorders⁴⁹, and cognitive dysfunction has been shown to be a relevant transdiagnostic dimension⁵⁰. There are also findings of shared brain structural abnormalities⁵¹ and alterations in connectivity⁵² across disorders. The p factor, or the general psychopathology factor, further points to a shared transdiagnostic dimension⁵³. Additionally, there has been increased evidence supporting transdiagnostic interventions, such as the effective use of aripiprazole across five disorders⁵⁴ and Unified Protocol for Emotional Disorders across six disorders⁵⁵.

While there has been an increase in transdiagnostic research, it still has a way to go to becoming a sound research design. Many transdiagnostic studies contain methodological weaknesses, and it is still necessary to further build and expand the base of solid evidence to deliver on the promises of a paradigm shift^{44,56}. For instance, many previous studies did not perform comparative analyses to determine whether transdiagnostic findings actually hold across diagnoses or are a result of group effects and differences in magnitude or direction of effects have sometimes been overlooked⁵⁶. Finding a common relationship or dimension across diagnoses does not automatically mean it is transdiagnostic. Nonetheless, the transdiagnostic

approach has potential, and recent methodological guidelines for transdiagnostic research can further guide in the acquisition of evidence.

An additional approach to conceptualize and investigate psychopathology is the network approach, which hypothesizes that psychopathology arises from the dynamic interaction of multiple factors that causally impact each other⁵⁷. Symptoms are then viewed as active elements of a causal system that develop or maintain psychopathology rather than as passive receptors of an underlying disorder. This differs from the latent approach, in which the disorder causes its observable symptoms. Figure 1 illustrates a basic schematic of the different approaches. In a network, symptoms may reinforce each other, such as in a feedback loop ($A \rightarrow B$ and $B \rightarrow A$), or impact multiple other symptoms, such as with a cascade effect ($A \rightarrow B \rightarrow C$). Networks also often focus on individual symptoms rather than sum-scores because symptoms are viewed as behaving in different ways and potentially even having different risk factors rather than being viewed as interchangeable and having equal weight in a disorder⁷. The network approach therefore enables the investigation of complex symptom-level interactions that can give insight into relative importance of different symptoms as well as differential impacts of symptoms on each other as well as on other factors.

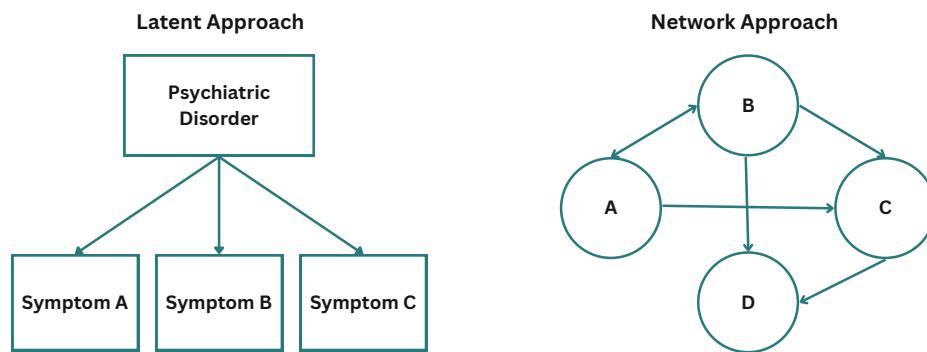


Figure 1. The latent vs network approach to psychopathology

Studies on psychopathology using the network approach have also proliferated in the past decade⁵⁸. There are network studies on a variety of specific psychiatric disorders and ones that investigate comorbidity between disorders⁵⁹. Some networks focus on core symptoms whereas others include other clinically-relevant factors, such as cognitive biases⁶⁰ and daily functioning⁶¹. However, while the network approach has gained considerable popularity, transdiagnostic networks are comparatively sparse. Borsboom, Epskamp, Kievit, Cramer, Schmittmann⁶² state that networks are inherently transdiagnostic, but many networks focus on *DSM* criteria and symptoms as variables and are conducted in psychiatric samples restricted to one or two *DSM*

diagnoses, which can essentially perpetuate the issues from which the network approach attempts to depart^{59,63}. The transdiagnostic and network approaches are highly compatible, however⁶². Both eschew diagnoses as the organizing principle and can take equinality and multifinality as well as comorbidity into account.

These approaches are then well-suited to investigate relationships between numerous dimensions of psychopathology that go beyond core symptoms in psychiatric samples with a variety of disorders. There is considerable consensus that psychopathology is multifactorial and complex, resulting from an interplay of various factors across levels (micro, mezzo, macro) and domains. Beyond symptoms, one can include variables on personality characteristics, biological measures, environmental factors, and more, which can expand the understanding of psychopathology^{59,64}.

A part of going beyond is expanding or re-incorporating different aspects of experiences around psychopathology. Recently, there has been renewed interest in further expanding the biopsychosocial model as well as the symptom-reduction model. For instance, there has been growing support for and implementation of the recovery-oriented framework⁶⁵ as well as recognition of mental health being more than the absence of symptoms or a disorder^{66,67}. In this sense, research, treatment, and recovery would include variables, targets, and outcomes that encompass clinical (e.g., symptom reduction), psychosocial (e.g., societal participation), and personal (e.g., self-worth) factors⁶⁸.

Additionally, expanding the biopsychosocial model can also mean integrating an existential dimension into psychiatry and the conceptualization of psychopathology^{69,70} as well as the recovery-oriented framework⁷¹. The existential dimension, or the way we relate to and reflect on our experiences, the world, and others, and conflicts therein can be considered a core aspect of many psychiatric disorders^{71,72}. Psychopathology may even be considered an existential experience in and of itself. For instance, depression can be viewed as a process of "risking existence" as individuals struggle with hope, belonging, and authenticity - concepts that are deeply existential⁷³. Including concepts related to existential and personal aspects in psychiatric research can lead to a more comprehensive understanding of and help contextualize psychopathology⁷⁴ rather than reducing it to a set of criteria.

The transdiagnostic and network approaches can aid in further contextualizing psychopathology and experiences of mental distress by taking symptom and non-symptom dimensions that do not adhere to diagnostic categories into account, reduce explanatory reductionism, and treating them as dynamic and complex. Psychiatric diagnostic classification systems, such as the *DSM*, have their usefulness, but have been limited on their own. Softening the grip of the current paradigm on research and exploring other approaches is therefore a necessity.

Aims

The aim of this thesis was to investigate the relationships between psychopathological symptoms, cognitive function, and other clinically-relevant factors (e.g., self-esteem, psychosocial functioning or existential concerns) through the use of the transdiagnostic and network approaches. This may provide further insight into dimension- or symptom-level rather than diagnostic-level relationships and elucidate transdiagnostic mechanisms and processes. The aim was also to demonstrate the feasibility, appropriateness, and value of the transdiagnostic and network approaches and to illustrate that they can provide insights that can further inform psychiatric practice and research. Ultimately, we strive to gain a better understanding of psychopathology and inform potential paths to improving treatment.

In **Chapter 2**, we described the protocol of the Across study, which details the background, rationale, and methodology of the study. The Across study is an ongoing transdiagnostic longitudinal study with a naturalistic patient population and consists of the assessment of cognitive performance, psychiatric symptoms, and collection of biological data.

In **Chapter 3**, we investigated the cross-sectional relationship between psychopathology and cognitive function. In a naturalistic transdiagnostic sample of patients with psychiatric disorders, we conducted network analyses with cognitive measures, symptoms, and other clinically-relevant factors, such as psychosocial functioning, as well as clustering and centrality analyses to determine how the variables cluster and identify important variables in the network.

In **Chapter 4**, we explored the relationship between resting-state EEG activity and cognitive function across multiple psychiatric disorders. Using random forest regression, we investigated resting-state EEG features associated with performance of multiple cognitive domains and diagnostic categories, and assessed differences in cognitive function over diagnoses as well as correlational association between cognitive domains and symptom dimensions.

In **Chapter 5**, we investigated the longitudinal two-wave relationships between psychopathological symptoms. We estimated a cross-lagged panel network model using individual depressive, anxious, and attenuated psychotic symptoms in a transdiagnostic sample of patients with various psychiatric disorders and conducted centrality analyses to identify which variables were most predictable and influential.

In **Chapter 6**, we explored cross-sectional relationships between existential concerns and psychopathology. In a transdiagnostic sample of patients with various psychiatric disorders, we used mixed graphical modeling with psychopathological symptom

domains and individual existential concerns and centrality metrics to gain insight on important variables in the network.

In **Chapter 7**, the main findings from the aforementioned studies are synthesized and discussed. Furthermore, the implications of the findings for psychiatric research and clinical practice along with potential avenues for future research are discussed.

References

1. Kinderman P, Allsopp K, Cooke A. Responses to the publication of the American Psychiatric Association's DSM-5. *Journal of Humanistic Psychology*. 2017;57(6):625-649.
2. Braslow JT, Brekke JS, Levenson J. Psychiatry's Myopia-Reclaiming the Social, Cultural, and Psychological in the Psychiatric Gaze. *JAMA Psychiatry*. 2020.
3. Kendler KS. DSM disorders and their criteria: how should they inter-relate? *Psychol Med*. 2017;47(12):2054-2060.
4. Kendler KS, Zachar P, Craver C. What kinds of things are psychiatric disorders? *Psychol Med*. 2011;41(6):1143-1150.
5. First MB, Rebello TJ, Keeley JW, et al. Do mental health professionals use diagnostic classifications the way we think they do? A global survey. *World Psychiatry*. 2018;17(2):187-195.
6. First MB, Erlich MD, Adler DA, et al. How the DSM Is Used in Clinical Practice. *J Nerv Ment Dis*. 2019;207(3):157-161.
7. Fried EI. Problematic assumptions have slowed down depression research: why symptoms, not syndromes are the way forward. *Front Psychol*. 2015;6.
8. *Diagnostic and statistical manual of mental disorders : DSM-IV*. Fourth edition. Washington, DC : American Psychiatric Association, [1994] ©1994; 1994.
9. Demyttenaere K, Heirman E. The blurred line between anxiety and depression: hesitations on comorbidity, thresholds and hierarchy. *Int Rev Psychiatry*. 2020;32(5-6):455-465.
10. Milos G, Spindler A, Schnyder U, Fairburn CG. Instability of eating disorder diagnoses: prospective study. *Br J Psychiatry*. 2005;187(6):573-578.
11. Cramer AOJ, Waldorp LJ, van der Maas HLJ, Borsboom D. Comorbidity: A network perspective. *Behav Brain Sci*. 2010;33(2-3):137-150.
12. Hyman SE. The diagnosis of mental disorders: the problem of reification. *Annu Rev Clin Psychol*. 2010;6:155-179.
13. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):617-627.
14. Krueger RF, Kotov R, Watson D, et al. Progress in achieving quantitative classification of psychopathology. *World Psychiatry*. 2018;17(3):282-293.
15. Widiger TA. A dimensional model of psychopathology. *Psychopathology*. 2005;38(4):211-214.
16. Simonsen E. The integration of categorical and dimensional approaches to psychopathology. *Contemporary directions in psychopathology: Scientific foundations of the DSM-V and ICD-11*. 2010:350-361.
17. Haslam N, Holland E, Kuppens P. Categories versus dimensions in personality and psychopathology: a quantitative review of taxometric research. *Psychol Med*. 2012;42(5):903-920.
18. Kraemer HC. Research Domain Criteria (RDoC) and the DSM—Two Methodological Approaches to Mental Health Diagnosis. *JAMA Psychiatry*. 2015;72(12):1163-1164.
19. Kendler KS. DSM disorders and their criteria: how should they inter-relate? *Psychol Med*. 2017;47(12):2054-2060.
20. Kenneth S. Kendler, M.D. The Phenomenology of Major Depression and the Representativeness and Nature of DSM Criteria. *Am J Psychiatry*. 2016;173(8):771-780.
21. Borsboom D. Psychometric perspectives on diagnostic systems. *J Clin Psychol*. 2008;64(9):1089-1108.
22. Borsboom D, Cramer AOJ, Schmittmann VD, Epskamp S, Waldorp LJ. The Small World of Psychopathology. *PLoS One*. 2011;6(11):e27407.
23. Kim NS, Ahn W-k. Clinical psychologists' theory-based representations of mental disorders predict their diagnostic reasoning and memory. *J Exp Psychol Gen*. 2002;131(4):451.
24. Nuijten M, Deserno M, Cramer A, Borsboom D. Mental disorders as complex networks. *Clin Neuropsychiatry*. 2016;13(4/5):68-76.
25. Zimmerman M, Ellison W, Young D, Chelminski I, Dalrymple K. How many different ways do patients meet the diagnostic criteria for major depressive disorder? *Compr Psychiatry*. 2015;56:29-34.

26. Fried EI, Nesse RM. Depression is not a consistent syndrome: An investigation of unique symptom patterns in the STAR*D study. *J Affect Disord.* 2015;172:96-102.
27. Park S-C, Kim J-M, Jun T-Y, et al. How many different symptom combinations fulfil the diagnostic criteria for major depressive disorder? Results from the CRESCEND study. *Nordic Journal of Psychiatry.* 2017;71(3):217-222.
28. Galatzer-Levy IR, Bryant RA. 636,120 ways to have posttraumatic stress disorder. *Perspect Psychol Sci.* 2013;8(6):651-662.
29. Fried EI, Nesse RM. Depression sum-scores don't add up: why analyzing specific depression symptoms is essential. *BMC Med.* 2015.
30. Bjarke J, Sinkeviciute I, Kroken RA, et al. Different response patterns in hallucinations and delusions to antipsychotic treatment. *Nordic Journal of Psychiatry.* 2020;74(7):497-504.
31. Bauer-Staeb C, Griffith E, Faraway JJ, Button KS. Trajectories of depression and generalised anxiety symptoms over the course of cognitive behaviour therapy in primary care: an observational, retrospective cohort. *Psychol Med.* 2022;1:9.
32. Cuijpers P. Targets and outcomes of psychotherapies for mental disorders: an overview. *World Psychiatry.* 2019;18(3):276-285.
33. Kinghorn W. Challenging the Hegemony of the Symptom: Reclaiming Context in PTSD and Moral Injury. *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine.* 2020;45(6):644-662.
34. Bakker GM. Psychotherapy outcome research: Implications of a new clinical taxonomy. *Clin Psychol Psychother.* 2022;29(1):178-199.
35. Cosgrove L, Troeger R, Karter JM. "Do antidepressants work?" A humanistic perspective on a long-standing and contentious debate. *The Humanistic Psychologist.* 2020;48(3):221.
36. Binder P-E, Holgersen H, Nielsen GHs. What is a "good outcome" in psychotherapy? A qualitative exploration of former patients' point of view. *Psychotherapy Research.* 2010;20(3):285-294.
37. Hasler G, Moergeli H, Schnyder U. Outcome of psychiatric treatment: What is relevant for our patients? *Compr Psychiatry.* 2004;45(3):199-205.
38. Chevance A, Ravaud P, Tomlinson A, et al. Identifying outcomes for depression that matter to patients, informal caregivers, and health-care professionals: qualitative content analysis of a large international online survey. *The Lancet Psychiatry.* 2020;7(8):692-702.
39. Oorschot M, Lataster T, Thewissen V, et al. Symptomatic remission in psychosis and real-life functioning. *Br J Psychiatry.* 2012;201(3):215-220.
40. McIntyre RS, Lee Y, Mansur RB. Treating to target in major depressive disorder: response to remission to functional recovery. *CNS Spectrums.* 2015;20(S1):17-31.
41. Rottenberg J, Kashdan TB. Well-Being After Psychopathology: A Transformational Research Agenda. *Curr Dir Psychol Sci.* 2022;31(3):280-287.
42. Kendler KS. The nature of psychiatric disorders. *World Psychiatry.* 2016;15(1):5-12.
43. Newby JM, McKinnon A, Kuyken W, Gilbody S, Dalgleish T. Systematic review and meta-analysis of transdiagnostic psychological treatments for anxiety and depressive disorders in adulthood. *Clin Psychol Rev.* 2015;40:91-110.
44. Fusar-Poli P, Solmi M, Brondino N, et al. Transdiagnostic psychiatry: a systematic review. *World Psychiatry.* 2019;18(2):192-207.
45. Walther S, Morrens M. What Can Be Learned from Dimensional Perspectives on Psychiatry? *Neuropsychobiology.* 2020;79(4-5):249-250.
46. Kotov R, Krueger RF, Watson D, et al. The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *J Abnorm Psychol.* 2017;126(4):454.
47. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry.* 2010.
48. Luca M. Maladaptive Rumination as a Transdiagnostic Mediator of Vulnerability and Outcome in Psychopathology. *Journal of Clinical Medicine.* 2019;8(3):314.
49. Cludius B, Mennin D, Ehring T. Emotion regulation as a transdiagnostic process. *Emotion.* 2020;20(1):37.
50. Abramovitch A, Short T, Schweiger A. The C Factor: Cognitive dysfunction as a transdiagnostic dimension in psychopathology. *Clin Psychol Rev.* 2021;86:102007.

51. Opel N, Goltermann J, Hermeszendorf M, Berger K, Baune BT, Dannlowski U. Cross-Disorder Analysis of Brain Structural Abnormalities in Six Major Psychiatric Disorders: A Secondary Analysis of Mega- and Meta-analytical Findings From the ENIGMA Consortium. *Biol Psychiatry*. 2020;88(9):678-686.
52. Buckholtz Joshua W, Meyer-Lindenberg A. Psychopathology and the Human Connectome: Toward a Transdiagnostic Model of Risk For Mental Illness. *Neuron*. 2012;74(6):990-1004.
53. Caspi A, Houts RM, Belsky DW, et al. The p factor: one general psychopathology factor in the structure of psychiatric disorders? *Clinical Psychological Science*. 2014;2(2):119-137.
54. Solmi M, Bodini L, Cocozza S, et al. Aripiprazole monotherapy as transdiagnostic intervention for the treatment of mental disorders: An umbrella review according to TRANSD criteria. *Eur Neuropsychopharmacol*. 2020;41:16-27.
55. Sakiris N, Berle D. A systematic review and meta-analysis of the Unified Protocol as a transdiagnostic emotion regulation based intervention. *Clin Psychol Rev*. 2019;72:101751.
56. Deanna M. Barch, Ph.D. What Does It Mean to Be Transdiagnostic and How Would We Know? *Am J Psychiatry*. 2020;177(5):370-372.
57. Borsboom D, Cramer AOJ. Network Analysis: An Integrative Approach to the Structure of Psychopathology. *Annu Rev Clin Psychol*. 2013;9(1):91-121.
58. Robinaugh DJ, Hoekstra RHA, Toner ER, Borsboom D. The network approach to psychopathology: a review of the literature 2008–2018 and an agenda for future research. *Psychol Med*. 2020;50(3):353-366.
59. Contreras A, Nieto I, Valiente C, Espinosa R, Vazquez C. The Study of Psychopathology from the Network Analysis Perspective: A Systematic Review. *Psychother Psychosom*. 2019;88(2):71-83.
60. Heeren A, McNally RJ. An integrative network approach to social anxiety disorder: The complex dynamic interplay among attentional bias for threat, attentional control, and symptoms. *J Anxiety Disord*. 2016;42:95-104.
61. Izquierdo A, Cabello M, Leal I, et al. The interplay between functioning problems and symptoms in first episode of psychosis: An approach from network analysis. *J Psychiatr Res*. 2021;136:265-273.
62. Borsboom D, Epskamp S, Kievit RA, Cramer AOJ, Schmittmann VD. Transdiagnostic Networks: Commentary on Nolen-Hoeksema and Watkins (2011). *Perspect Psychol Sci*. 2011;6(6):610-614.
63. Guloksuz S, Pries LK, van Os J. Application of network methods for understanding mental disorders: pitfalls and promise. *Psychol Med*. 2017;47(16):2743-2752.
64. Blanchard MA, Heeren A. 11.03 - Ongoing and Future Challenges of the Network Approach to Psychopathology: From Theoretical Conjectures to Clinical Translations. In: Asmundson GJG, ed. *Comprehensive Clinical Psychology (Second Edition)*. Oxford: Elsevier; 2022:32-46.
65. Pincus HA, Spaeth-Rublee B, Sara G, et al. A review of mental health recovery programs in selected industrialized countries. *International Journal of Mental Health Systems*. 2016;10(1):73.
66. Galderisi S, Heinze A, Kastrup M, Beechhold J, Sartorius N. Toward a new definition of mental health. *World Psychiatry*. 2015;14(2):231-233.
67. Fusar-Poli P, Salazar de Pablo G, De Michelis A, et al. What is good mental health? A scoping review. *Eur Neuropsychopharmacol*. 2020;31:33-46.
68. Van Weeghel J, van Zelst C, Boertien D, Hasson-Ohayon I. Conceptualizations, assessments, and implications of personal recovery in mental illness: A scoping review of systematic reviews and meta-analyses. *Psychiatric rehabilitation journal*. 2019;42(2):169.
69. Moore LJ, Goldner-Vukov M. The existential way to recovery. *Psychiatria danubina*. 2009;21(4):453-462.
70. van Os J, Guloksuz S, Vijn TW, Hafkenscheid A, Delespaul P. The evidence-based group-level symptom-reduction model as the organizing principle for mental health care: time for change? *World Psychiatry*. 2019;18(1):88-96.
71. Huguelet P. The Contribution of Existential Phenomenology in the Recovery-Oriented Care of Patients with Severe Mental Disorders. *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine*. 2014;39(4):346-367.
72. de Haan S. The existential dimension in psychiatry: an enactive framework. *Mental Health, Religion & Culture*. 2017;20(6):528-535.
73. Bygstad-Landro M, Giske T. Risking existence: The experience and handling of depression. *J Clin Nurs*. 2018;27(3-4):e514-e522.
74. van Os J, Pries L-K, ten Have M, et al. Context v. algorithm: evidence that a transdiagnostic framework of contextual clinical characterization is of more clinical value than categorical diagnosis. *Psychol Med*. 2021;1-9.



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Protocol Across study: Longitudinal transdiagnostic cognitive functioning, psychiatric symptoms, and biological parameters in patients with a psychiatric disorder

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Abstract

Background

Patients with psychiatric disorders, such as major depressive disorder, schizophrenia or obsessive-compulsive disorder, often suffer from cognitive dysfunction. The nature of these dysfunctions and their relation with clinical symptoms and biological parameters is not yet clear. Traditionally, cognitive dysfunction is studied in patients with specific psychiatric disorders, disregarding the fact that cognitive deficits are shared across disorders. The Across study aims to investigate cognitive functioning and its relation with psychiatric symptoms and biological parameters transdiagnostically and longitudinally.

Methods

The study recruits patients diagnosed with a variety of psychiatric disorders and has an observational longitudinal cohort design with an assessment at baseline and at one-year follow-up. The primary outcome measure is cognitive functioning. The secondary outcome measures include clinical symptoms, electroencephalographic, genetic and blood markers (e.g., fatty acids), and hair cortisol concentration levels.

Discussion

The Across study provides an opportunity for a transdiagnostic, bottom-up, data-driven approach of investigating cognition in relation to symptoms and biological parameters longitudinally in patients with psychiatric disorders. The study may help to find new clusters of symptoms, biological markers, and cognitive dysfunctions that have better prognostic value than the current diagnostic categories. Furthermore, increased insight into the relationship among cognitive deficits, biological parameters, and psychiatric symptoms can lead to new treatment possibilities.

Trial registration: Netherlands Trial Register (NTR): NL8170

Keywords: study protocol, transdiagnostic, cognitive functioning, psychiatric disorders

Background

Patients with psychiatric disorders often have cognitive deficits¹. These deficits have been associated with psychosocial dysfunction in a variety of disorders, including depression^{2,3}, schizophrenia⁴, and bipolar disorder⁵. Cognition encompasses a number of interrelated mental activities, such as attention, learning, memory, problem-solving, and planning¹, all of which are important for daily life functioning. In fact, cognitive dysfunctions may form an important underlying factor between psychiatric symptoms and functional outcomes^{6,7}. For instance, patients with schizophrenia have expressed a particular desire to treat cognitive deficits above the amelioration of their psychotic symptoms in order to function in daily life⁸. Cognitive deficits can also have an impact on other dimensions of psychiatric disorders by potentially contributing to and exacerbating cognitive biases⁹. However, cognitive dysfunction continues to be ineffectively treated because evidence-based treatments for cognitive dysfunction are scarce.

Previous research into cognitive dysfunction in psychiatric patients was mainly conducted in patient populations within specific diagnostic categories. However, high rates of comorbidity and heterogeneity are present across and within disorders¹⁰⁻¹². The heterogeneity within diagnostic categories and overlap of diagnostic criteria between disorders can be demonstrated by the fact that there are 227 ways to meet the criteria for major depressive disorder due to the polythetic definition of the disorder¹³, and that at least half of patients with depressive disorder have a comorbid anxiety disorder^{14,15}. Heterogeneity in and comorbidity across disorders manifest not only at the symptom level but also in behavior, physiology, and cognitive functioning. This could be a factor in lack of consensus regarding neuropsychological profiles for psychiatric disorders.

In addition, whether cognitive dysfunctions are generalized (i.e., global cognitive deficit) or more specific (i.e., psychotic disorders are associated with impairment in cognitive flexibility) is not yet clear. A reason why this may be difficult to determine is that studies often employ a limited assessment of cognition. Cognition is a multifaceted construct and consists of multiple domains, and some cognitive domains have sub-domains¹. For instance, executive functioning consists of different abilities, such as cognitive flexibility, verbal fluency, and strategy use, while it is often assessed with one test¹⁶. Memory encompasses immediate and delayed memory, and includes different mechanisms, such as retrieval and consolidation¹. The use of single assessments to measure such complex processes may give a limited view on cognition, corroborating the need for multiple tests that assess specific cognitive domains.

Additionally, there is a need for further investigation into which domains of cognition are trait- or state-dependent. Cognitive deficits that persist after remission suggest that certain cognitive domains may be trait-dependent. For instance, a review of cognitive functioning in young adults with major depressive disorder suggests that executive functioning and cognitive control deficits persist despite remission of clinical symptoms whereas other cognitive domains seem to be more dependent on clinical status¹⁷. Nonetheless, findings tend to be mixed and many studies investigated only one domain or are cross-sectional, so longitudinal studies with various cognitive domain assessments are necessary to assess any possible changes in functioning. Longitudinal investigations could elucidate whether certain domains of cognitive dysfunction are related to clinical state or whether they reflect, for instance, abnormal neurodevelopment and genetic vulnerabilities¹⁸. Furthermore, insight into potential causal relationships could be gained with a longitudinal approach, such as whether psychiatric symptoms or biological measurement outcomes impact cognitive functioning at a later time or vice versa.

Furthermore, biological mechanisms related to changes in cognition are not yet well-established. Inclusion of biological parameters may provide further insight into pathophysiological mechanisms associated with cognitive deficits and phenotypic expressions of disorders. For instance, cortisol awakening response is associated with memory deficits in patients with psychotic disorders¹⁹ and medicated patients with major depressive disorder²⁰. In addition, cognitive functioning shows a relationship with electroencephalogram (EEG) derivatives, such as the P300 and mismatch negativity (MMN) event-related potential, in individuals diagnosed with a variety of psychiatric disorders²¹⁻²³ and in healthy subjects^{24,25}. Other physiological parameters are also associated with cognition and psychopathology, such as inflammatory markers, which show an association with poor performance on memory, language, and attention tests in women with post-traumatic stress disorder²⁶. Recently, the role of polyunsaturated fatty acids (PUFAs) has also been garnering attention, and PUFA deficits have been transdiagnostically associated with diverse psychiatric disorders and cognition²⁷⁻³⁰. However, there has been a lack in solid findings regarding biomarkers associated with cognitive functioning in psychiatric disorders. This may once again be because studies analyze biological parameters focusing on specific psychiatric disorders, most often excluding those with comorbidity and thus possibly disregarding heterogeneity or subgroups within disorders. The inclusion of blood markers, EEG and cortisol as biological parameters in our study was informed by recent evidence of their transdiagnostic relationship with psychopathology³¹⁻³⁸.

Therefore, a transdiagnostic approach may be optimal to study the general role of cognition in psychiatric disorders. A transdiagnostic approach acknowledges

heterogeneity and comorbidity of symptoms because it does not view mental disorders as categorically distinct entities. As cognitive dysfunction occurs in patients with a variety of psychiatric disorders¹, it should be treated as a transdiagnostic dimension³⁹. Supporting this, the Research Domain Criteria (RDoC) framework also regards cognition as a transdiagnostic domain⁴⁰. A transdiagnostic approach therefore provides an opportunity for a bottom-up data-driven method of investigating cognition in relation to symptoms and biological parameters that is not bound to diagnostic categories.

Objectives

The objectives of the ongoing Across study are to: 1) investigate cognitive dysfunctions transdiagnostically across different psychiatric disorders, 2) link cognitive dysfunctions with psychiatric symptoms and biological parameters, and 3) investigate the longitudinal course of cognitive dysfunctions in relation to symptoms and biological parameters.

Due to the diverse measures included in this study, a wide-range of research questions can be investigated. Some hypotheses to be tested include: 1) executive functioning is impaired in psychiatric patients, 2) cortisol levels are associated with memory functioning, 3) lower concentrations of omega-3 PUFAs are associated with poorer cognitive functioning, and 4) verbal memory dysfunction persist despite improvements in psychiatric symptoms. Other research questions can be investigated with the acquired data.

The findings of the Across study could elucidate relationships among cognition, psychiatric symptoms, and biomarkers. This could lead to insight into mechanisms related to cognitive dysfunctions, which can be used as targets in treatment. Furthermore, longitudinal assessments can provide information on state and trait components of cognitive dysfunction.

Methods/Design

Study design and procedure

The Across study is an ongoing, observational longitudinal cohort study and consists of the assessment of cognitive performance, psychiatric symptoms, and collection of biological data (DOI 10.17605/OSF.IO/YHVTB)⁴¹. All patients visiting the Department of Psychiatry at the Amsterdam University Medical Centers (Amsterdam UMC), location Academic Medical Center (AMC) for an intake are referred to the study and can

choose which parts to participate in after they received information about the study and provide informed consent. All recruitment, testing, and data collection takes place at the Amsterdam UMC, which began in February 2016.

After intake, blood is drawn at a laboratory for the assessment of blood markers. On a later date, cognitive performance is assessed using a computerized battery, which is followed by the completion of self-report questionnaires on various symptom domains. This takes two to three hours to complete. After completion of the questionnaires, a hair sample is collected to measure cortisol levels, and 45 minutes of EEG recordings is obtained, which provides data on information-processing deficits. Underage participants (ages 14-17) complete a shorter version of the questionnaires and do not partake in the EEG data collection as EEG parameters are known to develop strongly during these periods^{42,43}. Participants are invited to be assessed again one year later if they consent to being contacted. The follow-up included the exact same measures, except for the blood donation.

The study protocol was approved by the Medical Ethical Review Committee and the Biobank Review Committee of the Amsterdam UMC (ABR no. NL55751.018.15). Biological data and material are stored in the Amsterdam UMC Biobank, a secured facility established specifically for the storage and management of biological materials. Patients are assigned a study number and patient data are stored securely to ensure confidentiality. All researchers undergo thorough training and receive extensive supervision to ensure quality of data collection.

Study population

The study population consists of individuals between the ages of 14 to 75 years who have a diagnosis of at least one psychiatric disorder. Participants are recruited through the tertiary care Department of Psychiatry at the Amsterdam UMC, location AMC, the Netherlands, if they meet the participation criteria (Table 1).

All patients receive a Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR or DSM-5 diagnosis^{44,45} from a trained psychiatrist within the Amsterdam UMC. As of September 2019, 1091 patients completed a baseline assessment and 272 patients completed a one-year follow-up assessment. On average, 14 patients agreed to participate in the Across study per month and the study will continue the coming years.

Table 1. Criteria for inclusion, exclusion, and discontinuation of participation

Inclusion criteria
1. Ability to give informed consent
2. DSM-IV-TR axis I or DSM-5 diagnosis
3. Aged 14 – 75 years at intake
4. For under-aged participants, consent will also be obtained from the participant's parents in addition to the participant's consent
5. Fluent in Dutch
6. Clinically stable
Exclusion criteria
1. High risk of suicide
2. Unstable medical disorder
3. Premorbid IQ < 70
4. History of a clinically significant abnormality of the neurological system (including dementia and other cognitive disorders or significant head injury) or any history of seizure (excluding febrile seizure)
Discontinuation criteria
1. Voluntary discontinuation by the patient who is at any time free to discontinue his or her participation in the study, without consequences to further treatment
2. Safety reasons as judged by the investigator
3. Severe non-compliance to the protocol as judged by the investigator
4. Incorrect enrolment (i.e., the patient did not meet or does no longer meet the required inclusion criteria) of the patient
5. Patient lost to follow-up due to no response
6. Development of exclusion criteria

The current sample has a mean (SD) premorbid IQ of 100.09 (13.3) and 86.5% of the sample were of Caucasian ethnicity. On average, the sample consisted of middle-aged adults with a mean (SD) age of 34.6 (14.1) years, and there was nearly an equal number of males and females (47.2% and 52.8%, respectively). The most common diagnoses are: disruptive, impulse-control, and conduct disorders (n=409), schizophrenia spectrum and other psychotic disorders (n=191), obsessive-compulsive spectrum disorders (n=164), depressive disorders (n=122), and anxiety disorders (n=64).

Measures

Demographic information, such as gender, ethnicity, age, and education, is obtained through self-report.

Primary outcome measures

The primary outcome measure is cognitive functioning, which is assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB)⁴⁶. The CANTAB

test battery is composed of the following subtests: Motor screening (MTS), Verbal Recognition Memory (VRM), Rapid Visual Information Processing (RVP), Intra/ Extradimensional Set Shift (IED), Choice reaction time (CRT), One Touch Stockings of Cambridge (OTS), Paired Associates Learning (PAL), Graded Naming Test (GNT), and Spatial Working Memory (SWM). Descriptions of the subtests can be found in Table 2.

Table 2. Description of Cambridge Neuropsychological Test Automated Battery subtests

Subtests	Description
Verbal Recognition Memory (VRM)	Assesses free recall, and immediate and delayed recognition memory for verbal information
Rapid Visual Information Processing (RVP)	Tests visual sustained attention and processing speed
Intra/ Extradimensional Set Shift (IED)	Assesses rule acquisition and attentional set shifting
Choice reaction time (CRT)	Measures alertness and motor speed
One Touch Stockings of Cambridge (OTS)	A planning test which gives a measure of frontal lobe functioning
Paired Associates Learning (PAL)	Assesses visual episodic memory and learning
Spatial Working Memory (SWM)	Assesses working memory and strategy use

In addition to CANTAB, the following tests are administered: the Dutch National Adult Reading Test (NART) to assess premorbid IQ ⁴⁷; the California Verbal Learning Test to measure episodic verbal learning and memory ⁴⁸; and the semantic Verbal Fluency of the Groninger Intelligence Test ⁴⁹.

Secondary outcome measures

These measures include psychometrically established self-report questionnaires on dimensions of psychopathology.

Substance use-related disorders are assessed with two questionnaires. The Alcohol Use Disorder Identification Test (AUDIT) consists of 10 items that assess alcohol consumption, drinking behaviors, and alcohol-related problems on scale of 0-4 ⁵⁰ with a median internal reliability of Cronbach alpha in the 0.80s across numerous studies ⁵¹. Cannabis use problems are screened with the Cannabis Use Disorder Identification Test (CUDIT), which consists of 10 items measuring frequency and dependence with a positive predictive power of 84.6% and sensitivity of 73.3% at a cut-off of 8 ⁵². In addition, participants are asked about the frequency of use for numerous substances, including coffee, cigarettes, stimulants (e.g., amphetamines), sedatives (e.g., barbiturates), opiates (e.g., heroin), and others.

The Prodromal Questionnaire (PQ-16) assesses the occurrence and severity of At Risk Mental State symptoms for a first psychosis with 2 items on negative symptoms,

5 items on unusual thought content/delusional ideas/paranoia, and 9 items on perceptual abnormalities/hallucinations⁵³. A previous study found a Cronbach's alpha for the total score of 0.77 and all item-total correlations of at least 0.31⁵³.

The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) measures the severity and type of obsessive-compulsive symptoms with 10 items⁵⁴. Item-total correlations were at least 0.36 with a mean Cronbach's alpha of 0.89 for internal consistency⁵⁴.

Anxiety-related symptoms are measured with two questionnaires. The Hamilton Anxiety Scale (HAM-A) assesses the severity of somatic, cognitive, and affective symptoms of anxiety with 13 items⁵⁵ and demonstrates good interrater reliability⁵⁵. Anxiety in social interactions and fear of scrutiny by others is assessed with the 20-item Social Interaction Anxiety Scale (SIAS)⁵⁶. The SIAS demonstrates high levels of internal consistency ($\alpha = 0.94$), test-retest reliability at 12 weeks ($r=0.92$), and sensitivity to change with treatment⁵⁶.

The severity of depressive symptoms is measured with Inventory of Depressive Symptomatology Self-Report (IDS-SR) with 30 items pertaining to mood, cognition, arousal, suicidality, and sleep⁵⁷. The IDS demonstrates good internal consistency ($\alpha = 0.85$) and is applicable to different types of depression⁵⁸.

Self-esteem in relation to social contact, achievements, and competency is assessed with the Self-esteem Rating Scale- Short Form (SERS-SR)⁵⁹. The SERS-SR demonstrates good test-retest reliability for the positive scale ($r= 0.90$) and the negative scale ($r= 0.91$) and high internal consistency for each scale (respectively, $\alpha= 0.91$ and $\alpha= 0.87$).

The Impact of Events Scale-Revised (IES-R) assesses subjective distress caused by traumatic events with 22 items and is composed of three subscales: avoidance, intrusions, and hyperarousal⁶⁰. The IES-R shows good internal consistency ($\alpha= 0.96$) and a cut-off score of 33 provided a sensitivity of 0.91, a specificity of 0.82, positive predictive power of 0.90, and negative predictive power of 0.84⁶⁰.

The Work and Social Adjustment Scale (WSAS) is a 5-item questionnaire that measures general impairment in different domains of daily life, including work, social activities, and leisure activities⁶¹. The WSAS is sensitive to disorder severity and treatment-related changes and demonstrated a test-retest correlation of 0.73 and internal consistency ranging from $\alpha= 0.70$ to 0.94 ⁶¹.

The Psychiatric Dimensions Questionnaire was developed at the Amsterdam UMC and contains 26 items, which assess a variety of transdiagnostic concepts such as

identity, autonomy, and self-control, that are commonly affected in patients with a psychiatric disorder.

Anhedonia is measured with the Anhedonia Scale⁶², in which participants rate 21 items related to pleasure from physical activity, hearing, seeing, touching, tasting, sex, and smelling.

The AUDIT, CUDIT, IES-R, Y-BOCS, WSAS and Anhedonia Scale are administered only to adult patients. These self-report questionnaires are administered on a computer with the Computer Diagnostic Leiden (CDL) program⁶³. Most tests and questionnaires include norms and cut-off scores that can aid in interpreting the range of performance. Patients are also asked about drug and medication use and their experience of participating in the study. Other information, such as the diagnosis and family history, is also collected during the clinical intake.

Biological measures

Blood markers

22 ml non-fasting blood samples are collected at baseline on the day of the intake at a laboratory within the Amsterdam UMC as part of standard blood collection for clinical purposes. Blood samples are stored in five tubes: 1) PAXgene for RNA; 2) EDTA 6ml for DNA; 3) EDTA 4ml for red blood cells, white blood cells, and platelets; 4) lithium heparin for plasma determinations (e.g., cholesterol and hormones); and 5) serum for antibodies and other proteins. After collection, the blood samples are stored in -80°C cryostorage at the Amsterdam UMC Biobank. The appropriate pre-processing steps (e.g., genotyping for DNA) will be conducted in order to analyze various blood markers, such as cytokines, DNA/RNA, and fatty acids. The methods to analyze fatty acids have been described previously in Mocking, Assies, Lok, Ruhé, Koeter, Visser, Bockting, Schene⁶⁴; in brief, erythrocytes are first separated, washed and frozen. Subsequently, fatty acid concentrations are analyzed using capillary gas chromatography and expressed in pmol/10⁶erythrocyte.

Electroencephalogram (EEG)

EEG is assessed with a WaveGuard cap with Ag/AgCl electrodes with standard 10/10 layout fed into the 64-channel ANT TMSI Refa amplifier, using Fpz as ground, horizontal EOG electrodes affixed to the outer canthus and vertical EOG electrodes affixed above and below the right eye, two mastoid channels (M1/M2). The vertex electrode (Cz) is used as the recording reference. The resting state EEG and auditory oddball task are recorded in a session of 45 minutes. Recordings were sampled at 512 Hz with a 128 Hz high-pass filter. Eyes-closed resting state recordings take 5 minutes,

eyes-opened resting state recordings take 3 minutes, and the auditory oddball task takes about 12 minutes. During the auditory oddball task, patients watch a nature documentary film as they listen to a series of beeps and press a button whenever there is a high-pitched beep. EEG data are collected only from adult patients.

Hair cortisol

A string of about 100 hairs is cut from the posterior vertex region of the scalp⁶⁵ to assess cortisol levels over the course of months in which 1 cm of hair is approximately equal to 1 month of mean cortisol levels^{66,67}. Hair samples are stored at room temperature at the Amsterdam UMC Biobank. To assess confounders, patients complete a questionnaire regarding hair-related characteristics, such as hair coloring, frequency of hair washing per week, use of hair products, and use of corticosteroids.

Power calculation

The power calculation was focused on the detection of a bivariate correlation between two quantitative measures as it will determine subsequent data reduction techniques. The proposed sample sizes are shown in Table 3, which would allow 80% power to detect a correlation of at least 0.08 at various alpha levels while accounting for an attrition rate of 20%. The necessary sample size could differ according to the number of tests and the minimum correlation we want to detect.

Table 3. Power calculation: Detect two-tailed bivariate correlation at 80% power

Correlation coefficient	Alpha	N ^a
0.08	0.0005	3492
0.14	0.0005	1134
0.2	0.0005	550
0.08	0.001	3192
0.014	0.001	1037
0.2	0.001	503
0.08	0.01	2184
0.14	0.01	709
0.2	0.01	345

^a Sample size accounting for a 20% attrition rate

Proposed statistical analyses

The association between cognitive dysfunctions, symptoms, and biological parameters will be analyzed. To elucidate models that most adequately explain the correlational patterns between variables, data reduction techniques will be employed

(e.g., factor analyses or network analyses) as determined by the structure of the correlational matrices. Other data reduction techniques, such as (graph) clustering analyses can be used, to determine whether symptom clusters match diagnosis.

Linear regression analyses will be conducted with cognition scores as the outcome measure and dummy coded diagnostic groups as the predictors to investigate cognitive deficits across different psychiatric disorders. Age, gender, education, ethnicity, and medication use will be included as covariates as deemed appropriate. Similar models will be built for the biological outcomes variables.

The longitudinal course of cognitive dysfunctions will be investigated with repeated measures analyses or a regression model using cognition change scores as the outcome variable and baseline cognition scores as predictor. Other predictors of changes will be investigated by conducting regression analyses with cognition change scores as the outcome measure and biological parameters and clinical symptoms as predictors with the baseline cognition scores as a covariate. Additionally, prediction of cognitive functioning and symptom course can be analyzed using machine learning. Age, gender, education, ethnicity, and medication use will also be included as covariates if deemed appropriate. If there are doubts about bias due to age-related effects, we will conduct sensitivity analyses.

Statistical analyses will be performed in IBM SPSS Statistics 24⁶⁸ or R⁶⁹.

Discussion

The objectives, study population characteristics, and assessment methods of the Across study are presented here to provide a detailed methodological reference for future Across papers. The aim of the study is to investigate cognitive functioning and its relation with symptoms and biological parameters transdiagnostically and longitudinally.

The Across study has a number of strengths. Firstly, the team of researchers and clinicians involved is multidisciplinary and has academic expertise in the specific topics of this study. Patients are seen during intakes by professionals with extensive clinical experience, and the research is set up and led by principal investigators with relevant expertise in genetics, EEG, and cognition research. Furthermore, the longitudinal design, large sample size, and transdiagnostic biopsychosocial approach add value to this study. The latter is especially important as it allows for a more comprehensive understanding of cognition in relation to biological parameters and psychiatric symptoms across disorders. In addition, the study utilizes a variety of instruments, providing researchers the opportunity to investigate different aspects

of cognition and psychiatric disorders. Cognition is also assessed as a complex and multifaceted construct with the use of tasks focusing on cognitive domains (and sub-domains). This also adds to the comprehensive nature of the study as cognition can be rather complex due to the numerous factors that interact on a variety of levels. Further, a relatively large transdiagnostic sample increases the ecological validity of this study as it includes minor and adult patients with various and comorbid psychiatric disorders, allowing for a better reflection of clinical reality. Moreover, there are relatively few exclusion criteria, and the inclusion criteria are broad, adding to the generalizability of the sample. Lastly, this study is performed at one institute, ensuring a more homogeneous approach than multicenter studies, which often encounter difficulty with merging data across centers and ensuring assessors are trained uniformly.

The study results should be interpreted with a few methodological considerations in mind. First, there may be a selection bias as the patients who are willing to participate may differ from patients who refuse. This is inherent to psychiatric research, and in order to obtain the most representative sample possible, lenient inclusion and exclusion criteria were used. Second, the quality of assessments may be influenced by the large number of research assistants involved, despite the investment in proper training. Quality checks are put into place to ensure that the protocol is being followed and that assistants carry out the assessments correctly. Third, the patients included in the study tend to have severe psychiatric disorders because the Amsterdam UMC is an institution that provides tertiary care based on specific referrals. This may reduce the generalizability of the results to less severely affected patients, and there may be both over- and under-representations of certain disorders. Findings may nonetheless still be representative for institutions similar to the Amsterdam UMC. Fourth, while a few hypotheses have already been determined, the vast dataset allows for the possibility of many other future research questions. Re-using datasets is a cost-effective and time saving way of doing research but on the other side leads to limitations in predefining the analysis plan. However, most biobank studies combine hypothesis-driven research with more general data-collection and data-driven analyses.

Although research into cognition is not necessarily sparse, much remains uncertain and unknown about the nature of cognitive dysfunctions in psychiatric patients. For example, a transdiagnostic construct such as anhedonia could be related to cognitive dysfunction. Cognitive dysfunctions remain undertreated as a result of the limited knowledge regarding the nature of cognitive deficits, despite its high occurrence in and heavy burden for psychiatric patients. The Across study may find new clusters of symptoms, biological markers, and cognitive dysfunctions that have better

prognostic value than the current diagnostic categories. Furthermore, increased insight into the relationship among cognitive deficits, biological parameters, and psychiatric symptoms can lead to new treatment possibilities.

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References

1. Millan MJ, Agid Y, Brüne M, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov.* 2012;11(2):141.
2. McIntyre RS, Cha DS, Soczynska JK, et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. *Depress Anxiety.* 2013;30(6):515-527.
3. Knight MJ, Air T, Baune BT. The role of cognitive impairment in psychosocial functioning in remitted depression. *J Affect Disord.* 2018;235:129-134.
4. Shamsi S, Lau A, Lencz T, et al. Cognitive and symptomatic predictors of functional disability in schizophrenia. *Schizophr Res.* 2011;126(1):257-264.
5. Depp CA, Mausbach BT, Harmell AL, et al. Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. *Bipolar Disord.* 2012;14(3):217-226.
6. Buist-Bouwman M, Ormel J, De Graaf R, et al. Mediators of the association between depression and role functioning. *Acta Psychiatr Scand.* 2008;118(6):451-458.
7. McIntyre RS, Soczynska JZ, Woldeyohannes HO, et al. The impact of cognitive impairment on perceived workforce performance: results from the International Mood Disorders Collaborative Project. *Compr Psychiatry.* 2015;56:279-282.
8. Hendriksen-Favier A, van Rooijen S, Vink L, Rijkaart A-M, Kroon H. Bridging the gap. Utrecht: Trimbos Instituut. 2012.
9. Ahern E, Bockting CL, Semkovska M. A Hot-Cold Cognitive Model of Depression: integrating the Neuropsychological Approach Into the Cognitive Theory Framework. *Clinical Psychology in Europe.* 2019;1:e34396.
10. Hyman SE. The diagnosis of mental disorders: the problem of reification. *Annu Rev Clin Psychol.* 2010;6:155-179.
11. Olbert CM, Gala GJ, Tupler LA. Quantifying heterogeneity attributable to polythetic diagnostic criteria: theoretical framework and empirical application. *J Abnorm Psychol.* 2014;123(2):452.
12. Sinden AM. The demands of comorbidity: implications for the explanation and classification of mental disorder. 2014.
13. Zimmerman M, Ellison W, Young D, Chelminski I, Dalrymple K. How many different ways do patients meet the diagnostic criteria for major depressive disorder? *Compr Psychiatry.* 2015;56:29-34.
14. Spinhoven P, van Balkom A, Nolen WA. Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the Netherlands Study of Depression and Anxiety (NESDA). *J Clin Psychiatry.* 2011;72:341-348.
15. Kessler RC, Sampson NA, Berglund P, et al. Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. *Epidemiol Psychiatr Sci.* 2015;24(3):210-226.
16. Suchy Y. Executive functioning: Overview, assessment, and research issues for non-neuropsychologists. *Ann Behav Med.* 2009;37(2):106-116.
17. Allott K, Fisher CA, Amminger GP, Goodall J, Hetrick S. Characterizing neurocognitive impairment in young people with major depression: state, trait, or scar? *Brain Behav.* 2016;6(10):e00527.
18. Alnæs D, Kaufmann T, Doan NT, et al. Association of heritable cognitive ability and psychopathology with white matter properties in children and adolescents. *JAMA psychiatry.* 2018;75(3):287-295.
19. Aas M, Dazzan P, Mondelli V, et al. Abnormal cortisol awakening response predicts worse cognitive function in patients with first-episode psychosis. *Psychol Med.* 2011;41(3):463-476.
20. Hinkelmann K, Muhtz C, Dettenborn L, et al. Association between cortisol awakening response and memory function in major depression. *Psychol Med.* 2013;43(11):2255-2263.
21. Näätänen R, Kujala T, Kreegipuu K, et al. The mismatch negativity: an index of cognitive decline in neuropsychiatric and neurological diseases and in ageing. *Brain.* 2011;134(12):3435-3453.
22. Nieman D, Koelman J, Linszen D, Bour L, Dingemans P, de Visser BO. Clinical and neuropsychological correlates of the P300 in schizophrenia. *Schizophr Res.* 2002;55(1):105-113.

23. Norra C, Pedersen A, Juckel G, Waniek S. Mismatch negativity generation deficits and selective monoaminergic treatments in patients with major depression. *Klinische Neurophysiologie*. 2011;42(01):P354.
24. Berka C, Levendowski DJ, Lumicao MN, et al. EEG correlates of task engagement and mental workload in vigilance, learning, and memory tasks. *Aviat Space Environ Med*. 2007;78(5):B231-B244.
25. Light GA, Swerdlow NR, Braff DL. Preattentive sensory processing as indexed by the MMN and P3a brain responses is associated with cognitive and psychosocial functioning in healthy adults. *J Cogn Neurosci*. 2007;19(10):1624-1632.
26. Imai R, Hori H, Itoh M, et al. Inflammatory markers and their possible effects on cognitive function in women with posttraumatic stress disorder. *J Psychiatr Res*. 2018;102:192-200.
27. Grosso G, Galvano F, Marventano S, et al. Omega-3 Fatty Acids and Depression: Scientific Evidence and Biological Mechanisms. *Oxid Med Cell Longev*. 2014;2014:313570.
28. Rangel-Huerta OD, Gil A. Effect of omega-3 fatty acids on cognition: an updated systematic review of randomized clinical trials. *Nutr Rev*. 2018;76(1):1-20.
29. Bos DJ, van Montfort SJ, Oranje B, Durston S, Smeets PA. Effects of omega-3 polyunsaturated fatty acids on human brain morphology and function: What is the evidence? *Eur Neuropsychopharmacol*. 2016;26(3):546-561.
30. Mocking R, Assies J, Ruhé H, Schene A. Focus on fatty acids in the neurometabolic pathophysiology of psychiatric disorders. *J Inherit Metab Dis*. 2018;1-15.
31. Amminger GP, Nelson B, Markulev C, et al. The NEURAPRO Biomarker Analysis: Long-Chain Omega-3 Fatty Acids Improve 6-Month and 12-Month Outcomes in Youths at Ultra-High Risk for Psychosis. *Biol Psychiatry*. 2020;87(3):243-252.
32. Firth J, Teasdale SB, Allott K, et al. The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials. *World Psychiatry*. 2019;18(3):308-324.
33. Emery S, Häberling I, Berger G, et al. Omega-3 and its domain-specific effects on cognitive test performance in youths: a meta-analysis. *Neurosci Biobehav Rev*. 2020.
34. Giacobbe J, Benoiton B, Zunszain P, Pariante CM, Borsini A. The anti-inflammatory role of omega-3 polyunsaturated fatty acids metabolites in pre-clinical models of psychiatric, neurodegenerative and neurological disorders. *Frontiers in Psychiatry*. 2020;11:122.
35. Grisanzio KA, Goldstein-Piekarski AN, Wang MY, Ahmed APR, Samara Z, Williams LM. Transdiagnostic symptom clusters and associations with brain, behavior, and daily function in mood, Anxiety, and trauma disorders. *JAMA psychiatry*. 2018;75(2):201-209.
36. Ferro MA, Gonzalez A. Hair cortisol concentration mediates the association between parent and child psychopathology. *Psychoneuroendocrinology*. 2020;114:104613.
37. Ketheesan S, Rinaudo M, Berger M, et al. Stress, Allostatic Load and Mental Health in Indigenous Australians. *Stress*. 2020(just-accepted):1-26.
38. Horwitz T, Lam K, Chen Y, Xia Y, Liu C. A decade in psychiatric GWAS research. *Mol Psychiatry*. 2019;24(3):378-389.
39. McTeague LM, Goodkind MS, Etkin A. Transdiagnostic impairment of cognitive control in mental illness. *J Psychiatr Res*. 2016;83:37-46.
40. Morris SE, Cuthbert BN. Research Domain Criteria: cognitive systems, neural circuits, and dimensions of behavior. *Dialogues Clin Neurosci*. 2012;14(1):29.
41. Nieman D, Vulink N, Chavez-Baldini U, Verweij K, Denys D. Across. <https://osf.io/yhvtb/>. Published 2019. Accessed.
42. Smit DJ, Boersma M, Schnack HG, et al. The brain matures with stronger functional connectivity and decreased randomness of its network. *PLoS One*. 2012;7(5):e36896.
43. Overbye K, Huster RJ, Walhovd KB, Fjell AM, Tamnes CK. Development of the P300 from childhood to adulthood: a multimodal EEG and MRI study. *Brain Struct Funct*. 2018;223(9):4337-4349.
44. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-5)*. Washington, DC: Author; 2013.
45. American Psychiatric Association. *Diagnostic and statistical manual-text revision (4th ed., text rev.)*. Washington, DC: Author; 2000.
46. CANTAB® [Cognitive assessment software] [computer program]. 2018.

47. Schmand B, Bakker D, Saan R, Louman J. The Dutch Reading Test for Adults: a measure of premorbid intelligence level. *Tijdschr Gerontol Geriatr.* 1991;22(1):15-19.
48. Delis DC, Kramer J, Kaplan E, Ober BA. *CVLT-II: California verbal learning test: adult version.* Psychological Corporation; 2000.
49. Luteijn F, Van der Ploeg FA. Groninger Intelligentie Test: Handleiding [Groninger Intelligence Test: Manual]. Swets, Zeitlinger BV: Lisse. 1983.
50. Saunders JB, Aasland OG, Babor TF, De la Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction.* 1993;88(6):791-804.
51. Reinert DF, Allen JP. The alcohol use disorders identification test (AUDIT): a review of recent research. *Alcoholism: Clinical and Experimental Research.* 2002;26(2):272-279.
52. Adamson SJ, Sellman JD. A prototype screening instrument for cannabis use disorder: the Cannabis Use Disorders Identification Test (CUDIT) in an alcohol-dependent clinical sample. *Drug Alcohol Rev.* 2003;22(3):309-315.
53. Ising HK, Veling W, Loewy RL, et al. The validity of the 16-item version of the Prodromal Questionnaire (PQ-16) to screen for ultra high risk of developing psychosis in the general help-seeking population. *Schizophr Bull.* 2012;38(6):1288-1296.
54. Goodman W, Price L, Rasmussen S, et al. Yale-brown obsessive compulsive scale (Y-BOCS): I. Development, use, and reliability. *Arch Gen Psychiatry.* 1989;46:1006-1011.
55. Hamilton M, Schutte N, Malouff J. Hamilton anxiety scale (HAMA). *Sourcebook of Adult Assessment: Applied Clinical Psychology.* 1976:154-157.
56. Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. *Behav Res Ther.* 1998;36(4):455-470.
57. Rush AJ, Giles DE, Schlessser MA, Fulton CL, Weissenburger J, Burns C. The inventory for depressive symptomatology (IDS): preliminary findings. *Psychiatry Res.* 1986;18(1):65-87.
58. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The inventory of depressive symptomatology (IDS): psychometric properties. *Psychol Med.* 1996;26(3):477-486.
59. Lecomte T, Corbière M, Laisné F. Investigating self-esteem in individuals with schizophrenia: relevance of the Self-Esteem Rating Scale-Short Form. *Psychiatry Res.* 2006;143(1):99-108.
60. Weiss D, Marmar C. The Impact of Event Scale-Revised. In: Wilson J, Keane T, eds. *Assessing Psychological Trauma and PTSD.* New York, NY, US: Guilford Press; 1997.
61. Mundt JC, Marks IM, Shear MK, Greist JM. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *Br J Psychiatry.* 2002;180(5):461-464.
62. Rombouts R, Van-Kuilenburg CJ. Hedonie, de ontwikkeling van een vragenlijst [Development of a questionnaire designed to measure hedonism]. *Gedrag en Gezondheid.* 1988;16:117-123.
63. CDLJava [Computer software] [computer program]. Lelystad: BuroTesteR; 2002.
64. Mocking R, Assies J, Lok A, et al. Statistical methodological issues in handling of fatty acid data: percentage or concentration, imputation and indices. *Lipids.* 2012;47(5):541-547.
65. Sauvé B, Koren G, Walsh G, Tokmakejian S, Van Uum SH. Measurement of cortisol in human hair as a biomarker of systemic exposure. *Clinical & Investigative Medicine.* 2007;30(5):183-191.
66. Russell E, Koren G, Rieder M, Van Uum S. Hair cortisol as a biological marker of chronic stress: current status, future directions and unanswered questions. *Psychoneuroendocrinology.* 2012;37(5):589-601.
67. Stalder T, Kirschbaum C. Analysis of cortisol in hair-state of the art and future directions. *Brain Behav Immun.* 2012;26(7):1019-1029.
68. IBM SPSS Statistics for Windows, Version 24.0 [computer program]. Armonk, NY: IBM Corp; 2016.
69. R: A Language and Environment for Statistical Computing [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2017.



3

The relationship between cognitive functioning and psychopathology in patients with psychiatric disorders: A transdiagnostic network analysis

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Abstract

Background

Patients with psychiatric disorders often experience cognitive dysfunction, but the precise relationship between cognitive deficits and psychopathology remains unclear. We investigated the relationships between domains of cognitive functioning and psychopathology in a transdiagnostic sample using a data-driven approach.

Methods

Cross-sectional network analyses were conducted to investigate the relationships between domains of psychopathology and cognitive functioning and detect clusters in the network. This naturalistic transdiagnostic sample consists of 1016 psychiatric patients who have a variety of psychiatric diagnoses, such as depressive disorders, anxiety disorders, obsessive-compulsive and related disorders, and schizophrenia spectrum and other psychotic disorders. Psychopathology symptoms were assessed using various questionnaires. Core cognitive domains were assessed with a battery of automated tests.

Results

Network analysis detected three clusters that we labelled: general psychopathology, substance use, and cognition. Depressive and anxiety symptoms, verbal memory, and visual attention were the most central nodes in the network. Most associations between cognitive functioning and symptoms were negative, i.e. increased symptom severity was associated with worse cognitive functioning. Cannabis use, (subclinical) psychotic experiences, and anhedonia had the strongest total negative relationships with cognitive variables.

Conclusions

Cognitive functioning and psychopathology are independent but related dimensions, which interact in a transdiagnostic manner. Depression, anxiety, verbal memory, and visual attention are especially relevant in this network and can be considered independent transdiagnostic targets for research and treatment in psychiatry. Moreover, future research on cognitive functioning in psychopathology should take a transdiagnostic approach, focusing on symptom-specific interactions with cognitive domains rather than investigating cognitive functioning within diagnostic categories.

Keywords: transdiagnostic, cognitive function, psychopathology, network analysis

Introduction

It is becoming increasingly accepted that psychiatric diagnostic categories are pragmatic, man-made constructs that should be interpreted as guidelines for clinical communication rather than true representations of underlying disorders¹. Symptom expression is not disorder-specific, possibly explaining findings of high rates of comorbidity, general treatment effects, heterogeneity within disorders, and a lack of objective biomarkers²⁻⁴.

To remedy this, a transdiagnostic approach has been put forth to advance the understanding of psychopathology in which mental disorders are not deemed categorically distinct entities. This transdiagnostic approach acknowledges that expression of symptoms can manifest across disorders and takes into account other clinically relevant dimensions, including cognitive functioning. Consortiums and research initiatives, such as the Research Domain Criteria (RDoC) framework⁵ and the Hierarchical Taxonomy of Psychopathology (HiTOP) consortium⁶, have been created with the goal to elucidate the nature of psychopathology without being bound to diagnostic categories. The Across study is among these research initiatives in its effort to employ a transdiagnostic approach to increase insight into the relationship among cognitive functioning, psychiatric symptoms, and biological parameters across psychiatric disorders⁷.

Previous research indicates that individuals with mental disorders often experience cognitive deficits^{8,9}. For instance, executive dysfunction and memory deficits are apparent in patients with schizophrenia, depression, obsessive-compulsive disorder, post-traumatic stress disorder, and bipolar disorder¹⁰⁻¹². Cognitive dysfunction cuts across disorders and should therefore be considered a transdiagnostic dimension^{13,14}. Additionally, cognitive dysfunction associated with psychiatric disorders has been shown to persist into remission^{9,15,16} and is predictive for recurrences¹⁷, suggesting that it is a construct partly independent from psychiatric symptoms. However, the psychopathological component of psychiatric disorders tends to garner the most attention while cognitive functioning remains neglected. Cognitive deficits, nonetheless, have been associated with psychosocial dysfunction in patients with schizophrenia¹⁸, bipolar disorder¹⁹, and depression²⁰. The transdiagnostic nature of cognitive dysfunction and its heavy impact on daily functioning makes it therefore an important target for treatment⁸. Treating cognitive dysfunction in addition to psychopathology could lead to better outcomes for patients.

One statistical method ideally suited for transdiagnostic research is network analysis²¹. Network analysis has been at the forefront of the broader paradigm shift in psychiatry as an alternative to the more traditional perspective of disorders

as latent causes of symptoms. A network approach to psychopathology instead views disorders as constituted by symptoms which cause and interact directly with each other²¹. By assessing the relationship between symptoms, network analysis can provide insights into which symptoms are more central, which symptoms cluster together, and which symptoms bridge different clusters^{22,23}. This has resulted in network models showing how symptoms, such as psychotic and depressive symptoms²⁴, interact with each other. Network analysis can also elucidate interactions of symptoms with other clinically-relevant factors, such as anxiety with attentional bias²⁵ and cognition with stress as assessed with cortisol levels²⁶. Although some network analyses on the relationship between cognitive functioning and psychopathology have been conducted^{25,27}, there is still a lack of research using a transdiagnostic network approach combining cognitive functioning and psychopathology.

The present study aims to elucidate the relationship between domains of cognitive functioning (i.e., visual attention, executive function, verbal and episodic memory, and alertness) and psychiatric symptoms (e.g., depression and anxiety) using a transdiagnostic approach (i.e., across disorders). In a large naturalistic transdiagnostic sample of patients with psychiatric disorders, we aim to (1) conduct a network analysis with cognitive measures and psychiatric symptoms, (2) perform a centrality analysis to detect which variables are important within the network, and (3) detect clusters using exploratory graph analysis.

Methods

Sample

The naturalistic sample consists of 1016 psychiatric patients recruited during intakes at outpatient clinic of the Department of Psychiatry at the Amsterdam University Medical Centers (UMC), location Academic Medical Center (AMC), in Amsterdam, the Netherlands. Inclusion criteria were: age 14-75 years, ability to give informed consent, having a DSM-IV-TR or DSM-V diagnosis as determined by a trained psychiatrist, and being fluent in Dutch. Exclusion criteria were: acute high risk of suicide, unstable medical disorder, premorbid IQ<70, history of seizure or clinically significant abnormality of the neurological system. Written informed consent was obtained from patients and their parents (if underage). Patients could discontinue participation from the study at any time.

Procedure

The Across study is an ongoing, observational longitudinal cohort study and consists of the assessment of cognitive performance, psychiatric symptoms, and collection of biological data (DOI 10.17605/OSF.IO/YHVTB). The study instruments and procedures are described in Nieman, Chavez-Baldini, Vulink, Smit, van Wingen, de Koning, Sutterland, Mocking, Bockting, Verweij, Lok, Denys⁷. Patients underwent extensive psychiatric and medical assessments at the outpatient clinic, performed by experienced psychiatrists and psychologists, and were then invited to participate in the study. The current study used cross-sectional data on cognitive performance and psychiatric symptoms. Cognitive performance was assessed with a computerized battery, followed by self-report questionnaires about various symptoms that were filled out on a computer. Patients were not required to abstain from substance or medication use before participation and were able to participate at any point of their clinical trajectory (e.g., before, during, or after treatment), which could influence their cognitive functioning and/or symptomatology. However, this is an observational, naturalistic study that aims to reflect the reality of patients regular functioning. The study protocol was approved by the Medical Ethical Review Committee of the Amsterdam UMC (ABR no. NL55751.018.15), and data are stored according European to privacy laws.

Materials

Table 1 shows the instruments used to assess the different variables (nodes). For a detailed description of the instruments, see Table S1 in the Supplementary Materials. To aid interpretability, cognitive variables were coded positively (higher is better) and psychopathology/substance use variables were coded negatively (higher is worse). All variables were continuous.

Network analysis

The analyses consisted of network estimation and visualization, cluster detection, and centrality analysis performed in R Version 1.2.5042⁴³. The network estimation procedure resulted in a set of relationships between variables that can be visualized in a network in which the variables are nodes that are connected by a set of edges representing the estimated relationships. Network estimation was conducted with the R package *qgraph*⁴⁴. The procedure started with a partial correlation network, in which correlations between two variables are corrected for all the other variables in the network. The extended Bayesian information criterion graphical least absolute shrinkage (EBICglasso) procedure⁴⁵⁻⁴⁸ was then applied to select edges by using a penalty, which decreases the strength of some of the parameter estimates, while others are set to zero. Following earlier network analyses, we used a g of 0.5 for an

optimal balance between density and sparseness⁴⁹. This resulted in a sparse network, in which the absence of an edge is interpreted as the conditional independence of two nodes given other variables⁴⁵.

Table 1. Overview of measures

Domains and variables	Instruments	Nodes ^a
Cognitive functioning	Cambridge Neuropsychological Test Automated Battery (CANTAB) ²⁸	CANTAB subtest scores: Choice Reaction Time (CRT), Intra/Extradimensional Set Shift (IED), One Touch Stockings of Cambridge (OTS), Paired Associates Learning (PAL), Rapid Visual Processing (RVP), Spatial Working Memory (SWM), Verbal Recognition Memory (VRM)
	California Verbal Learning Test (CVLT) ²⁹	CVLT total learning achievement
	Groninger Intelligence Test (GIT) ³⁰	GIT verbal fluency (animals)
Intelligence	Dutch National Adult Reading Test (NART) ³¹	Premorbid IQ score
Substance use	Alcohol Use Disorder Identification Test (AUDIT) ^{32,b}	AUDIT total score
	Cannabis Use Disorder Identification Test (CUDIT) ^{33,b}	CUDIT total score
Psychopathology	Prodromal Questionnaire-16 (PQ-16) ³⁴	PQ-16 total score
	Yale-Brown Obsessive Compulsive Scale (Y-BOCS) ^{35,b}	Y-BOCS total score
	Hamilton Anxiety Scale (HAM-A) ³⁶	HAM-A total score
	Inventory of Depressive Symptomatology Self-Report (IDS-SR) ³⁷	IDS-SR total score
	Impact of Events Scale- Revised (IES-R) ^{38,b}	IES-R total score
	Hedonism Scale ^{39,b}	Hedonism total score
	Self-esteem Rating Scale- Short Form (SERS-SR) ⁴⁰	SERS-SR total score
	Work and Social Adjustment Scale (WSAS) ^{41,b}	WSAS total score
	Social Interaction Anxiety Scale SIAS) ⁴²	SIAS total score

^aThe psychopathology and substance use nodes in this study were sum scores of symptom domains rather than individual symptoms.

^bAssessed only for adult patients (18-75 years old) and put as missing in analyses for underage patients

Visualization of the network was performed with *graph*⁴⁴, using the Fruchterman-Reingold algorithm⁵⁰, which placed nodes that are more connected closer together and nodes which have higher centrality indices closer to the center of the graph. Stronger edges were depicted as thicker lines between nodes. Positive associations were depicted in green and negative associations in red. Due to the coding, we expected most edges between domains of cognitive functioning and

psychopathology to be red whereas edges between psychopathology nodes and edges between cognitive nodes were expected to be green.

Analysis of the network stability⁵¹ was conducted (see Appendix 1 in the Supplementary Materials) to give an indication of how reliable the estimated network is.

We computed the centrality index strength^{51,52} using *graph*⁴⁴. Strength is calculated as the total of all edges of that node and indicates the degree of association of that node to its neighbors and the relative importance of each node in the full network. A node that has high strength is a node that has many and/or strong connections to its neighbors, whereas lower strength indicates a node with fewer and/or weaker connections.

Cluster detection was conducted with an exploratory graph analysis (EGA) as implemented in the R-package *EGA*⁵³. EGA uses the ‘walktrap’ algorithm, which uses random walks to quantify the distance between any two nodes or clusters in a network⁵⁴. Proximity between two nodes is defined as the degree of similarity of the distance of two nodes to the rest of the network. The walktrap algorithm then uses an agglomerative approach, grouping together the closest nodes or clusters step by step until all nodes are part of a cluster. The final step determines the point during the agglomeration in which the fraction of the strength of internal connections within the clusters compared to the external connections between clusters is optimized. This determines how the clusters within the network are finally defined. This step allowed us to identify subgroups of nodes that cluster together due to strong interconnectedness.

Results

Sample characteristics

Data of 1016 patients were included in the analyses. Overall, patients had an average premorbid IQ and a majority of the sample were of Caucasian ethnicity. On average, the sample consisted mostly of young and middle-aged adults and about half were male. The distribution of the primary diagnosis reflects the naturalistic patient population of the Amsterdam UMC, an expertise center for misophonia, early psychosis, anxiety and depressive disorders. Further results are presented in Table 2. Cognitive and psychopathology variables scores are shown in Table S2 and CANTAB standard scores are shown in Table S3 in the Supplementary Materials. Differences in cognitive and psychopathology variable scores per medication category are shown in Table S4 in the Supplementary Materials. Except for alcohol use, cognitive flexibility, and alertness, there were significant differences in scores over types of medication,

suggesting a possible influence of medication on cognitive and psychopathology variables. Generally, antidepressants, benzodiazepines, and sleep medication differed significantly and were related to worse symptomatology. Furthermore, antipsychotic medication differed significantly and was related to worse cognitive function.

Table 2. Demographic and clinical characteristics of participants

Measure	Values (N= 1016)
Age (years), mean (SD)	34.7 (14.2)
Gender, male, No. (%)	478 (47.1)
Education, No. (%)	
Higher education	340 (33.5)
Vocational education	205 (20.2)
Secondary education	345 (40.0)
Primary education	47 (4.6)
No education	32 (3.1)
Unknown	47 (4.6)
Premorbid IQ (NART), mean (SD)	100.09 (13.3)
Ethnicity, Caucasian, No. (%)	878 (86.5)
Marital status, married, No. (%)	316 (31.1)
DSM diagnostic category ^a , No. (%)	
Schizophrenia spectrum and other psychotic disorders	185 (18.2)
Depressive disorder	111 (10.9)
Anxiety disorder	60 (5.9)
Obsessive-compulsive and related disorders	177 (17.5)
Impulse-control disorder NOS (misophonia)	353 (34.7)
Other disorders ^b	130 (12.8)
Medication use, No. (%)	
Antidepressants	213 (21.0)
Antipsychotics	169 (16.6)
Benzodiazepines	30 (3.0)
Sleep medication	15 (1.5)
Mood stabilizers	8 (0.8)
Psychostimulants	8 (0.8)
Other	168 (16.5)
None	392 (38.6)
Unknown	13 (1.3)

Abbreviations: NART= Dutch National Adult Reading Test, DSM= Diagnostic and Statistical Manual of Mental Disorders, NOS= not otherwise specified.

^a Diagnostic category is only for the primary diagnosis.

^b Other disorder category includes: substance use disorders (n = 20) , eating disorders (n = 5), neurodevelopmental disorders (n = 29), sexual disorders (n = 2), sleep disorders (n = 2), dissociative disorders (n = 1), adjustment disorders (n = 4), bipolar disorders (n = 28), and personality disorders (n = 12).

Network analysis

The network of the cognitive functioning and psychopathology domains is visualized in Figure 1. Three clusters were detected, indicated by different colors in the figure which were labelled: general psychopathology symptoms (blue), substance use (yellow), and cognition (purple). A weights matrix of the network can be seen in Table S5 in the Supplementary Materials. The stability analysis revealed that most of the edges in the network were stable, indicating that the estimated network was robust (Figure S4 in the Supplementary Materials). Variables with the highest strength were depression, anxiety, verbal memory, and visual attention.

As expected, within-cluster edges between psychopathology and within-cluster edges between cognitive domain were mostly positive. Cross-cluster edges between cognitive domains and psychopathology contained mostly negative edges, in which increased symptom severity was associated with worse cognitive functioning. The total strengths of edges within clusters are notably higher than the total strength of edges between clusters, which is in line with our expectations because nodes cluster together due to strong interconnectedness. An overview of the edges in the network can be seen in Table 3. Closer inspection of the edges between cognitive domains and psychopathology showed that cognitive nodes have both positive and negative associations with different psychopathology nodes, whereas psychopathology nodes have either positive or negative associations with different cognitive nodes (Table S6 in the Supplementary Materials). The obsessive-compulsive symptoms node was the only exception. Furthermore, (subclinical) psychotic experiences, cannabis use, and anhedonia had the strongest total negative relationships with cognitive variables while alcohol use had the strongest total positive relationship with cognitive variables (Table S6 in the Supplementary Materials).

Table 3. Overview of the edges in the network^a

	Total	Positive, No. (%)	Negative, No. (%)	Total Strength	Positive Strength	Negative Strength
All edges	76	50 (66)	26 (34)	4.79	5.61	-0.82
Between psychopathology nodes^b	25	23 (92)	2 (8)	3.16	3.27	-0.10
Between cognitive nodes	32	32 (100)	0 (0)	3.49	3.49	0.00
Psychopathology-cognition interaction	29	7 (24)	22 (76)	-0.33	0.19	-0.52

^aFirst three columns are the number of edges, whereas the last three columns are the sums of the strengths of the edges. Rows indicate the set of edges under consideration.

^b Substance use nodes are included.

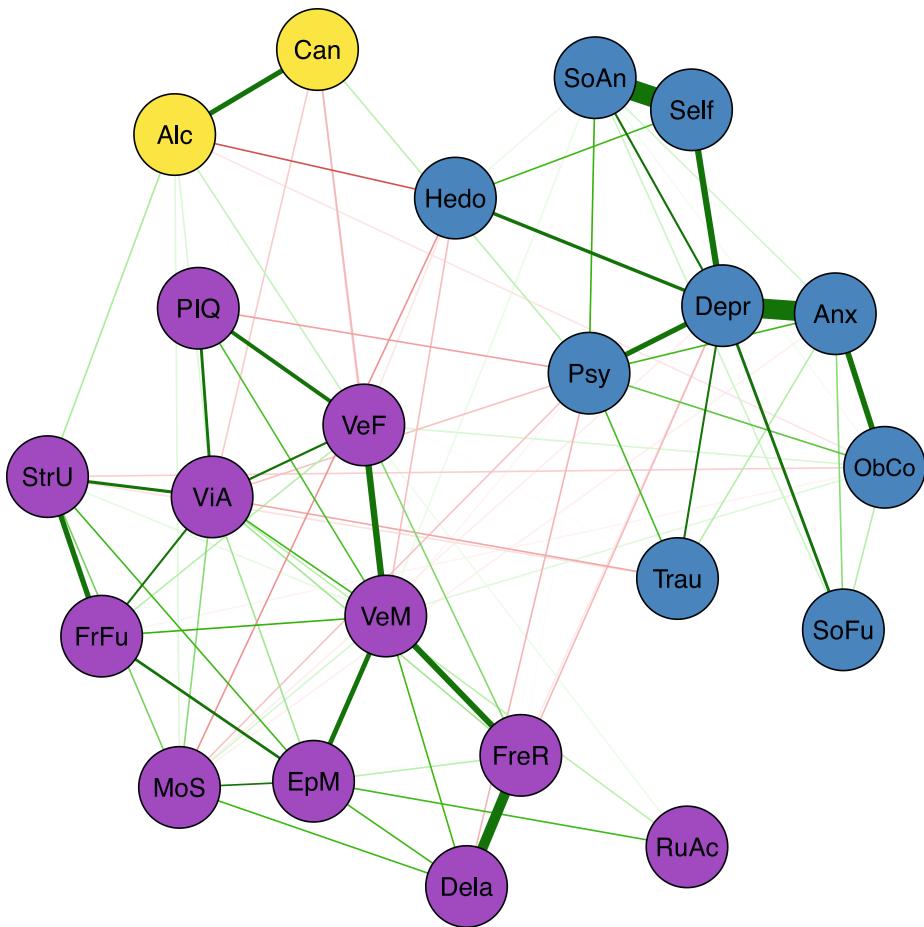


Figure 1. Transdiagnostic network of cognitive and psychopathology domains (N = 1016). Nodes represent the variables included in the network and edges indicate an association between two nodes. Green edges represent positive associations whereas red edges represent negative associations, and thickness of an edge represents the strength of association between two nodes. The color of each node indicates to which cluster it belongs according to the EGA: cognition (purple), general psychopathology (blue), or substance use (yellow).

Abbreviations: **Psychopathology domains:** Alc = alcohol (ab)use (AUDIT); Anx= anxiety symptoms (HAM-A); Can = cannabis (ab)use (CUDIT); Depr = depressive symptoms (IDS); Hed = hedonism questionnaire; ObCo = obsessive-compulsive symptoms (Y-BOCS); Psy = (subclinical) psychotic experiences (PQ-16); Self = self-esteem (SERS-SF); SoAn = social anxiety symptoms (SIAS); SoFu = poor psychosocial functioning (WSAS) ; Trau = post-traumatic stress symptoms (IES-R). **Cognitive domains:** Dela = verbal recognition memory-delayed (VRM); EpM = episodic memory and learning (PAL); FreR = verbal recognition memory-immediate (VRM); FrFu = planning test (OTS); MoS = alertness and motor speed (CRT); PIQ = premorbid IQ (NART); RuAc = rule acquisition and attentional set shifting, cognitive flexibility (IED); StrU = strategy use (SWM); VeF = verbal fluency (GIT); VeM = verbal memory (CVLT); ViA = sustained visual attention and processing speed (RVP).

To further assess the stability of the cluster detection in our analyses, we performed a bootstrap analysis of the EGA procedure for all networks, including the control networks. This analysis revealed that amongst all the networks, the original network exhibited the most stable cluster structure (Table S7 in the Supplementary Materials). Stability checks also demonstrated that networks were stable despite changes in sample size, indicating that sample size did not largely influence this (Figure S5 in the Supplementary Materials).

Lastly, further network analyses were conducted as controls: one using binarized data to control for differences in measurement methods and scales and others to account for sample variation in the variables based on diagnostic category, age, sex, education level, and medication use (Appendices 1 and 2 in the Supplementary Materials). All the control networks reproduced the original three-cluster network, except for one diagnostic network (without depressive disorders) and the without medication network, which produced four clusters. In both of these networks (without depressive disorders and without medication), the psychopathology cluster was split into two separate clusters. The separation of cognitive and psychopathological variables remained in all control networks (Figures S6-14 in the Supplementary Materials).

Discussion

The present study used a network approach to investigate how domains of cognitive functioning and psychopathology cluster and interact in a large transdiagnostic sample of patients with psychiatric disorders. This resulted in a fully connected network, showing that the domains are all closely associated. Cluster analysis detected three clusters in the network, labelled: cognition, general psychopathology, and substance use.

Cognitive functioning and psychopathology each form their own clusters, indicating that they are independent but related dimensions. The edges between the cognition and psychopathology clusters were relatively weak, which emphasizes their independence and further supports that cognitive function should be investigated in addition to and separately from psychiatric symptoms. Nonetheless, any associations, even if weak, may still be an important part of the etiology. The separation of these clusters also held across the control networks that were conducted to check the possible influence of diagnostic categories, suggesting that this interaction between cognitive domains and psychopathology domains is transdiagnostic and does not adhere to traditional diagnostic boundaries.

The formation of the separate clusters is in line with the hot-cold cognitive model in depression^{17,55,56}, in which “cold” cognition is information processing without emotional influence (e.g., attentional control) and “hot” cognition is information processing with emotional influence (e.g., mood-congruent attentional bias). The hot-cold cognitive model posits that non-affective cold cognitive dysfunctions contributes to the development of hot cognition (e.g., negative/catastrophic thoughts/beliefs), subsequently leading to psychiatric symptoms and further exacerbating cold cognitive dysfunctions. While we did not specifically measure hot cognition, it could be theorized that the psychiatric symptoms in our sample could also arise from cold cognitive deficits through hot cognition. Future research could investigate whether hot cognition acts as a bridge between cold cognition and symptoms. This model could be extended to other disorders as cognitive-affective processes are transdiagnostic^{9,57}. Although temporal relationships cannot be assessed in the current study, this also supports our result regarding the association between worse cognitive functioning and higher symptom severity.

Another possibility for the separate clusters is that cognitive functioning and psychopathology follow different clinical trajectories, as suggested by findings of premorbid and persisting cognitive deficits despite symptom remission^{15,16,58,59}. This could further tie in with the hot-cold cognitive model, in which premorbid cognitive deficits lead to psychiatric symptoms, and explain how cognitive functioning and psychopathology are related despite different trajectories.

Within the general psychopathology cluster, self-esteem, depressed mood, and (social) anxiety were strongly related. Low self-esteem can be considered a general transdiagnostic risk and maintenance factor in psychopathology⁶⁰ and is often related to depression and anxiety⁶¹. The depressive symptoms node had the highest number of edges and highest total edge strength within the psychopathology cluster, meaning that it had the most relationships with other psychopathology domains. Depressive symptoms are often reported in patients with a variety of other disorders, such as subclinical psychosis, bipolar disorder, and obsessive-compulsive disorders⁶²⁻⁶⁴. Depressive symptoms could be considered a normal response to living with a psychiatric disorder, which can induce lowered self-esteem⁶⁵, (self)stigma, and reduced possibilities in life. Successful treatment of the psychiatric disorder may subsequently reduce the depressive symptoms. There is also the possibility of bidirectional relationships between depressive symptoms and other clinical factors; however, this cannot be inferred with the current undirected network.

The substance use cluster is composed of the AUDIT and CUDIT. The formation of this cluster may have been influenced by the fact that the scales measure closely

related constructs and are highly similar in form (i.e., the CUDIT was developed from the AUDIT) and/or because of the low prevalence of cannabis and alcohol use (i.e., a high number of individuals scored zeros on both scales). These possibilities were controlled for and the results led us to conclude that the original three clusters represent the most reliable clusters. This suggests substance use is related to the general psychopathology cluster but exhibits a certain independence at the same time. The general psychopathology cluster mostly contains affective symptoms, and while affective symptoms and substance (ab)use are related^{66,67}, they are nonetheless different psychometrically and conceptually (emotions versus behavior) and fall under different spectra (internalizing versus externalizing)⁶.

Within the cognition cluster, the verbal memory node had the highest number of edges and the highest total edge strength, indicating that verbal memory was related to many other cognitive domains. Verbal memory had the strongest association with verbal fluency. Interestingly, verbal memory has been shown to be predictive of remission for at-risk mental states individuals⁶⁸ and treatment response for PTSD⁶⁹ and comorbid depression-anxiety⁷⁰. This may suggest that it could be beneficial to improve verbal memory deficits in patients with psychiatric disorders to improve treatment response and increase the chance of remission. Many therapies are verbal and verbal memory deficits may hamper therapeutic success because patients have more difficult remembering the content of their therapy sessions.

Depression, anxiety, verbal memory, and visual attention have the highest strength in the network, implying that they play a central role in psychiatric disorders. These nodes have a strong influence on other nodes, and could have a significant impact on overarching psychopathology. A common factor here may be stress, which plays a role in the development and maintenance of many disorders^{71,72}. Dysregulation of the central stress response system, the hypothalamic-pituitary-adrenal (HPA) axis, can lead to memory deficits⁷³. Stress is also implicated in the etiology of emotional disturbances^{74,75}, including excess of negative emotion and distress, explaining the relative importance of depression and anxiety symptoms, which are often observed across psychiatric disorders⁷⁶.

Attentional deficits are also evident in patients with psychiatric disorders transdiagnostically⁸. In the network, visual attention displays the strongest associations with strategy use (working memory), verbal fluency, and planning ability, which is in line with the executive-attention framework^{8,77}. Previous studies have shown that dorsolateral prefrontal-cingulate-parietal network underpins the executive-attention framework framework^{8,77}. Atypical connectivity within this network is often found across disorders, which may contribute to deficits in working

memory, attention, and cognitive control⁷⁷. Furthermore, associations of the visual cortex with the frontoparietal and default mode networks have been implicated in information processing (e.g., attention)⁷⁸. In addition, hyperconnectivity between visual association cortex and both frontoparietal and default mode networks has been associated with a general liability for mental illness (i.e., p-factor)⁷⁹. This could provide an underlying mechanism for the shared cognitive deficits that are present across disorders.

Interestingly, we found that nodes representing psychopathology tended to have consistent relationships with cognitive domains, while nodes representing cognitive domains had mixed relationships with psychopathology. For instance, depression was consistently related to worse functioning across cognitive domains. However, verbal memory functioning had different relationships to certain psychopathology domains: (subclinical) psychotic experiences were related to worse verbal memory, whereas obsessions and compulsions were related to better verbal memory. This encourages future research to focus on symptom-specific interactions with different cognitive domains, rather than investigating cognitive functioning within diagnostic categories. Research within diagnostic categories could also explain why clear findings on cognitive functioning in psychiatric diagnostic categories are hard to come by: specific symptoms and cognitive deficits may vary considerably within one diagnostic category, and patterns could emerge more clearly by investigating relationships between cognitive functioning and symptoms directly, rather than comparing them across categories.

Cannabis use, (subclinical) psychotic experiences, and anhedonia had the strongest overall negative association with cognitive functioning. Both (subclinical) psychotic-like experiences and cannabis use have been associated with cognitive dysfunction^{80,81}. The relation between anhedonia and worse cognitive functioning, specifically motor speed, verbal memory, and fluency, may be partly explained by decreased connectivity within reward-related brain regions⁸². Interestingly, psychosocial functioning was included in the symptom cluster and demonstrated no associations with cognitive functioning. This is somewhat unexpected because psychosocial functioning tends to be more strongly associated with cognitive functioning than with psychiatric symptoms¹⁸⁻²⁰, although associations with psychopathology, such as depression⁸³ have been reported.

The main strengths of the current analysis are the inclusion of various cognitive and psychopathology domains and the large transdiagnostic sample. This means that the results may be generalizable to patients with a wide range of psychiatric disorders. The main limitation of the current study is the cross-sectional design, meaning that

neither causal interactions nor the direction of relationships can be assessed. Using cross-sectional data is a problem in most network papers published so far, and the results must be interpreted with caution⁸⁴. However, cross-sectional networks could still give insight into the co-occurrence of symptoms⁸⁵. The Across study is ongoing; hence, future analyses will entail longitudinal data and biological markers. Another limitation is that sum scores of questionnaires were used. This was done to reduce the number of nodes in the network at the expense of losing information about relationships between individual items. Questionnaires also had differences in scoring and scaling properties, which could have influenced the pattern of edges and clusters detected. Most questionnaires were also self-reported, introducing a possible interpretation and self-report bias. However, the self-report questionnaires that were used are psychometrically valid and provide important information from the patients' perspective. Additionally, due to the naturalistic character of our sample and the fact that our department does not specialize in treatment for these patient groups, some diagnostic groups were relatively underrepresented in our sample (e.g., substance use and neurodevelopmental disorders) and were therefore grouped together in an "Other disorders" category.

Furthermore, the lack of a healthy control group is a limitation in the paper. Although we attempt to use a dimensional approach when assessing the psychiatric domains included in this study, we cannot capture the entire continuum without a healthy control or general population group. Due to a lack of a well-matched healthy control group, it is not clear to what extent cognitive deficits are present and whether these deficits are clinically relevant. A further limitation is that the network was not adjusted for medication use, which can impact cognitive function. This is, however, a naturalistic study of patients with psychiatric disorders, reflecting clinical reality of medication use. We would also like to note that there probably is an interaction effect between the disorder, clinical severity, and medication use, which would make it difficult to disentangle the effect of medication and the effect of the disorder on cognitive functioning.

Moreover, while the use of a transdiagnostic approach is a strength, we recognize the potential shortcoming of not analyzing specific relationships across diagnostic categories. However, control networks with diagnostic categories removed demonstrated that the structure of network is fairly robust to potential differences between subgroups. Finally, labelling of clusters is, as always with such techniques, rather subjective. Altogether, this study should be seen as a first investigation of the structure of the relationship between psychopathology and cognitive functioning. Future exploration can focus on parts of the network to investigate how specific items relate to each other and to cognitive measures.

The results of this study support the notion that cognitive functioning and psychopathology are independent but related dimensions, which interact in a transdiagnostic manner. Thus, it cannot be assumed that treating symptoms will alleviate cognitive deficits, and future studies should specifically assess if typical treatments influence cognitive dysfunction. Cognitive deficits, however, are usually undertreated, suggesting a need for treatments specifically targeting cognitive dysfunction in patients with psychiatric disorders, regardless of diagnosis. Interventions for cognitive dysfunction, such as cognitive remediation, which tend to be heavily geared towards patients with schizophrenia or bipolar disorders, should perhaps be considered transdiagnostic. Furthermore, depression, anxiety, verbal memory, and visual attention seem to play central roles across disorders and should therefore be the focus of transdiagnostic research and treatment.

References

1. Marshall M. The hidden links between mental disorders. *Nature*. 2020;581:19-21.
2. Hyman SE. The diagnosis of mental disorders: the problem of reification. *Annu Rev Clin Psychol*. 2010;6:155-179.
3. Olbert CM, Gala GJ, Tupler LA. Quantifying heterogeneity attributable to polythetic diagnostic criteria: theoretical framework and empirical application. *J Abnorm Psychol*. 2014;123(2):452.
4. Ofrat S, Krueger RF. How research on the meta-structure of psychopathology aids in understanding biological correlates of mood and anxiety disorders. *Biology of Mood & Anxiety Disorders*. 2012;2(1):13.
5. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010.
6. Kotov R, Krueger RF, Watson D, et al. The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *J Abnorm Psychol*. 2017;126(4):454.
7. Nieman DH, Chavez-Baldini U, Vulink NC, et al. Protocol Across study: longitudinal transdiagnostic cognitive functioning, psychiatric symptoms, and biological parameters in patients with a psychiatric disorder. *BMC Psychiatry*. 2020;20(1):212.
8. Millan MJ, Agid Y, Brüne M, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov*. 2012;11(2):141.
9. Iosifescu DV. The relation between mood, cognition and psychosocial functioning in psychiatric disorders. *Eur Neuropsychopharmacol*. 2012;22:S499-S504.
10. Snyder HR, Miyake A, Hankin BL. Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. *Front Psychol*. 2015;6:328.
11. Czepielewski LS, Massuda R, Goi P, et al. Verbal episodic memory along the course of schizophrenia and bipolar disorder: A new perspective. *Eur Neuropsychopharmacol*. 2015;25(2):169-175.
12. Dere E, Pause BM, Pietrowsky R. Emotion and episodic memory in neuropsychiatric disorders. *Behav Brain Res*. 2010;215(2):162-171.
13. McTeague LM, Goodkind MS, Etkin A. Transdiagnostic impairment of cognitive control in mental illness. *J Psychiatr Res*. 2016;83:37-46.
14. East-Richard C, R-Mercier A, Nadeau D, Cellard C. Transdiagnostic neurocognitive deficits in psychiatry: A review of meta-analyses. *Canadian Psychology/Psychologie canadienne*. 2019.
15. Balanzá-Martínez V, Tabarés-Seisdedos R, Selva-Vera G, et al. Persistent cognitive dysfunctions in bipolar I disorder and schizophrenic patients: a 3-year follow-up study. *Psychother Psychosom*. 2005;74(2):113-119.
16. Semkovska M, Quinlivan L, O'Grady T, et al. Cognitive function following a major depressive episode: a systematic review and meta-analysis. *The Lancet Psychiatry*. 2019;6(10):851-861.
17. Ahern E, Bockting CL, Semkovska M. A Hot-Cold Cognitive Model of Depression: integrating the Neuropsychological Approach Into the Cognitive Theory Framework. *Clinical Psychology in Europe*. 2019;1:e34396.
18. Shamsi S, Lau A, Lenz T, et al. Cognitive and symptomatic predictors of functional disability in schizophrenia. *Schizophr Res*. 2011;126(1):257-264.
19. Depp CA, Mausbach BT, Harmell AL, et al. Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. *Bipolar Disord*. 2012;14(3):217-226.
20. McIntyre RS, Cha DS, Soczynska JK, et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. *Depress Anxiety*. 2013;30(6):515-527.
21. Borsboom D. A network theory of mental disorders. *World Psychiatry*. 2017;16(1):5-13.
22. Cramer AOJ, Waldorp LJ, van der Maas HLJ, Borsboom D. Comorbidity: A network perspective. *Behav Brain Sci*. 2010;33(2-3):137-150.
23. Blanken TF, Deserno MK, Dalege J, et al. The role of stabilizing and communicating symptoms given overlapping communities in psychopathology networks. *Sci Rep*. 2018;8(1):5854.
24. van Rooijen G, Isvoranu A-M, Kruijt OH, et al. A state-independent network of depressive, negative and positive symptoms in male patients with schizophrenia spectrum disorders. *Schizophr Res*. 2017.

25. Heeren A, McNally RJ. An integrative network approach to social anxiety disorder: the complex dynamic interplay among attentional bias for threat, attentional control, and symptoms. *J Anxiety Disord.* 2016;42:95-104.
26. Hinkelmann K, Moritz S, Botzenhardt J, et al. Cognitive Impairment in Major Depression: Association with Salivary Cortisol. *Biol Psychiatry.* 2009;66(9):879-885.
27. Galderisi S, Rucci P, Kirkpatrick B, et al. Interplay among psychopathologic variables, personal resources, context-related factors, and real-life functioning in individuals with schizophrenia: a network analysis. *JAMA psychiatry.* 2018;75(4):396-404.
28. CANTAB® [Cognitive assessment software] [computer program]. 2018.
29. Delis DC, Kramer J, Kaplan E, Ober BA. *CVLT-II: California verbal learning test: adult version.* Psychological Corporation; 2000.
30. Luteijn F, Van der Ploeg FA. Groninger Intelligentie Test: Handleiding [Groninger Intelligence Test: Manual]. Swets, Zeitlinger BV: Lisse. 1983.
31. Schmand B, Bakker D, Saan R, Louman J. The Dutch Reading Test for Adults: a measure of premorbid intelligence level. *Tijdschr Gerontol Geriatr.* 1991;22(1):15-19.
32. Saunders JB, Aasland OG, Babor TF, De la Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction.* 1993;88(6):791-804.
33. Adamson SJ, Sellman JD. A prototype screening instrument for cannabis use disorder: the Cannabis Use Disorders Identification Test (CUDIT) in an alcohol-dependent clinical sample. *Drug Alcohol Rev.* 2003;22(3):309-315.
34. Ising HK, Veling W, Loewy RL, et al. The validity of the 16-item version of the Prodromal Questionnaire (PQ-16) to screen for ultra high risk of developing psychosis in the general help-seeking population. *Schizophr Bull.* 2012;38(6):1288-1296.
35. Goodman W, Price L, Rasmussen S, et al. Yale-brown obsessive compulsive scale (Y-BOCS): I. Development, use, and reliability. *Arch Gen Psychiatry.* 1989;46:1006-1011.
36. Hamilton M, Schutte N, Malouff J. Hamilton anxiety scale (HAMA). *Sourcebook of Adult Assessment: Applied Clinical Psychology.* 1976:154-157.
37. Rush AJ, Giles DE, Schlessier MA, Fulton CL, Weissenburger J, Burns C. The inventory for depressive symptomatology (IDS): preliminary findings. *Psychiatry Res.* 1986;18(1):65-87.
38. Weiss D, Marmar C. The Impact of Event Scale-Revised. In: Wilson J, Keane T, eds. *Assessing Psychological Trauma and PTSD.* New York, NY, US: Guilford Press; 1997.
39. Rombouts R, Van-Kuilenburg CJ. Hedonie, de ontwikkeling van een vragenlijst [Development of a questionnaire designed to measure hedonism]. *Gedrag en Gezondheid.* 1988;16:117-123.
40. Lecomte T, Corbière M, Laisné F. Investigating self-esteem in individuals with schizophrenia: relevance of the Self-Esteem Rating Scale-Short Form. *Psychiatry Res.* 2006;143(1):99-108.
41. Mundt JC, Marks IM, Shear MK, Greist JM. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *Br J Psychiatry.* 2002;180(5):461-464.
42. Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. *Behav Res Ther.* 1998;36(4):455-470.
43. R: A Language and Environment for Statistical Computing [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2020.
44. Epskamp S, Cramer AO, Waldorp LJ, Schmittmann VD, Borsboom D. qgraph: Network visualizations of relationships in psychometric data. *Journal of Statistical Software.* 2012;48(4):1-18.
45. Friedman J, Hastie T, Tibshirani R. Sparse inverse covariance estimation with the graphical lasso. *Biostatistics.* 2008;9(3):432-441.
46. Chen J, Chen Z. Extended Bayesian information criteria for model selection with large model spaces. *Biometrika.* 2008;95(3):759-771.
47. Epskamp S, Fried EI. A tutorial on regularized partial correlation networks. *Psychol Methods.* 2018.
48. Foygel R, Drton M. Extended Bayesian information criteria for Gaussian graphical models. Paper presented at: Advances in neural information processing systems2010.
49. van Borkulo CD, Boschloo L, Borsboom D, Penninx BW, Waldorp LJ, Schoevers RA. Association of symptom network structure with the course of depression. *JAMA psychiatry.* 2015;72(12):1219-1226.
50. Fruchterman TM, Reingold EM. Graph drawing by force-directed placement. *Software: Practice and experience.* 1991;21(11):1129-1164.

51. Epskamp S, Borsboom D, Fried EI. Estimating psychological networks and their accuracy: A tutorial paper. *Behav Res Methods*. 2018;50(1):195-212.
52. Bringmann LF, Elmer T, Epskamp S, et al. What do centrality measures measure in psychological networks? *The journal of abnormal psychology*. 2019.
53. Golino HF, Epskamp S. Exploratory graph analysis: A new approach for estimating the number of dimensions in psychological research. *PLoS One*. 2017;12(6):e0174035.
54. Pons P, Latapy M. Computing communities in large networks using random walks. *J Graph Algorithms Appl*. 2006;10(2):191-218.
55. Roiser JP, Sahakian BJ. Hot and cold cognition in depression. *CNS spectrums*. 2013;18(3):139-149.
56. De Raedt R, Koster EHW. Understanding vulnerability for depression from a cognitive neuroscience perspective: A reappraisal of attentional factors and a new conceptual framework. *Cognitive, Affective, & Behavioral Neuroscience*. 2010;10(1):50-70.
57. Mansell W, Harvey A, Watkins ER, Shafran R. Cognitive Behavioral Processes Across Psychological Disorders: A Review of the Utility and Validity of the Transdiagnostic Approach. *Int J Cogn Ther*. 2008;1(3):181-191.
58. Allott K, Fisher CA, Amminger GP, Goodall J, Hetrick S. Characterizing neurocognitive impairment in young people with major depression: state, trait, or scar? *Brain Behav*. 2016;6(10):e00527.
59. Caspi A, Reichenberg A, Weiser M, et al. Cognitive performance in schizophrenia patients assessed before and following the first psychotic episode. *Schizophr Res*. 2003;65(2):87-94.
60. Zeigler-Hill V. The connections between self-esteem and psychopathology. *Journal of Contemporary Psychotherapy*. 2011;41(3):157-164.
61. Sowislo JF, Orth U. Does low self-esteem predict depression and anxiety? A meta-analysis of longitudinal studies. *Psychol Bull*. 2013;139(1):213.
62. Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK. Comorbid Depressive and Anxiety Disorders in 509 Individuals With an At-Risk Mental State: Impact on Psychopathology and Transition to Psychosis. *Schizophr Bull*. 2012;40(1):120-131.
63. Goldberg D, Fawcett J. The importance of anxiety in both major depression and bipolar disorder. *Depress Anxiety*. 2012;29(6):471-478.
64. Quarantini LC, Torres AR, Sampaio AS, et al. Comorbid major depression in obsessive-compulsive disorder patients. *Compr Psychiatry*. 2011;52(4):386-393.
65. Silverstone PH, Salsali M. Low self-esteem and psychiatric patients: Part I – The relationship between low self-esteem and psychiatric diagnosis. *Annals of General Hospital Psychiatry*. 2003;2(1):2.
66. Boden JM, Fergusson DM. Alcohol and depression. *Addiction*. 2011;106(5):906-914.
67. Kedzior KK, Laeber LT. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies. *BMC Psychiatry*. 2014;14(1):136.
68. Simon AE, Grädel M, Cattapan-Ludewig K, et al. Cognitive functioning in at-risk mental states for psychosis and 2-year clinical outcome. *Schizophr Res*. 2012;142(1):108-115.
69. Scott JC, Harb G, Brownlow JA, Greene J, Gur RC, Ross RJ. Verbal memory functioning moderates psychotherapy treatment response for PTSD-Related nightmares. *Behav Res Ther*. 2017;91:24-32.
70. Braund TA, Tillman G, Palmer DM, Harris AWF. Verbal memory predicts treatment outcome in syndromal anxious depression: An iSPOT-D report. *J Affect Disord*. 2020;260:245-253.
71. Nolen-Hoeksema S, Watkins ER. A Heuristic for Developing Transdiagnostic Models of Psychopathology:Explaining Multifinality and Divergent Trajectories. *Perspect Psychol Sci*. 2011;6(6):589-609.
72. Conway CC, Raposa EB, Hammen C, Brennan PA. Transdiagnostic pathways from early social stress to psychopathology: a 20-year prospective study. *Journal of Child Psychology and Psychiatry*. 2018;59(8):855-862.
73. Wingenfeld K, Wolf OT. Stress, memory, and the hippocampus. In: *The Hippocampus in Clinical Neuroscience*. Vol 34. Karger Publishers; 2014:109-120.
74. Pechtel P, Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology*. 2011;214(1):55-70.

75. McLaughlin KA, Conron KJ, Koenen KC, Gilman SE. Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: a test of the stress sensitization hypothesis in a population-based sample of adults. *Psychol Med.* 2010;40(10):1647-1658.
76. Kring AM. Emotion disturbances as transdiagnostic processes in psychopathology. *Handbook of emotion.* 2008;3:691-705.
77. Buckholtz Joshua W, Meyer-Lindenberg A. Psychopathology and the Human Connectome: Toward a Transdiagnostic Model of Risk For Mental Illness. *Neuron.* 2012;74(6):990-1004.
78. Chadick JZ, Gazzaley A. Differential coupling of visual cortex with default or frontal-parietal network based on goals. *Nat Neurosci.* 2011;14(7):830-832.
79. Elliott ML, Romer A, Knott AR, Hariri AR. A connectome-wide functional signature of transdiagnostic risk for mental illness. *Biol Psychiatry.* 2018;84(6):452-459.
80. Lindgren M, Manninen M, Laajasalo T, et al. The relationship between psychotic-like symptoms and neurocognitive performance in a general adolescent psychiatric sample. *Schizophr Res.* 2010;123(1):77-85.
81. Volkow ND, Swanson JM, Evins A, et al. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: A review. *JAMA Psychiatry.* 2016;73(3):292-297.
82. Felger JC, Li Z, Haroon E, et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. *Mol Psychiatry.* 2015;21:1358.
83. Fried EI, Nesse RM. The impact of individual depressive symptoms on impairment of psychosocial functioning. *PLoS One.* 2014;9(2).
84. Guloksuz S, Pries L, Van Os J. Application of network methods for understanding mental disorders: pitfalls and promise. *Psychol Med.* 2017;47(16):2743-2752.
85. Bos FM, Snippe E, de Vos S, et al. Can We Jump from Cross-Sectional to Dynamic? Interpretations of Networks Implications for the Network Perspective in Psychiatry. *Psychother Psychosom.* 2017;86(3):175-177.

Supplementary Materials

Appendix 1. Methods

Stability check

We performed a stability check implemented in the R package ‘bootnet’ to assess the robustness of the networks we estimated; the full procedure has been described previously with instructions of Epskamp, Borsboom, Fried ⁵¹. Altogether, this stability check allows one to assess three different aspects of the estimated network: (1) the accuracy of edge weights, (2) test for differences between different edges and different centralities and (3) assess the stability of centralities.

The procedure of (1) and (2) involve a method called non-parametric bootstrapping (hereafter simply referred to as bootstrapping). Bootstrapping is a method in which one generates a new sample by sampling from one’s data with replacement ⁸⁶. This means that you can draw a certain patient multiple times and that the probability of sampling a patient does not change after sampling that patient. For example, if your data consists out of 100 patients, the probability of selecting any patient p_x after you start and selected the first patient remains 1/100, whereas whilst sampling without replacement it would become 0 for the patient p_x already selected, and 1/99 for all the remaining patients. This procedure results in a new sample that has the same size as the original sample but contains certain patients multiple times. This procedure can be repeated n times, to generate n new samples, in our case we used n = 1000 to generate 1000 new samples.

The next step is to estimate a network for each of the new samples using the same EBICglasso procedure ^{45,46,48}. These 1000 networks can be used to generate a distribution of various network attributes, such as edge weights. A 95% confidence interval of the edge weights can be obtained by sorting the 1000 values from the networks and taking the 0.025th and the 0.975th value. The width of this interval is an indication of (1) the accuracy of the edge weights (see Figure S2 below).

To obtain (2) the difference tests for edge weights (for example comparing edge A-B to edge A-C) one uses the same 1000 networks obtained from bootstrapping, but this time one calculates the differences between two edges in each network. These 1000 differences can be used to construct a 95% confidence interval in the same way as described above. If the interval does not contain zero this means that the edges differ at the $\alpha = 0.05$ level (Figure S2 below contains a visualization of the results of this test). The same procedure can be used to test differences between the strength of two nodes (see Figure S3 below for a visualization).

The final procedure to (3) assess the stability of the centralities of the network is a bit different from above. This procedure uses a method called the *m out of n bootstrap*⁸⁷. In this procedure, a certain percentage of the sample is randomly removed, ‘dropped’, to yield a new sample, which can be repeated a certain number of times. The next step is the estimation of a network for each sample and the calculation of centralities⁸⁸. The metric of interest that will be calculated next is the correlation between the centralities of each ‘dropped’ network and the centralities of the original network, this correlation is an indication of the stability of the order of the centralities rather than a measure of the absolute sameness of the centralities⁵¹. Correlations above 0.7 are acceptable and indicate that the centralities are still stable after dropping the given percentage of people.

This means that the centralities are considered stable up to a point where dropping that percentage of patients will include a correlation of 0.7 in the 95% confidence interval. Figure S5 is a visualization of the average correlation to the original centralities after dropping a certain percentage of patients and the shaded areas indicate the 95% confidence intervals.

We also followed a similar procedure to assess the stability of the results of the clustering analysis using EGA. The *EGA* package has the function *bootEGA* which uses non-parametric bootstrapping based on resampling, the same as used in procedures (1) and (2) above⁵³. By resampling and performing the *EGA* analysis 1000 times allows one to get a distribution of the number of dimensions in the bootstraps of a network. We performed this procedure for the main network (Figure 1 in the main article) and for the networks that were created as controls for the cluster analysis (see paragraph 1.2 below for further explanation of these networks). The results of the cluster stability analysis can be seen in Table S7.

Control networks for cluster analysis

The cluster analysis of the main network (Figure 1 in the main article) revealed one minor cluster: substance use. There are two factor that may have influenced the formation of these clusters: (a) many of the patients in our sample had no scores (i.e., zero's) on any of the domains in this cluster and (b) the subdomains of this cluster may have been separated unfairly and should have left together in one variable since the subdomains essentially measure the same construct. To control for these possible confounding situations, we created two control networks for each this cluster: one in which all patients were removed that have only zero's in all the items in that cluster and another one where the subdomains were not separated. We conducted all the analyses for the control networks in the same way as was done for the unchanged network: network estimation, stability analysis, cluster detection, and cluster stability

analysis as described in the supplementary method above. The resulting networks can be seen in Figure S6, the stability analysis of the edges can be seen in Figure S7 and the results of the cluster stability analysis can be seen in Table S7.

Control networks for the interaction between cognition and psychopathology

The main analysis exhibited a pattern in which cognition variables interacted mostly with other cognition variables and psychopathology variables interacted mostly with other psychopathology variables. There were two possible confounding properties of the data that could artificially generate such a pattern: (a) differences in measurement methods and used scales between the cognitive and psychopathological measures could result in different distributions in the variables and may thereby result in weaker network edges between those domains, and (b) sample variation in the level of cognitive functioning could weaken the statistical covariation of cognition with psychopathology.

In order to control for the first possibility (a), we binarized the data by setting for each variable all values that were above the median of that variable to 1 and everything equal or below the median to zero. Binarization thereby removes any differences between cognitive and psychopathological variables in distribution or scaling. Networks were computed from the binarized data using the *IsingFit* function from the *IsingFit* package, was explicitly developed as a binary alternative to the partial correlation method⁸⁹. The resulting network can be seen in Figure S12.

In order to control for the second possibility (b) we split the data into two groups based on prior educational level: high and low⁹⁰. This resulted in two groups with a more similar level of prior cognitive functioning and might reveal more covariation between cognitive functioning and psychopathology. We computed networks for these groups using the same procedure as the main analysis. Similar analyses were conducted for male versus female patients and younger (up to 31 years old) versus older (31 years old and above) patients. Finally, to assess the impact of patient diagnosis on cluster structure we conducted a jackknife sensitivity analysis by leaving out patients belonging to 6 major categories: anxiety disorders, depressive disorders, misophonia, obsessive-compulsive and related disorders, schizophrenia spectrum and other psychotic disorders, and other disorders.

Appendix 2. Control network results

Cluster control conditions

In our main analysis, we detected 1 smaller cluster: substance use. We noted that this cluster may have been formed due to confounding factors: many patients with only zeros on the substance use items or the undue splitting of substance use into cannabis use and alcohol. To control for these potential confounding factors, we created two control conditions for the substance use cluster: removing patients with zeros on all items in the cluster and conducting the analysis without splitting substance use into subscales. The results of the control conditions can be seen in Figure S6. To assess the stability of the clustering in these networks, we furthermore conducted a bootstrapping analysis as described above, the results of which can be seen in Table S7. Fusing of the cannabis and alcohol use scales resulted in fusion of the substance use cluster with the psychopathology cluster. Interestingly, removing the patients that had zeros on both substance use scales resulted in the same cluster structure as in the original network.

The analysis of these control conditions shows how important it is to be careful with choices regarding the inclusion and fusion of nodes in the network. Undue fusion of two nodes that are in fact too dissimilar will result in loss of signal due to the mixing, while undue separation of subscales will create a very strong separate cluster. Therefore, it is important to incorporate cluster stability analysis, and to plot and check all the different networks to assess their feasibility.

Control networks for the interaction between cognition and psychopathology

The Ising network (Figure S12) estimated from binarized data to control for confounding effects of differences in variable distribution revealed a very weak pattern of interaction between cognition and psychopathology. This leads us to conclude that differences in variable distribution between cognitive and psychopathological variables did not reduce the pattern of interaction that we found.

The EBICglasso networks that we estimated for patients with a higher educational level (Figure S8a) and with a lower educational level (Figure S8b) separately did not reveal differences in cluster structure regarding cognitive and psychopathological variables. This leads us to conclude that prior differences in educational level did not reduce the pattern of interaction that we found between cognition and psychopathology. Similarly, control networks for male (Figure S8c) versus female (Figure S8d) patients and younger (up to 31, Figure S8e) versus older (31 and above, Figure S8f) patients demonstrated no differences in cluster structure. Finally, diagnostic categories also did not reveal differences in cluster structure regarding

cognitive and psychopathological variables (Figure S10): anxiety disorders (10a), depressive disorders (10b), misophonia (10c), obsessive-compulsive and related disorders (10d), schizophrenia spectrum and other psychotic disorders (10e), and other disorders (10f).

Table S1. Detailed overview of instruments

Instrument	Description	Outcome Measure
Cambridge Neuropsychological Test Automated Battery (CANTAB) ²⁸	Assesses cognitive functioning and is composed of the following subtests:	
Verbal Recognition Memory-immediate (VRM)	Assesses immediate free recall and recognition memory for verbal information	Free recall- total correct: Total number of distinct words correctly recalled.
Rapid Visual Information Processing (RVP)	Tests visual sustained attention	A: Measure of how good the subject is at detecting target sequences.
Intra/ Extradimensional Set Shift (IED)	Assesses rule acquisition and attentional set shifting	Completed stage errors: Number of intra-dimensional and extra-dimensional shift errors made on stages successfully completed.
Choice reaction time (CRT)	Measures alertness and motor speed	Mean correct latency: Mean latency of response (from stimulus appearance to button press).
Verbal Recognition Memory (VRM-delayed)	Assesses delayed recognition memory for verbal information	Recognition- total correct: Total number of words that the subject correctly recognizes.
One Touch Stockings of Cambridge (OTS)	A planning test which gives a measure of frontal lobe functioning	Problems solved on first choice: Number of problems which were solved on the subject's first choice.
Paired Associates Learning (PAL)	Assesses episodic memory and learning	Total errors (adjusted): Total number of errors adjusted for number of trials completed.
Spatial Working Memory (SWM)	Assesses working memory and strategy use	Strategy: Number of times the subject begins a new search.
Dutch National Adult Reading Test (NART) ³¹	Measures premorbid IQ	Total score
California Verbal Learning Test (CVLT) ²⁹	Assesses episodic verbal learning and memory	Performance level List A: Overall performance level on the first 5 trials.
Groninger Intelligence Test (GIT) ³⁰	Measures level of verbal fluency	Number of words named (animal category)
Alcohol Use Disorder Identification Test (AUDIT) ³²	Assesses alcohol consumption, drinking behaviors, and alcohol-related problems	Total score

Table S1. (continued)

Instrument	Description	Outcome Measure
Cannabis Use Disorder Identification Test (CUDIT) ³³	Screens for cannabis use problems	Total score
Prodromal Questionnaire-16 (PQ-16) ³⁴	Screens for the risk of psychosis	Total score
Yale-Brown Obsessive Compulsive Scale (Y-BOCS) ³⁵	Measures the severity and type of obsessive-compulsive symptoms	Total score
Hamilton Anxiety Scale (HAM-A) ³⁶	Assess severity of somatic, cognitive, and affective symptoms in anxiety	Total score
Inventory of Depressive Symptomatology Self-Report (IDS-SR) ³⁷	Measures the severity of depressive symptoms	Total score
Impact of Events Scale- Revised (IES-R) ³⁸	Assesses subjective distress caused by traumatic events	Total score
Hedonism Scale ³⁹	Measures degree of pleasure from physical activity, hearing, seeing, touching, tasting, sex and smelling	Total score
Self-esteem Rating Scale- Short Form (SERS-SF) ⁴⁰	Assesses self-esteem in relation to social contact, achievements, and competency	Total score
Work and Social Adjustment Scale (WSAS) ⁴¹	Measures general impairment in different domains of daily life	Total score
Social Interaction Anxiety Scale (SIAS) ⁴²	Assess anxiety in social interactions and fear of scrutiny by others	Total score

Table S2. Cognitive and psychopathology domain scores of all patients (original scaling): Mean (SD), range

Measure	All patients (N=1016)	SZ (n=185)	Depressive disorders (n=111)	Anxiety disorders (n=60)	OCD (n=177)	Misophonia (n=353)	Other disorders ^a (n=30)
Anxiety symptoms (HAM-A) ^b	13.24 (10.0), 0-52	9.27 (9.2), 0-52	19.42 (9.8), 1-50	21.09 (10.6), 1-42	16.73 (10.0), 0-45	9.97 (7.8), 0-36	13.88 (10.4), 0-40
Depressive symptoms (IDS-SR) ^b	23.13 (14.0), 0-72	19.37 (13.2), 0-59	36.63 (14.2), 0-72	29.12 (13.0), 4-57	25.23 (12.4), 3-68	17.35 (11.0), 0-53	24.90 (13.6), 1-59
Subclinical psychotic symptoms (PQ-16) ^b	5.56 (5.7), 0-33	7.03 (7.3), 0-33	6.95 (6.5), 0-29	6.75 (5.5), 0-24	5.50 (6.0), 0-31	4.18 (4.1), 0-22	5.77 (5.7), 0-32
Alcohol use (AUDIT) ^b	5.15 (4.9), 0-37	5.40 (6.0), 0-37	4.28 (4.1), 0-17	3.88 (4.2), 0-19	4.22 (4.3), 0-24	5.56 (4.0), 0-22	6.42 (6.6), 0-35
Cannabis use (CUDIT) ^b	1.51 (4.7), 0-35	4.46 (8.1), 0-33	1.10 (2.9), 0-19	0.80 (3.4), 0-24	0.64 (2.1), 0-14	0.43 (1.8), 0-16	2.33 (6.2), 0-35
Self-esteem (SERS-SF) ^c	12.19 (20.2), -54-60	15.84 (20.0), -48-58	-1.00 (18.2), -45-45	9.71 (22.6), -44-50	6.73 (20.7), -54-45	18.88 (17.6), -46-60	9.55 (18.9), -32-53
Social anxiety (SIAS) ^b	23.55 (15.4), 0-75	20.00 (13.9), 0-66	32.96 (15.7), 2-69	26.88 (18.7), 3-66	26.40 (15.9), 0-75	19.79 (13.0), 0-62	24.94 (15.6), 0-60
Psychosocial functioning (WSAS) ^b	17.43 (8.9), 0-40	17.61 (9.1), 0-40	20.94 (9.4), 2-39	17.85 (8.2), 0-36	19.46 (9.2), 2-40	15.06 (7.9), 0-34	17.55 (9.0), 0-36
Hedonism Scale ^c	58.07 (11.2), 21-84	59.35 (11.3), 21-84	49.07 (10.6), 29-78	53.14 (12.7), 21-80	57.31 (10.4), 25-84	62.02 (9.6), 21-83	57.07 (10.0), 23-83
OC symptoms (Y-BOCS) ^b	6.61 (9.5), 0-39	3.37 (7.4), 0-34	5.21 (8.1), 0-31	8.48 (9.9), 0-37	17.25 (10.4), 0-38	3.23 (6.4), 0-39	6.07 (8.2), 0-32
PTS symptoms (IES-R) ^b	9.40 (17.7), 0-88	10.42 (18.4), 0-81	17.05 (22.4), 0-72	16.64 (22.6), 0-68	8.63 (17.3), 0-88	5.69 (13.5), 0-69	9.27 (17.2), 0-65
CRT Mean correct latency ^b	343.61 (93.0), 220-1629	345.21 (99.2), 229-168	372.82 (100.3), 233-806	356.65 (118.4), 220-971	346.85 (86.9), 221-953	328.56 (59.5), 223-716	346.90 (133.5), 225-1629
RVP A ^c	0.90 (0.1), 0.6-1.0	0.87 (0.1), 0.6-1.0	0.89 (0.1), 0.7-1.0	0.89 (0.1), 0.8-1.0	0.90 (0.1), 0.8-1.0	0.91 (0.1), 0.8-1.0	0.90 (0.1), 0.7-1.0
VRM free recall-immediate ^c	6.95 (2.7), 0-16	6.45 (2.3), 0-15	6.39 (2.8), 1-16	6.88 (2.8), 3-14	6.90 (3.0), 0-14	7.43 (2.5), 0-15	6.94 (2.7), 0-14

Table S2. (continued)

Measure	All patients (N=1016)	SZ (n=185)	Depressive disorders (n=111)	Anxiety disorders (n=60)	OCD (n=177)	Misophonia (n=333)	Other disorders ^a (n=130)
VRM recognition-delayed ^c	32.36 (3.0), 20-36	32.30 (3.0), 20-36	31.46 (3.4), 21-36	32.05 (3.1), 21-36	32.47 (3.0), 20-36	32.76 (2.6), 24-36	32.21 (3.2), 20-36
PAL Total errors adjusted ^b	100.09 (13.3), 36-143	93.28 (13.8), 36-127	101.25 (14.5), 50-131	102.05 (12.2), 80-135	102.21 (14.5), 55-143	101.70 (11.1), 66-129	100.47 (12.9), 63-127
IED Completed stage errors ^b	13.21 (20.1), 0-129	18.59 (25.9), 0-129	19.13 (25.1), 0-118	15.45 (23.9), 0-126	14.73 (21.1), 0-116	8.11 (12.0), 0-115	11.21 (16.3), 0-125
Verbal memory (CVLT) ^c	13.15 (8.0), 0-59	15.26 (9.2), 0-54	12.05 (6.5), 2-42	12.80 (8.6), 2-59	12.86 (8.3), 1-53	12.90 (7.3), 2-42	12.32 (7.6), 1-44
Verbal fluency (GIT) ^c	24.22 (6.4), 7-49	19.92 (6.2), 7-41	23.81 (5.7), 10-42	23.54 (6.4), 11-39	26.07 (6.7), 9-41	25.78 (5.7), 13-49	24.13 (6.9), 7-41

Abbreviation: SZ= Schizophrenia spectrum and other psychotic disorders, OCD= Obsessive-compulsive and related disorders, Misophonia= Misophonia= Impulse-control disorder NOS (misophonia), AUDIT= Alcohol Use Disorder Identification Test, CUDIT = Cannabis Use Disorder Identification Test, PQ-16 = Prodromal Questionnaire, Y-BOCS = Yale-Brown Obsessive Compulsive Scale, HAM-A = Hamilton Anxiety Scale, IDS-SR = Inventory of Depressive Symptomatology Self-Report, IES-R = Impact of Events Scale- Revised, SERS-SF = Self-esteem Rating Scale- Short Form, WSAS = Work and Social Adjustment Scale, SIAS = Social Interaction Anxiety Scale, CRT = Choice Reaction Time, CLVT= California Verbal Learning Test, GIT= Groninger Intelligence Test, IED = Intra/ Extradimensional Set Shift, NARI= Dutch National Adult Reading Test, OTS = One Touch Stockings of Cambridge, PAL = Paired Associates Learning, RVP = Rapid Visual Processing, SWM = Spatial Working Memory, VRM = Verbal Recognition Memory.

^a Other disorder category includes: substance use disorders, eating disorders, neurodevelopmental disorders, sexual disorders, sleep disorders, dissociative disorders, adjustment disorders, bipolar disorders, and personality disorders.

^b Scaling: higher is worse.

^c Scaling: higher is better.

Table S3. CANTAB Standard Scores^a

Variable	Standard Score (M, SD)	Range	Deficit ^b , yes, No. (%)
CRT Mean correct latency ^c	-	-	-
RVP A'	-0.42 (1.2)	-5.95 – 2.50	202 (19.9)
VRM free recall-immediate ^c	-	-	-
VRM recognition-delayed ^c	-	-	-
PAL Total errors adjusted	-0.0023 (1.8)	-23.03 – 1.52	83 (8.2)
OTS Problems solved on first choice ^c	-	-	-
SWM Strategy use	0.16 (1.1)	-2.94 – 3.73	61 (6.0)
IED Completed stage errors	-0.03 (1.1)	-7.56 – 2.08	116 (11.4)

Abbreviation: CRT = Choice Reaction Time, IED = Intra/ Extradimensional Set Shift, OTS = One Touch Stockings of Cambridge, PAL = Paired Associates Learning, RVP = Rapid Visual Processing, SWM = Spatial Working Memory, VRM = Verbal Recognition Memory.

^aStandard scores should be interpreted with caution as they are calculated with normative data that is not matched by age and premorbid IQ.

^bDeficit: no > -1.5, yes < -1.5

^cNo normative data available.

Table S4. Cognitive domain scores and medication (original scaling); Mean (SD)

Variable	None (n= 392)	Anti-depressants (n= 213)	Benzo-diazepines (n= 30)	Anti-psychotics (n= 169)	Mood stabilizers (n= 8)	Psycho-stimulants (n= 8)	Sleep medication (n= 15)	Other* (n= 168)	Test Statistic	p
Anxiety symptoms (HAM-A) ^b	11.55 (9.3)	16.42 (9.4)	20.84 (10.8)	10.15 (9.7)	15.29 (8.1)	20.86 (12.4)	20.93 (10.1)	13.36 (10.4)	F= 11.29, df= 7	<.001
Depressive symptoms (IDS-SR) ^b	20.02 (12.7)	28.74 (13.7)	30.11 (14.8)	20.92 (13.6)	31.14 (13.9)	33.00 (21.8)	34.07 (15.1)	22.65 (14.0)	F= 11.84, df= 7	<.001
Subclinical psychotic symptoms (PQ-16) ^b	3.50 (2.9)	3.84 (3.2)	4.70 (2.9)	4.61 (3.7)	3.29 (2.1)	6.14 (5.2)	4.85 (3.3)	3.61 (3.1)	F= 3.00, df= 7	.004
Alcohol use (AUDIT) ^b	5.51 (4.9)	4.63 (4.9)	4.40 (4.5)	5.60 (6.0)	4.29 (5.7)	5.43 (3.3)	4.79 (3.7)	4.71 (3.7)	F= 1.10, df= 7	.359
Cannabis use (CUDIT) ^b	1.30 (4.6)	1.07 (3.6)	2.20 (4.6)	3.56 (7.3)	0.57 (1.5)	1.00 (2.6)	1.07 (2.8)	0.45 (1.7)	F= 6.03, df= 7	<.001
Self-esteem (SEPS-SF) ^c	16.30 (19.3)	6.66 (20.3)	11.44 (19.2)	12.40 (21.2)	5.00 (18.5)	5.14 (16.6)	3.86 (21.0)	11.07 (19.7)	F= 5.27, df= 7	<.001
Social anxiety (SIAS) ^b	21.26 (14.4)	27.40 (16.3)	24.48 (15.0)	21.92 (15.2)	28.43 (15.6)	32.00 (19.1)	30.93 (19.1)	24.41 (15.2)	F= 4.34, df= 7	<.001
Psychosocial functioning (WSAS) ^b	16.15 (8.6)	18.92 (8.7)	18.62 (9.0)	17.74 (9.5)	19.29 (7.0)	15.43 (10.2)	22.15 (8.8)	17.22 (8.6)	F= 2.65, df= 7	.01
Hedonism Scale ^c	59.88 (10.9)	54.31 (11.1)	55.27 (11.6)	58.55 (12.1)	48.14 (9.1)	54.14 (10.3)	54.64 (12.9)	59.66 (9.3)	F= 6.82, df= 7	<.001
OC symptoms (Y-BOCS) ^b	5.25 (8.3)	10.28 (10.7)	6.27 (10.6)	4.94 (9.3)	8.86 (11.9)	13.29 (8.7)	7.93 (9.6)	6.06 (8.8)	F= 7.23, df= 7	<.001
PTS symptoms (IES-R) ^b	7.77 (16.0)	12.00 (19.6)	21.67 (23.2)	9.55 (17.4)	9.86 (26.1)	10.71 (27.0)	15.57 (23.8)	7.22 (15.5)	F= 3.60, df= 7	.001
CRT Mean correct latency ^b	334.49 (95.1)	350.98 (99.9)	378.81 (79.6)	341.93 (75.6)	339.68 (37.0)	371.44 (175.9)	341.87 (78.5)	349.97 (95.6)	F= 1.56, df= 7	.144
RVP A ^c	0.91 (0.1)	0.89 (0.1)	0.88 (0.1)	0.88 (0.1)	0.86 (0.1)	0.88 (0.1)	0.90 (0.1)	0.90 (0.1)	F= 5.66, df= 7	<.001
VRM free recall-immediate ^c	7.37 (2.6)	6.73 (2.8)	6.23 (2.5)	6.30 (2.3)	6.13 (3.5)	7.63 (3.7)	6.13 (2.3)	7.14 (2.8)	F= 3.93, df= 7	<.001
VRM recognition-delayed ^c	32.65 (2.9)	31.79 (3.3)	31.59 (2.5)	32.10 (2.8)	33.29 (2.1)	32.50 (4.7)	31.43 (2.7)	32.80 (2.7)	F= 2.97, df= 7	.004
Premorbid IQ (NART) ^c	100.87 (12.4)	100.98 (13.4)	100.80 (14.1)	95.26 (14.8)	93.63 (18.0)	93.38 (7.3)	95.87 (12.0)	102.26 (12.4)	F= 4.95, df= 7	<.001
PAL Total errors adjusted ^b	9.76 (17.5)	16.97 (23.0)	20.57 (23.4)	18.93 (24.1)	9.13 (7.4)	5.88 (3.8)	10.27 (7.3)	10.55 (16.4)	F= 6.06, df= 7	<.001
OTS Problems solved on first choice ^c	18.35 (3.0)	17.25 (3.0)	15.293 (4.7)	16.11 (3.9)	18.33 (2.3)	19.40 (2.2)	18.00 (2.4)	18.08 (2.8)	F= 9.88, df= 7	<.001

Table S4. (continued)

Variable	None (n= 392)	Anti-depressants (n= 213)	Benzo-diazepines (n= 30)	Anti-psychotics (n= 169)	Mood stabilizers (n= 8)	Psycho-stimulants (n= 8)	Sleep medication (n= 15)	Other ^a (n= 168)	Test Statistic	p
SWM Strategy use ^b	30.12 (6.0)	31.50 (6.5)	34.93 (5.3)	33.12 (6.0)	35.00 (5.0)	30.29 (7.0)	31.53 (5.0)	31.45 (6.6)	F= 6.08, df= 7	<.001
IED Completed stage errors ^b	13.29 (8.1)	12.61 (7.6)	12.00 (7.9)	14.04 (8.7)	14.63 (6.1)	13.25 (6.6)	12.53 (6.7)	13.02 (7.8)	F= 0.60, df= 7	.757
Verbal memory (CVLT) ^c	59.82 (10.1)	58.97 (10.6)	55.57 (10.7)	49.39 (11.9)	59.00 (10.2)	60.86 (9.5)	58.33 (8.0)	59.60 (10.6)	F= 17.90, df= 7	<.001
Verbal fluency (GIT) ^c	24.55 (6.1)	25.26 (6.4)	22.97 (6.3)	20.95 (6.5)	23.71 (6.0)	23.71 (3.4)	22.71 (5.0)	25.77 (6.1)	F= 9.01, df= 7	<.001

Abbreviation: AUDIT= Alcohol Use Disorder Identification Test, CUDIT = Cannabis Use Disorder Identification Test, HAM-A = Hamilton Anxiety Scale, IDS-SR = Inventory of Depressive Symptomatology Self-Report, IES-R = Impact of Events Scale- Revised, PQ-16 = Prodromal Questionnaire, SERS-SF = Self-esteem Rating Scale- Short Form, SIAS = Social Interaction Anxiety Scale, WSAS = Work and Social Adjustment Scale, Y-BOCS = Yale-Brown Obsessive Compulsive Scale; CRT = Choice Reaction Time, CLVT= California Verbal Learning Test, GIT= Groninger Intelligence Test, IED = Intra/ Extradiimensional Set Shift, OTS = One Touch Stockings of Cambridge, PAL = Paired Associates Learning, RVP = Rapid Visual Processing, SWM = Spatial Working Memory, VRM = Verbal Recognition Memory.

^aOther medication: Anti-epileptic drugs, anti-inflammatory drugs, antihistamines, bronchodilators, cholesterol medication, contraceptives, corticosteroids, dopamine-agonists, hormone therapy, insulin, and migraine medications.
^bScaling: higher is worse.
^cScaling: higher is better.

Table S5. Edge weights of the main network.

	Anx	Depr	Psy	Alc	Can	Self	SoAn	SoFu	Hedo	ObCo	Trau	MoS	ViA	FrR	PtQ	EpM	FrFu	StrU	Dela	RuAc	VeM	VeF
Anx	0																					
Depr	.528	0																				
Psy	.104	.201	0																			
Alc	0	0	0	0																		
Can	0	0	.042	.198	0																	
Self	0	.224	0	0	0	0																
SoAn	.028	.132	.118	0	0	.545	0															
SoFu	.065	.149	0	0	0	0	.032	0														
Hedo	0	.161	0	-.087	0	.11	.014	0	0													
ObCo	.211	0	.083	-.015	0	0	.008	.045	0	0												
Trau	.045	.13	.092	0	0	0	0	0	0	0	0											
MoS	-.008	-.009	-.031	.021	0	0	0	0	-.056	0	0	0										
ViA	0	0	-.033	.023	-.028	0	0	0	0	0	0	-.045	.065	0								
FrR	0	-.011	-.001	0	0	0	0	0	0	0	0	.004	.054	0								
PtQ	0	0	-.05	0	-.001	0	0	0	0	0	0	-.002	0	.149	0	0						
EpM	0	0	0	0	0	0	0	0	0	0	0	.122	.055	.043	0	0						
FrFu	0	0	0	0	0	0	0	0	0	0	-.006	0	0	.131	0	0	.145	0				
StrU	0	0	.05	0	0	0	0	0	-.026	-.017	.073	.153	0	0	.102	.202	0					
Dela	0	-.037	-.04	0	0	0	0	0	0	0	.106	0	.314	0	.104	0	0	0	0	0	0	
RuAc	0	0	0	0	0	0	0	0	0	0	0	.042	0	0	.096	0	0	0	0	0	0	
VeM	0	0	-.005	0	-.028	0	.014	0	-.035	.02	0	.026	.105	.219	.089	.192	.119	.016	.108	0	0	
VeF	0	0	.037	-.037	0	0	0	-.013	.024	0	0	.134	.068	.173	0	.044	0	0	.012	.228	0	

Abbreviations: Anx = anxiety symptoms; Depr = depressive symptoms; Psy = subclinical psychotic symptoms; Alc = alcohol use; Can = cannabis use; Self = self-esteem; SoAn = social anxiety symptoms; SoFu = psychosocial functioning; Hedo = Hedonism Questionnaire; ObCo = obsessive-compulsive symptoms; Trau = post-traumatic stress symptoms; MoS = alertness and motor speed; ViA = sustained visual attention and processing speed; FrR = verbal recognition memory-immediate; PtQ = premorbid IQ; EpM = episodic memory and learning; FrFu = planning test; StrU = strategy use; Dela = verbal memory test; RuAc = rule acquisition and attentional set shifting, cognitive flexibility; VeM = verbal memory; VeF = verbal fluency.

Table S6. Edge weights of the associations between cognitive domains and psychopathology domains^a

Variable	Anx	Depr	Psy	Alc	Can	Self	SoAn	SoFu	Hedo	ObCo	Trau	Sum
MoS	-.008	-.009	-.031	.021	0	0	0	0	-.056	0	0	-.083
ViA	0	0	-.033	.023	-.028	0	0	0	0	0	-.045	-.083
FreR	0	-.011	-.001	0	0	0	0	0	0	0	0	-.012
PIQ	0	0	-.05	0	-.001	0	0	0	0	0	-.002	-.053
EpM	0	0	0	0	0	0	0	0	0	0	0	0
FrFu	0	0	0	0	0	0	0	0	0	-.006	0	-.006
StrU	0	0	0	.05	0	0	0	0	0	-.026	-.017	.007
Dela	0	-.037	-.04	0	0	0	0	0	0	0	0	-.077
RuAc	0	0	0	0	0	0	0	0	0	0	0	0
VeM	0	0	-.005	0	-.028	0	.014	0	-.035	.02	0	-.034
VeF	0	0	0	.037	-.037	0	0	0	-.013	.024	0	.011
Sum	-.008	-.057	-.16	.131	-.094	0	.014	0	-.104	.012	-.064	

^aRows represent cognitive domains and columns indicate psychopathology domains. The final column and row represent sums. The table corresponds with Table S3.

Table S7. Results of the bootstrap analysis of the EGA clustering^a

Dimensions	2	3	4	5	6	7	8	39	Median	SD
Main network (n= 1016)	2	745	237	15	1	-	-	-	3	.49
High education (n= 538)	2	90	299	293	142	58	52	64	5	1.75
Low education (n= 431)	5	415	437	116	25	2	-	-	4	.78
Substance use fused (n= 1016)	178	640	165	17	-	-	-	-	3	.64
No zero substance use (n= 570)	60	271	354	226	52	24	8	5	4	1.19
Male patients (n= 478)	78	477	279	126	32	8	-	-	3	.97
Female patients (n= 537)	-	154	731	83	26	6	-	-	4	.63
No Anxiety Disorders (n= 956)	1	635	341	23	-	-	-	-	3	.53
No Depressive Disorders (n= 905)	1	723	194	67	14	1	-	-	3	.68
No Misphonia (n= 663)	-	283	620	91	6	-	-	-	4	.60
No OCD (n= 839)	11	891	94	4	-	-	-	-	3	.34
No SZ Disorders (n= 831)	3	398	492	79	23	5	-	-	4	.75
No Other Disorders (n= 886)	20	628	311	36	5	-	-	-	3	.61
Older patients (n= 519)	21	217	344	253	107	52	6	-	4	1.18
Younger patients (n= 497)	10	373	382	167	48	16	4	-	4	.99
Without medication use (n= 392)	-	34	149	213	171	135	99	199	6	2.35
With medication use (n= 611)	27	225	558	163	24	3	-	-	4	0.78

Abbreviation: SZ= Schizophrenia spectrum and other psychotic disorders, OCD= Obsessive-compulsive and related disorders, Misophonia= Impulse-control disorder NOS (misophonia).

^aTable shows the number of bootstraps for each number of dimensions per condition and the median number of dimensions per condition. The maximum number of conditions is 17.

Table S8. Results of the bootstrap analysis of the EGA clustering- Node placement^a

Cluster	Nodes
1	MoS, ViA, FrR, PIQ, EpM, FrF, StU, Del, RuA, VeM, VeF
2	Anx, Depr, Psy, Self, SoAn, SoFu, Hedo, ObCo, Trau
3	Alc, Can

Abbreviations: Anx = anxiety symptoms (HAM-A); Depr = depressive symptoms (IDS-SR); Psy = subclinical psychotic symptoms (PQ-16); Alc = alcohol use (AUDIT); Can = cannabis Use (CUDIT); Self = self-esteem (SER-SR); SoAn = social anxiety symptoms (SIAS); SoFu = psychosocial functioning (WSAS); Hedo = Hedonie Questionnaire; ObCo = obsessive-compulsive symptoms (Y-BOCS); Trau = post-traumatic stress symptoms (IES-R); MoS = alertness and motor speed (CRT); ViA = sustained visual attention and processing speed (RVP); FreR = verbal recognition memory-immediate (VRM); PIQ = premorbid IQ (NART); EpM = episodic memory and learning (PAL); FrFu = planning test (OTS); StrU = strategy use (SWM); Dela = verbal recognition memory- delayed (VRM); RuAc = rule acquisition and attentional set shifting, cognitive flexibility (IED); VeM = verbal memory (CVLT); VeF = verbal fluency (GIT).

^aTable that demonstrates to which cluster all the nodes in the network belonged in the median network as obtained by bootstrapping.

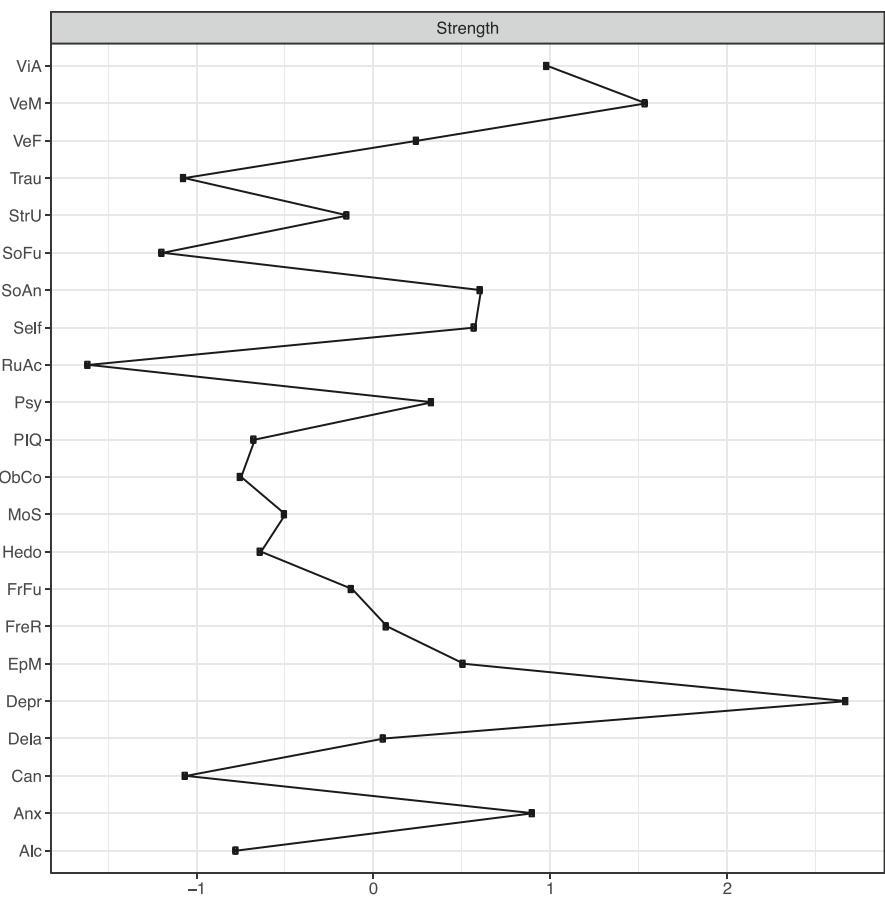


Figure S1. Strength centrality measure of psychopathology and cognitive domains. Strength indicates the degree of association of that node to its neighbors. See Figure S5 below regarding the stability of the centrality indices.

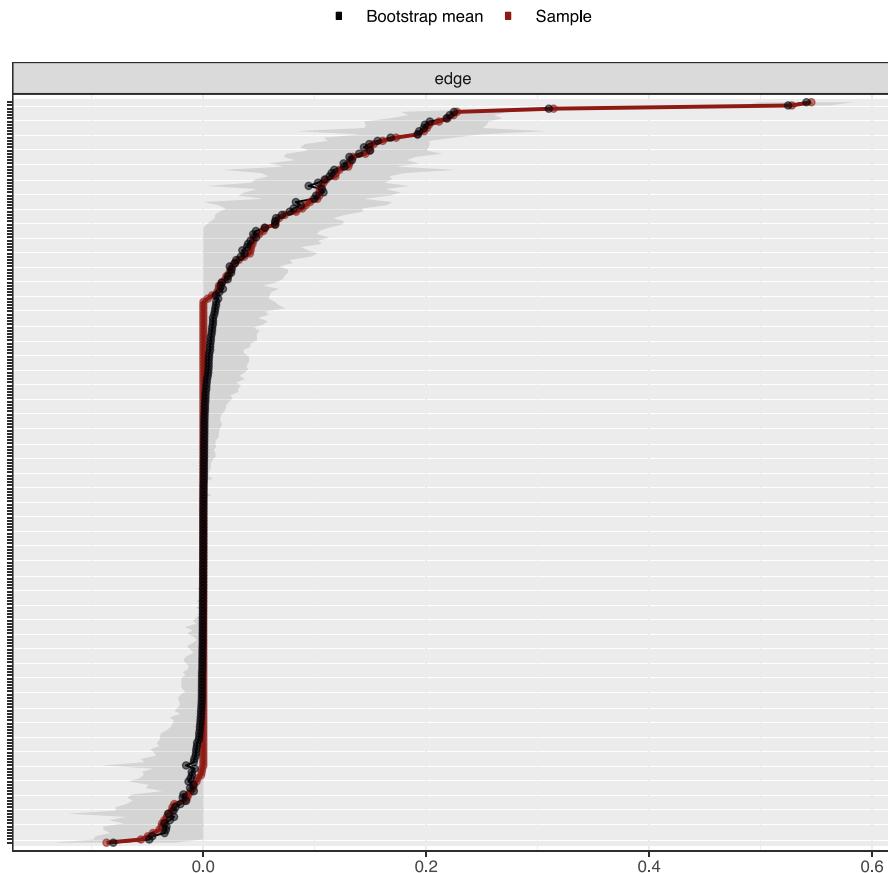


Figure S2. Accuracy of the estimated edges of the network. The x-axis shows the strength of the edge. The edges from the original network are shown in red and are arranged from most negative to most positive along the y-axis. The grey area represents confidence intervals based on the bootstrapped networks.

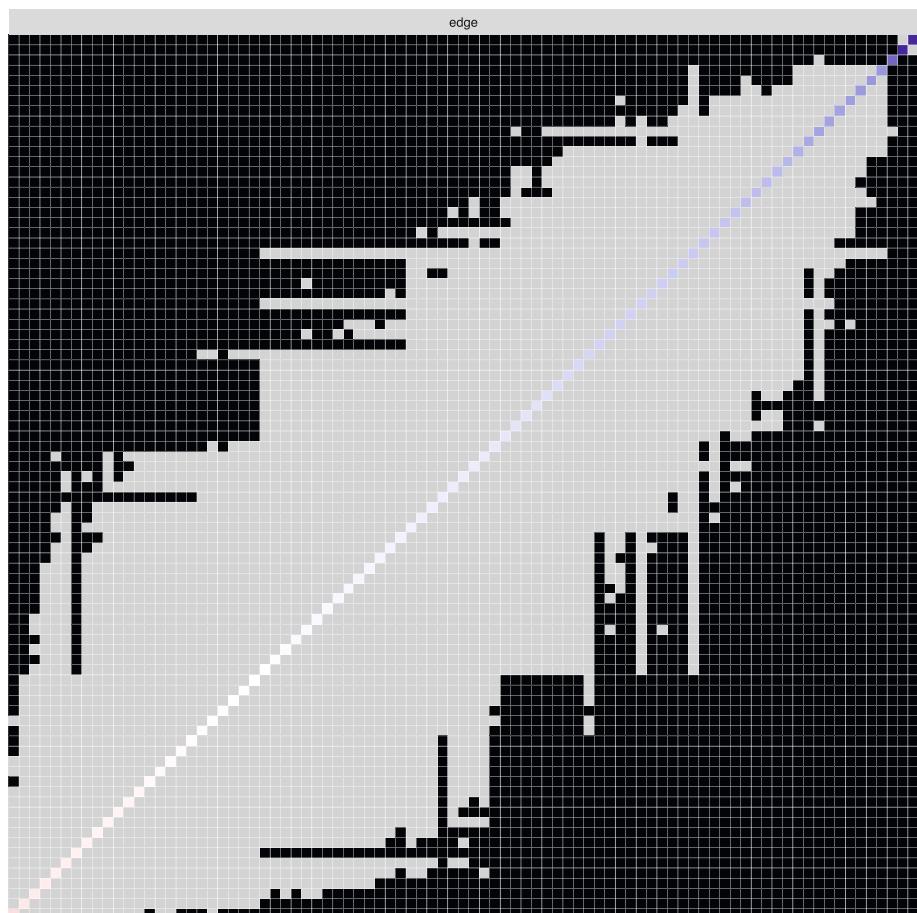


Figure S3. Difference tests of edges in the network. Rows and columns represent the different edges in the network, with edges ordered from most negative weight (left, bottom) to most positive (right, top). Black dots indicate that two edges differ from each other at the $\alpha = 0.05$ level.

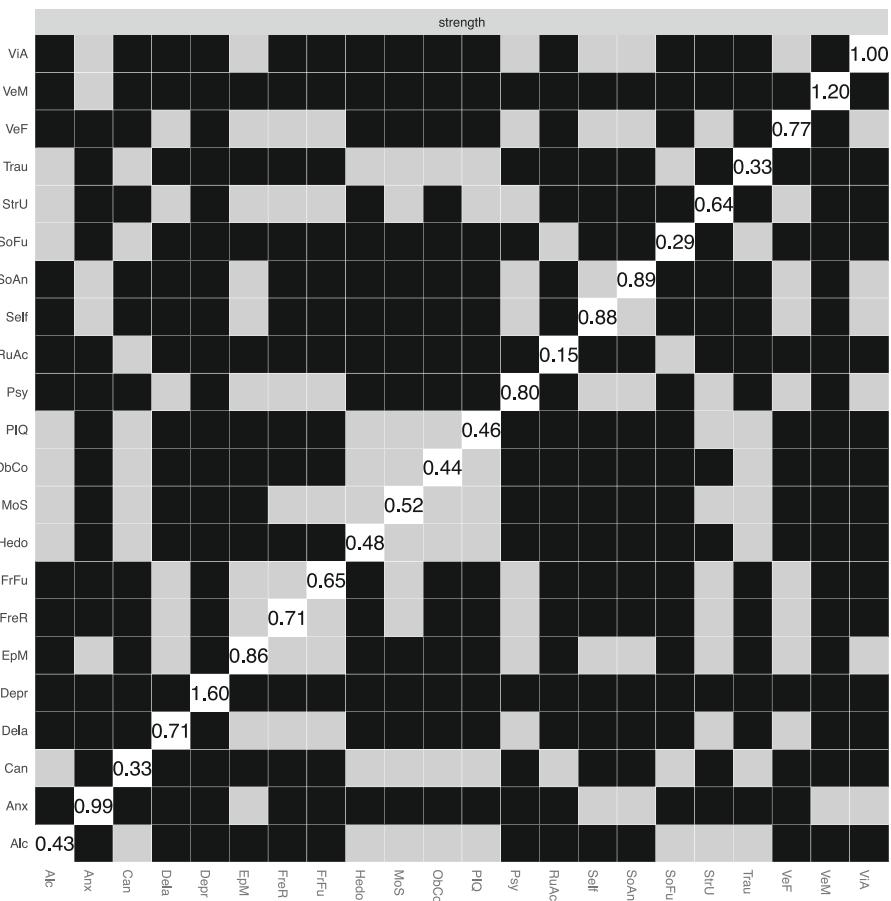


Figure S4. Difference test of total strength per node in the network. Black dots represent significant differences at the $\alpha = 0.05$ level. The diagonal line contains the centrality index.

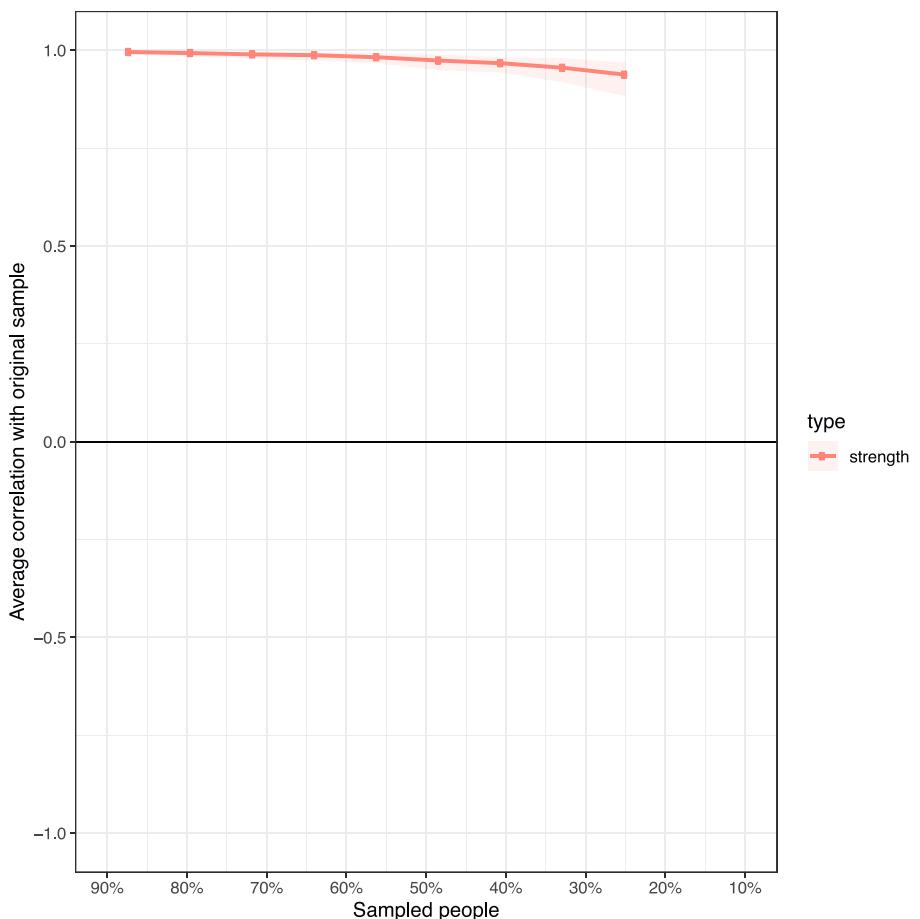
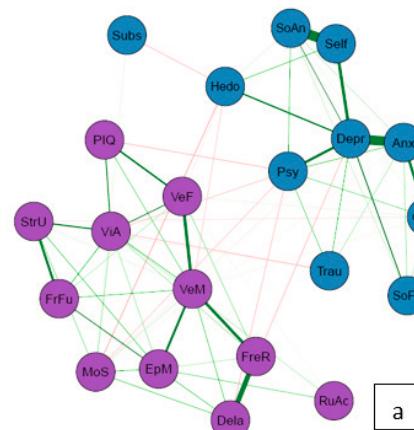


Figure S5. Stability of centrality indices of the network after 'dropping' a part of the patients. The x-axis shows the percentage of patients that was dropped. The y-axis shows the correlation of the centralities after dropping to the original centralities. The shaded areas indicate the 95% confidence interval. The centralities are considered stable as long as the 95% confidence interval does not reach 0.7.

Number of patients = 1016, Number of clusters = 2



Number of patients = 570, Number of clusters = 3

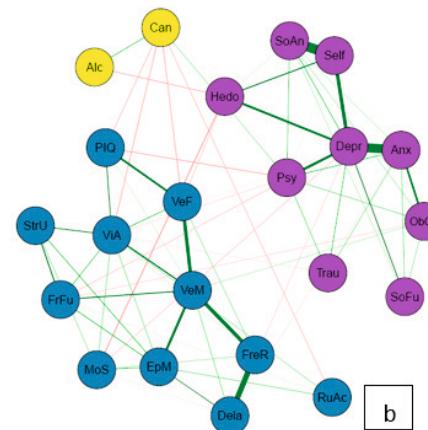


Figure S6. Networks for substance use fused (a) and no zero substance use (b). Nodes represent the variables included in the network and edges indicate an association between two nodes. Green edges represent positive associations whereas red edges represent negative associations, and thickness of an edge represents the strength of association between two nodes. Colors represent cluster membership as determined by the EGA algorithm.

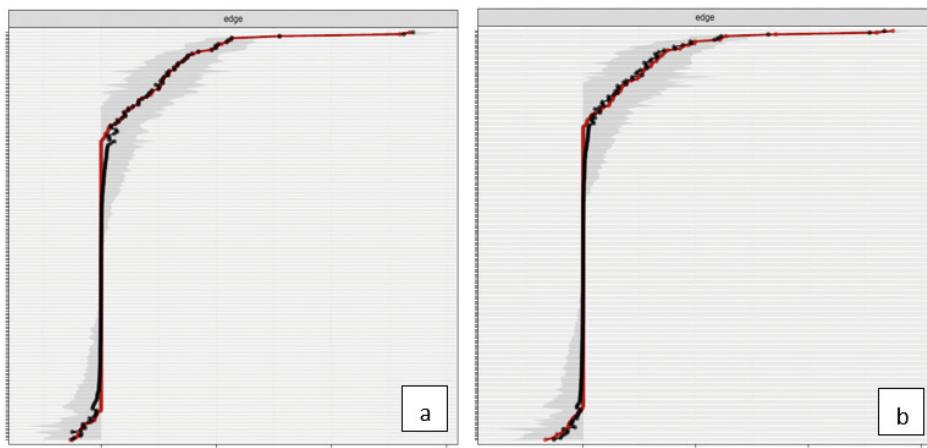


Figure S7. Accuracy of the estimated edges of substance use control networks. Networks: substance use fused (a) and no zero substance use (b). The x-axis shows the strength of the edge. The edges from the original network are shown in red and the bootstrapped means are shown in black. Edges are arranged from most negative to most positive along the y-axis. The grey area represents confidence intervals based on the bootstrapped networks.

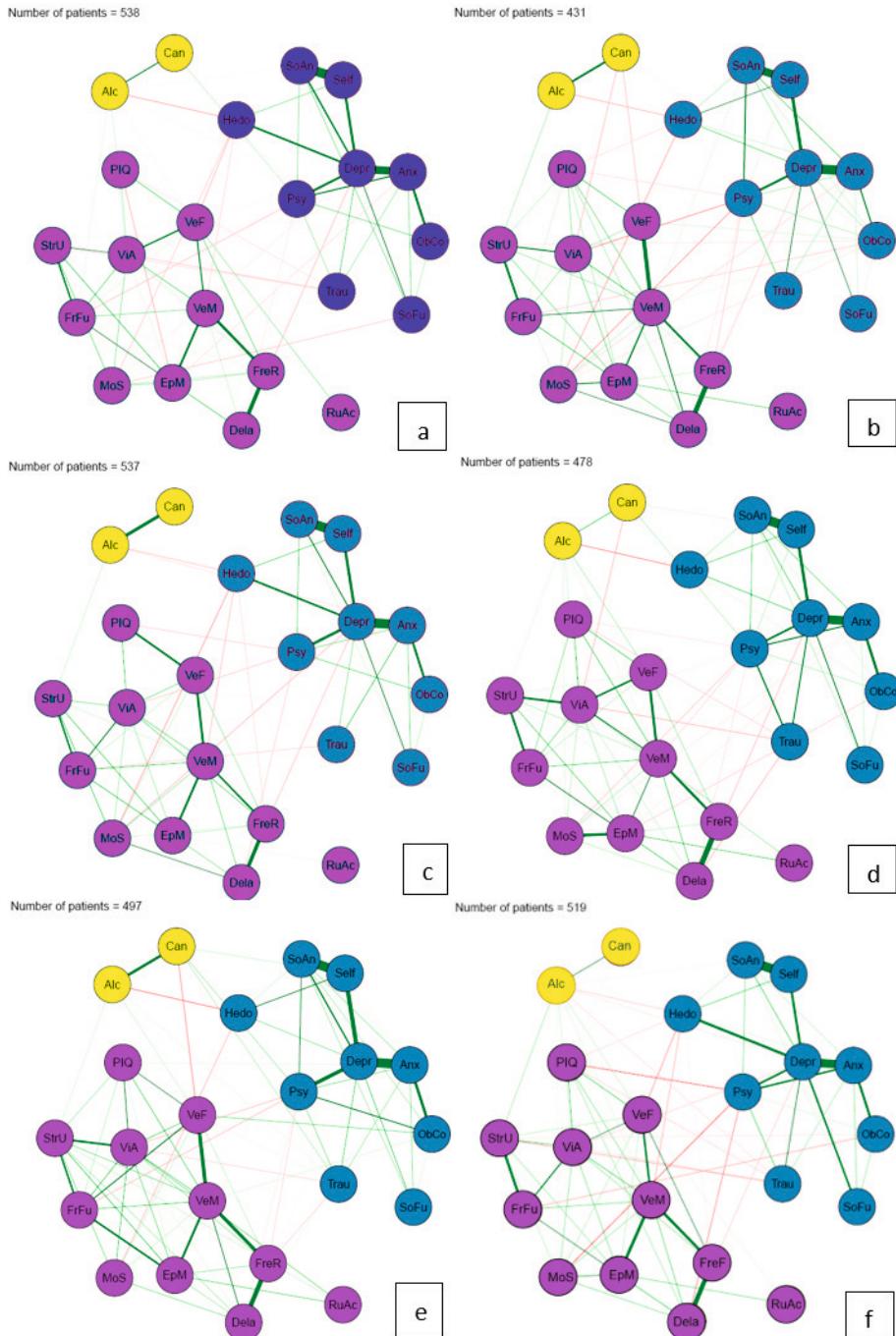


Figure S8. Network for subsamples of high educational level (a), patients with low educational level (b), female patients (c), male patients (d), younger patients aged 14-30 years (e), and older patients aged 31-75 years (f).



Figure S9. Accuracy of the estimated edges of demographic control networks: high education (a), low education (b), female patients (c), male patients (d), younger patients (e), and older patients (f).

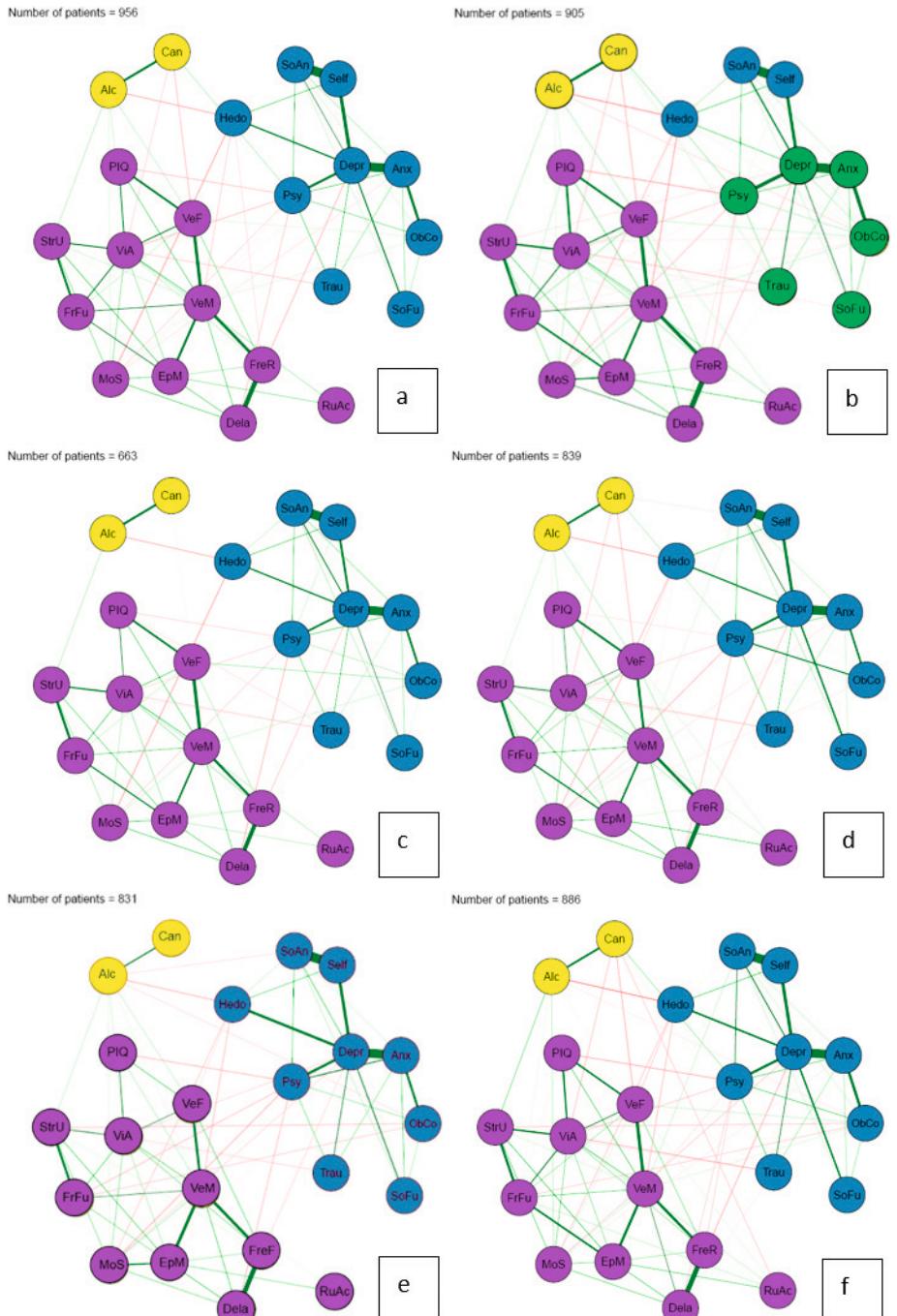


Figure S10. Networks of jackknife diagnostic categories subsamples without anxiety disorders (a), depressive disorders (b), misophonia (c), obsessive-compulsive and related disorders (d), schizophrenia spectrum and other psychotic disorders (e), and other disorders (f).

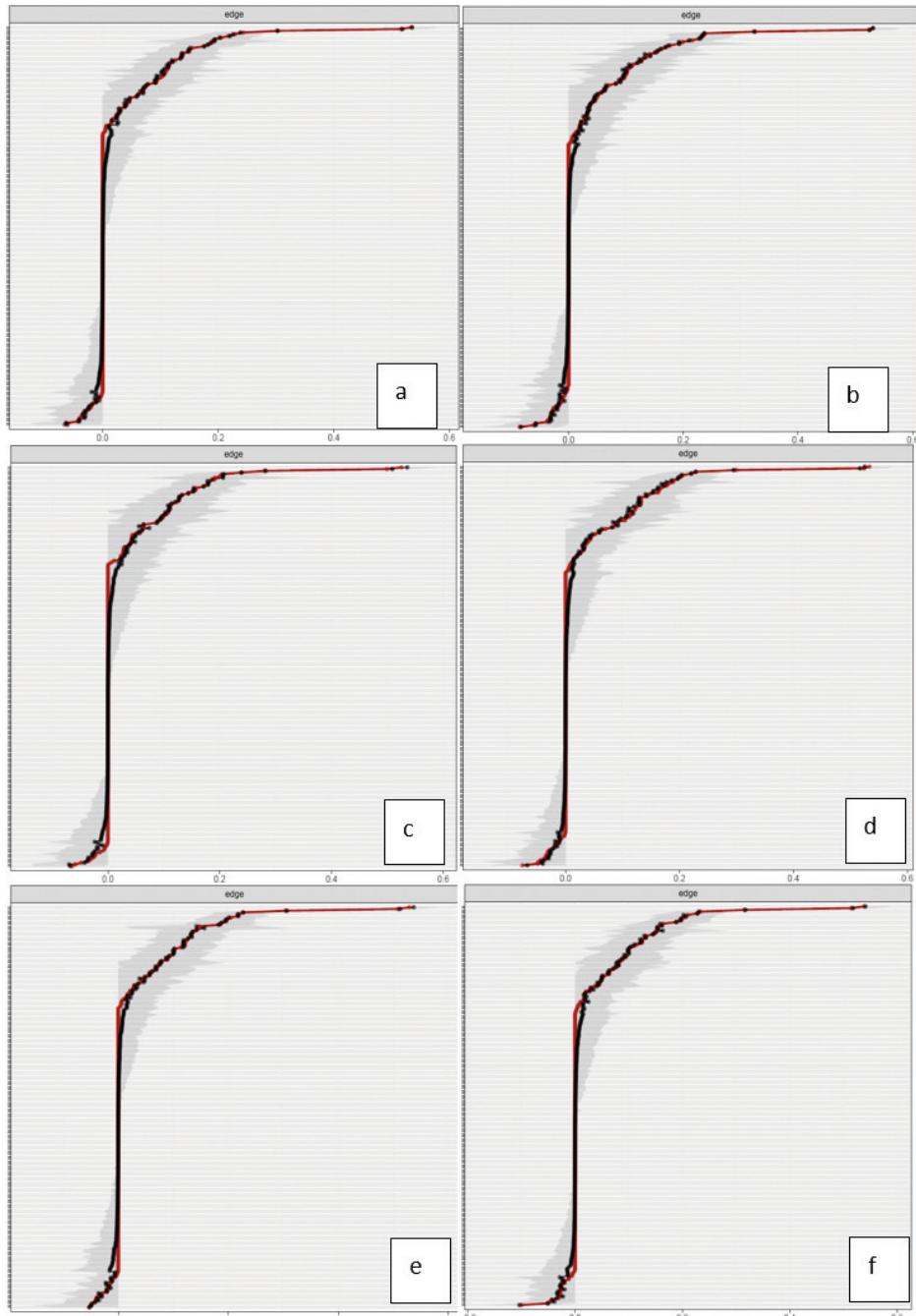


Figure S11. Accuracy of the edges of diagnostic subsample control networks: without anxiety disorders (a), depressive disorders (b), misophonia (c), obsessive-compulsive and related disorders (d), schizophrenia spectrum and other psychotic disorders (e), and other disorders (f).

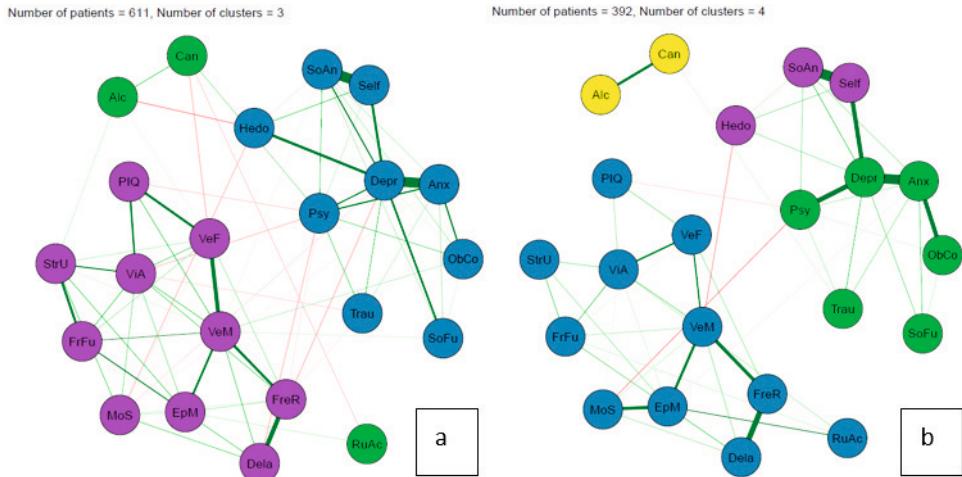


Figure S12. Networks of subsamples without medication use (a) and patients with medication use (b). Nodes represent the variables included in the network and edges indicate an association between two nodes. Green edges represent positive associations whereas red edges represent negative associations, and thickness of an edge represents the strength of association between two nodes. Colors represent cluster membership as determined by the EGA algorithm.

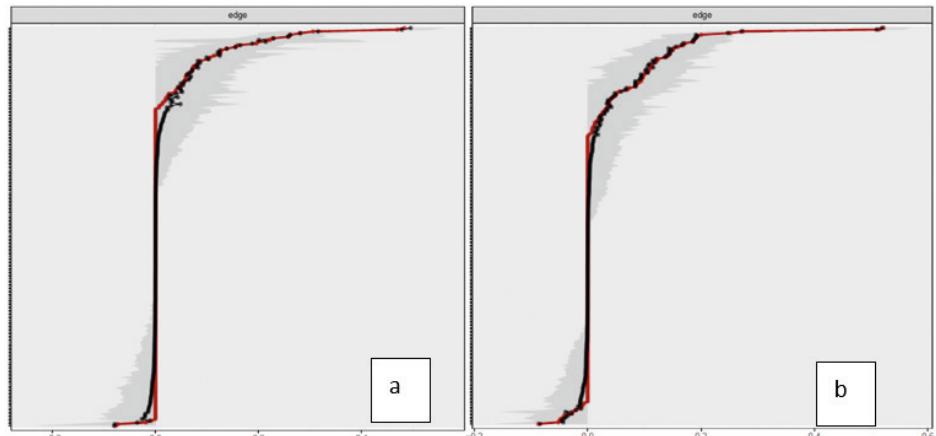


Figure S13. Accuracy of the edges of medication use subsample control networks without medication use (a) and with medication use (b). The x-axis shows the strength of the edge. The edges from the original network are shown in red and the bootstrapped means are shown in black. Edges are arranged from most negative to most positive along the y-axis. The grey area represents confidence intervals based on the bootstrapped networks.

Ising network, number of patients = 690

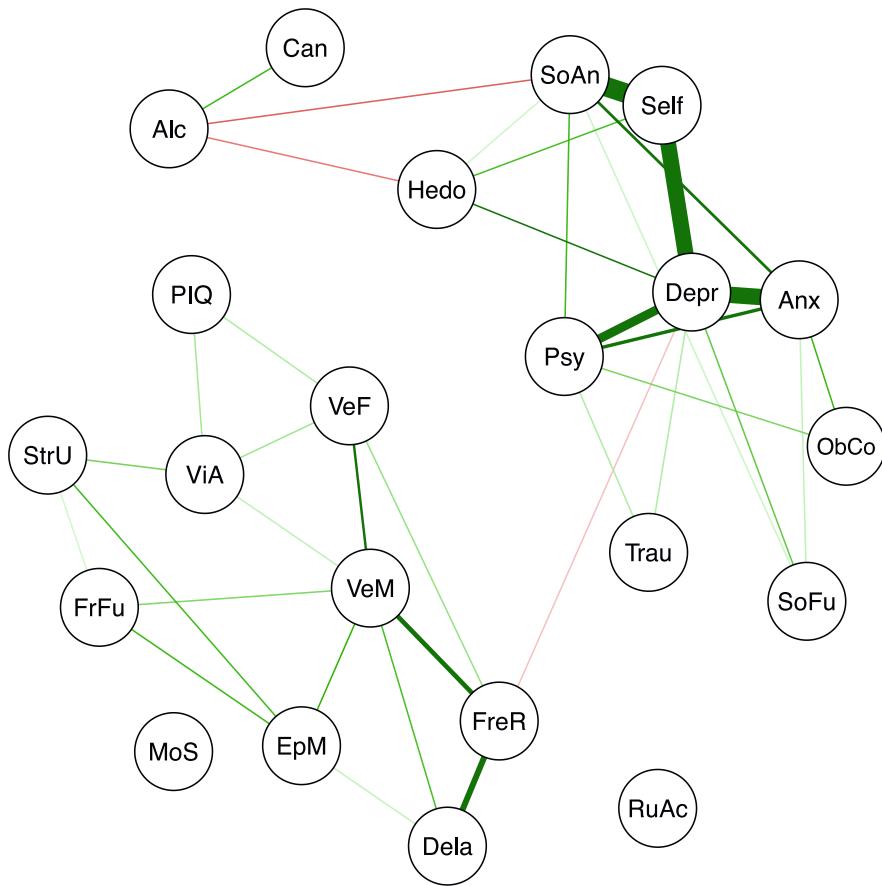


Figure S14. Ising network of 690 patients using binarized data and the *IsingFit* package. Nodes represent the variables included in the network and edges indicate an association between two nodes. Green edges represent positive associations whereas red edges represent negative associations, and thickness of an edge represents the strength of association between two nodes.



4

Resting-state brain oscillations predict cognitive function in psychiatric disorders: A transdiagnostic machine learning approach

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Abstract

Background

Cognitive dysfunction is widespread in psychiatric disorders and can significantly impact quality of life. Deficits cut across traditional diagnostic boundaries, necessitating new approaches to understand how cognitive function relates to large-scale brain activity and psychiatric symptoms across the diagnostic spectrum.

Objective

Using random forest regression, we aimed to identify transdiagnostic patterns linking cognitive function to resting-state EEG oscillations.

Methods

216 participants recruited through an outpatient psychiatric clinic completed the Cambridge Neuropsychological Test Automated Battery and underwent a 5-minute eyes-closed resting state EEG recording. We built random forest regression models to predict performance on each cognitive test using the resting-state EEG power spectrum as input, and we compared model performance to a sampling distribution constructed with random permutations. For models that performed significantly better than chance, we used feature importance estimates to identify features of the EEG power spectrum that are predictive of cognitive functioning.

Results

Random forest models successfully predicted performance on measures of episodic memory and associative learning (Paired Associates Learning, PAL), information processing speed (Choice Reaction Time, CRT), and attentional set-shifting and executive function (Intra-Extra Dimensional Set Shift, IED). Oscillatory power in the upper alpha range was associated with better performance on PAL and CRT, while low alpha power was associated with worse CRT performance. Beta power predicted poor performance on all three tests. Theta power was associated with good performance on PAL, and delta and theta oscillations were identified as predictors of good performance on IED. No differences in cognitive performance were found between diagnostic categories.

Conclusion

Resting oscillations are predictive of certain dimensions of cognitive function across various psychiatric disorders. These findings may inform treatment development to improve cognition.

Keywords: resting-state EEG, transdiagnostic psychiatry, machine learning, cognitive function

Introduction

While psychiatric research and treatment have traditionally focused on the affective changes that characterize mental disorders, cognitive function is gaining increasing attention as a relevant dimension of psychiatric illness. Cognitive deficits are widespread across disorders and can significantly impact overall functioning and quality of life¹. As such, cognitive difficulties are often a primary complaint for which patients seek treatment². Understanding the neurobiological mechanisms underlying cognitive function should therefore be a central goal in efforts to improve treatment and enhance quality of life for patients.

Cognitive function encompasses a broad range of domains including memory, attention, language, problem solving and decision making. Every major diagnostic category in the Diagnostic and Statistical Manual of Mental Disorders (DSM) is associated with altered cognitive functioning in at least one domain¹. Perturbations in executive function occur across multiple disorders, affecting various subdomains including planning and decision making (e.g. depressive disorders)³, cognitive flexibility (e.g. autism spectrum disorder (ASD))⁴, and inhibitory control (e.g. obsessive-compulsive disorder (OCD))⁵ and bipolar disorder⁶. Executive function is most severely compromised in individuals with schizophrenia, who have deficits in all of these subdomains^{7,8}. Deficits in working memory and semantic memory are also common in schizophrenia⁹, while episodic memory is compromised in depression, bipolar disorder, schizophrenia, ASD, posttraumatic stress disorder (PTSD) and OCD¹. Changes in attention are also associated with most disorders, including attention deficit hyperactivity disorder (ADHD)¹⁰, PTSD¹¹, OCD¹², and generalized anxiety disorder (GAD)¹³.

It is difficult to disentangle disorder-specific patterns of cognitive impairment from general deficits transcending diagnostic categories. Cognitive function is highly complex, involving multiple cognitive domains that interact with each other and with emotional and social processing, making it difficult to isolate individual cognitive processes for scientific study. Furthermore, psychiatric disorders themselves are not clearly delineated but instead have broad symptom overlap and high rates of comorbidity. To address this issue, recent research initiatives have attempted to elucidate biological processes underlying psychopathology more broadly without being bound to traditional diagnostic categories (e.g., Research Domain Criteria (RDoc)¹⁴; Hierarchical Taxonomy of Psychopathology (HiTOP)¹⁵). Such transdiagnostic approaches focus on specific domains such as cognition, arousal, and emotion regulation, which are implicated in psychopathology across the diagnostic spectrum and are more closely linked to basic biological processes than complex

and heterogeneous psychiatric disorders are. By taking a fine-grained, bottom-up approach to link specific dimensions of functioning with biological parameters, we may develop a more biologically grounded understanding of psychiatric illness across the diagnostic spectrum.

Cognitive function can be understood in biological terms as precisely orchestrated interactions of brain regions and networks. Breakdowns in the coordination of brain activity are also associated with diverse forms of psychopathology, as evidenced by aberrant network organization in all major psychiatric disorders¹⁶. Measuring large-scale neural activity can therefore provide important insights into brain function subserving cognition and implicated in psychopathology.

Electroencephalography (EEG) provides millisecond temporal resolution in measuring ongoing electrical activity, which constitutes the basis of information exchange across the brain in the form of synchronized oscillations¹⁷. These oscillations are evident in the EEG power spectrum, particularly in specific frequency ranges referred to as alpha (8-13 Hz), beta (13-30 Hz), gamma (30 - 90 Hz), theta (4-8 Hz), and delta (1-4 Hz). A significant proportion of the EEG literature in psychiatric illness focuses on oscillatory power in these frequency bands, with the EEG signals typically recorded in the resting-state. The changes observed between psychiatric cases and controls are, however, highly variable within disorders and not diagnostically specific (for review see Newson, Thiagarajan¹⁸). Resting-state EEG power changes likely hold important information about brain function in psychiatric illness, but it is unclear what specific pathophysiological processes such changes reflect. Thus, taking a more fine-grained approach to link specific EEG changes to specific domains of functioning may offer new interpretations of neurophysiological abnormalities in psychiatric disorders.

This study takes a transdiagnostic approach to explore the relationship between resting-state EEG activity and cognitive function across multiple psychiatric disorders. 216 participants with disorders across seven diagnostic categories were recruited from an outpatient psychiatric clinic and included in the study. Machine learning methods are becoming increasingly employed to identify novel patterns in large datasets, and are particularly well suited for the emerging field of transdiagnostic computational psychiatry to mine information-rich biological signals such as EEG and identify relationships with symptom domains across disorders. One study of patients with schizophrenia employed machine learning methods to identify task-based EEG features that predict working memory performance¹⁹, highlighting the utility of machine learning methods for extracting relevant features from high-dimensional EEG data. The present study employs a similar approach, using random forest regression to identify resting-state EEG features associated with

cognitive performance across multiple cognitive domains and psychiatric disorders. This approach may shed light on the neurobiological basis and clinical relevance of cognitive dysfunction in psychiatric illness.

Materials and methods

Sample

Data are reported from 216 participants who were recruited through an outpatient clinic of the Department of Psychiatry at the Amsterdam University Medical Centers (UMC) in Amsterdam, the Netherlands. Inclusion criteria were: age 18-75 years, ability to give informed consent, having a DSM-IV-TR or DSM-V diagnosis, being clinically stable, and being fluent in Dutch. Exclusion criteria were: high risk of suicide, unstable medical disorder, premorbid IQ<70, history of seizures or neurological disorder. Informed consent was obtained from all participants. Of 955 patients who participated in the Across study, 256 participants agreed to participate in the EEG substudy. 6 participants were excluded because their EEG data were unusable due to technical issues. Of the remaining participants, 216 completed the CANTAB battery and were included in analyses.

4

Procedure

The Across study is an ongoing, observational longitudinal cohort study and consists of the assessment of cognitive performance, psychiatric symptoms, and collection of biological data (DOI 10.17605/OSF.IO/YHVTB). All instruments and procedures are described in Nieman, Chavez-Baldini, Vulink, Smit, van Wingen, de Koning, Sutterland, Mocking, Bockting, Verweij, Lok, Denys²⁰. Participants underwent an extensive psychiatric and medical assessment at the outpatient clinic, performed by experienced psychiatrists and psychologists. The current study uses baseline data from the computerized cognitive assessment, EEG recordings, and symptomatology questionnaires (see Supplementary Material). The study protocol was approved by the Medical Ethical Review Committee of the Amsterdam UMC (ABR no. NL55751.018.15), and data is stored according to privacy laws.

Cognitive assessment

Cognitive functioning was assessed with the Cambridge Neuropsychological Test Automated Battery²¹. The CANTAB test battery is composed of the following subtests: Verbal Recognition Memory (VRM), Rapid Visual Information Processing (RVP), Intra/Extradimensional Set Shift (IED), Choice Reaction Time (CRT), One Touch

Stockings of Cambridge (OTS), Paired Associates Learning (PAL), and Spatial Working Memory (SWM). Descriptions of the subtests are found in Table 1.

Table 1. Description of Cambridge Neuropsychological Test Automated Battery subtests

Subtest	Description
Verbal Recognition Memory (VRM)	Assesses free recall, and immediate and delayed recognition memory for verbal information
Rapid Visual Information Processing (RVP)	Tests visual sustained attention and processing speed
Intra/ Extradimensional Set Shift (IED)	Assesses rule acquisition and attentional set shifting
Choice reaction time (CRT)	Measures alertness and motor speed
One Touch Stockings of Cambridge (OTS)	A planning test measuring frontal lobe functioning
Paired Associates Learning (PAL)	Assesses visual episodic memory and learning
Spatial Working Memory (SWM)	Assesses working memory and strategy use

EEG acquisition and processing

EEG was recorded with a WaveGuard cap with Ag/AgCl electrodes with standard 10/10 layout fed into the 64-channel ANT TMSi Refa amplifier, using Fpz as ground, horizontal EOG electrodes affixed to the outer canthus and vertical EOG electrodes affixed above and below the right eye, and two mastoid channels (M1/M2). The vertex electrode (Cz) was used as the recording reference. Eyes-closed resting state EEG was recorded for 5 minutes, in addition to eyes-open resting state and an auditory oddball task for a total recording session of 45 minutes. Eyes-closed resting state was used for the current analysis, since the majority of studies of EEG oscillations in psychiatric disorders report data from eyes-closed recording¹⁸. Recordings were sampled at 512 Hz with a 128 Hz low-pass filter.

All analyses were performed in MATLAB R2018b. EEG preprocessing was performed for each subject using EEGLAB²². Data were re-referenced offline to an average reference and filtered using a FIR bandpass filter from 1- 50 Hz. Bad channels were removed and interpolated. Data were epoched into 2-second segments to manually reject artifactual epochs, after which data were re-concatenated into continuous data. Independent component analysis was performed to manually identify and reject noise components. Ocular and muscular artifacts were removed using blind source separation and canonical correlation analysis techniques implemented in the AAR plugin for EEGLAB²³.

For all 64 channels, a fast Fourier transform was computed after applying a 512-point Hanning window. The resulting power spectrum was segmented into bins of 1 Hz, ranging from 1-50 Hz (50 bins) and log-transformed. To control for the effects of age and gender, power spectra for all electrodes were regressed on age and gender, and residual scores were used as corrected power values for all analyses.

Random forest prediction

To estimate performance on each CANTAB cognitive test, we used a random forest model with power at each channel in 1-Hz bins from 1-50 Hz as input features after correcting for age and gender. Random forest is one of the most popular machine learning algorithms for classification and regression²⁴, and is particularly suited for high dimensional data. The algorithm creates a large number of decision trees, where each tree is trained on a bootstrap sampling of the data with a random subsample of features. The algorithm builds a maximally informative decision tree for each sampling, with each level moving into a branch based on a critical value for an input feature. After multiple decisions, each tree leads to end nodes that are associated with a classification into either of two groups. In the regression extension, each decision tree assigns a value for the outcome variable based on decisions made for the sampled features falling above or below a certain threshold. After all decision trees are run and the forest of trees is created, the prediction of the random forest is the average prediction of the individual trees. Bootstrap aggregation or “bagging” of decision trees means that each tree is trained on a subsample of the data, so the performance of each model on its left-out samples (“out-of-bag” observations) when averaged provides an estimate of model accuracy. In this way, out-of-bag performance provides a metric of generalization performance that is very similar to cross-validation.

Because our primary aim was to identify EEG features associated with cognitive performance, our choice of random forest regression among various machine learning techniques was primarily due to its utility in estimating feature importance. Besides being versatile in prediction of continuous and categorical outcomes, random forest naturally allows for the inspection of predictor importance. Due to its randomization and ‘bagging’ component, it will result in a gradual distribution of importance of features, in contrast with, for example, penalized regressions that will result in sparse weights across space and frequency, especially when features are highly correlated. This is crucial for visualizing scalp topography of predictor importance.

For each cognitive test, we built a random forest with the number of trees set to 20,000 and with the number of predictors to sample set to 12. These hyperparameters were selected not to optimize model performance *per se*, but rather to optimize predictor importance estimates to determine which EEG features are most predictive of cognitive functioning. We found that predictor importance estimates were highly variable with fewer than 5,000 trees, and predictor importance estimates became steadily less variable as the number of trees was increased to 20,000. Model

performance did not improve above 5,000 trees, and neither model performance nor predictor importance estimates improved with greater than 12 predictors sampled.

Model performance was evaluated using the coefficient of determination or Nash-Sutcliffe efficiency (NSE), reflecting model fit between observed cognitive scores and predicted scores for out-of-bag observations. NSE is computed as $NSE = 1 - \frac{\sum(Y_m - Y_p)^2}{\sum(Y_m - \bar{Y})^2}$, where Y_m and Y_p are observed and predicted values, respectively, and \bar{Y} is the mean of observations. NSE ranges from $-\infty$ to 1.

For each model, permutation testing was conducted to determine if the model performed significantly better than chance. Cognitive test scores were randomly permuted and a random forest model was built for each permutation, thus obtaining a null distribution of the NSE statistic. The p-value is the frequency of random models that perform equal to or better than the original model, reflecting the probability of obtaining equal or better model performance due to chance alone. The significance threshold was set at $p = 0.00714$ ($0.05/7$, correcting for number of cognitive tests), and 2000 permutations were performed to provide a p-value resolution of 0.0005 ($1/2000 = 0.0005$).

For models that performed significantly better than chance, predictor importance was estimated for EEG features as the increase in prediction error if the values of the predictor are randomly permuted for out-of-bag observations. To identify frequencies with the highest predictor importance for each model, we plotted predictor importance by frequency (averaged across electrodes) and selected peaks, defined as local maxima exceeding one standard deviation above the mean predictor importance estimate. To investigate the direction of effect for each frequency predictor on cognitive outcome, we identified the top three channels with greatest predictor importance within each selected frequency and examined their relationships with cognitive performance using univariate regression models.

Statistical analysis

Follow-up analyses were performed to assess differences among diagnostic groups. For cognitive tests that were found to be predictable from EEG data (based on significance of permutation testing), a Welch's ANOVA was performed to determine if cognitive scores differed among diagnostic groups. Welch's ANOVA was used due to unequal variances across groups. We first corrected the scores by residualizing them for age and gender across the whole sample as in the random forest models. Next, the Welch's ANOVA included diagnostic groups with $n > 10$ (see Table 2). Further analyses to investigate possible effects of medication and diagnostic category on predictor-outcome relationships are included in Supplementary Material (suppl.

Tables 2 and 3). An important and clinically relevant question is how cognitive (dys)function interacts with other dimensions of psychiatric illness. We decided to investigate the relationship between cognitive function and other symptom dimensions in order to more effectively interpret the relationship between EEG activity and cognition. We therefore performed a series of Pearson correlations between CANTAB scores and symptom scores on five symptom dimensions. These symptom dimensions were identified using factor analysis of self-report symptom questionnaires (see Supplementary Material) and were labeled as social/interpersonal, anxious, depressive, somatic, and anomalous (psychosis-spectrum symptoms). To rule out the possibility that predictability of cognitive performance is related to specific diagnosis, we used the same model parameters to build random forest models to predict each diagnosis and assessed performance using the same methods described above.

Results

Table 2 shows demographic information and CANTAB cognitive test scores for 216 participants. Further medication data are presented in Supplementary Table 1.

Table 3 shows random forest model performance statistics for each cognitive test. NSE (ranging from $-\infty$ to 1) reflects model fit between observed scores and predicted scores for out-of-bag observations. The p-value is the frequency of random permutation models that perform equal to or better than the original model, reflecting the probability of obtaining equal or better model performance due to chance alone. For models that performed significantly better than chance, predictor importance was estimated for EEG features.

Table 3. Random forest model performance for each cognitive test

	NSE	p-value*
VRM	-0.0018	0.0560
RVP	-0.0487	0.5605
IED	0.0226	0.0070
CRT	0.0242	0.0065
OTS	-0.0419	0.4500
PAL	0.0348	0.0055
SWM	-0.0434	0.4805

*Significant p-values (<.00714) shown in bold

Table 2. Participant demographics and CANTAB scores

	Total	MDD	BP	PSY	OCD	GAD	ASD	ID-NOS
n	216	34	4	15	49	9	4	101
Age mean (SD)	38.6 (15.0)	41.5 (15.7)	38.0 (18.3)	29.3 (10.6)	43.7 (14.8)	45.1 (16.3)	26.3 (6.3)	36.5 (14.4)
Gender # male (%)	83 (38.4)	14 (41.2)	2 (50.0)	8 (53.3)	21 (42.9)	4 (44.4)	3 (75.0)	31 (30.7)
Medication status # medicated (%)	68 (31.5)	16 (47.1)	1 (25.0)	9 (60.0)	14 (28.6)	4 (44.4)	0 (0.0)	24 (23.8)
Premorbid IQ mean (SD)	103.1 (13.1)	102.9 (15.2)	100.5 (13.2)	105.8 (16.0)	106.1 (14.6)	95.7 (11.7)	99.5 (17.3)	102.2 (11.3)
CRT mean (SD)	351 (87.9)	395 (118)	337 (61.9)	305 (41.8)	351 (63.8)	393 (22.1)	322 (40.0)	340 (66.9)
IED mean (SD)	26.4 (27.4)	29.7 (40.0)	21.8 (23.0)	30.4 (26.9)	30.8 (31.0)	39.2 (38.8)	9.50 (2.65)	22.2 (18.1)
OTS mean (SD)	1.39 (0.255)	1.39 (0.270)	1.42 (0.373)	1.35 (0.202)	1.45 (0.281)	1.58 (0.384)	1.49 (0.212)	1.34 (0.219)
PAL mean (SD)	12.3 (18.9)	18.1 (26.6)	11.3 (13.7)	10.2 (11.5)	11.9 (13.0)	24.0 (29.4)	9.50 (10.1)	9.87 (18.0)
RvP mean (SD)	0.898 (0.054)	0.876 (0.068)	0.870 (0.066)	0.884 (0.053)	0.903 (0.042)	0.868 (0.053)	0.952 (0.005)	0.908 (0.050)
SWM mean (SD)	21.0 (18.5)	24.9 (20.4)	27.3 (12.1)	27.9 (25.7)	25.3 (20.9)	28.0 (18.4)	9.25 (13.3)	16.2 (14.3)
VRM mean (SD)	6.75 (2.70)	6.29 (2.60)	9.25 (3.59)	6.13 (2.45)	7.00 (3.19)	5.78 (2.17)	5.25 (2.22)	6.92 (2.49)

Note: MDD = Major depressive disorder; BP = Bipolar disorder; PSY = Psychosis spectrum disorders; OCD = Obsessive-compulsive disorder; CAD = Generalized anxiety disorder; ASD = Autism spectrum disorder; ID-NOS = impulse-control disorder, not otherwise specified (misophonia). Note: large ID-NOS sample is due to specialized misophonia research group located at the AUMC. Premorbid IQ assessed with National Adult Reading Test (NART)²⁵. CRT = Choice Reaction Time, mean correct latency; IED = Intra-Extra Dimensional Set Shift, total errors adjusted; OTS = One Touch Stockings of Cambridge, mean choices to correct; PAL = Paired Associates Learning, total errors adjusted; RvP = Rapid Visual Information Processing, A-prime; SWM = Spatial Working Memory, between errors; VRM = Verbal Recognition Memory, free recall total correct.

Paired Associate Learning

The random forest model performed significantly better than chance predicting PAL score from EEG data. Figure 1A shows the observed NSE value relative to the null distribution of permuted NSE statistics. Figures 1B – F show predictor importance estimates, computed for each predictor as the increase in prediction error if the values of the predictor are randomly permuted for out-of-bag observations. Topography of predictor importance estimates for each frequency (1-50 Hz in 1 Hz bins) are shown in Supplementary Material Figure 1. Figures 1D – F show a selection of topographical maps corresponding to frequency peaks, identified at 6 Hz, 13 Hz, and 17 Hz. These peaks were selected for subsequent analyses to determine directions of effects.

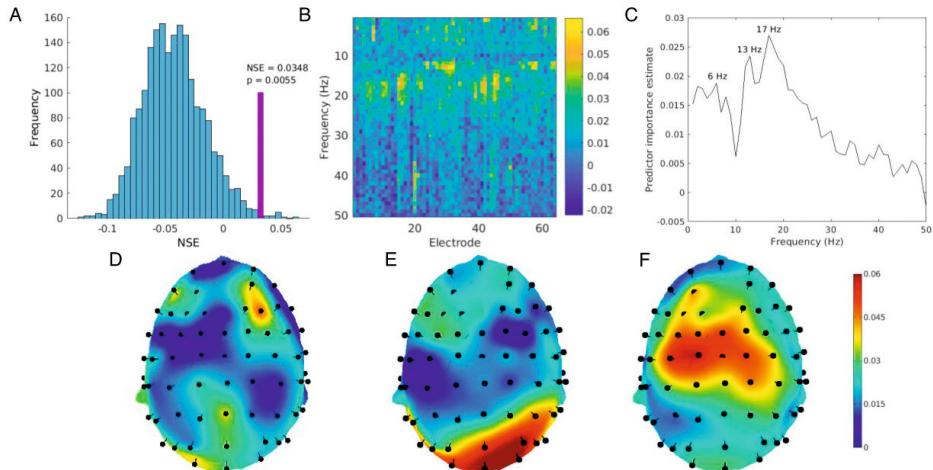


Figure 1: (A) Distribution of NSE values from 2000 permutations of random forest model with PAL scores randomly shuffled. Observed NSE shown in purple. 11 out of 2000 permutations exceeded the observed NSE value, yielding a p-value of 0.0055 (B) PAL predictor importance estimates for all 3200 predictors (electrode x frequency). (C) Estimated predictor importance by frequency (averaged across electrodes). (D) Topography of predictor importance at 6 Hz (corresponding to predictor importance peak at 6 Hz, see C). (E) Topography of predictor importance at 13 Hz. (F) Topography of predictor importance at 17 Hz.

To assess the direction of effect for frequencies with high predictor importance, linear regression models were used with power as independent variables and PAL score (total errors adjusted) as the dependent variable. For each peak frequency, three channels with the highest predictor importance were tested in univariate models. 6 Hz power at F4, AF4 and O1 all exhibited inverse relationships with PAL errors (greater power associated with better performance; $\beta_{F4} = -.49$, $\beta_{AF4} = -.41$, $\beta_{O1} = -.25$). 13 Hz power also showed an inverse relationship with PAL errors ($\beta_{Oz} = -.27$, $\beta_{O2} = -.29$, $\beta_{PO4} = -.30$). 17 Hz power exhibited a positive relationship with PAL errors (greater power associated with worse performance; $\beta_{C1} = .48$, $\beta_{C3} = .49$, $\beta_{FCz} = .52$).

Choice Reaction Time

The random forest model performed significantly better than chance predicting CRT scores from EEG data. Figure 2A shows the observed NSE value relative to the null distribution of permuted NSE statistics. Figures 2B – F show predictor importance estimates. Topography of predictor importance estimates for each frequency (1-50 Hz in 1 Hz bins) are shown in Supplementary Material Figure 2. Figures 2D – F show a selection of topographical maps corresponding to frequency peaks, identified at 8 Hz, 12 Hz, and 17 Hz. These peaks were selected for subsequent analyses to determine directions of effects.

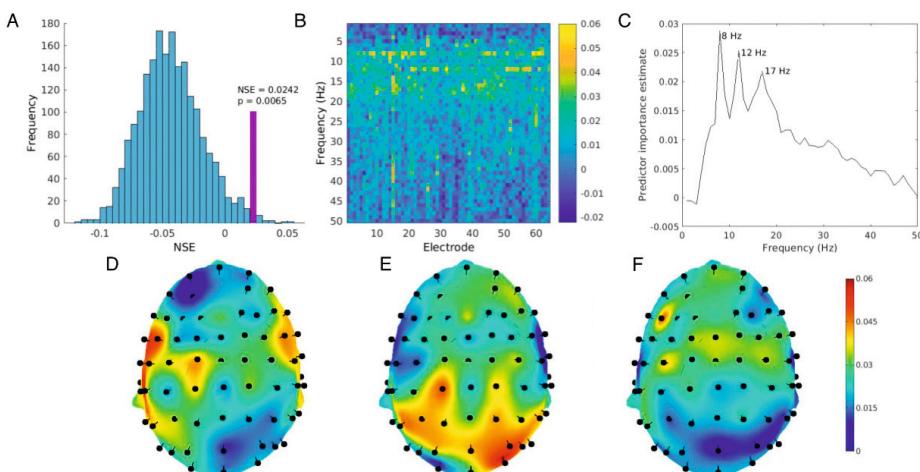


Figure 2: (A) Distribution of NSE values from 2000 permutations of random forest model with CRT scores randomly shuffled. Observed NSE shown in purple. 13 out of 2000 permutations exceeded the observed NSE value, yielding a p-value of 0.0065 (B) CRT predictor importance estimates for all 3200 predictors (electrode x frequency). (C) Estimated predictor importance by frequency (averaged across electrodes). (D) Topography of predictor importance at 8 Hz (corresponding to predictor importance peak at 8 Hz, see C). (E) Topography of predictor importance at 12 Hz. (F) Topography of predictor importance at 17 Hz.

To assess the direction of effect for frequencies with high predictor importance, linear regression models were used with power as independent variables and CRT score (mean correct latency) as the dependent variable. For each peak frequency, three channels with the highest predictor importance were tested in univariate models. 8 Hz power at FC5, FT7, and TP7 all exhibited positive relationships with CRT latency (greater power associated with worse performance; $\beta_{FC5} = .30$, $\beta_{FT7} = .39$, $\beta_{TP7} = .32$). 17 Hz power also exhibited a positive relationship with CRT latency ($\beta_{C1} = 0.47$, $\beta_{C3} = 0.56$, $\beta_{C2} = 0.41$). 12 Hz power exhibited an inverse relationship with CRT latency (greater power associated with better performance; $\beta_{CPI} = -.07$, $\beta_{O2} = -.20$, $\beta_{PO6} = -.21$).

Intra-Extra Dimensional Set Shift

The random forest model performed significantly better than chance predicting IED score from EEG data. Figure 3A shows the observed NSE value relative to the null

distribution of permuted NSE statistics. Figures 3B – F show predictor importance estimates. Topography of predictor importance estimates for each frequency (1-50 Hz in 1 Hz bins) are shown in Supplementary Material Figure 3. Figures 3D – F show a selection of topographical maps corresponding to frequency peaks, identified at 2 Hz, 5 Hz, and 22 Hz. These peaks were selected for subsequent analyses to determine directions of effects.

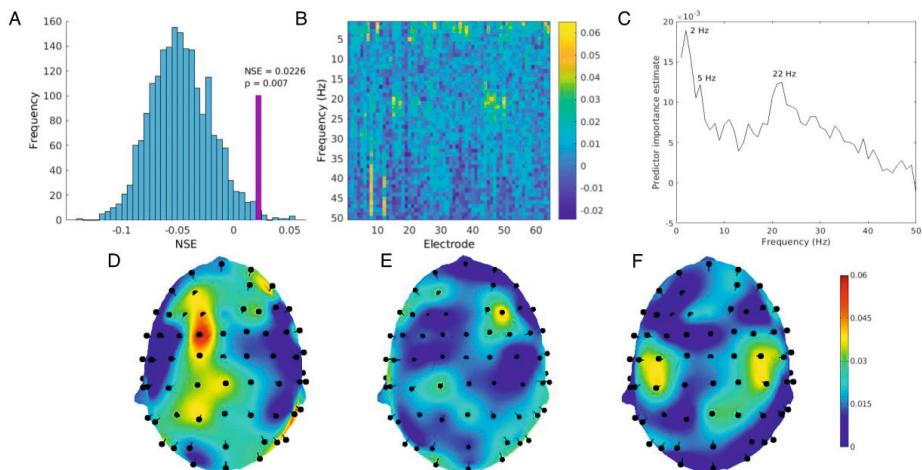


Figure 3: (A) Distribution of NSE values from 2000 permutations of random forest model with IED scores randomly shuffled. Observed NSE shown in purple. 14 out of 2000 permutations exceeded the observed NSE value, yielding a p -value of 0.007 (B) IED predictor importance estimates for all 3200 predictors (electrode x frequency). (C) Estimated predictor importance by frequency (averaged across electrodes). (D) Topography of predictor importance at 2 Hz (corresponding to predictor importance peak at 2 Hz, see C). (E) Topography of predictor importance at 5 Hz. (F) Topography of predictor importance at 22 Hz.

To assess the direction of effect for frequencies with high predictor importance, linear regression models were used with power as independent variables and IED score (total errors adjusted) as the dependent variable. For each peak frequency, three channels with the highest predictor importance were tested in univariate models. 2 Hz power at F1, FC1 and P8 all exhibited inverse relationships with IED errors (greater power associated with better performance; $\beta_{F1} = -.35$, $\beta_{FC1} = -.50$, $\beta_{P8} = -.44$). 5 Hz power also showed an inverse relationship with IED errors ($\beta_{F4} = -.47$, $\beta_{CP1} = -.38$, $\beta_{CP5} = -.38$). 22 Hz power exhibited a positive relationship with IED errors (greater power associated with worse performance; $\beta_{C4} = .34$, $\beta_{CP3} = .13$, $\beta_{CP4} = .19$).

Follow-up analyses: Clinical relationships

To assess whether PAL, CRT, and IED scores differed among diagnostic groups, we performed a Welch's ANOVA for each cognitive test controlling for age and gender, including only diagnostic groups with $n > 10$ (MDD, PSY, OCD, and ID-NOS). For all three cognitive tests, scores did not differ significantly among diagnostic groups (PAL: $F(3,53.14) = 1.27$, $p = 0.30$; CRT: $F(3,55.17) = 2.45$, $p = 0.07$; IED: $F(3,46.32) = 1.09$, $p = 0.36$). There were no significant correlations between CANTAB scores and symptom scores for any of the five symptom dimensions, as seen in Table 4.

Table 4. Correlations between CANTAB scores and symptom dimension scores

	PAL		CRT		IED	
	r	p	r	p	r	p
Social/interpersonal	-.128	.080	.138	.058	-.012	.869
Anxious	-.075	.305	-.073	.352	-.060	.411
Depressive	-.040	.585	-.080	.271	.029	.691
Somatic	.092	.207	.113	.121	.071	.333
Anomalous	-.048	.515	-.001	.990	-.084	.252

We next tested whether a random forest model would also successfully predict diagnosis, which could suggest that the relationship between EEG oscillations and cognition is secondary to the relationship between EEG oscillations and specific psychopathology. We built a random forest model to predict each diagnosis, with the same model parameters that were used to predict cognitive scores. Although a classification model is generally used to predict a binary target variable (diagnosis or no diagnosis), we used a regression model to maintain methodological consistency with the continuous prediction of cognitive scores and to allow graded (continuous) prediction values, perhaps reflecting disorder severity. Table 5 shows NSE and p-values for each model. No model performed better than chance in predicting diagnosis.

Table 5. Random forest model performance for diagnostic categories

Diagnosis	NSE	p-value
MDD	-0.0299	0.2753
BP	-0.0158	0.1325
PSY	-0.0470	0.5345
OCD	-0.0355	0.3545
GAD	-0.0097	0.0950
ID-NOS	-0.0362	0.3630

Discussion

The aim of this study was to identify correlates of cognitive function in the resting EEG power spectrum, across various psychiatric disorders and multiple cognitive domains. Using resting EEG data as input, random forest models performed significantly better than chance in predicting performance in tasks measuring episodic memory and associative learning (PAL), information processing speed (CRT), and attentional set-shifting and executive function (IED). Power in the upper alpha range (12-13 Hz) was associated with better performance on PAL and CRT, while power in the beta frequency range was associated with poorer performance on all three tests. Theta oscillations were associated with better performance on PAL, and

theta and delta oscillations were associated with better IED performance. Random forest models with the same hyperparameters were unable to predict diagnosis at a level above chance. Scores for PAL, CRT, and IED did not differ significantly among diagnostic groups.

Resting oscillations and cognition

Alpha oscillations

We found that better performance on PAL and CRT was associated with greater power in the upper alpha range, while increased power in the lower alpha range was associated with worse CRT performance. Resting alpha power, particularly in the high-alpha range, has been found to correlate with cognitive performance and memory in particular²⁶⁻²⁹. Several studies also provide evidence that individual alpha frequency (IAF) is an indicator for speed of cognitive processes^{27,30-32}, which may explain why power in the low alpha range was associated with worse CRT performance.

Alpha oscillations have been traditionally thought to reflect idling or inhibition of task-irrelevant cortical areas, given that they desynchronize in response to most task demands. However, recent findings that alpha oscillations increase in certain conditions, particularly in working memory tasks^{33,34}, have led to a revised understanding that ascribes alpha oscillations an active role in cognitive processing. Alpha oscillations serve a critical top-down modulatory role by acting as a selective inhibitory filter³⁵ and by controlling rhythmic changes in neural excitability^{36,37}. This enables the precise timing of neuronal firing rates as a function of alpha phase and modulates higher frequency oscillations³⁸. High resting alpha power may therefore reflect effective top-down cognitive control that allows for efficient information processing³⁵. This function may be compromised in psychiatric illness, as alpha oscillations are reduced across multiple disorders (see Newson, Thiagarajan¹⁸ for review). Given the critical role of alpha oscillations in modulating and maintaining global brain dynamics, further work should attempt to clarify whether reduced alpha oscillations in psychiatric disorders relate specifically to cognitive dysfunction, or if alpha reductions underlie broad network disruptions leading to diverse symptoms.

Beta oscillations

We found that resting beta power was associated with poor performance on PAL, CRT, and IED. While beta oscillations are classically considered to be related to sensorimotor functions through the maintenance of steady muscle contractions³⁹, work in the last few decades suggests that beta oscillations play a parallel role in cognition through the maintenance of ongoing cognitive operations⁴⁰. Engel

and Fries⁴¹ offer a unifying hypothesis of beta oscillations serving to maintain the current sensorimotor and cognitive set, or “status quo”. Engel and Fries predict that pathological enhancement of beta activity is likely to result in deterioration of flexible cognitive control and efficient information processing. This could explain why elevated resting beta is associated with poorer performance on flexible set shifting (IED) and slower processing of novel stimuli (CRT). Beta oscillations may maintain the current cognitive state in part by inhibiting oscillations in other frequencies⁴¹. Given evidence that associative learning is accomplished through the synchronous firing of different populations of neurons at gamma frequency⁴², this may explain why elevated baseline beta activity is associated with poorer performance on associative learning and memory (PAL).

Theta and delta oscillations

We found that theta oscillations were associated with better performance on PAL, and theta and delta oscillations were associated with better IED performance. These findings are somewhat surprising, given that resting theta power has been associated with poorer cognitive performance (see Klimesch⁴³ for review), while increased delta oscillations at rest are commonly considered to indicate brain pathology and are observed in a number of neurological and psychiatric conditions including schizophrenia, ADHD, Alzheimer’s disease, Parkinson’s disease, Down syndrome, depression, anxiety, and OCD (see Knyazev⁴⁴ for review). Delta and theta power also increase with normal aging (see Rossini, Rossi, Babiloni, Polich⁴⁵ for review). However, age-dependent changes in the relationship between cognition and resting oscillations could offer a possible interpretation of the current findings. Several studies have found that enhanced delta and theta power show a positive relationship with cognitive performance in older, but not younger, adults^{46,47}. It is possible that while increases in delta and theta power are observed in aging and a range of pathological conditions, this serves a compensatory function when faster oscillations (particularly alpha) are compromised. In this sense, patients with various psychiatric disorders may have a general pathology that results in increased delta and theta oscillations, but these oscillations may paradoxically preserve cognitive function.

Cognitive function across disorders

Performance on PAL, CRT, and IED did not differ significantly among diagnostic groups. This may suggest that executive function, episodic memory, and processing speed reflect transdiagnostic factors that are broadly affected across diagnostic categories. This is supported by a recent review of meta-analyses of neurocognitive impairment in psychiatric disorders, which found that deficits in executive function and episodic memory are the most severe and most frequently reported across

disorders⁴⁸ (MDD, schizophrenia, ASD, ADHD, bipolar, OCD, and PTSD were considered in the review). The authors suggest that deficits in executive function and episodic memory constitute key transdiagnostic neurocognitive impairments and may reflect common pathophysiological mechanisms across disorders. They suggest that a common cognitive factor may underlie various cognitive deficits across the diagnostic spectrum, akin to the “p factor” proposed by Caspi, Houts, Belsky, Goldman-Mellor, Harrington, Israel, Meier, Ramrakha, Shalev, Poulton⁴⁹ that reflects an overall susceptibility to psychopathology. An impaired common cognitive factor could produce different cognitive deficits in different psychiatric disorders, and certain domains such as executive function and episodic memory may be more centrally related to a common cognitive factor and thus more often impaired. While processing speed was not identified as a central neurocognitive impairment, well-established associations between processing speed and oscillatory frequency (particularly alpha) suggest there may be a direct relationship between the speed of oscillatory and cognitive processes. This may explain why random forest models in the current study successfully identified neuro-oscillatory correlates of executive function, episodic memory, and processing speed, but not other cognitive domains. Deficits that are less severe or less ubiquitous across disorders may have simply been too slight to identify biological correlates.

The concept of a common cognitive factor also implies that cognitive dysfunction is a core mechanism in the pathophysiology of psychiatric illness, rather than a peripheral symptom. Cognition depends on the precise orchestration of cerebral activity, and cognitive dysfunction may therefore be the most direct and immediate consequence of pathophysiological alterations in cerebral networks in psychiatric disorders. It is therefore not surprising that EEG activity would be more strongly associated with cognitive function than with other symptoms or with disorders as a whole.

Limitations

The aim of the Across study is to examine dimensions of functioning without the categorical distinction between healthy, ‘normal’ control subjects and ill psychiatric patients. There is a broad range in cognitive functioning both in patient populations and among individuals without psychiatric diagnoses and this categorical distinction is a theoretical assumption that does not reflect clinical reality. However, since individuals without psychiatric diagnoses were not included in the current study it is unclear if our results reflect a general link between resting-state oscillations and cognitive function, or if our findings are specific to patients with psychiatric diagnoses and reflect a transdiagnostic pathological mechanism (i.e. biological correlates of cognitive dysfunction).

As such, we suggest that future transdiagnostic studies would benefit from the inclusion of healthy individuals not as comparison subjects per se, but to examine the full range of variability in cognition and other dimensions of functioning.

Finally, as is often the case in psychiatric research, medication status may influence the results. While this is mainly problematic in the comparison of individuals with psychiatric diagnoses to unmedicated controls, medication status may still introduce confounding effects that are difficult to control for given the diverse range of medications used in a transdiagnostic sample.

Clinical significance and implications

Resting state EEG is a widely used tool in psychiatric research, with a considerable number of studies linking specific disorders to power changes in specific frequency bands. Our results show that resting EEG oscillations are predictive of cognitive performance across several domains, but EEG data could not be used to predict diagnosis at a level above chance. Researchers should therefore be cautious when interpreting power abnormalities associated with psychiatric disorders. Without controlling for cognitive variables, it is possible that group differences in EEG frequency bands are driven by specific factors such as cognitive function that are not necessarily disorder specific.

While this may present a challenge to psychiatry's search for disorder-specific EEG biomarkers, it could compel a transition to new approaches that link EEG features to more basic dimensions of functioning. For example, anhedonia has been considered a candidate endophenotype of depression and schizophrenia and is strongly linked to reduced electrophysiological responsiveness to reward^{50,51}. We may develop a more biologically grounded understanding of (transdiagnostic) psychiatric illness by isolating cognitive, emotional, or social processes and linking these processes to specific neurophysiological correlates. By taking a fine-grained, bottom-up approach to link dimensions of psychiatric illness with biological parameters, we may discover novel patterns and identify new targets for treatment.

The current results could implicate resting-state oscillations as a potential treatment target to improve cognition for patients with severe deficits. In fact, existing research shows that neurofeedback training to increase resting upper alpha power can improve cognitive performance⁵². Given the severe impact of cognitive impairment on general functioning and overall wellbeing, researchers and clinicians are calling for increased attention to cognitive deficits in psychiatric disorders. Some have suggested that efforts should be made to develop pharmacological therapies that specifically target cognitive deficits in psychiatric disorders⁵³. Efforts to identify the

neurobiological correlates of cognitive function may be the first step in the endeavor to develop such therapies and improve quality of life for patients.

Acknowledgements

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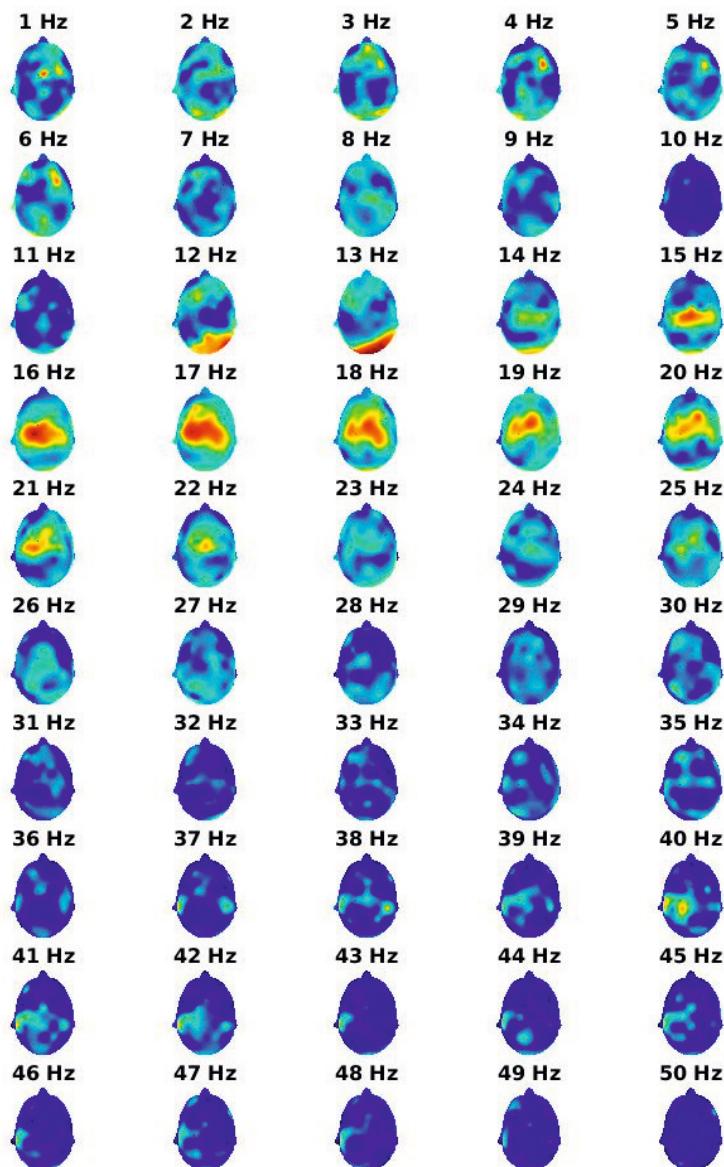
References

1. Millan MJ, Agid Y, Brüne M, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov.* 2012;11(2):141.
2. Nieman D. *Prevention in mental health care: Time for a new approach.* Routledge; 2016.
3. Marazziti D, Consoli G, Picchetti M, Carlini M, Faravelli L. Cognitive impairment in major depression. *Eur J Pharmacol.* 2010;626(1):83-86.
4. Robinson S, Goddard L, Dritschel B, Wisley M, Howlin P. Executive functions in children with autism spectrum disorders. *Brain Cogn.* 2009;71(3):362-368.
5. Penades R, Catalan R, Rubia K, Andres S, Salamero M, Gasto C. Impaired response inhibition in obsessive compulsive disorder. *Eur Psychiatry.* 2007;22(6):404-410.
6. Kurtz MM, Gerraty RT. A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. *Neuropsychology.* 2009;23(5):551.
7. Dickinson D, Harvey PD. Systemic hypotheses for generalized cognitive deficits in schizophrenia: a new take on an old problem. *Schizophr Bull.* 2009;35(2):403-414.
8. Kalkstein S, Hurford I, Gur RC. Neurocognition in schizophrenia. *Behavioral neurobiology of schizophrenia and its treatment.* 2010:373-390.
9. Barnett JH, Robbins TW, Leeson VC, Sahakian BJ, Joyce EM, Blackwell AD. Assessing cognitive function in clinical trials of schizophrenia. *Neurosci Biobehav Rev.* 2010;34(8):1161-1177.
10. Vaidya CJ, Stollstorff M. Cognitive neuroscience of attention deficit hyperactivity disorder: current status and working hypotheses. *Developmental disabilities research reviews.* 2008;14(4):261-267.
11. McNally RJ. Cognitive abnormalities in post-traumatic stress disorder. *Trends Cogn Sci.* 2006;10(6):271-277.
12. Burdick KE, Robinson DG, Malhotra AK, Szeszko PR. Neurocognitive profile analysis in obsessive-compulsive disorder. *J Int Neuropsychol Soc.* 2008;14(4):640-645.
13. Castaneda AE, Tuilio-Henriksson A, Marttunen M, Suvisaari J, Lönnqvist J. A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. *J Affect Disord.* 2008;106(1-2):1-27.
14. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry.* 2010.
15. Kotov R, Krueger RF, Watson D, et al. The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *J Abnorm Psychol.* 2017;126(4):454.
16. Buckholtz Joshua W, Meyer-Lindenberg A. Psychopathology and the Human Connectome: Toward a Transdiagnostic Model of Risk For Mental Illness. *Neuron.* 2012;74(6):990-1004.
17. Başar E, Başar-Eroglu C, Karakaş S, Schürmann M. Gamma, alpha, delta, and theta oscillations govern cognitive processes. *Int J Psychophysiol.* 2001;39(2-3):241-248.
18. Newson JJ, Thiagarajan TC. EEG frequency bands in psychiatric disorders: a review of resting state studies. *Front Hum Neurosci.* 2019;12:521.
19. Johannessen JK, Bi J, Jiang R, Kenney JG, Chen C-MA. Machine learning identification of EEG features predicting working memory performance in schizophrenia and healthy adults. *Neuropsychiatric electrophysiology.* 2016;2(1):1-21.
20. Nieman DH, Chavez-Baldini U, Vulink NC, et al. Protocol Across study: longitudinal transdiagnostic cognitive functioning, psychiatric symptoms, and biological parameters in patients with a psychiatric disorder. *BMC Psychiatry.* 2020;20(1):212.
21. CANTAB® [Cognitive assessment software] [computer program]. 2018.
22. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods.* 2004;134(1):9-21.
23. De Clercq W, Vergult A, Vanrumste B, Van Paesschen W, Van Huffel S. Canonical correlation analysis applied to remove muscle artifacts from the electroencephalogram. *Ieee T Bio-Med Eng.* 2006;53(12):2583-2587.
24. Breiman L. Random forests. *Mach Learn.* 2001;45(1):5-32.
25. Schmand B, Bakker D, Saan R, Louman J. The Dutch Reading Test for Adults: a measure of premorbid intelligence level. *Tijdschr Gerontol Geriatr.* 1991;22(1):15-19.

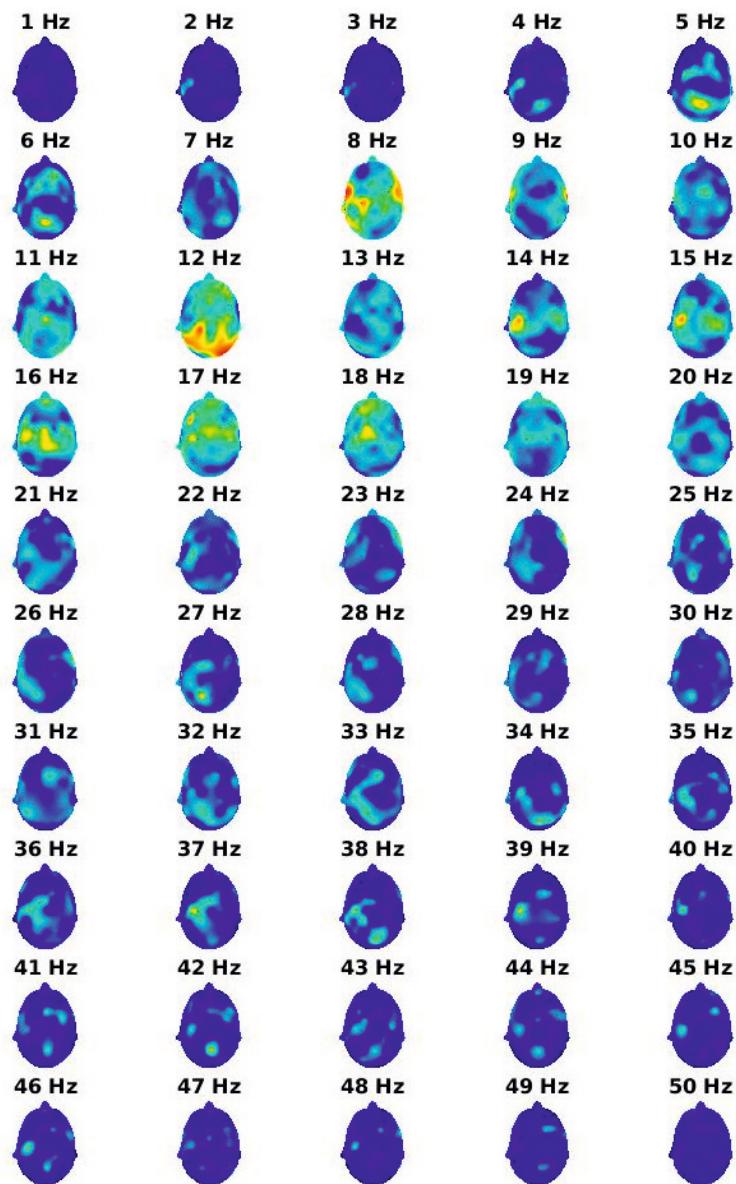
26. Vogt F, Klimesch W, Doppelmayr M. High-frequency components in the alpha band and memory performance. *J Clin Neurophysiol.* 1998;15(2):167-172.
27. Klimesch W, Doppelmayr M, Pachinger T, Ripper B. Brain oscillations and human memory: EEG correlates in the upper alpha and theta band. *Neurosci Lett.* 1997;238(1-2):9-12.
28. Mahjoory K, Cesnaite E, Hohlfeld FU, Villringer A, Nikulin VV. Power and temporal dynamics of alpha oscillations at rest differentiate cognitive performance involving sustained and phasic cognitive control. *Neuroimage.* 2019;188:135-144.
29. Prat CS, Yamasaki BL, Kluender RA, Stocco A. Resting-state qEEG predicts rate of second language learning in adults. *Brain Lang.* 2016;157-158:44-50.
30. Surwillo WW. The relation of simple response time to brain-wave frequency and the effects of age. *Electroencephalogr Clin Neurophysiol.* 1963;15:105-114.
31. Surwillo WW. The Relation of Decision Time to Brain Wave Frequency and to Age. *Electroencephalogr Clin Neurophysiol.* 1964;16:510-514.
32. Klimesch W, Doppelmayr M, Schimke H, Pachinger T. Alpha frequency, reaction time, and the speed of processing information. *J Clin Neurophysiol.* 1996;13(6):511-518.
33. Smit DJ, Posthuma D, Boomsma DI, De Geus EJ. Phenotypic and genetic correlations between evoked EEG/ERP measures during the response anticipation period of a delayed response task. *Psychophysiology.* 2009;46(2):344-356.
34. Palva JM, Monto S, Kulashekhar S, Palva S. Neuronal synchrony reveals working memory networks and predicts individual memory capacity. *Proc Natl Acad Sci U S A.* 2010;107(16):7580-7585.
35. Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Res Rev.* 2007;53(1):63-88.
36. Mathewson KE, Prudhomme C, Fabiani M, Beck DM, Lleras A, Gratton G. Making Waves in the Stream of Consciousness: Entrainment Oscillations in EEG Alpha and Fluctuations in Visual Awareness with Rhythmic Visual Stimulation. *J Cognitive Neurosci.* 2012;24(12):2321-2333.
37. Sadaghiani S, Kleinschmidt A. Brain Networks and proportional to-Oscillations: Structural and Functional Foundations of Cognitive Control. *Trends in Cognitive Sciences.* 2016;20(11):805-817.
38. Palva S, Palva JM. New vistas for alpha-frequency band oscillations. *Trends Neurosci.* 2007;30(4):150-158.
39. Baker SN. Oscillatory interactions between sensorimotor cortex and the periphery. *Curr Opin Neurobiol.* 2007;17(6):649-655.
40. Buschman TJ, Miller EK. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science.* 2007;315(5820):1860-1862.
41. Engel AK, Fries P. Beta-band oscillations--signalling the status quo? *Curr Opin Neurobiol.* 2010;20(2):156-165.
42. Gruber T, Keil A, Muller MM. Modulation of induced gamma band responses and phase synchrony in a paired associate learning task in the human EEG. *Neurosci Lett.* 2001;316(1):29-32.
43. Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Res Rev.* 1999;29(2-3):169-195.
44. Knyazev GG. EEG delta oscillations as a correlate of basic homeostatic and motivational processes. *Neurosci Biobehav Rev.* 2012;36(1):677-695.
45. Rossini PM, Rossi S, Babiloni C, Polich J. Clinical neurophysiology of aging brain: from normal aging to neurodegeneration. *Prog Neurobiol.* 2007;83(6):375-400.
46. Finnigan S, Robertson IH. Resting EEG theta power correlates with cognitive performance in healthy older adults. *Psychophysiology.* 2011;48(8):1083-1087.
47. Vlahou EL, Thurm F, Kolassa I-T, Schlee W. Resting-state slow wave power, healthy aging and cognitive performance. *Sci Rep.* 2014;4(1):1-6.
48. East-Richard C, R-Mercier A, Nadeau D, Cellard C. Transdiagnostic neurocognitive deficits in psychiatry: A review of meta-analyses. *Canadian Psychology/Psychologie canadienne.* 2019.
49. Caspi A, Houts RM, Belsky DW, et al. The p factor: one general psychopathology factor in the structure of psychiatric disorders? *Clinical Psychological Science.* 2014;2(2):119-137.
50. Padrao G, Mallorqui A, Cucurell D, Marco-Pallares J, Rodriguez-Fornells A. Neurophysiological differences in reward processing in anhedonics. *Cogn Affect Behav Neurosci.* 2013;13(1):102-115.
51. Pizzagalli DA. Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annu Rev Clin Psychol.* 2014;10:393-423.

52. Hanslmayr S, Sauseng P, Doppelmayr M, Schabus M, Klimesch W. Increasing individual upper alpha power by neurofeedback improves cognitive performance in human subjects. *Appl Psychophysiol Biofeedback*. 2005;30(1):1-10.
53. Etkin A, Gyurak A, O'Hara R. A neurobiological approach to the cognitive deficits of psychiatric disorders. *Dialogues Clin Neurosci*. 2013;15(4):419-429.
54. Hamilton M, Schutte N, Malouff J. Hamilton anxiety scale (HAMA). *Sourcebook of Adult Assessment: Applied Clinical Psychology*. 1976:154-157.
55. Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. *Behav Res Ther*. 1998;36(4):455-470.
56. Ising HK, Veling W, Loewy RL, et al. The validity of the 16-item version of the Prodromal Questionnaire (PQ-16) to screen for ultra high risk of developing psychosis in the general help-seeking population. *Schizophr Bull*. 2012;38(6):1288-1296.
57. Rush AJ, Giles DE, Schlessier MA, Fulton CL, Weissenburger J, Burns C. The inventory for depressive symptomatology (IDS): preliminary findings. *Psychiatry Res*. 1986;18(1):65-87.
58. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The inventory of depressive symptomatology (IDS): psychometric properties. *Psychol Med*. 1996;26(3):477-486.
59. Rombouts R, Van-Kuilenburg CJ. Hedonie, de ontwikkeling van een vragenlijst [Development of a questionnaire designed to measure hedonism]. *Gedrag en Gezondheid*. 1988;16:117-123.
60. Revelle WR. psych: Procedures for personality and psychological research. 2017.
61. R: A Language and Environment for Statistical Computing [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2020.
62. Costello AB, Osborne JW. Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. *Practical assessment, research & evaluation*. 2005;10(7):1-9.
63. Fabrigar LR, Wegener DT, MacCallum RC, Strahan EJ. Evaluating the use of exploratory factor analysis in psychological research. *Psychol Methods*. 1999;4(3):272.
64. Matsunaga M. How to factor-analyze your data right: do's, don'ts, and how-to's. *International Journal of Psychological Research*. 2010;3(1):97-110.
65. Netemeyer RG, Bearden WO, Sharma S. *Scaling procedures: Issues and applications*. Sage Publications; 2003.
66. Tabachnick B, Fidell L. Using Multivariate Statistics, Allyn and Bacon, Boston, MA. *Using Multivariate Statistics, 4th ed* Allyn and Bacon, Boston, MA. 2001:-.

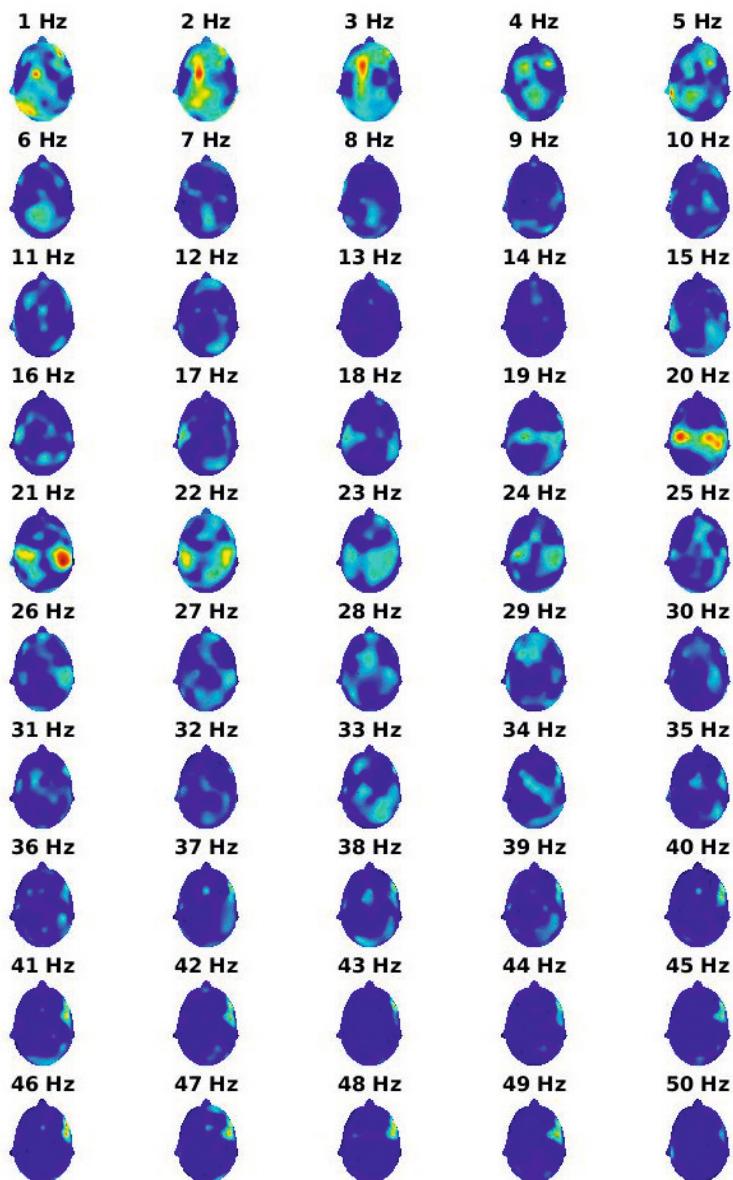
Supplementary Material



Supplementary Figure 1: Topography of PAL predictor importance at each frequency (1-50 Hz) in 1 Hz bins



Supplementary Figure 2: Topography of CRT predictor importance at each frequency (1-50 Hz) in 1 Hz bins



Supplementary Figure 3: Topography of IED predictor importance at each frequency (1-50 Hz) in 1 Hz bins

Supplementary Table 1. Medications and dosages

Medication type	Total	MDD	BP	PSY	OCD	GAD	ASD	Num-Dosage ber (mg) mean (%) (SD)	ID-NOS				
	Num-Dosage ber (%) (SD)	Num-Dosage ber (%) (SD)	Num-Dosage ber (%) (SD)	Num-Dosage ber (%) (SD)	Num-Dosage ber (%) (SD)	Num-Dosage ber (%) (SD)							
SSRIs	37 (17.1)	73.5 (72.1)	9 (26.5) (52.1)	72.2	—	—	—	8 (16.3) (69.1)	70.0 (44.4) (61.8)	4 (62.5)	—	—	16 (81.3) (91.0)
TCAs	3 (1.4)	158.3 (62.9)	1 (2.9) (0.0)	100.0	—	—	—	1 (2.0) (0.0)	150.0 (0.0)	—	—	—	1 (225.0) (0.0)
MAOIs	1 (0.5)	70.0 (0.0)	—	—	—	—	—	—	—	—	—	—	1 (70.0) (1.0)
Typical antipsychotics	3 (1.4)	2.7 (1.5)	1 (2.9) (0.0)	3.0	—	—	1 (6.6) (0.0)	4.0 (2.0) (0.0)	1 (1.0) (0.0)	—	—	—	—
Atypical antipsychotics	14 (6.5)	156.2 (227.0)	1 (2.9) (0.0)	400.0	1 (25.0) (0.0)	10.0	8 (53.3) (268.0)	196.5 (6.0) (114.6)	3 (67.7)	—	—	—	1 (2.0) (0.0)
Benzodiazepines	6 (2.8)	7.8 (7.2)	1 (2.9) (0.0)	1.0	—	—	—	—	1 (2.0) (0.0)	20.0	—	—	—
Psychostimulants	2 (0.9)	25.0 (21.2)	1 (2.9) (0.0)	10.0	—	—	—	—	—	—	—	—	1 (40.0) (1.0)
Anticonvulsants	2 (0.9)	45.0 (212.1)	2 (2.9) (212.1)	450.0	—	—	—	—	—	—	—	—	—
All medications	68 (31.5)	93.7 (138.3)	16 (47.1)	129.0	1 (25.0) (0.0)	10.0	9 (60.0) (258.7)	175.1 (28.6) (75.1)	14 (44.4) (61.8)	66.7	4 (62.5)	—	24 (69.3) (23.8) (86.5)

Note: MDD = Major depressive disorder; BP = Bipolar disorder; PSY = Psychosis spectrum disorders; OCD = Obsessive-compulsive disorder; GAD = Generalized anxiety disorder; ASD = Autism spectrum disorder; ID-NOS = Impulse-control disorder, not otherwise specified (misophonia); SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; MAOIs = monoamine oxidase inhibitor

Medication Effects

We investigated whether medication effects influenced relationships between EEG predictors and cognitive outcomes. This was to ensure that random forest regression results were not driven by stronger predictor-outcome relationships within a medicated (or unmedicated) subset of the sample. We selected EEG predictors by selecting each frequency peak identified for each cognitive test and calculating average power across the top three channels with highest predictor importance. This resulted in three EEG predictors per cognitive test. We then performed an ANCOVA for each EEG predictor to test for slope differences in predictor-outcome relationships among unmedicated patients ($n=148$), patients taking SSRIs ($n=37$), and patients taking atypical antipsychotics ($n=14$). Other medication classes were not included in the analysis due to small sample sizes. Slopes did not differ significantly among groups for any of the predictor-outcome effects.

Supplementary Table 2 shows ANCOVA results.

Supplementary Table 2. ANCOVA Test of predictor-outcome slope differences among medication classes

		Unmedicated	SSRIs	Antipsychotics	$F(2,210)$	p-value
		β (SE)	β (SE)	β (SE)		
PAL	6 Hz	-0.64 (0.34)	0.37 (0.45)	-0.13 (0.51)	1.45	0.24
	13 Hz	-0.46 (0.18)	0.20 (0.23)	-0.02 (0.27)	2.54	0.08
	17 Hz	0.24 (0.32)	1.16 (0.39)	0.72 (0.55)	1.75	0.18
CRT	8 Hz	0.31 (0.29)	0.67 (0.33)	-0.36 (0.49)	0.96	0.38
	12 Hz	-0.14 (0.19)	-0.21 (0.23)	-0.65 (0.30)	0.66	0.52
	17 Hz	0.37 (0.39)	0.99 (0.46)	1.24 (0.69)	0.99	0.37
IED	2 Hz	-0.36 (0.40)	-1.35 (0.50)	-1.02 (0.64)	1.34	0.27
	5 Hz	-0.39 (0.39)	-1.04 (0.50)	-0.52 (0.59)	0.46	0.63
	22 Hz	0.07 (0.35)	1.11 (0.42)	0.81 (0.57)	2.81	0.06

Effects of diagnosis on predictor-outcome relationships

Due to the large percentage of ID-NOS patients in the sample, we investigated whether relationships between EEG predictors and cognitive outcomes differed between ID-NOS patients and the rest of the sample. This was to ensure that random forest regression results were not driven by stronger predictor-outcome relationships within a subset of the sample. Using the same EEG predictors described above, we performed an ANCOVA for each EEG predictor to test for slope differences in predictor-outcome relationships between ID-NOS and non-ID-NOS patients. Slopes did not differ significantly between ID-NOS and non-ID-NOS patients for any of the predictor-outcome effects. Supplementary Table 3 shows ANCOVA results.

While we tested whether cognitive performance differed among diagnostic groups, three diagnostic groups (BP, ASD, and GAD) were not included in the analysis due to their small sample sizes. To ensure that random forest regression results were not driven by these smaller groups, which in some cases had more extreme cognitive scores, we repeated the random forest regression and permutation procedure with only larger diagnostic groups included. All models still performed significantly better than chance, with the significance threshold at $p=.0167$ (.05/3 to correct for number of tests): PAL: NSE = .033, $p = .0060$; CRT: NSE = .0151, $p = .0155$; IED: NSE = .018, $p = .0135$. While model performance decreased somewhat for all tests, this may be due in part to the lower sample size.

Supplementary Table 3. ANCOVA test of predictor-outcome slope differences between ID-NOS and non-ID-NOS patients

		ID-NOS	Other diagnoses	F (1, 212)	p-value
		β (SE)	β (SE)		
PAL	6 Hz	-0.59 (0.22)	-0.26 (0.22)	0.60	0.44
	13 Hz	-0.24 (0.12)	-0.28 (0.12)	0.02	0.88
	17 Hz	0.45 (0.17)	0.59 (0.17)	0.16	0.69
CRT	8 Hz	0.01 (0.17)	0.59 (0.17)	3.01	0.08
	12 Hz	-0.15 (0.12)	-0.19 (0.12)	0.03	0.87
	17 Hz	0.31 (0.20)	0.66 (0.20)	0.78	0.38
IED	2 Hz	-0.28 (0.24)	-0.77 (0.24)	1.02	0.31
	5 Hz	-0.25 (0.24)	-0.66 (0.24)	0.72	0.40
	22 Hz	0.27 (0.20)	0.21 (0.20)	0.02	0.89

Symptom Dimensions

Objective

Questionnaires on psychiatric symptoms often capture various underlying components of a psychiatric disorder and symptoms can cut across disorders, meaning that using sum-scores be inefficient as they can lead to a loss of information, such as on heterogeneity (i.e., two individual with the same score can endorse different symptoms). Furthermore, a questionnaire on depressive symptoms, for instance, could also ask about anxiety symptoms, and vice versa, potentially inflating comorbidity. The objective of this analysis was to identify transdiagnostic symptom dimensions by investigating the underlying structure of individual items of self-report psychiatric symptom questionnaires using data from participants with psychiatric disorders. Performing a factor analysis on individual symptoms of questionnaires can group related symptoms into smaller transdiagnostic dimensions, which could potentially be more precise than using sum-scores of categorical disorders.

Materials and methods

Sample

955 participants with psychiatric disorders from the Across study (Nieman et al., 2020). 45.1% of the sample were men and the mean age was 34.86 years ($SD = 14.36$). Inclusion criteria were: age 14-75 years, ability to give informed consent, have a DSM-IV-TR or DSM-5 diagnosis, clinically stability, and fluency in Dutch. Exclusion criteria were: high risk of suicide, unstable medical disorder, premorbid IQ < 70, history of seizure or clinically significant abnormality of the neurological system. Informed consent is obtained from patients and their parents if patients are underage. Patients are able to discontinue participation from the study at any time.

Materials

*Hamilton Anxiety Scale (HAM-A)*⁵⁴. The HAM-A assesses the severity of somatic, cognitive, and affective symptoms of anxiety with 13 items. It consists of two subscales, psychological anxiety and somatic anxiety, and demonstrates good interrater reliability.

*Social Interaction Anxiety Scale (SIAS)*⁵⁵. The SIAS measures anxiety in social interactions and fear of scrutiny by others with the 20-item and demonstrates high levels of internal consistency ($\alpha = 0.94$), test-retest reliability at 12 weeks ($r = 0.92$), and sensitivity to change with treatment (Mattick & Clarke, 1998).

*Prodromal Questionnaire-16 (PQ-16)*⁵⁶. The occurrence and severity of At Risk Mental State symptoms for a first psychosis is assessed with the PQ-16. It consists of 2 items on negative symptoms, 5 items on unusual thought content/delusional ideas/paranoia, and 9 items on perceptual abnormalities/hallucinations. Cronbach's alpha for the total score was 0.77 and all item-total correlations were at least 0.31⁵⁶.

*Inventory of Depressive Symptomatology Self-Report (IDS-SR 30)*⁵⁷. The IDS measures the severity of depressive symptoms pertaining to mood, cognition, suicidality, arousal, and sleep with 30 items. It demonstrates good internal consistency ($\alpha = 0.85$) and is applicable for different types of depression⁵⁸.

*Hedonism Scale*⁵⁹. The Hedonism Scale consists of 21 items and measures the degree of pleasure from physical activity, hearing, seeing, touching, tasting, sex and smelling.

Statistical analysis

An exploratory factor analysis (EFA) was conducted for data reduction using the *psych* package version 1.7.8⁶⁰ of the R statistical program⁶¹. A correlation matrix was first created and tested with the Kaiser-Meyer-Olkin (KMO) test and Bartlett's Test of Sphericity to

determine the suitability of the items and data for EFA. Principal axis factoring was used as the extraction method due to the significantly non-normal distribution of the items⁶²⁻⁶⁴. The number of factors retained was determined with parallel analysis, and oblique rotation was used to allow for correlation among factors^{62,64} as it is reasonable to expect this. The cut-off score for each item factor loading was 0.30⁶². Items with a communality lower than 0.3 were removed. From the parallel analysis, factor reduction was determined by the absence of Heywood cases (i.e., in which the communality is greater than or equal to 1) and a minimum of three items per factor.

Results

As per the KMO test, the overall Measure of Sampling Adequacy (MSA) for the correlation matrix of 46 items was 0.96, which is deemed adequate^{65,66}. Furthermore, the Bartlett's Test of Sphericity was significant, demonstrating the suitability of the sample for analysis.

The parallel analysis identified 7 factors, which were reduced to 5, labelled: Social/Interpersonal, Depressive, Somatic, Anxious, and Anomalous. The factor loadings are shown in Table 1.

Supplementary Table 4. Factor Loadings

Item	Social/ Inter- personal	Depres- sive	Somatic	Anxious	Anoma- lous
I felt uninterested in the things I used to enjoy (PQ-16)	0.02	0.68	0.01	-0.07	0.11
I get extremely worried when I first meet people (PQ-16)	0.53	0.04	0.00	0.05	0.21
I have seen things that other people apparently can't see (PQ-16)	-0.01	0.08	0.01	-0.03	0.60
I have heard things other people can't hear like voices of people whispering or talking (PQ-16)	0.06	0.06	0.04	-0.06	0.55
I have had the sense that some person or force is around me, even though I could not see anyone (PQ-16)	0.07	0.06	0.05	0.03	0.55
Feeling Sad (IDS-SR)	0.07	0.61	-0.04	0.28	-0.05
Feeling Anxious or Tense (IDS-SR)	0.11	0.16	0.09	0.59	-0.07
Response of Your Mood to Good or Desired Events (IDS-SR)	0.02	0.60	-0.04	0.15	0.07
Concentration/Decision Making (IDS-SR)	0.10	0.45	0.06	0.15	-0.04
View of Myself (IDS-SR)	0.23	0.41	-0.05	0.18	-0.08
View of My Future (IDS-SR)	0.10	0.60	0.03	0.09	-0.11
Thoughts of Death or Suicide (IDS-SR)	0.08	0.57	-0.01	0.08	-0.01
General Interest (IDS-SR)	-0.01	0.77	0.05	-0.01	0.09
Energy Level (IDS-SR)	0.03	0.45	0.27	0.08	0.04
Capacity for Pleasure or Enjoyment (excluding sex) (IDS-SR)	-0.01	0.75	0.08	0.03	0.09

Supplementary Table 4. (continued)

Item	Social/ Inter- personal	Depres- sive	Somatic	Anxious	Anoma- lous
Interest in Sex (IDS-SR)	0.05	0.55	0.09	-0.06	-0.06
Aches and pains (IDS-SR)	0.03	0.05	0.66	-0.07	-0.11
Other bodily symptoms (IDS-SR)	0.01	-0.01	0.66	0.07	0.06
Panic/Phobic symptoms (IDS-SR)	0.00	-0.06	0.15	0.62	0.04
Interpersonal Sensitivity (IDS-SR)	0.42	0.06	0.08	0.23	-0.06
I get nervous if I have to speak with someone in authority (SIAS)	0.63	-0.01	0.04	0.08	-0.02
I have difficulty making eye contact with others (SIAS)	0.62	0.02	0.00	0.03	0.18
I become tense if I have to talk about myself or my feelings (SIAS)	0.58	0.08	0.04	0.03	-0.06
I find it difficult to mix comfortably with the people I work with (SIAS)	0.61	0.09	-0.03	0.12	0.05
I find it easy to make friends my own age (SIAS)	0.57	0.16	0.03	-0.18	-0.08
I tense up if I meet an acquaintance in the street (SIAS)	0.66	0.00	-0.11	0.14	0.15
When mixing socially, I am uncomfortable (SIAS)	0.71	0.09	0.06	-0.03	0.00
I feel tense if I am alone with just one other person (SIAS)	0.64	0.02	-0.02	0.09	0.07
I am at ease meeting people at parties, etc (SIAS)	0.57	0.24	0.06	-0.16	-0.09
I have difficulty talking with other people (SIAS)	0.73	0.11	0.01	-0.11	0.01
I find myself worrying that I won't know what to say in social situations (SIAS)	0.75	0.01	-0.01	-0.02	0.00
I am nervous mixing with people I don't know well (SIAS)	0.83	-0.05	0.03	-0.03	-0.05
When mixing in a group, I find myself worrying I will be ignored (SIAS)	0.76	-0.10	0.01	0.04	-0.10
I am tense mixing in a group (SIAS)	0.82	-0.03	0.06	0.03	-0.04
I am unsure whether to greet someone I know only slightly (SIAS)	0.71	-0.11	-0.02	0.06	0.11
Anxious mood (HAM-A)	0.04	0.12	0.06	0.71	0.01
Tension (HAM-A)	0.07	0.22	0.11	0.59	0.00
Fears (HAM-A)	0.04	0.00	0.07	0.68	0.03
Insomnia (HAM-A)	-0.04	0.21	0.46	0.03	-0.02
Depressed mood (HAM-A)	0.06	0.50	0.04	0.37	-0.07
Somatic (muscular) (HAM-A)	0.01	0.10	0.65	-0.07	-0.06
Somatic (sensory) (HAM-A)	-0.01	0.00	0.65	0.06	0.09
Cardiovascular symptoms (HAM-A)	0.00	-0.05	0.60	0.13	0.04
Respiratory symptoms (HAM-A)	0.09	-0.12	0.56	0.09	0.10
Gastrointestinal symptoms (HAM-A)	0.06	-0.10	0.48	0.14	0.01
Hedonism (Hedonism Scale)	-0.04	-0.61	0.02	0.09	0.06
SS loadings	8.36	5.82	3.54	3.47	1.25
Proportion variance	0.18	0.13	0.08	0.08	0.03

Note: PQ-16 = Prodromal Questionnaire-16, IDS-SR= Inventory of Depressive Symptomatology Self-Report, SIAS= Social Interaction Anxiety Scale, HAM-A= Hamilton Anxiety Scale. Loadings above 0.3 are bolded.



5

The interplay between psychopathological symptoms: A transdiagnostic cross-lagged panel network model

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Abstract

Background

Recent paradigm shifts suggest that psychopathology manifests through dynamic interactions between individual symptoms.

Aims

To investigate the longitudinal relationships between symptoms in a transdiagnostic sample of patients with psychiatric disorders.

Method

A two-wave, cross-lagged panel network model of 15 nodes representing symptoms of depression, (social) anxiety and attenuated psychotic symptoms was estimated, using baseline and 1-year follow-up data of 222 individuals with psychiatric disorders. Centrality indices were calculated to determine important predictors and outcomes.

Results

Our results demonstrated that the strongest relationships in the network were between (a) more suicidal ideation predicting more negative self-view, and (b) autoregressive relationships of social anxiety symptoms positively reinforcing themselves. Negative self-view was the most predictable node in the network as it had the highest 'in-expected influence' centrality, and may be an important transdiagnostic outcome symptom.

Conclusions

The results give insight into longitudinal interactions between symptoms, which interact in ways that do not adhere to broader diagnostic categories. Our results suggest that self-view can also be a transdiagnostic outcome of psychopathology rather than just a predictor, as is normally posited, and may especially have an important relationship with suicidal ideation. Overall, our study demonstrates the dynamic complexity of psychopathology, and further supports the importance of investigating symptom interactions of different psychopathological dimensions over time and across disorders.

Keywords: *transdiagnostic; longitudinal; network analysis; psychopathology; symptom network*

Introduction

The conceptualization of psychopathology has shifted over the last decade to a dynamic systems perspective, in which a disorder is the result of the dynamic interactions between various mechanisms^{1,2}. This dynamic systems perspective is embodied in the network approach, which posits that psychopathology arises from a network of symptoms that interact over time³. While the dynamic systems perspective and network approach have gained more traction, there is still little research investigating psychopathology as a dynamic system transdiagnostically, which acknowledges that symptoms can cut across diagnoses. A study assessing the network structure of symptoms from 12 DSM-IV diagnoses in a community sample found that some symptoms of one disorder were also connected to symptoms of different disorders⁴. Networks with a variety of symptom across various disorders should therefore be further investigated. Additionally, to investigate the dynamic nature of psychopathology, it is important to move cross-sectional to longitudinal network designs, such as temporal, contemporaneous, or cross-lagged panel networks e.g.,^{5,6}. This could give insight into the interplay of psychopathological dimensions over time at the symptom level by elucidating how observations at one time point predict observations at the next time point and into transdiagnostic mechanisms by identifying symptoms that play a predictive or influential role in the network⁷. This could also elucidate important symptom-symptom interactions, which could indicate potential causal relationships and points of intervention to disrupt negative processes⁶.

Relationships between psychopathological symptoms

Some core symptom dimensions of psychopathology include depression, anxiety, and psychotic-like symptoms, which may be considered transdiagnostic. Depressive and anxiety symptoms are often reported in patients with various disorders e.g.,^{8,9}, and psychotic-like experiences can also occur in patients with non-psychotic disorders¹⁰. Previous cross-sectional networks demonstrated relationships between (social) anxiety and depression symptoms^{11,12} and between psychotic and depression symptoms¹³. In a cross-sectional network analysis with a transdiagnostic sample, we found that sum-scores of depression, (social) anxiety, and sub-clinical psychotic symptom dimensions were all interrelated¹⁴. It remains necessary, however, to investigate these relationships over time.

Study aims

The present study therefore investigated two-wave longitudinal relationships over an average of 12 months between individual depression, (social) anxiety, and attenuated

psychotic symptoms in a transdiagnostic sample of patients with various psychiatric disorders. The aim was to investigate how symptoms impact each other over time and to identify important predictor and outcome symptoms. We modelled the longitudinal relationships between symptoms with a cross-lagged panel network (CLPN) and investigated the predictability and influence of each item in the network. It was hypothesized that individual symptoms will interact in ways that do not adhere to broader diagnostic categories.

Methods

Sample

The sample consisted of 222 patients with psychiatric disorders recruited during intakes at the outpatient clinic of the Department of Psychiatry at the Amsterdam University Medical Centers (UMC), location Academic Medical Center (AMC), which is an expertise center for misophonia, early psychosis, anxiety, and depressive disorders. 1134 patients participated in the first measurement, of which 304 completed the follow-up measurement. 82 were excluded because the follow-up measure was not completed within the appropriate time frame.

Inclusion criteria were: age 14-75 years, ability to give informed consent, having a *DSM-IV-TR* or *DSM-V* diagnosis, fluent in Dutch, and completion of follow-up measurement between 6 to 18 months. Exclusion criteria were: acute high risk of suicide (i.e., suicidal behavior requiring immediate and urgent attention), unstable medical disorder, premorbid IQ<70, history of seizure or clinically significant abnormality of the neurological system.

Procedure

The Across study is an ongoing, longitudinal research project that collects data on cognitive functioning, psychopathology symptoms, and biological parameters (<https://osf.io/yhvtb/>). The full study procedure is described in Nieman, Chavez-Baldini, Vulink, Smit, van Wingen, de Koning, Sutterland, Mocking, Bockting, Verweij, Lok, Denys ¹⁵. After an intake at the Department of Psychiatry of the Amsterdam UMC, location AMC, patients were invited to participate in the study after being briefed. This study was performed in accordance with the Declaration of Helsinki and was approved by Medical Ethical Review Committee and the Biobank Review Committee of the Amsterdam UMC (ABR no. NL55751.018.15). All participants and all parents or guardians of minors provided written informed consent to participate in this study. Participants were able to participate at any point of their clinical trajectory (e.g., before, during, or after treatment) and could discontinue participation from

the study or parts of the study at any time. For the one-year follow-up, additional consent was obtained.

Participants filled in questionnaires on psychopathological symptoms on a computer, which took 30 minutes to an hour to complete. The current study had a two-wave longitudinal design and used baseline (T1) and one-year follow-up (T2) questionnaires data.

Measures

Psychopathological symptoms included in this study were assessed with the Hamilton Anxiety Scale (HAM-A), the Social Interaction Anxiety Scale (SIAS), the Inventory of Depressive Symptomatology Self-Report (IDS-SR₃₀), which are validated and psychometrically-sound questionnaires. Moreover, we administered the Psychiatric Dimensions Questionnaire, which was developed at the Amsterdam UMC¹⁶. The HAM-A measures the severity of somatic, cognitive, and affective symptoms of anxiety¹⁷. It consists of 13 items that are rated on a scale of 0 (not present) to 4 (severe). The SIAS assesses anxiety in social interactions and fear of scrutiny by others¹⁸. It consists of 20 items and each item is rated on a scale of 0 (not at all characteristic of me) to 4 (extremely characteristic of me). The IDS-SR measures the severity of depressive symptoms pertaining to mood, cognition, arousal, suicidality, and sleep¹⁹. It consists of 30 items that are rated on a scale from 0 (symptom is not present) to 3 (strongest impairment). The Psychiatric Dimensions Questionnaire consists of 26 items and assesses a variety of transdiagnostic concepts that are commonly affected in patients with a psychiatric disorder: affect, volition, identity, cognition, reality, and vitality^{15,16}. Only items from the Reality subscale, in which participants rate questions pertaining to attenuated psychotic symptoms, i.e., exceptional experiences and anomalous self-experiences, on a scale of 0 (never) to 8 (continuously), are included in the network. Exceptional experiences and anomalous self-experiences refer to experiential deviations, such as déjà-vu, inexplicable auditory or visual perceptions, or difficulty in grasping taken-for-granted meanings^{20,21}. Other subscales items were not included because they are covered by the other questionnaires or were not part of the aforementioned core dimensions. Only the psychological items from the questionnaires were included, meaning any somatic or physical symptoms were excluded.

Age, gender, diagnostic category, and presence of treatment were included as covariates in the network. Age and gender were obtained from a demographic questionnaire. Diagnostic category and treatment were obtained from the participants' medical records. The diagnosis is determined by a psychiatrist and categorized into 7 categories: schizophrenia spectrum and other psychotic disorders, depressive disorders, anxiety disorders, obsessive-compulsive and

related disorders, impulse-control disorder NOS (misophonia), bipolar disorder, and other disorders. Specific diagnoses under each category can be viewed in Table S1 in the Supplementary materials. Presence of treatment was measured with two variables: treatment at T1 with 0= no treatment before or during the research phase and 1= started treatment before T1, and treatment between T1 and T2 with 0= no treatment before or during the research phase and 1= started treatment between T1 and T2. Treatment included both psychotropic medication use (e.g., anti-depressants) and psychological treatment or support (e.g., cognitive-behavioral therapy).

Individual items that were used in the analyses can be viewed in Table 1. Each node represents a single item from a questionnaire, except for three items which were combined, which is indicated in the rightmost column. A two-step item selection procedure was performed before the analyses using content-based selection as recommended by Rhemtulla, van Bork, Cramer²² and weighted topological overlap approach, which is detailed in the Supplementary Appendix 1. This reduced the total number of items from 79 to 15.

Table 1. Symptom nodes and labels

Node	Label	Items	Measure (item no.)
Cog	Cognitive problems	Concentration/Decision Making; Intellectual: Difficulty in concentration, poor memory	IDS-SR (15) + HAM-A (5)
WAD	Weight/appetite decrease	Change in appetite: decreased; Change in weight: decreased	IDS-SR (11 + 13)
WAI	Weight/appetite increase	Change in appetite: increased; Change in weight: increased	IDS-SR (12 + 14)
Ealn	Early insomnia	Falling asleep	IDS-SR (1)
HyIn	Hypersomnia	Sleeping too much	IDS-SR (4)
EaWa	Early/frequent wakening	Sleep during the night; Waking up too early	IDS-SR (2 + 3)
Sad	Sad	Feeling sad	IDS-SR (5)
Self	Self-view	View of myself (Negative) ^a	IDS-SR (16)
Sui	Suicidality	Thoughts of death or suicide ^b	IDS-SR (18)
Int	Interest	General interest (negative)	IDS-SR (19)
Ener	Energy	Energy level (negative)	IDS-SR (20)
Ret	Psychomotor retardation	Feeling slowed down	IDS-SR (23)
Agi	Psychomotor agitation	Feeling restless	IDS-SR (24)
EyCon	Difficulty making eye contact	I have difficulty making eye contact with others.	SIAS (2)
DifCo	Difficulty mixing with co-workers	I find it difficult to mix comfortably with the people I work with.	SIAS (4)
SocT	Social tension	I tense up if I meet an acquaintance in the street; I feel tense if I am alone with just one other person.	SIAS (6 + 8)

Table 1. (continued)

Node	Label	Items	Measure (item no.)
Talk	Difficulty talking with others	I have difficulty talking with other people.	SIAS (10)
Dis	Difficulty disagreeing	I find it difficult to disagree with another's point of view.	SIAS (13)
AnxT	Anxious tension	Anxious mood: Worries, anticipation of the worst, fearful anticipation, irritability; Tension: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.	HAM-A (1 + 2)
Fear	Fears	Fears: Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.	HAM-A (3)
Som	Somatic (muscular)	Somatic (muscular): Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.	HAM-A (7)
PerAn	Perceptual anomalies	To what extent can you perceive things that others cannot perceive?	Dimensions (10)
Perplx	Perplexity; Lack of natural self-evidence	Do you feel that the natural self-evidence of the world around you has been lost? Do you have the profound experience that you have to think about the most obvious things, such as about everyday actions or objects?	Dimensions (11 + 12)
AbSal	Aberrant salience	Has your perception changed, making everything more meaningful?	Dimensions (13)
Threat	Feeling threatened or paranoid	Do you feel that others want to harm you?	Dimensions (14)

Note: In the "Measure (item no.)" column, the questionnaire and the item number that each node represents is noted. Variables are coded so that a higher score on an item implies greater severity.

Abbreviations: IDS-SR= Inventory of Depressive Symptomatology Self-Report, SIAS= Social Interaction Anxiety Scale, HAM-A= Hamilton Anxiety Scale, Dimensions = Psychiatric Dimensions Questionnaire.

^aView of myself is measured negatively with higher scores depicting a more negative self-view based on self-blaming and ruminating on personal shortcomings and defects.

^bSuicidality is a broad concept and is measured as suicidal ideation and intent. It ranges in mild infrequency of thoughts of death and suicide to more severe suicidal intent, such as making plans or attempting suicide.

Statistical Analyses

Analyses were performed in R version 3.6.1 ²³. We modelled the longitudinal relationships between variables with a cross-lagged panel network (CLPN), a model designed by Rhemtulla, van Bork, Cramer ²², which combines network modeling with cross-lagged panel modeling. This allows individual items to impact other items over time using two-wave panel data by measuring cross-lagged (i.e., the effect of a symptom at T1 on another symptom at T2) and autoregressive (i.e., the effect of a symptom at time 1 on itself at time 2) effects. Age at T1, gender, diagnostic category, and treatment were included as covariates. 22 participants had missing data, which was missing at random according to Little's MCAR test ($\chi^2=130.55$, DF= 155, p= 0.92).

CLPN modeling requires complete case analysis, so missing data was imputed using random forest imputation algorithm implemented with the R-package *missForest*²⁴.

To estimate the CLPN, we computed auto-regressive and cross-lagged coefficients with a series of regularized regressions using the penalized maximum likelihood with a LASSO penalty²⁵. This results in a sparse network, which reduces overfitting and false positive edges by shrinking all edge weights and setting the smallest to zero. The network was estimated with the R-package *glmnet*²⁶. After estimation, the network was visualized as a directed network with the R-package *qgraph*²⁷. Arrows demonstrate the direction of temporal relationships: green arrows represent positive relationships, red arrows represent negative relationships, and thicker lines represents stronger relationships between nodes. Placement of the nodes is determined by the Fruchterman-Reingold algorithm²⁸, in which nodes that are more connected are placed closer together.

Two measures of centrality were computed using the R-package *bootnet*²⁹: cross-lagged out expected influence (out-EI) and cross-lagged in-expected influence (in-EI). Out-EI is calculated as the sum of all outgoing edge strengths connected to a node, measuring how much a node influences other nodes. In-EI is calculated as the sum of all incoming edge strengths connected to a node, measuring how much a node is influenced by other others. Clinically, out-EI could be considered a treatment target whereas in-EI could be considered an important treatment outcome.

Stability checks were conducted to assess the accuracy of edge weights, differences between edges and centralities, and the stability of centralities using *bootnet* as detailed in Epskamp, Borsboom, Fried²⁹ and with a custom function developed by Funkhouser, Chacko, Correa, Kaiser, Shankman⁵.

As sensitivity analyses, a control network without misophonia was estimated, given that it was the largest group (39.6% of the sample) and may impact the whole sample estimates. Centralities were computed and stability checks were conducted for this control network. Similarities between the main and control network were evaluated using the correlation between edge lists as a global measure of network similarity, the percentage of individual edges that are replicated, correlations of centralities between networks, and replication of the most central symptoms.

Results

Sample characteristics

Data from 222 participants collected between 2012 and 2022 were included in the analyses. The distribution of the primary diagnosis reflects the naturalistic patient population of the Amsterdam UMC. Sample characteristics can be seen in Table 2. Symptom variables scores are shown in Table S2 in the Supplementary materials. Furthermore, participants who completed both measurements were compared to participants who completed only the first measurement as a sensitivity analysis. Results can be viewed in Table S4 of the Supplementary Materials. There was a significant difference in age and in the distribution of diagnosis and medication. Except for feeling threatened or paranoid, there were no significant differences in symptom severity.

Table 2. Demographic and clinical characteristics of participants

Characteristics	Baseline
Age (years), mean (SD)	
Baseline	39.1 (15.6)
Follow-up	40.1 (15.6)
Months between measures, mean (SD)	12.1 (2.7)
Gender, women, No. (%)	117 (55.5)
Completed education ^a , No. (%)	
Low	19 (9.0)
Middle	49 (23.2)
High	134 (63.5)
Unknown	9 (4.3)
DSM diagnostic category, No. (%)	
Schizophrenia spectrum and other psychotic disorders	17 (8.9)
Depressive disorder	34 (16.1)
Anxiety disorder	9 (4.3)
Obsessive-compulsive and related disorders	37 (17.5)
Misophonia (Impulse-control disorder NOS)	86 (40.8)
Bipolar disorder	14 (6.6)
Other disorders	11 (5.2)
Comorbidity, No. (%)	50 (23.7)
Presence of treatment, No. (%)	
None	13 (6.2)
Before T1	147 (69.7)
Between T1 and T2	51 (24.2)

Table 2. (continued)

Characteristics	Baseline
Medication, No. (%)	
Antidepressants	57 (27.0)
Antipsychotics	24 (11.4)
Benzodiazepines	3 (1.4)
Psychostimulants	4 (1.9)
Mood stabilizers	4 (1.9)
Other (non-psychotropic) ^b	42 (19.9)
None	77 (36.5)
Psychotherapy and treatments, No. (%) ^c	
Evidence-based treatments	167 (79.2)
Supplementary or alternative interventions	153 (72.5)

Note: SD= standard deviation, DSM= Diagnostic and Statistical Manual of Mental Disorders, NOS= not otherwise specified.

^a Based on the Verhage coding of educational levels: low (1 through 4: less than or equal to primary education or low-level secondary education), middle (5: average-level secondary education), high (6 and 7: high-level secondary education or university degree).

^b Other medication includes: anti-inflammatory, anti-histamines, anti-epilepsy, contraceptives, cholesterol medication, corticosteroids, dopamine-agonists, and various supplements.

^c Participants often followed multiple types of treatment. Evidence-based treatments include cognitive and behavioral therapies, trauma therapies, system therapy, schema therapy, and psychotherapies. Supplementary or alternative interventions include talk therapy, counseling, coaching, expressive or creative therapies, skills trainings, psychodynamic therapy, reintegration support, peer support, ambulant care, and lifestyle interventions.

Cross-lagged Panel Network Analysis

The CLPN of psychopathological symptoms is visualized in Figure 1, which presents cross-lagged and autoregressive relationships.

All nodes had at least one connection to another node, whether as predictor or outcome, resulting in 79 non-zero cross-lagged edges of which 92.4% were positive. The strongest cross-lagged edge was between more baseline suicidal ideation (SI) predicting higher follow-up negative self-view ($B = 0.36$). The strongest autoregressive relationships pertained to social anxiety items: difficulty making eye contact ($B = 0.57$), difficulty disagreeing with others ($B = 0.54$), and social tension ($B = 0.53$). These were observed as the strongest edges in the matrix of the edge weights (i.e., regression coefficients), which can be seen in Table S3. There are some other notable connections representing potential feedback loops between sadness and suicidal ideation, between difficulty disagreeing with others and difficulty mixing with coworkers, between feeling threatened (paranoia) and difficulty disagreeing with others, and between feeling threatened and difficulty making eye contact. These are expanded upon and discussed in the Supplementary Appendix 2.

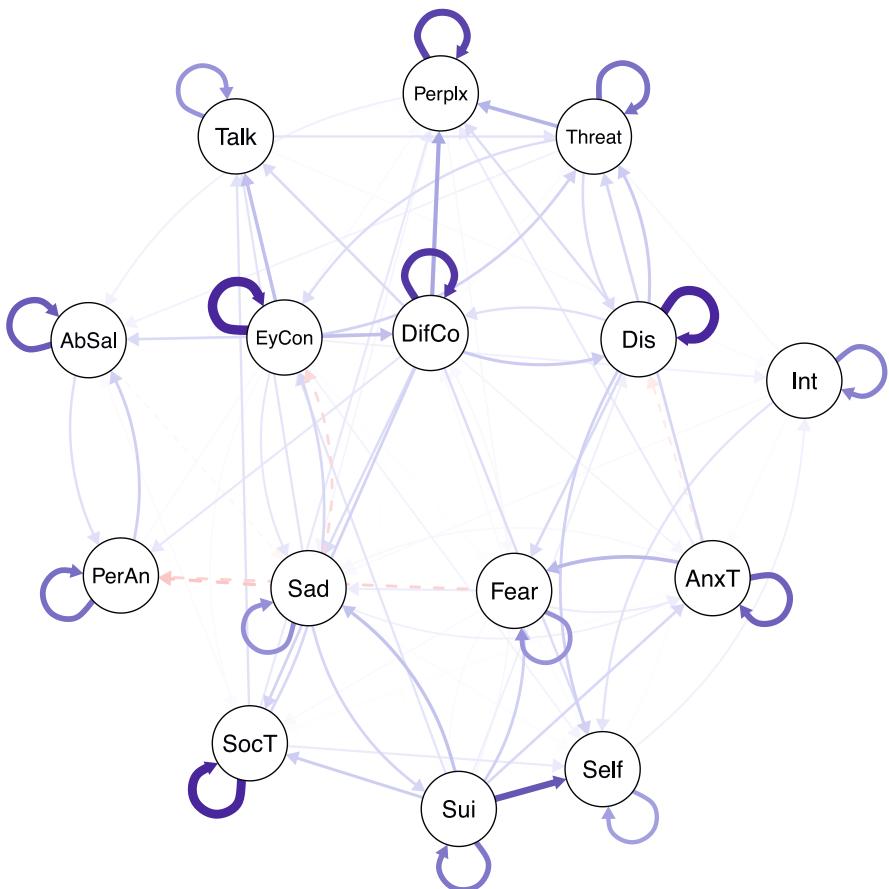


Figure 1. Transdiagnostic cross-lagged panel network of symptoms. Nodes represent the variables included in the network and edges with arrows indicate a directed association between nodes.

Abbreviations: AbSal = aberrant salience, Agi = psychomotor agitation, AnxT = anxious tension, Cog = cognitive problems, DifCo = difficulty mixing with co-workers, Talk = difficulty talking with others, Dis = difficulty disagreeing, Ealm = early insomnia, EaWa = early/frequent awakening, Ener = energy, EyCon = difficulty making eye contact, Fear = fears, Hyn = hypersomnia, Int = interest, PerAn = perceptual anomalies, Perplx = perplexity; lack of natural evidence, Ret = psychomotor retardation, Sad = sad, Self = self-view, Som = somatic (muscular), Sui = suicidality, SocT = social tension, Threat = feeling threatened; paranoia, WAD = weight/appetite decrease, WAI = weight/appetite increase.

The effects of the covariates can be seen in Table S3. Treatment had the most effect on symptoms in the network whereas age, gender, and diagnosis had few relationships with symptoms. Presence of treatment before T1 was related to increased severity of a couple of symptoms, mostly related anxiety, whereas presence of treatment between T1 and T2 was related to decreased severity of a couple of symptoms, mostly related to depression. Neither treatment covariate had an effect on attenuated psychotic symptoms.

The centrality plots can be seen in Figure 2. Stability was low for out-El, but strong for in-El (CS coefficient= 0.21 and 0.52, respectively). A CS coefficient should not be below 0.25 and preferably above 0.5²⁹. Therefore, out-El is not interpreted. Negative self-view had the highest predictability and had significantly higher in-El than 10 out of 15 other symptoms (Figure S3), suggesting that self-view tends to be influenced by other symptoms.

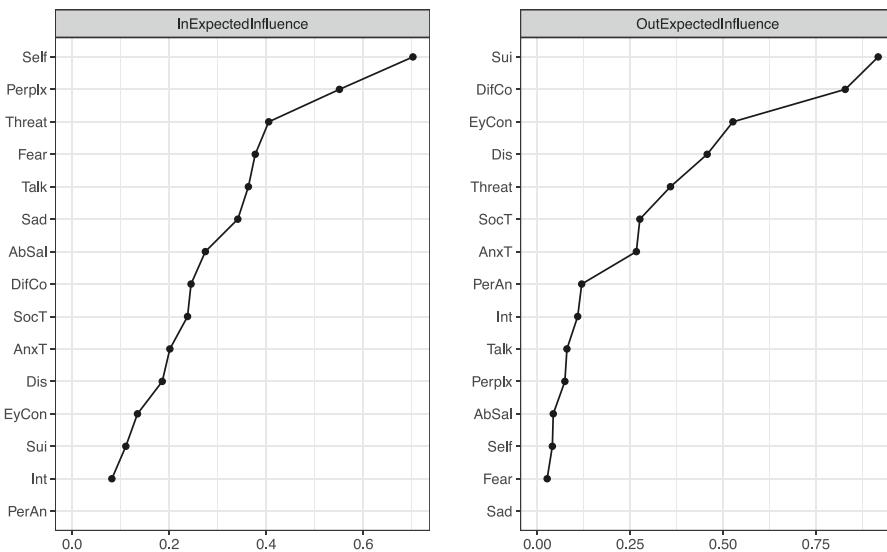


Figure 2. Cross-lagged centrality plots of out-expected influence and in-expected influence. The nodes are denoted on the y-axis and the standardized centrality coefficients are denoted on the x-axis. Higher z-scores indicate higher centrality.

Abbreviations: AbSal = aberrant salience, Agi = psychomotor agitation, AnxT = anxious tension, Cog = cognitive problems, DifCo = difficulty mixing with co-workers, Talk = difficulty talking with others, Dis = difficulty disagreeing, Ealn = early insomnia, EaWa= early/frequent awakening, Ener = energy, EyCon = difficulty making eye contact, Fear = fears, Hyln = hypersomnia, Int = interest, PerAn = perceptual anomalies, Perplx = perplexity; lack of natural evidence, Ret = psychomotor retardation, Sad = sad, Self = self-view, Som = somatic (muscular), Sui = suicidality, SocT = social tension, Threat = feeling threatened; paranoia, WAD = weight/appetite decrease, WAI= weight/appetite increase.

The control network without misophonia (n=134) replicated the relationship between baseline SI and follow-up self-view as the strongest edge ($B= 0.33$). The strongest autoregressive relationships of social tension ($B= 0.64$), difficulty making eye contact ($B= 0.54$), and difficulty disagreeing with others ($B= 0.51$) were also replicated. The edges of the main and control network were strongly correlated ($r= 0.81$). 90% of the edges in the control network were replicated in the main network and 64% of the edges in the main network were replicated in the control network. Negative self-view also had the highest predictability (in-El) and correlation of overall out-El

is $r= 0.77$ and in-EI is $r= 0.98$ between the main and control networks. However, the CS coefficients for the control network are low, so results on centralities should not be interpreted (out-EI= 0.13, in-EI= 0.21). This is most likely due to the small sample size. The control network, centrality plots, and stability and difference tests can be viewed in the Supplementary Materials (Figures S5-S10).

Discussion

This study aimed to investigate two-wave longitudinal relationships over an average of 12 months between individual symptoms using a cross-lagged panel network model in a transdiagnostic sample of individuals with psychiatric disorders. Interactions between symptoms from the different dimensions were also observed in the network, further supporting the co-occurrence of depression, (social) anxiety, and attenuated psychotic symptoms. The strongest cross-lagged and autoregressive edges (SI predicting negative self-view and self-reinforcing social anxiety symptoms) will be the focus of the discussion. Centrality analyses also detected self-view as a highly predictable node. These results were obtained by accounting for diagnosis as a control variable and were replicated in the control network without misophonia, which may potentially suggest that they are transdiagnostic. This supports the expectation that symptoms interact in ways that do not adhere to diagnostic categories.

An interesting relationship in the network was between more baseline SI predicting higher follow-up negative self-view. As a note, SI is measured in this study as a broad concept that ranges from thoughts of death to suicide attempts and should be interpreted with caution as it does not clearly differentiate between ideation and actual attempts (see Table 1). While research supports an association between SI and self-esteem, longitudinal studies find that self-esteem predicts SI^{30,31}, which is opposite of what we find. A potential explanation for our finding is that individuals may feel shame or embarrassment for contemplating or attempting suicide^{32,33}, also known as self-stigma, which is tied to lower self-esteem³⁴. Additionally, SI is often associated with feelings of burdensomeness³⁵, which are related to low self-esteem and self-hate³⁶. Negative self-view may possibly be a reflection of self-stigma and perceived burdensomeness as a result of SI. Focusing on self-compassion as an intervention for dealing with suicidality may be worthwhile as it can potentially influence self-esteem and other related factors, such as self-stigma and perceived burdensomeness^{37,38}. Due to the conflation of within- and between-subject effects prevalent in CLPN models, cross-lagged edges should be interpreted with caution.

Other strong edges pertained to social anxiety symptoms, especially difficulty making eye contact, difficulty disagreeing with others, and social tension, which had

the strongest autoregressive effects. This suggests they are the most self-reinforcing symptoms in the network. Models of social anxiety point to a self-perpetuating cycle in interpersonal situations, such that an individual might behave in anticipation of or according to their expectations of how another individual might react or behave^{39,40}. Cognitive biases and using safety behaviors, such as avoiding eye contact or seeking approval, reinforce and maintain social anxiety⁴¹. Furthermore, the strength of these symptoms could indicate their relevance in a transdiagnostic manner. For instance, social anxiety is prevalent in individuals with other disorders, such as psychosis⁴², bipolar⁴³, or depression⁴⁴. These could reflect more general difficulties with social interaction⁴⁵.

Self-view was a main transdiagnostic outcome in this network as suggested by its high predictability. This means that transdiagnostically, many other symptoms influenced self-view, and participants had a lower self-view when they experienced these other symptoms. While more attention is given to self-esteem as risk factor or development mechanism for psychopathology, self-esteem may also be an outcome of psychopathology^{46,47}. The current finding is in line with the scar model, which posits that psychopathology tends to deplete psychological resources, leaving scars that distort an individual's self-concept. Having a psychiatric disorder could potentially lower self-esteem⁴⁸. The vulnerability model, in which self-esteem predicts psychopathology, has more support⁴⁹, but our result does not align with this. However, the scar and vulnerability models are not mutually exclusive, and a bidirectional relationship is possible⁴⁷.

In our network, self-view was mostly predicted by nodes related to depression and social anxiety symptoms. Considering that depression and social anxiety symptoms can impact many areas of life, such as psychosocial functioning^{50,51}, a negative self-view might not be a direct outcome of these factors. Instead, it might be a reflection of the negative consequences of living with a psychiatric disorder. Individuals with psychiatric disorders often have limited access to work, education, and social activities; activities which often are considered meaningful. For instance, employment is associated with higher self-esteem⁵². Not being able to participate in society could therefore lead to loss of self-esteem. Living with psychiatric disorders can also lead to demoralization, as accepting the realities of mental illness and its consequences can affect self-esteem⁵³. This is especially so if one internalizes that mental illness means inadequacy, incompetence, and that there is something inherently wrong with oneself⁵⁴. Emphasizing psychosocial rehabilitation and recovery-oriented care concepts such as empowerment, hope, and inclusion in recovery may lead to better long-term outcomes, including improvements in self-esteem⁵⁵.

Of the covariates, treatment was mostly strongly related with symptoms. Treatment before the baseline measurement was related to higher sadness and (social) anxiety symptoms. A potential reason for this may be due to an increased self-reflection and insight, which can have a paradoxical effect of increasing symptoms, perhaps through self-stigma⁵⁶. The AMC is also a tertiary care institution and tends to treat individuals with more severe cases who typically have a previous history of treatment. Treatment between the baseline and follow-up measurements was related to lower symptom severity, especially negative self-view, lack of interest, and suicidal ideation. Considering the transdiagnostic nature, this may be related to general improvements in well-being and quality of life. Factors, such as duration and type of treatment, were not included in the treatment covariates, so these findings must be interpreted cautiously.

Strengths and Limitations

A main strength of this study is that it employs a transdiagnostic approach that cuts across multiple diagnostic spectra and focuses on individual symptoms rather than on sum-scores or diagnoses. Broad categories, whether sum-scores or diagnoses, can lead to a loss of information on how specific symptoms or mental states, irrespective of diagnosis, interact with each other. Furthermore, the analyses were controlled for diagnoses and were repeated in a diagnostic subsample without misophonia to check for the potential influence of misophonia, which is the largest group. However, future research should conduct analyses of individual diagnostic categories to determine a true transdiagnostic nature. Lastly, conducting a CLPN model is a step forward from cross-sectional partial correlation networks as it allows for directed relationships. Longitudinal investigations are necessary to investigate the dynamic nature of psychopathology, and determining temporal order is one step towards determining causality.

The results of this paper should be interpreted with the following limitations in mind. First, CLPNs can be influenced by limitations pertaining to traditional cross-lagged panel models and network models as explained in Rhemtulla, van Bork, Cramer²². A main limitation is that CLPN models conflate within- and between-subject effects, which can bias results if variables contain stable individual differences. This means that cross-lagged effects may be produced amongst correlated variables that have no causal relationships. Methods that can separate these effects require at least three waves of data and require more research, but include mean-centering data across time points or fitting a latent factor to repeated observations in a random-intercept cross-lagged panel model. Furthermore, estimates can be impacted by sampling frequency, so relationships in this network should be interpreted in light of the one-year time lag represented in this study. Moreover, two time points do not

allow for analyzing dynamic bidirectional relationships. Future research therefore could include intensive time-series designs to measure hourly or daily fluctuations and multi-wave longitudinal studies to measure longer-term changes to account for differences in frequency of change. Furthermore, the small sample size is a limitation, which did not allow us to compare individual networks per diagnostic category. However, diagnosis was included as a covariate in the network to account for potential differences. The small sample size may have also impacted the stability estimates and should therefore be interpreted cautiously. Another potential limitation is selection bias. Participants who completed both measurements may differ from participants who completed only the first measurement, especially as completing the follow-up measurement was not necessary for participation in the study. For instance, we found a difference in age, diagnosis, medication, and feeling threatened or paranoid. This further contributed to the small sample size. Furthermore, misophonia comprised a large percentage of the sample, which may also be a selection bias. However, the control network without the misophonia subsample demonstrated a moderate correlation with the main network and substantially replicated the main findings. Participants could also participate at any point of their treatment trajectory, which could impact stationarity but we controlled for this in the network. This reflects the naturalistic nature of the study, which can more closely reflect clinical reality, but also introduce more variability in variables, such as age, treatment, and diagnostic category. Lastly, most of the nodes contained only one item, which might not be sufficient to capture some of the more complex concepts, including suicidal ideation.

Conclusion

To conclude, this study gives insight into two-wave longitudinal interactions between individual symptoms, which cut across diagnostic categories. Overall, all nodes in the network both predicted and were influenced by at least one other node, which resulted in numerous unique associations. This demonstrates the dynamic complexity of psychopathology and further supports the importance of investigating symptom-symptoms interactions of different psychopathological dimensions over time and across disorders. Potential mechanisms of these relationships need to be elucidated and models should be extended to include measures of psychosocial functioning and daily life to investigate how these are impacted by symptoms.

References

1. Borsboom D. Psychometric perspectives on diagnostic systems. *J Clin Psychol*. 2008;64(9):1089-1108.
2. Kendler KS, Zachar P, Craver C. What kinds of things are psychiatric disorders? *Psychol Med*. 2011;41(6):1143-1150.
3. Borsboom D. A network theory of mental disorders. *World Psychiatry*. 2017;16(1):5-13.
4. Boschloo L, van Borkulo CD, Rhemtulla M, Keyes KM, Borsboom D, Schoevers RA. The Network Structure of Symptoms of the Diagnostic and Statistical Manual of Mental Disorders. *PLoS One*. 2015;10(9):e0137621.
5. Funkhouser CJ, Chacko AA, Correa KA, Kaiser AJ, Shankman SA. Unique longitudinal relationships between symptoms of psychopathology in youth: A cross-lagged panel network analysis in the ABCD study. *J Child Psychol Psychiatr*. 2021;62(2):184-194.
6. Epskamp S, van Borkulo CD, van der Veen DC, et al. Personalized Network Modeling in Psychopathology: The Importance of Contemporaneous and Temporal Connections. *Clinical Psychological Science*. 2018;6(3):416-427.
7. Bringmann LF, Vissers N, Wichers M, et al. A Network Approach to Psychopathology: New Insights into Clinical Longitudinal Data. *PLoS One*. 2013;8(4):e60188.
8. Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK. Comorbid Depressive and Anxiety Disorders in 509 Individuals With an At-Risk Mental State: Impact on Psychopathology and Transition to Psychosis. *Schizophr Bull*. 2012;40(1):120-131.
9. Goldberg D, Fawcett J. The importance of anxiety in both major depression and bipolar disorder. *Depress Anxiety*. 2012;29(6):471-478.
10. Hanssen M, Peeters F, Krabbendam L, Radstake S, Verdoux H, Van Os J. How psychotic are individuals with non-psychotic disorders? *Soc Psychiatry Psychiatr Epidemiol*. 2003;38(3):149-154.
11. Heeren A, Jones PJ, McNally RJ. Mapping network connectivity among symptoms of social anxiety and comorbid depression in people with social anxiety disorder. *J Affect Disord*. 2018;228:75-82.
12. Beard C, Millner AJ, Forgeard MJC, et al. Network analysis of depression and anxiety symptom relationships in a psychiatric sample. *Psychol Med*. 2016;46(16):3359-3369.
13. van Rooijen G, Isvoranu A-M, Kruyt OH, et al. A state-independent network of depressive, negative and positive symptoms in male patients with schizophrenia spectrum disorders. *Schizophr Res*. 2018;193:232-239.
14. Chavez-Baldini U, Nieman DH, Keestra A, et al. The relationship between cognitive functioning and psychopathology in patients with psychiatric disorders: a transdiagnostic network analysis. *Psychol Med*. 2021;1-10.
15. Nieman DH, Chavez-Baldini U, Vulink NC, et al. Protocol Across study: longitudinal transdiagnostic cognitive functioning, psychiatric symptoms, and biological parameters in patients with a psychiatric disorder. *BMC Psychiatry*. 2020;20(1):212.
16. Nieman DH, Vulink NC, Chavez-Baldini U, Verweij K, Denys D. Psychiatric Dimensions Questionnaire. <https://osf.io/6s48a/>. Published 2021. Accessed.
17. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50-55.
18. Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. *Behav Res Ther*. 1998;36(4):455-470.
19. Rush AJ, Giles DE, Schlessser MA, Fulton CL, Weissenburger J, Burns C. The inventory for depressive symptomatology (IDS): preliminary findings. *Psychiatry Res*. 1986;18(1):65-87.
20. Haug E, Øie M, Andreassen OA, et al. High levels of anomalous self-experience are associated with longer duration of untreated psychosis. *Early Interv Psychiatry*. 2017;11(2):133-138.
21. Landolt K, Wittwer A, Wyss T, et al. Help-Seeking in People with Exceptional Experiences: Results from a General Population Sample. *Front Public Health*. 2014;2.
22. Rhemtulla M, van Bork R, Cramer A. Cross-lagged network models. *Multivariate Behav Res*. 2020.
23. R: A Language and Environment for Statistical Computing [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2017.
24. Nonparametric missing value imputation using random forest [computer program]. 2016.

25. Friedman J, Hastie T, Tibshirani R. Sparse inverse covariance estimation with the graphical lasso. *Biostatistics*. 2008;9(3):432-441.
26. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *J Stat Softw*. 2010;33(1):1.
27. Epskamp S, Cramer AO, Waldorp LJ, Schmittmann VD, Borsboom D. qgraph: Network visualizations of relationships in psychometric data. *J Stat Softw*. 2012;48(4):1-18.
28. Fruchterman TM, Reingold EM. Graph drawing by force-directed placement. *Softw Pract Exp*. 1991;21(11):1129-1164.
29. Epskamp S, Borsboom D, Fried EI. Estimating psychological networks and their accuracy: A tutorial paper. *Behav Res Methods*. 2018;50(1):195-212.
30. Stange JP, Kleiman EM, Sylvia LG, et al. SPECIFIC MOOD SYMPTOMS CONFER RISK FOR SUBSEQUENT SUICIDAL IDEATION IN BIPOLAR DISORDER WITH AND WITHOUT SUICIDE ATTEMPT HISTORY: MULTI-WAVE DATA FROM STEP-BD. *Depress Anxiety*. 2016;33(6):464-472.
31. McGee R, Williams S, Nada-Raja S. Low Self-Esteem and Hopelessness in Childhood and Suicidal Ideation in Early Adulthood. *J Abnorm Child Psychol*. 2001;29(4):281-291.
32. Burton Denmark A, Hess E, Becker MS. College Students' Reasons for Concealing Suicidal Ideation. *Journal of College Student Psychotherapy*. 2012;26(2):83-98.
33. Blanchard M, Farber BA. "It is never okay to talk about suicide": Patients' reasons for concealing suicidal ideation in psychotherapy. *Psychother Res*. 2020;30(1):124-136.
34. Park K, MinHwa L, Seo M. The impact of self-stigma on self-esteem among persons with different mental disorders. *Int J Soc Psychiatry*. 2019;65(7-8):558-565.
35. Rath D, de Beurs D, Hallensleben N, Spangenberg L, Glaesmer H, Forkmann T. Modelling suicide ideation from beep to beep: Application of network analysis to ecological momentary assessment data. *Internet Interv*. 2019;18:100292-100292.
36. Van Orden KA, Witte TK, Cukrowicz KC, Braithwaite SR, Selby EA, Joiner TE, Jr. The interpersonal theory of suicide. *Psychol Rev*. 2010;117(2):575-600.
37. Cleare S, Gumley A, O'Connor RC. Self-compassion, self-forgiveness, suicidal ideation, and self-harm: A systematic review. *Clin Psychol Psychother*. 2019;26(5):511-530.
38. Wong CCY, Knee CR, Neighbors C, Zvolensky MJ. Hacking Stigma by Loving Yourself: a Mediated-Moderation Model of Self-Compassion and Stigma. *Mindfulness*. 2019;10(3):415-433.
39. Alden LE, Wallace ST. Social phobia and social appraisal in successful and unsuccessful social interactions. *Behav Res Ther*. 1995;33(5):497-505.
40. Alden LE, Taylor CT. Interpersonal processes in social phobia. *Clin Psychol Rev*. 2004;24(7):857-882.
41. Taylor CT, Alden LE. To see ourselves as others see us: an experimental integration of the intra and interpersonal consequences of self-protection in social anxiety disorder. *J Abnorm Psychol*. 2011;120(1):129-141.
42. McEnery C, Lim MH, Tremain H, Knowles A, Alvarez-Jimenez M. Prevalence rate of social anxiety disorder in individuals with a psychotic disorder: A systematic review and meta-analysis. *Schizophr Res*. 2019;208:25-33.
43. Levy B, Tsay E, Brodt M, Petrosyan K, Malloy M. Stigma, social anxiety, and illness severity in bipolar disorder: Implications for treatment. *J Affect Disord*. 2015;27(1):55-64.
44. Adams GC, Balbuena L, Meng X, Asmundson GJG. When social anxiety and depression go together: A population study of comorbidity and associated consequences. *J Affect Disord*. 2016;206:48-54.
45. Kennedy DP, Adolphs R. The social brain in psychiatric and neurological disorders. *Trends Cogn Sci*. 2012;16(11):559-572.
46. Zeigler-Hill V. The Connections Between Self-Esteem and Psychopathology. *J Contemp Psychother*. 2011;41(3):157-164.
47. Steiger AE, Fend HA, Allemand M. Testing the vulnerability and scar models of self-esteem and depressive symptoms from adolescence to middle adulthood and across generations. *Dev Psychol*. 2015;51(2):236.
48. Silverstone PH, Salsali M. Low self-esteem and psychiatric patients: Part I – The relationship between low self-esteem and psychiatric diagnosis. *Ann Gen Psychiatry*. 2003;2(1):2.
49. Sowislo JF, Orth U. Does low self-esteem predict depression and anxiety? A meta-analysis of longitudinal studies. *Psychol Bull*. 2013;139(1):213.

50. Eng W, Coles ME, Heimberg RG, Safren SA. Domains of life satisfaction in social anxiety disorder: relation to symptoms and response to cognitive-behavioral therapy. *J Anxiety Disord.* 2005;19(2):143-156.
51. Fried EI, Nesse RM. The Impact of Individual Depressive Symptoms on Impairment of Psychosocial Functioning. *PLoS One.* 2014;9(2):e90311.
52. Van Dongen CJ. Quality of life and self-esteem in working and nonworking persons with mental illness. *Community Ment Health J.* 1996;32(6):535-548.
53. Cavelti M, Rüsch N, Vauth R. Is Living With Psychosis Demoralizing?: Insight, Self-stigma, and Clinical Outcome Among People With Schizophrenia Across 1 Year. *J Nerv Ment Dis.* 2014;202(7):521-529.
54. Yanos PT, Roe D, Lysaker PH. The Impact of Illness Identity on Recovery from Severe Mental Illness. *Am J Psychiatr Rehabil.* 2010;13(2):73-93.
55. Winsper C, Crawford-Docherty A, Weich S, Fenton S-J, Singh SP. How do recovery-oriented interventions contribute to personal mental health recovery? A systematic review and logic model. *Clin Psychol Rev.* 2020;76:101815.
56. Fowler CA, Rempfer MV, Murphy ME, Barnes AL, Hoover ED. Exploring the paradoxical effects of insight and stigma in psychological recovery. *North American Journal of Psychology.* 2015;17(1):151-174.
57. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry.* 2003;54(5):573-583.
58. Peters L, Sunderland M, Andrews G, Rapee RM, Mattick RP. Development of a short form Social Interaction Anxiety (SIAS) and Social Phobia Scale (SPS) using nonparametric item response theory: the SIAS-6 and the SPS-6. *Psychol Assess.* 2012;24(1):66.
59. Bech P. *Clinical psychometrics.* John Wiley & Sons; 2012.
60. Golino H, Christensen A, Moulder R. EGAnet: Exploratory Graph Analysis: A framework for estimating the number of dimensions in multivariate data using network psychometrics. *R package version 09.* 2020;2.
61. Kuipers J, Moffa G, Kuipers E, Freeman D, Bebbington P. Links between psychotic and neurotic symptoms in the general population: an analysis of longitudinal British National Survey data using Directed Acyclic Graphs. *Psychol Med.* 2019;49(3):388-395.
62. Ben-Zeev D, Young MA, Depp CA. Real-time predictors of suicidal ideation: Mobile assessment of hospitalized depressed patients. *Psychiatry Res.* 2012;197(1):55-59.
63. Thompson WK, Gershon A, O'Hara R, Bernert RA, Depp CA. The prediction of study-emergent suicidal ideation in bipolar disorder: a pilot study using ecological momentary assessment data. *Bipolar Disord.* 2014;16(7):669-677.
64. Yamokoski CA, Scheel KR, Rogers JR. The Role of Affect in Suicidal Thoughts and Behaviors. *Suicide Life Threat Behav.* 2011;41(2):160-170.
65. Moreno-Küstner B, Jones R, Švab I, et al. Suicidality in primary care patients who present with sadness and anhedonia: a prospective European study. *BMC Psychiatry.* 2016;16(1):94.
66. Michail M, Birchwood M. Social anxiety disorder in first-episode psychosis: incidence, phenomenology and relationship with paranoia. *Br J Psychiatry.* 2009;195(3):234-241.
67. Combs DR, Penn DL. The role of subclinical paranoia on social perception and behavior. *Schizophr Res.* 2004;69(1):93-104.
68. Newman Taylor K, Stopa L. The Fear of Others: A Pilot Study of Social Anxiety Processes in Paranoia. *Behav Cogn Psychother.* 2013;41(1):66-88.
69. Reno RR, Kenny DA. Effects of Self-Consciousness and Social Anxiety on Self-Disclosure among Unacquainted Individuals: An Application of the Social Relations Model. *J Pers.* 1992;60(1):79-94.
70. Orr EMJ, Moscovitch DA. Blending in at the Cost of Losing Oneself: Dishonest Self-Disclosure Erodes Self-Concept Clarity in Social Anxiety. *Journal of Experimental Psychopathology.* 2015;6(3):278-296.
71. Chambliss DL, Hunter K, Jackson A. Social anxiety and assertiveness: a comparison of the correlations in phobic and college student samples. *Behav Res Ther.* 1982;20(4):403-404.

72. Swee MB, Butler RM, Ross BV, Horenstein A, O'Day EB, Heimberg RG. Interpersonal Patterns in Social Anxiety Disorder: Predictors and Outcomes of Cognitive-Behavioral Therapy. *Cognit Ther Res.* 2021;45(4):614-627.
73. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry.* 2003;160(1):13-23.
74. Wright A, Nelson B, Fowler D, Greenwood K. Perceptual biases and metacognition and their association with anomalous self experiences in first episode psychosis. *Conscious Cogn.* 2020;77:102847.
75. Cicero DC, Docherty AR, Becker TM, Martin EA, Kerns JG. Aberrant Salience, Self-Concept Clarity, and Interview-Rated Psychotic-Like Experiences. *Journal of Personality Disorders.* 2015;29(1):79-99.

Supplementary Materials

Appendix 1. Item Selection Procedure

Following Rhemtulla, van Bork, Cramer²²'s recommendation, an item selection procedure was performed, in which the number of items was reduced. This is done to make the network results more interpretable as many items may have conceptual overlap. This item selection was done before any analyses were conducted and was based on a combination of content-based and data-driven reduction. If available, we first used short-form versions of questionnaires to guide item selection: QIDS-SR₁₆⁵⁷, SIAS-6⁵⁸, and HAM-A₆⁵⁹. This reduced the total number of items from all questionnaires combined from 79 to 32. Next, we selected items that pertained to psychological symptoms, meaning we removed items pertaining to somatic or physical symptoms, such as sleep. This further reduced the number of items to 18. Next, we performed a node redundancy procedure using a weighted topological overlap approach and adaptive alpha multiple comparisons correction to determine which items are redundant. This procedure was conducted with the node.redundant function available in the *EGAnet* package⁶⁰. Item wording and theory was also taken into consideration when determining which nodes to combine as was suggested in Rhemtulla, van Bork, Cramer²². This further reduced the 18 items to 15 items. The final list of items can be viewed in Table 1 in the main manuscript.

Appendix 2. Feedback loops

Results

A couple of potential feedback loops were present in the current network. More sadness at baseline predicted more suicidal ideation at follow-up ($B= 0.10$) and more suicidal ideation at baseline predicted more sadness at follow-up ($B= 0.14$). Feeling more threatened at baseline predicted more difficulty disagreeing with others at follow-up ($B= 0.08$) and more difficulty disagreeing with others at baseline predicted feeling more threatened at follow-up ($B= 0.12$). Feeling more threatened at baseline also predicted more difficulty making eye contact at follow-up ($B= 0.08$) and more difficulty making eye contact at baseline predicted feeling more threatened at follow-up ($B= 0.10$). More difficulty disagreeing with others at baseline predicted more difficulty mixing with co-workers ($B= 0.07$) and more difficulty mixing with co-workers predicted more difficulty disagreeing with others ($B= 0.12$). Lastly, more perceptual anomalies predicted more aberrant salience ($B= 0.11$) and more aberrant salience predicted more perceptual anomalies ($B= 0.07$). These could suggest tentative feedback loops as explained in Kuipers, Moffa, Kuipers, Freeman, Bebbington⁶¹. If variable A at baseline affects variable B at follow-up, and B at baseline affects A at

follow-up, we could potentially infer a feedback loop. Disentangling the effect of synchronous correlation ('A1B1 'A2B2) from causal cross-item influence is difficult, however, so this should be interpreted cautiously. Furthermore, at least three waves are necessary to detect true feedback loops.

Discussion

A couple of potential transdiagnostic feedback loops were observed in the network. One positive feedback loop was between sadness and suicidal ideation. Sadness and negative affect have been shown to relate to and predict suicidal thoughts⁶²⁻⁶⁴. Unfortunately, there is a dearth of research investigating suicidal ideation as a predictor as it is often considered an outcome. Moreno-Küstner, Jones, Švab, Maaroos, Xavier, Geerlings, Torres-González, Nazareth, Motrico-Martínez, Montón-Franco, Gil-de-Gómez, Sánchez-Celaya, Díaz-Barreiros, Vicens-Caldentey, King⁶⁵ found that suicidal ideation predicted persistent depression, and considering that sadness is a core symptom of depression, it may suggest that suicidal ideation could predict sadness. However, more bidirectional research is necessary between negative affect and suicidal ideation.

Two other positive feedback loops were between feeling threatened and difficulty disagreeing with others between feeling threatened and difficulty making eye contact. A link between social anxiety and exceptional or psychotic-like experiences related to anticipating harm from others, paranoia, and persecutory delusions has been demonstrated in previous research⁶⁶⁻⁶⁸, which support these two feedback loops found in the network. A fear of others characterized by social threat is an underlying common factor for those with social anxiety and paranoia or persecutory delusions⁶⁸ and may explain these relationships.

The potential feedback loop between difficulty disagreeing with others and difficulty mixing with co-workers could be explained by an overarching relationship between social anxiety and self-protective strategies, including reduce self-disclosure and less assertiveness⁶⁹⁻⁷². Mingling with others, including co-workers, can involve self-disclosure, and expressing disagreement is not only a form of disclosing one's opinions, it also requires asserting oneself. As such, these self-protective strategies could lead to feedback loops of negative behaviors that perpetuate each other.

Lastly, aberrant salience and perceptual anomalies has a well-established link in the literature. Models of psychosis posit that aberrant salience can lead to perceptual biases and psychotic-like experiences e.g.,^{73,74} and are especially related to positive psychotic symptoms and experiences⁷⁵. While there is support for aberrant salience leading to perceptual anomalies and generally positive psychotic-like experiences, there is a lack of research on the converse relationship. Given that aberrant salience refers to giving excessive attention or importance to neutral or irrelevant stimuli, perceptual

anomalies, or perceiving what others cannot perceive, could increase aberrant salience by making that perception more important in that individual's mind.

While these relationships only indicate potential feedback loops rather than reflect true feedback loops, these findings further point to the dynamic nature of psychopathology.

Table S1. Specific diagnoses per diagnostic category

Diagnosis	n
Schizophrenia spectrum and other psychotic disorders (n=21)	
Schizophrenia, Paranoid Type	7
Schizophrenia or Psychotic Disorder NOS	10
Schizopreniform Disorder	1
Schizoaffective Disorder	2
Delusional Disorder	1
Depressive disorders (n=37)	
Major Depressive Disorder, Recurrent	19
Major Depressive Disorder, Single Episode	9
Dysthymic Disorder	3
Cyclothymic Disorder	1
Depressive Disorder NOS	5
Anxiety disorders (n=9)	
Generalized Anxiety Disorder	3
Panic Disorder	1
Posttraumatic Stress Disorder	4
Anxiety Disorder NOS	1
Obsessive-compulsive and related disorders (n=41)	
Body Dysmorphic Disorder	3
Skin Picking (Excoriation Disorder)	1
Trichotillomania	4
Obsessive-Compulsive Disorder	33
Misophonia (Impulse control disorder NOS)	
Misophonia	88
Bipolar disorders (n=14)	
Bipolar I Disorder	6
Bipolar II Disorder	7
Bipolar Disorder NOS	1
Other disorders (n=12)	
Substance use disorders	3
Neurodevelopmental disorders	5
Impulse control disorders	3
Adjustment disorder	1

Note: Misophonia is not an official DSM diagnosis.

Table S2. Symptom scores: Mean (SD), range

Measure	All (N=222) (n=21)	SZ (n= 21)	Depression (n= 37)	Anxiety (n= 9)	OCD (n= 41)	Misophonia (n= 88)	Bipolar (n= 14)	Other (n= 12)	Missing (%)
Baseline									
Sad	1.05 (0.9), 0-3	0.81 (0.87), 0-3	1.97 (0.93), 0-3	1 (0.5), 0-2	1.12 (0.95), 0-3	0.73 (0.7), 0-3	0.5 (0.65), 0-2	1.42 (1.16), 0-3	13.33
Self-view	1.12 (1.2), 0-3	0.86 (1.28), 0-3	1.97 (1.09), 0-3	1 (1), 0-3	1.39 (1.28), 0-3	0.66 (1.03), 0-3	1 (1.24), 0-3	1.58 (1.38), 0-3	13.33
Suicidal ideation	0.53 (0.8), 0-3	0.24 (0.54), 0-2	1.38 (1.01), 0-3	0.44 (0.73), 0-2	0.44 (0.74), 0-3	0.23 (0.55), 0-2	0.57 (0.94), 0-3	0.83 (1.11), 0-3	13.33
Interest	0.69 (0.9), 0-3	0.71 (0.78), 0-3	1.65 (1.11), 0-3	1.11 (0.93), 0-3	0.57 (0.8), 0-3	0.24 (0.47), 0-2	0.86 (0.86), 0-3	1 (1.04), 0-3	13.33
Difficulty making eye contact	0.8 (1.1), 0-4	1.05 (1.32), 0-4	1.3 (1.41), 0-4	0.78 (1.3), 0-3	0.76 (0.97), 0-4	0.58 (0.96), 0-3	0.64 (1.08), 0-3	0.83 (0.94), 0-3	13.33
Difficulty mixing with co-workers	0.88 (1), 0-4	1.05 (1.24), 0-3	1.62 (1.23), 0-4	0.78 (1.2), 0-3	0.76 (0.89), 0-3	0.58 (0.8), 0-3	0.86 (0.86), 0-2	1 (0.95), 0-3	13.33
Social tension	1.14 (1.2), 0-4	0.71 (0.87), 0-3.5	1.5 (0.98), 0-4	0.56 (0.77), 0-2	0.76 (0.91), 0-3	0.54 (0.71), 0-3	0.64 (0.72), 0-2	0.88 (0.86), 0-2.5	13.33
Difficulty talking with others	0.78 (0.9), 0-4	0.76 (0.94), 0-4	1.68 (1.18), 0-4	0.56 (1.13), 0-3	0.66 (0.76), 0-2	0.8 (0.87), 0-3	0.79 (0.89), 0-3	0.83 (1.27), 0-4	13.33
Difficulty disagreeing	0.91 (1), 0-4	0.67 (1.1), 0-4	2.03 (1.26), 0-4	0.89 (1.36), 0-4	1.22 (1.15), 0-4	0.93 (1.07), 0-4	1 (0.88), 0-3	0.92 (1.08), 0-3	13.33
Anxious tension	1.19 (1.2), 0-4	0.81 (1.21), 0-4	1.96 (1.44), 0-4	2.33 (0.94), 1-3.5	1.35 (1.16), 0-4	0.83 (0.94), 0-3.5	0.93 (1.22), 0-4	1.04 (1.16), 0-3	16.67
Fear	0.89 (1.2), 0-4	0.43 (0.75), 0-3	1.51 (1.48), 0-4	1.44 (1.42), 0-4	1.24 (1.2), 0-4	0.61 (1.02), 0-4	0.79 (1.19), 0-4	0.42 (0.5), 0-1	16.67
Perceptual anomalies	1.42 (1.9), 0-8	1.85 (1.77), 0-7	0.93 (1.65), 0-6	2.72 (2.5), 0-6	0.87 (1.73), 0-8	1.83 (2.15), 0-8	0.57 (1.16), 0-4	1.04 (1.39), 0-4	43.33
Perplexity	2.05 (2), 0-8	2.18 (2.1), 0-7	2.92 (2.32), 0-8	2.78 (2.83), 0-7	2.25 (1.92), 0-8	1.43 (1.48), 0-6	2.14 (2.1), 0-7.5	2.36 (1.67), 0-6.5	43.33
Aberrant salience	1.48 (1.9), 0-8	2.12 (2.25), 0-8	1.18 (1.42), 0-5	2.49 (2.83), 0-7	1.24 (2.03), 0-8	1.42 (1.62), 0-8	1.5 (2.24), 0-8	1.63 (1.98), 0-6	43.33
Threatened; paranoia	0.83 (1.4), 0-8	1.51 (2.25), 0-8	1.13 (1.76), 0-7	0.52 (0.71), 0-2	1.04 (1.5), 0-8	0.52 (0.74), 0-3	0.29 (0.73), 0-2	1.12 (1.91), 0-6	43.33

Table S2. (continued)

Measure	All (N=222)	SZ (n= 21)	Depression (n= 37)	Anxiety (n= 9)	OCD (n=41)	Misophonia (n= 88)	Bipolar (n=14)	Other (n=12)	Missing (%)
	Follow-up								
Sad	0.8 (0.8), 0-3	0.81 (0.81), 0-3	1.23 (0.91), 0-3	0.44 (0.53), 0-1	0.81 (0.84), 0-3	0.62 (0.71), 0-3	1 (1.04), 0-3	0.75 (0.62), 0-2	20.00
Self-view	0.86 (1.2), 0-3	0.48 (0.93), 0-3	1.92 (1.25), 0-3	0.33 (0.5), 0-1	0.85 (1.21), 0-3	0.43 (0.88), 0-3	1.29 (1.38), 0-3	1.42 (1.31), 0-3	20.00
Suicidal ideation	0.38 (0.7), 0-3	0.43 (0.81), 0-2	0.86 (0.88), 0-3	0.56 (0.88), 0-2	0.25 (0.66), 0-3	0.17 (0.45), 0-2	0.64 (0.84), 0-2	0.42 (0.79), 0-2	20.00
Interest	0.48 (0.8), 0-3	0.67 (1.02), 0-3	0.86 (0.82), 0-3	0.22 (0.44), 0-1	0.47 (0.67), 0-2	0.22 (0.51), 0-3	0.71 (0.91), 0-3	0.83 (1.11), 0-3	20.00
Difficulty making eye contact	0.69 (1.1), 0-4	0.9 (1.22), 0-4	0.99 (1.24), 0-4	0.44 (1.01), 0-3	0.61 (0.95), 0-4	0.61 (1.05), 0-4	0.57 (1.09), 0-3	0.58 (0.67), 0-2	16.67
Difficulty mixing with co-workers	0.7 (1), 0-4	0.86 (1.15), 0-3	1.16 (1.19), 0-4	0.56 (1.33), 0-4	0.56 (0.81), 0-3	0.53 (1), 0-4	0.79 (0.7), 0-2	0.67 (0.78), 0-2	16.67
Social tension	0.72 (0.9), 0-4	0.64 (0.9), 0-3	1.36 (1.05), 0-3	0.39 (0.82), 0-2	0.25 (0.68), 0-2	0.3 (0.56), 0-2	0.68 (0.64), 0-2	0.54 (0.78), 0-2	20.25
Difficulty talking with others	0.81 (0.9), 0-4	0.95 (0.97), 0-3	1.32 (1.01), 0-3	0.56 (1.13), 0-3	0.61 (0.67), 0-2	0.69 (0.89), 0-4	0.71 (0.83), 0-3	0.92 (0.79), 0-2	16.67
Difficulty disagreeing	1.04 (1.2), 0-4	0.57 (0.87), 0-3	1.79 (1.3), 0-4	0.44 (0.88), 0-2	1.32 (1.25), 0-4	0.86 (1.09), 0-4	0.79 (0.7), 0-2	0.67 (0.78), 0-2	16.67
Anxious tension	0.89 (1.1), 0-4	0.43 (0.84), 0-2	1.35 (1.22), 0-4	1.33 (1.32), 0-4	1.01 (1.18), 0-4	0.71 (0.95), 0-4	0.86 (1.23), 0-3	0.35 (0.79), 0-2	16.67
Fear	0.65 (1), 0-4	0.29 (0.56), 0-2	1.25 (1.34), 0-4	0.78 (1.39), 0-4	0.85 (1.13), 0-4	0.41 (0.71), 0-4	0.71 (1.14), 0-3	0.33 (0.49), 0-1	16.67
Perceptual anomalies	1.16 (1.8), 0-8	1.38 (2.13), 0-8	0.72 (1.3), 0-6	1.56 (2.6), 0-6	0.78 (1.6), 0-8	1.52 (1.95), 0-7	0.93 (1.64), 0-6	0.83 (1.53), 0-5	16.67
Perplexity	1.76 (1.8), 0-7.5	1.62 (1.77), 0-7	2.44 (1.85), 0-7	1.83 (2.32), 0-6	1.71 (1.78), 0-7.5	1.36 (1.37), 0-7	2.54 (2.52), 0-7	2.12 (1.76), 0-5	16.67
Aberrant salience	1.39 (1.9), 0-8	1.57 (1.99), 0-6	1.36 (1.82), 0-7	2 (2.5), 0-6	1.15 (1.9), 0-8	1.55 (2.03), 0-8	1.14 (1.92), 0-7	0.67 (0.98), 0-3	16.67
Threatened; paranoia	0.81 (1.3), 0-8	0.9 (1.22), 0-4	1.13 (1.15), 0-7	1 (2.65), 0-8	0.83 (1.24), 0-6	0.53 (0.82), 0-4	0.86 (0.86), 0-2	1.5 (1.83), 0-5	16.67

Note: The Psychiatric Dimensions Questionnaire was introduced into the study at a later point, which explains the higher rates of missing data in the baseline scores of the attenuated psychotic symptoms.

Table S3. Edge weights matrix

	Sad	Self	Sui	Int	EyCon	DifCo	SocT	Talk	Dis	AnxT	Fear	PerAn	Perplx	AbSal	Threat
Sad	.242	.010	.096	.000	-.097	.000	.000	.064	.000	.034	.000	-.140	.000	.000	.000
Self	.000	.209	.000	.037	.000	.000	.000	.000	.004	.000	.000	.000	.000	.000	.000
Sui	.136	.358	.287	.000	.062	.017	.110	.000	.037	.089	.108	.000	.000	.000	.000
Int	.014	.066	.000	.269	.000	.000	.000	.000	.000	.009	.000	.000	.000	.000	.018
EyCon	.056	.029	.000	.035	.566	.142	.011	.145	.000	.000	.004	.000	.000	.003	.101
DifCo	.079	.077	.002	.000	.000	.422	.099	.085	.118	.024	.000	.055	.194	.086	.009
SocT	.000	.051	.000	.000	.091	.000	.528	.069	.000	.000	.000	.000	.054	.012	.000
Talk	.000	.000	.000	.010	.000	.000	.000	.234	.000	.000	.000	.000	.003	.000	.066
Dis	.000	.104	.000	.000	.000	.071	.000	.000	.542	.000	.087	.000	.077	.000	.118
AnxT	.017	.000	.000	.000	.000	.000	.005	.000	-.057	.332	.161	.000	.048	.000	.092
Fear	.046	.007	.012	.000	.000	.014	.012	.000	.000	.045	.233	-.110	.000	.000	.000
PerAn	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.306	.012	.107	.000	.000
Perplx	.021	.000	.000	.000	.000	.000	.000	.000	.000	.018	.000	.394	.035	.000	.000
AbSal	-.027	.000	.000	.000	.000	.000	.000	.000	.000	.000	.074	-.003	.347	.000	.000
Threat	.000	.000	.000	.000	.078	.000	.000	.000	.083	.000	.000	.000	.166	.031	.301
Age	.000	.000	.000	.000	-.004	.000	.000	.000	.000	.000	.000	.011	.000	.000	.001
Gender	.035	.003	.000	.000	.000	.058	.020	.000	.180	.000	.000	.000	.000	.000	.000
Diagnosis	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.056	.000	.000	.000
Treat1	.056	.000	.000	.000	.000	.061	.000	.000	.173	.000	.047	.000	.000	.000	.000
Treat2	.000	-.112	-.107	-.103	.000	.000	.000	-.006	.000	.000	.000	.000	.000	.000	.000

Note: Independent variables are in rows and dependent variables are in columns. Autoregressive edges are presented along the diagonal. Covariates are presented in the last five rows. Abbreviations: AbSal = aberrant salience, AnxT = anxious tension, DifCo = difficulty mixing with co-workers, Talk = difficulty talking with others, Dis = difficulty disagreeing, EyCon = difficulty making eye contact, Fear = fears, Int = interest, PerAn = perceptual anomalies, Perplx = perplexity; lack of natural evidence, Sad = sad, Self = self-view, Sui = suicidal ideation, SocT = social tension, Threat = feeling threatened; paranoia.

Table S4. Comparison between participants with and without follow-up measure

Variable (Baseline)	Test statistic
Age	t(322.43)= -4.84***
Gender	$\chi^2(1)= 0.01$
Diagnosis	$\chi^2(6)= 26.09^{***}$
Comorbidity	$\chi^2(1)= 1.61$
Medication	$\chi^2(5)= 13.28^*$
Sad	t(353.40)= 0.18
Self	t(350.51)= 0.30
Sui	t(341.82)= -0.87
Int	t(361.57)= 1.04
EyCon	t(361.28)= 1.32
DifCo	t(378.27)= 0.75
SocT	t(383.93)= 1.43
Talk	t(365.62)= -0.14
Dis	t(351.89)= -1.20
AnxT	t(358.53)= 0.46
Fear	t(377.59)= 1.40
PerAn	t(378.91)= 0.55
Perplx	t(361.70)= 0.59
AbSal	t(390.05)= 1.60
Threat	t(400.67)= 2.28*

Note: Significance codes are * P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001

Participations without a follow-up measure (group 1) were younger than those with a follow-up measure (group 2). Differences in the distribution of the diagnostic category were minimal except that group 1 also had notably more patients with schizophrenia spectrum and other psychotic disorders. Group 1 also had a higher use of anti-depressants and benzodiazepines.

Edge Weight Confidence Intervals

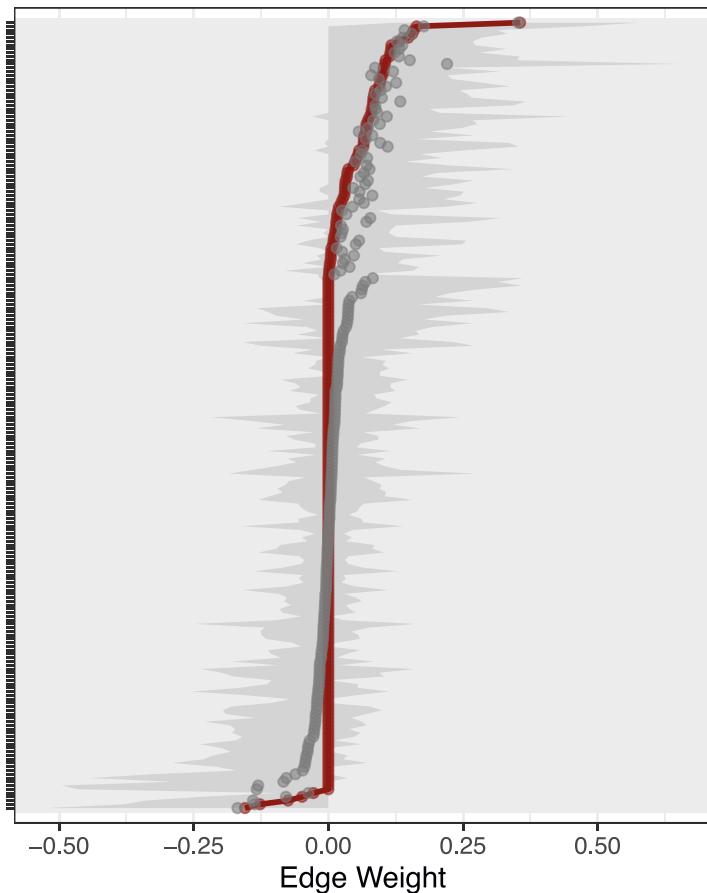


Figure S1. Accuracy of the estimated edges. The x-axis shows the strength of the edge. The edges from the original network are shown in red and are arranged from most negative to most positive along the y-axis. The grey area represents confidence intervals based on the bootstrapped networks.

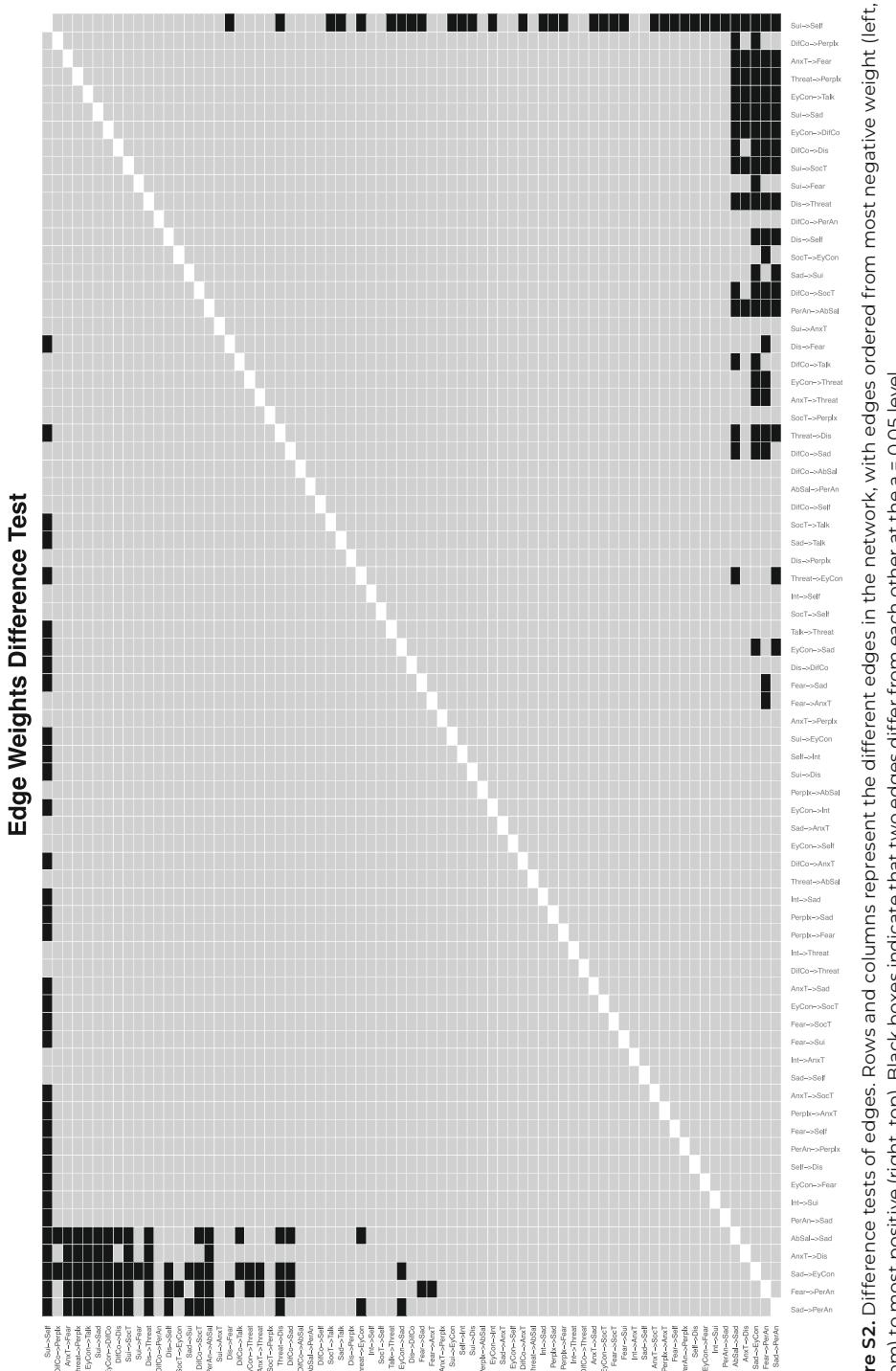


Figure S2. Difference tests of edges. Rows and columns represent the different edges in the network, with edges ordered from most negative weight (left, bottom) to most positive (right, top). Black boxes indicate that two edges differ from each other at the $\alpha = 0.05$ level.

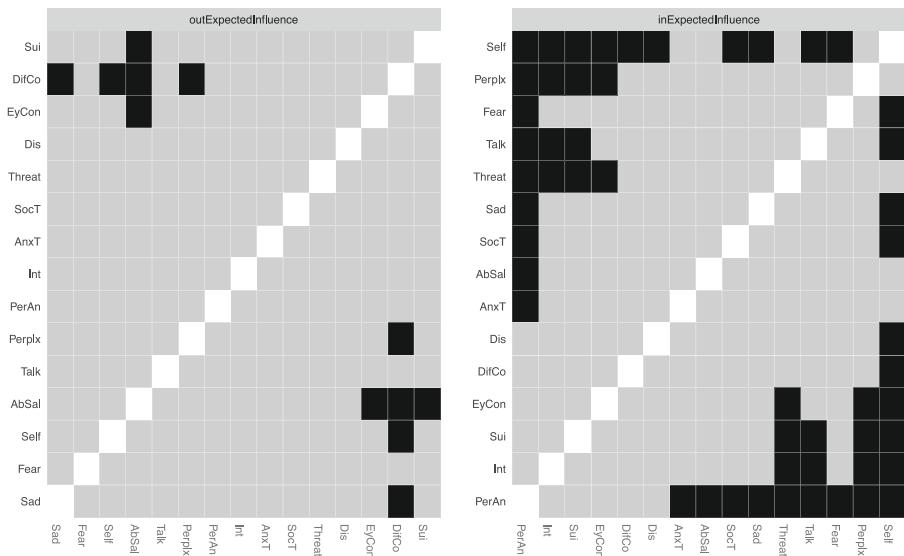


Figure S3. Difference tests of centralities. Rows and columns represent the nodes in the network. Black boxes represent significant differences at the $\alpha = 0.05$ level.

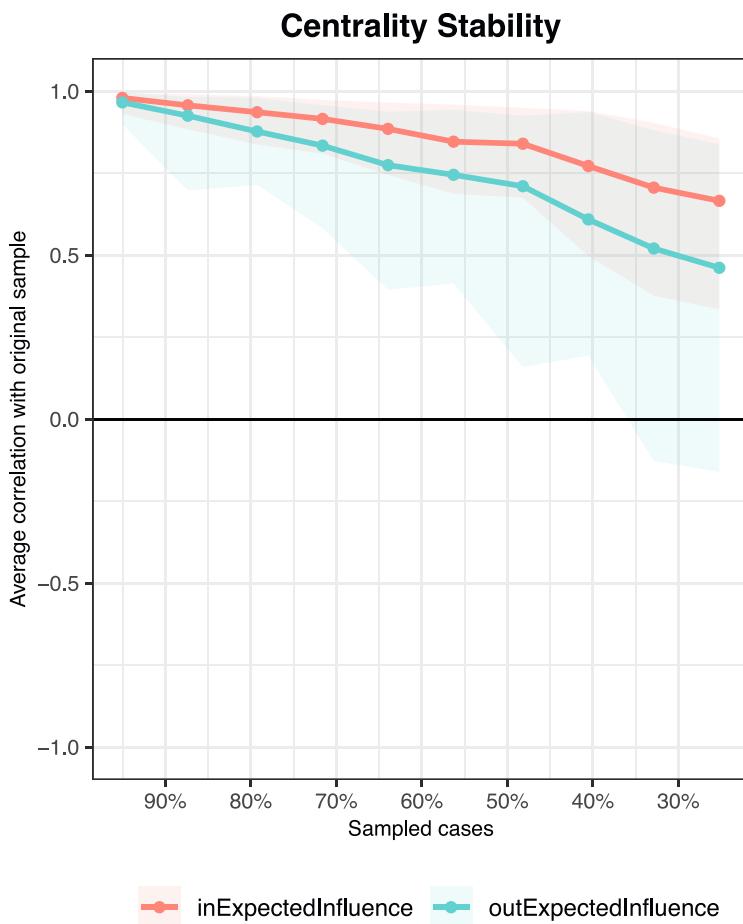


Figure S4. Stability of the centrality measures. The x-axis shows the percentage of patients that was dropped. The y-axis shows the correlation of the centralities after dropping to the original centralities. The shaded areas indicate the 95% confidence interval.

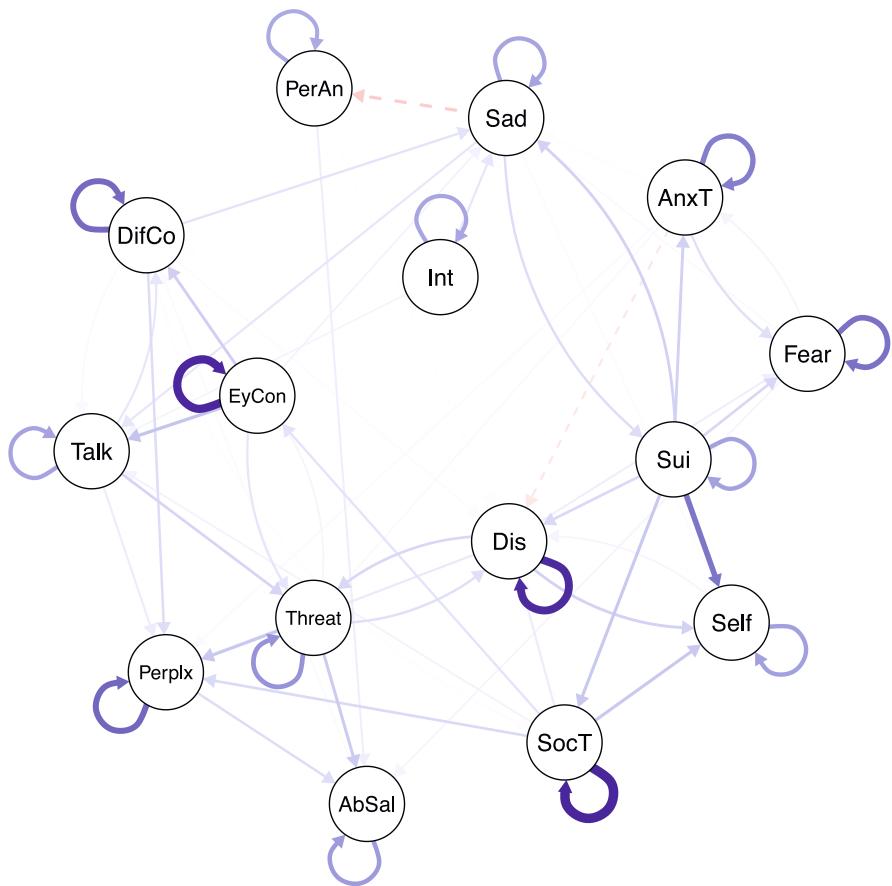


Figure S5. Control cross-lagged network without misophonia with autoregressive effects. Nodes represent the variables included in the network and edges with arrows indicate a directed association between nodes. Solid edges represent positive associations while dashed edges represent negative associations.

Abbreviations: AbSal = aberrant salience, AnxT = anxious tension, DifCo = difficulty mixing with co-workers, Talk = difficulty talking with others, Dis = difficulty disagreeing, EyCon = difficulty making eye contact, Fear = fears, Int = interest, PerAn = perceptual anomalies, Perplx = perplexity; lack of natural evidence, Sad = sad, Self = self-view, Sui = suicidal ideation, SocT = social tension, Threat = feeling threatened; paranoia.

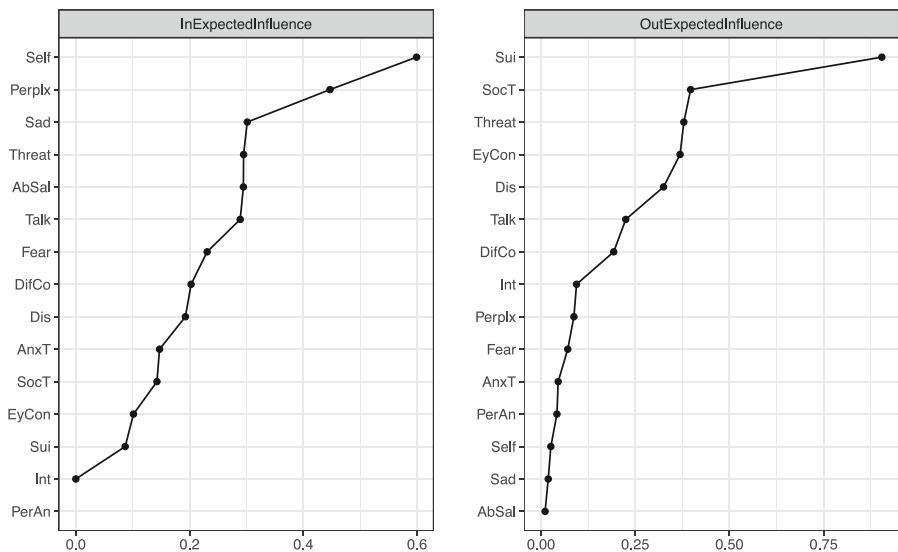


Figure S6. Cross-lagged centrality plots for control network without misophonia. The nodes are denoted on the y-axis and the standardized centrality coefficients are denoted on the x-axis. Higher z-scores indicate higher centrality.

Abbreviations: AbSal = aberrant salience, AnxT = anxious tension, DifCo = difficulty mixing with co-workers, Talk = difficulty talking with others, Dis = difficulty disagreeing, EyCon = difficulty making eye contact, Fear = fears, Int = interest, PerAn = perceptual anomalies, Perplx = perplexity; lack of natural evidence, Sad = sad, Self = self-view, Sui = suicidal ideation, SocT = social tension, Threat = feeling threatened; paranoia.

Edge Weight Confidence Intervals

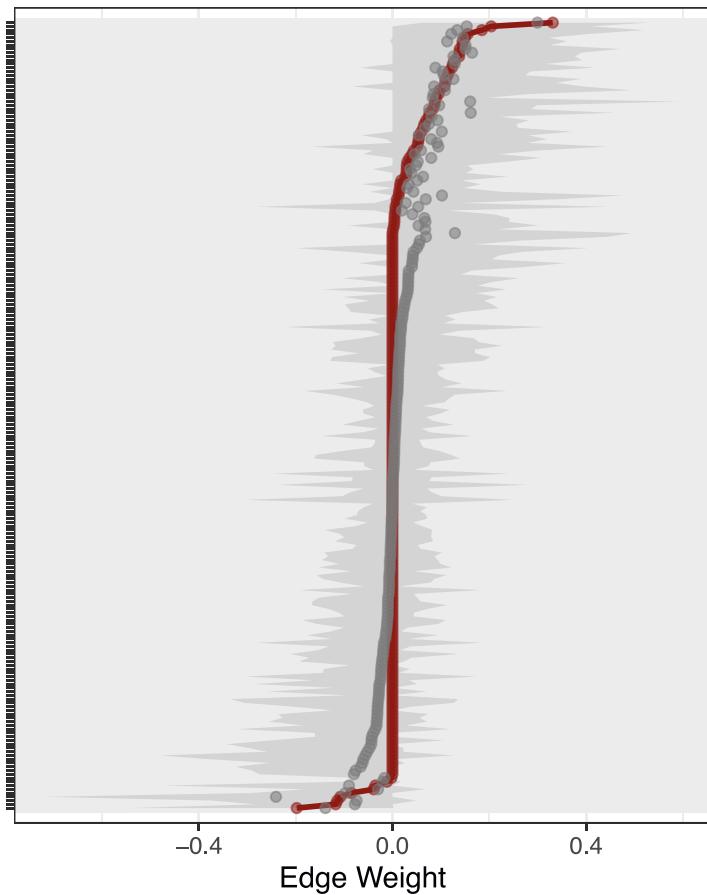


Figure S7. Accuracy of the estimated edges for control network without misophonia. The x-axis shows the strength of the edge. The edges from the original network are shown in red and are arranged from most negative to most positive along the y-axis. The grey area represents confidence intervals based on the bootstrapped networks.

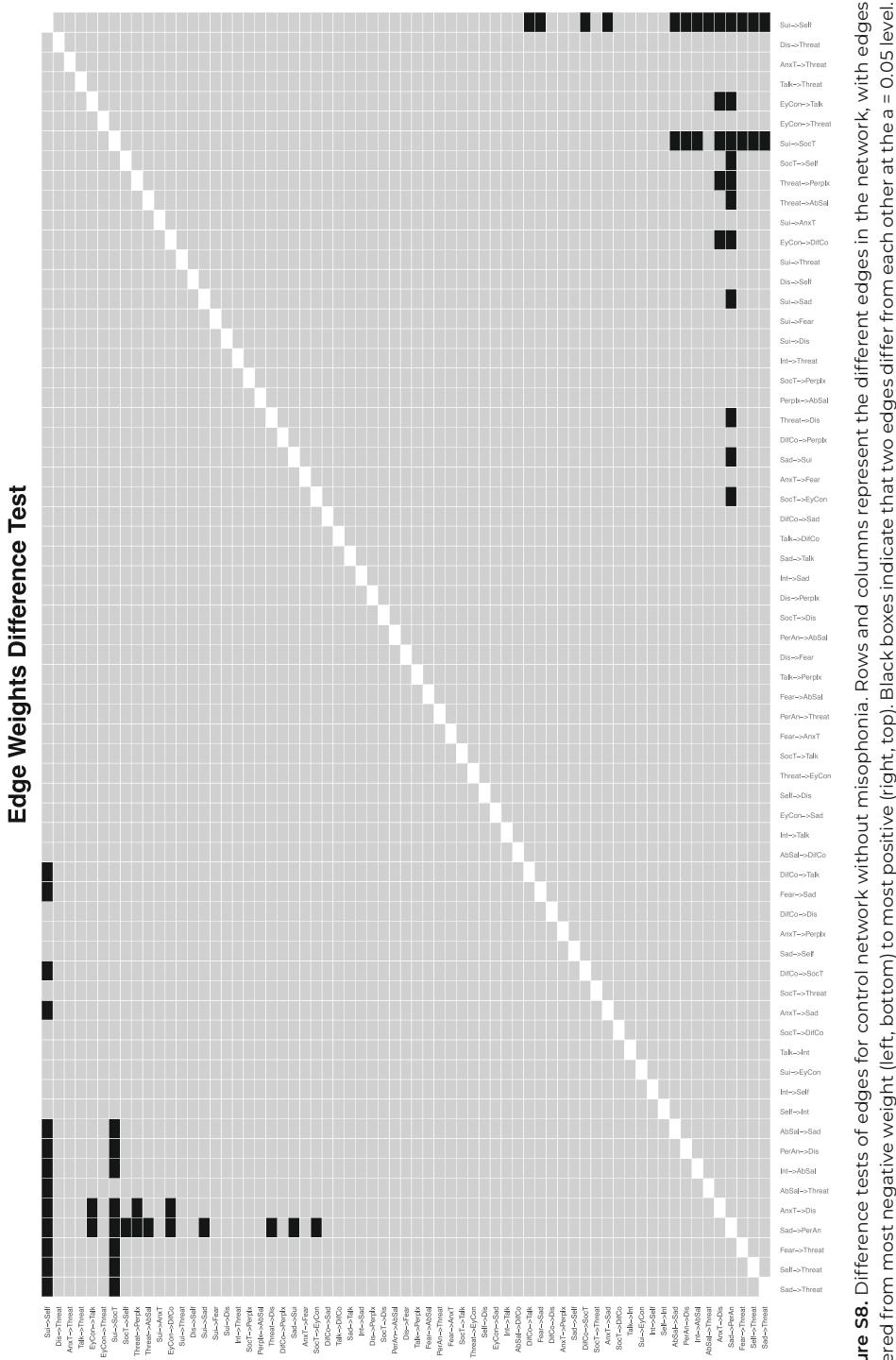


Figure S8. Difference tests of edges for control network without misophonias. Rows and columns represent the different edges in the network, with edges ordered from most negative weight (left, bottom) to most positive (right, top). Black boxes indicate that two edges differ from each other at the $\alpha = 0.05$ level.

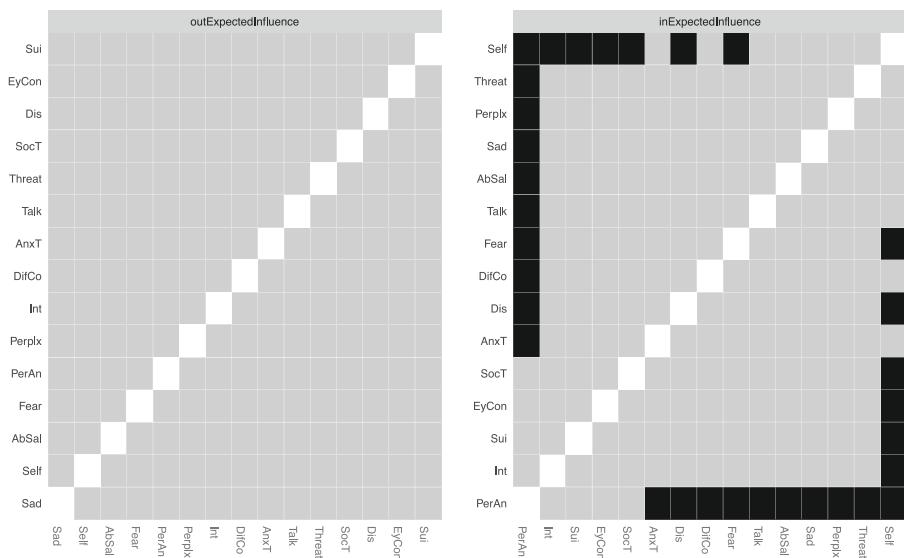


Figure S9. Difference tests of centralities for control network without misophonia. Rows and columns represent the nodes in the network. Black boxes represent significant differences at the $\alpha = 0.05$ level.

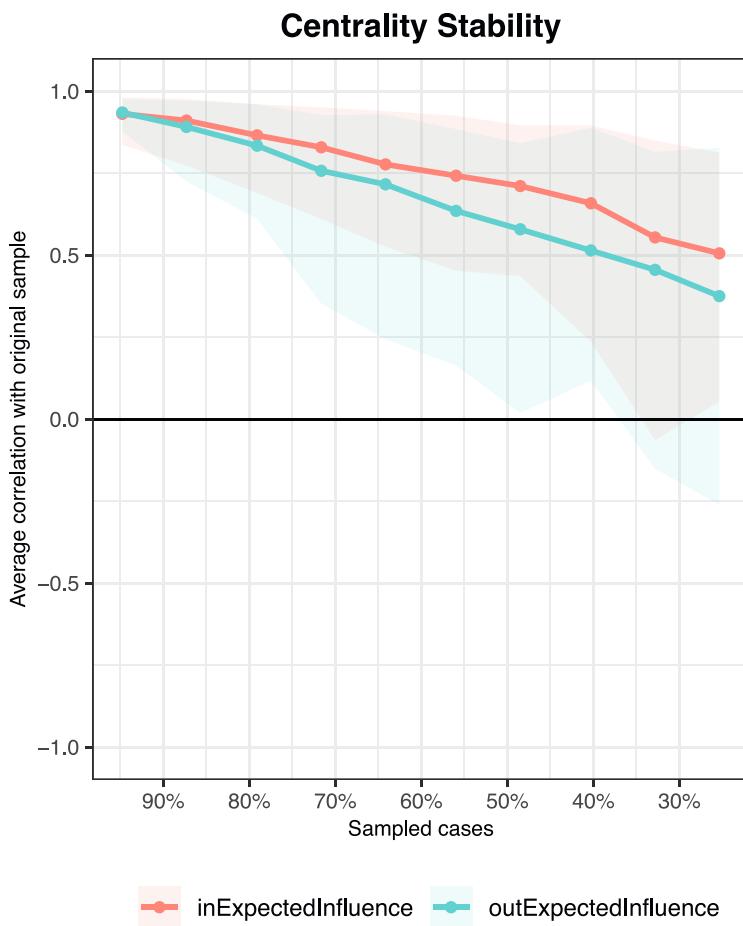


Figure S10. Stability of the centrality measures for control network without misophonia. The x-axis shows the percentage of patients that was dropped. The y-axis shows the correlation of the centralities after dropping to the original centralities. The shaded areas indicate the 95% confidence interval.



6

Existential concerns in psychiatry: A transdiagnostic network analysis

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Under submission

Abstract

Background

Existential concerns, such as autonomy and identity, are often overlooked although they play an important role in psychiatric research and practice. The aims of this study are to investigate how existential concerns relate to psychopathological symptoms and to identify important existential concerns.

Methods

A cross-sectional mixed graphical model of 11 nodes (4 existential and 3 symptom domains) with 4 covariates was estimated in a sample of 996 individuals with various psychiatric disorders. Symptom nodes were derived from questionnaires on psychopathological symptoms and existential nodes from questionnaires on transdiagnostic psychiatric dimensions and self-esteem. The centrality metric, expected influence, was calculated to determine nodes' cumulative influence in the network.

Results

Existential concerns were related to worse psychopathology overall, but most strongly to depressive and anxiety symptoms whereas psychosis was only related to identity. The strongest cross-domain relationship was between anxiety and recognition of psychiatric disorder. Of the existential concerns, autonomy and identity were the most central nodes in the network.

Conclusions

Existential concerns play a role in psychopathology and lived experiences of individuals with psychiatric disorders. Our results advocate to address existential concerns in clinical practice and research on top of symptom reduction. Conveying individual responses to experiencing psychopathology, such as recognition of disorder, and supporting autonomy or positive identity formation may be areas for intervention.

Keywords: Transdiagnostic, psychopathology, existential concerns, network approach

Introduction

Existential concerns have psychological, medical, and philosophical significance, but the increased focus on behavioral psychology and biomedical models over the past decades has largely ignored existential concerns in psychiatry ¹. Existential psychology is derived from existentialism and largely concerns itself with how people face and cope with the experience of human existence ^{2,3}. The existential dimension then can broadly refer to the way we relate to and reflect on our experiences and conflicts that may arise thereof ^{1,4}. According to existentialism-inspired psychology and psychotherapy, death, freedom, isolation, identity, and meaning are the major overarching existential concerns that humans face, and it is posited that these concerns can have a significant impact on well-being ^{3,5}. Existential concerns are complex to define and can have intricate relationships with psychopathology. For instance, they can play a constitutive or modulatory role in or be an integral part of psychopathology ⁴.

Everyone contends with existential concerns to some degree, but more so individuals with psychiatric disorders who express feelings of loneliness and yearning for social connection and belonging, feeling a loss of dignity and self, fearing change and responsibility, needs for personal development, and searching for meaning ⁶⁻⁹. As such, one could argue that many if not all of the existential concerns are transdiagnostic constructs, meaning that they are not specific to a particular condition or psychiatric disorder. For example, death anxiety ¹⁰, existential suffering ¹¹, and emptiness ¹² have been shown to be transdiagnostic existential concerns related to many psychiatric conditions. Of the existential concerns identified by existential psychology, we focus on identity (e.g., the struggle of maintaining a clear sense of who one is while facing uncertainties surrounding self-perception), freedom (e.g., the experience of free will versus constraints and the responsibility of one's choices), and isolation (e.g., the need for social connection versus experiences of rejection and feeling isolated in one's subjective experience of reality) ^{1,3}. Individuals with psychiatric disorders also often describe a loss of self and identity and of struggling with reconciling with their illness identity ^{13,14}. While identity problems can be a risk factor for psychopathology ¹⁵, psychopathology can also impact identity as one may question if the psychiatric disorder is part of the self ⁴. Additionally, a compromised or lack of autonomy e.g., ^{16,17,18} as well as social isolation and loneliness e.g., ^{3,19,20} can be associated with psychopathology. Associated with a sense of will and responsibility, compromised autonomy can have consequences on one's ability to act in accordance with one's goals or desires ²¹. Threats to freedom and autonomy may often be considered external, but psychopathology can itself also be a barrier to autonomy ¹⁸. Lastly, social isolation can be both interpersonal and existential in a way that reflects

a lack of social connections or worth therein but also a sense of feeling different from others, misunderstood, or alone in one's experiences²². Connectedness is often considered necessary for mental health e.g.,²³, but connectedness could be hindered by psychopathology, such as through shame of having a psychiatric disorder⁴. Given that psychopathology can itself be considered an existential experience e.g.,^{3,4}, we also included the recognition of that experience as an existential concern.

Studies that more directly investigate the interrelations between various existential concerns and symptoms are sparse but demonstrate that they are indeed related^{24,25}. It remains therefore necessary to further explore relationships between existential concerns and symptoms and do so with a transdiagnostic approach. Depressive, anxious, and psychotic symptoms can be considered core symptom dimensions, and they have been shown to be transdiagnostic in nature. For instance, anxiety and depression can occur in numerous disorders, such as misophonia²⁶, obsessive-compulsive disorder²⁷, and psychosis²⁸, and psychotic symptoms have also been reported in non-psychotic disorders²⁹.

Individuals with psychiatric disorders have expressed that recovery and remission are more than the reduction of symptoms^{30,31} and that existential concerns are as - or even more - important and urgent than symptom reduction^{8,32}. Consequently, there has been renewed recognition that these concerns should be acknowledged and addressed as part of routine care^{9,33,34} and that the existential dimension should be emphasized in the bio-psycho-social model^{4,35,36}. Further understanding of the role of existential concerns in psychiatry and their relation with psychopathological symptoms is therefore of importance. There remains however a dearth of quantitative research on the relationship between psychopathology and existential concerns, especially in a transdiagnostic manner.

A network approach could be useful for investigating how these existential concerns and symptoms interrelate. This approach posits that psychopathology manifests due to a complex interplay of symptoms and other clinically-relevant biopsychosocial factors, such as cognitions and daily functioning³⁷, which is represented by a network of nodes (variables) and edges (relationships between nodes). Although cross-sectional network analyses do not allow for causal inference, they can elucidate numerous relationships between nodes in one model as well as nodes that are most central, or most strongly connected, in the network, and can be useful for hypothesis generation.

The present study aims to explore cross-sectional relationships between existential concerns (i.e., autonomy, identity, recognition of psychiatric disorder, and social connection) and psychopathological symptoms (i.e., depressive, anxiety, and psychotic symptoms) in a transdiagnostic sample of individuals with psychiatric

disorders by estimating a network model of existential and symptom domains and performing centrality analysis to detect which variables are important within the network. Considering the agnostic and exploratory nature of the network approach, there were no hypotheses regarding specific relationships or centrality. It was however generally expected that stronger existential concerns (e.g., lower autonomy) would be related to worse symptom severity (e.g., worse depressive symptoms).

Methods

Sample

The sample consists of 996 patients with psychiatric disorders recruited during intakes at the outpatient clinic of the Department of Psychiatry at the Amsterdam University Medical Centers (UMC), location Academic Medical Center (AMC). The Amsterdam UMC is an expertise center for obsessive-compulsive related disorders, depressive disorders, psychosis, and misophonia. Inclusion criteria were: age 14-75 years, ability to give informed consent, a *DSM-IV-TR* or *DSM-5* diagnosis as determined by a trained psychiatrist, and fluent in Dutch. Exclusion criteria were: acute high risk of suicide (i.e., suicidal behavior requiring immediate and urgent attention), premorbid IQ<70, history of seizure or clinically significant abnormality of the neurological system.

Procedure

The Across study is an ongoing, longitudinal research project that collects data on cognitive functioning, psychopathology symptoms, and biological parameters (<https://osf.io/yhvtb/>). The full study and procedure are described in Nieman, Chavez-Baldini, Vulink, Smit, van Wingen, de Koning, Sutterland, Mocking, Bockting, Verweij, Lok, Denys ³⁸. After an intake at the Department of Psychiatry of the Amsterdam UMC, location AMC, patients were invited to participate after being briefed about the study, and written informed consent was obtained from participants if they agreed to participate. Participants were able to participate at any point of their clinical trajectory (e.g., before, during, or after treatment); note that one-third to one-half of patients who have an intake at the Amsterdam UMC do not start treatment. Participants could discontinue participation from the study or parts of the study at any time.

The current study used data from baseline questionnaires on psychopathological symptoms and other clinically-relevant factors, such as self-esteem. Questionnaires were administered on a computer during a research session, which took about 30 minutes to an hour to complete. The study protocol was approved by the Medical

Ethical Review Committee of the Amsterdam UMC (ABR no. NL55751.018.15), and data are stored according to European privacy laws.

Measures

At the time the Across study was designed, there was not a validated questionnaire that comprehensively covered different existential concerns. Therefore, items related to existential domains of identity, autonomy, recognition of psychiatric disorder, and social functioning and connection were selected from the Psychiatric Dimensions Questionnaire and the Self-esteem Rating Scale- Short Form (SERS-SF) to create a limited inventory of existential concerns. The Psychiatric Dimensions Questionnaire assesses a variety of transdiagnostic concepts that are commonly affected in patients with a psychiatric disorder: affect, volition, identity, cognition, reality, and vitality^{38,39}. It was developed at the Amsterdam UMC³⁹ and consists of 26 items. The SERS-SF measures self-esteem in relation to self-worth, social competence, abilities, self-competence, and worth compared with others⁴⁰. It consists of 20 items that are rated on a scale from 0 (strongly disagree) to 6 (strongly agree). The SERS-SF demonstrates high internal consistency for the positive and negative scales (respectively, $\alpha = 0.91$ and $\alpha = 0.87$) and good test-retest reliability for each scale (respectively, $r = 0.90$ and $r = 0.91$)⁴⁰.

Psychopathological symptoms included in this study were assessed with the Hamilton Anxiety Scale (HAM-A), the Inventory of Depressive Symptomatology Self-Report (IDS-SR₃₀), and Prodromal Questionnaire 16 (PQ-16), which are validated and psychometrically-sound questionnaires. The HAM-A measures the severity of somatic, cognitive, and affective symptoms of anxiety⁴¹. It consists of 13 items that are rated on a scale of 0 (not present) to 4 (severe). The HAM-A demonstrates satisfactory interrater reliability and concurrent validity⁴². The IDS-SR measures the severity of depressive symptoms pertaining to mood, cognition, arousal, suicidality, and sleep⁴³. It consists of 30 items that are rated on a scale from 0 (symptom is not present) to 3 (strongest impairment). The IDS-SR also demonstrates good internal consistency ($\alpha = 0.85$) and satisfactory psychometric properties⁴⁴. Because a number of items from the IDS- SR₃₀ and HAM-A overlap (e.g., both ask about depressed and anxious mood), total scores of the shortened versions which focus on core symptoms of each domain were used to avoid multicollinearity: Quick IDS-SR QIDS-SR-16;⁴⁵ and HAM-A₆⁴⁶. Both the QIDS-SR⁴⁵ HAM- A₆⁴⁷ also demonstrate satisfactory psychometric properties. The PQ-16 assesses the occurrence and severity of At Risk Mental State symptoms for a first psychosis⁴⁸. It consists of 16 items (2 negative symptoms, 5 unusual thought content/delusional ideas/paranoia, and 9 on perceptual abnormalities/hallucinations) which participants first endorse the

presence of a symptom (true or false) and then rate the severity from 0 (no distress) to 3 (severe distress). The PQ-16 demonstrates an all item-total correlations of at least 0.31 and good internal consistency ($\alpha = 0.77$)⁴⁸.

Age, gender, diagnostic category, and use of psychotropic medication were included as covariates in the network. Age and gender were obtained from a demographic questionnaire. Diagnostic category and treatment were obtained from the participants' medical records. The diagnosis is determined by a psychiatrist and categorized into 7 categories: schizophrenia spectrum and other psychotic disorders, depressive disorders, anxiety disorders, obsessive-compulsive and related disorders, misophonia (impulse-control disorder NOS), bipolar disorder, and other disorders. Use of psychotropic medication includes antidepressants, antipsychotics, benzodiazepines, psychostimulants, and mood stabilizers and is coded as a binary variable of 0 (no) and 1 (yes).

Nodes that were included in the network can be viewed in Table 1, excluding covariates. Each node represents either an existential factor or a symptom domain. To create the existential factor nodes, individual items were collapsed with content-based selection and weighted topological overlap approach using the R-package *EGAnet*⁴⁹.

Table 1. Nodes and labels.

Node Label	Items	Measure (item no.)
Aut Autonomy	Do you feel you are in control of yourself? (reversed); Do you feel that you can choose freely when you have to make a decision? (reversed); Do you have the motivation and drive to start new activities? (reversed)	Dimensions (3 + 8 + 9)
Rec Recognition of psychiatric disorder	Do you suffer because of your current mental state?; I have a psychiatric disorder	Dimensions (7 + 16)
Id Identity	Do you feel like you are a stranger to yourself?; I wish that I were someone else	Dimensions (17) + SERS-SR (20)
Soc Social	I feel confident in my ability to deal with people (reversed); My friends value me a lot (reversed)	SERS-SR (2 + 14)
Anx Anxiety symptoms	Total score	HAM-A ₆ (total score)
Dep Depression symptoms	Total score	QIDS-SR (total score)
Psy (Subclinical) psychotic symptoms	Total score (severity)	PQ-16 (severity score)

Note: In the "Measure (item no.)" column, the questionnaire and the item number that each node represents is noted. Variables are coded so that a higher score on an item implies greater severity.

Abbreviations: Dimensions = Psychiatric Dimensions Questionnaire, QIDS-SR= Quick Inventory of Depressive Symptomatology Self-Report, HAM-A= Hamilton Anxiety Scale, PQ-16 = Prodromal Questionnaire 16, SERS-SR= Self-esteem Rating Scale- Short Form.

Data Analyses

Analyses were conducted using R version 3.6.1⁵⁰. We estimated cross-sectional regularized networks of existential concerns (continuous), psychopathological symptoms (continuous), and covariates (continuous and categorical). In a network, variables are represented by nodes and the relationship between variables are represented by edges. To account for continuous and categorical variables, we estimated mixed graphical models (MGM) using the R-package *mgm*⁵¹, in which edges are statistically defined by the nodewise regression coefficient. MGM uses casewise deletion for analyses⁵¹, so participants with at least one missing data point were removed. To create sparse networks, models were estimated with the least absolute shrinkage and selection operator (LASSO), using the Extended Bayesian Information Criterion (EBIC) and a gamma of 0.5, which reduces false positive edges by shrinking all edge weights and setting the smallest to zero. This produces a network with non-zero edges, or edges that have a weight greater than zero as an edge weight of zero indicates that there is no edge. After estimation, networks were visualized as undirected networks with the R-package *qgraph*⁵², using the “circle” layout and colorblind theme.

The centrality metric of expected influence (EI) was computed using the R-packages *qgraph*⁵². EI assesses a node’s cumulative influence in a network and is calculated as the summed weight of its edges while taking into account negative edges⁵³. EI can give insight into a node’s role in the “activation, persistence, and remission of the network”⁵³. To check for the influence of variable properties on centrality, EI was correlated with infrequency of endorsement, means, variance, and standard deviations of variables^{54,55}.

To assess the accuracy of edge weights, differences between edges and centralities, and the stability of centralities, stability checks were conducted using *bootnet* as detailed in Epskamp, Borsboom, Fried⁵⁶. This results in bootstrapped non-parametric confidence intervals based on 1,000 bootstrap samples, which are used to indicate the accuracy of the edge weights and differences between edges and centralities. Case-drop bootstrapping based on 1,000 bootstrap samples produces a correlation-stability (CS) coefficient, which indicate the stability of centralities. A CS coefficient should not be below 0.25 and preferably above 0.5⁵⁶.

As sensitivity analyses, a control network without misophonia was estimated, given that it was the largest group (35.7% of the sample) and may impact the whole sample estimates. Centralities were computed and stability checks were conducted for this control network. Given differences in estimation methods (i.e., differing diagnostic variable levels), a network comparison test cannot be used to compare the main

and control network. Therefore, similarities between the main and control network were evaluated using the correlation between edge lists as a global measure of network similarity, the percentage of individual edges that are replicated, correlations of centralities between networks, and replication of the most central symptoms.

Results

Sample characteristics

Data from 996 participants collected between 2012 and 2022 were included in the analyses. 4.5% of measurements took place after the start of COVID-19, meaning that a majority of measurements took place beforehand. 1155 patients participated in the study, but 159 were excluded because of missing data. Data was determined to be missing at random (MAR) through inspection and according to Little's Missing Completely at Random (MCAR) test ($\chi^2=36.7$, DF= 32, $p=0.261$). The distribution of the primary diagnosis reflects the naturalistic patient population of the Amsterdam UMC. Sample characteristics can be seen in Table 2. Variables' scores are shown in Table S2 in the Supplementary materials.

Network analysis

The network of existential concerns and symptoms is visualized in Figure 1.

The whole sample network contained 14 non-zero edges out of 21 possible edges (excluding edges with and between covariates), 100% of which were positive. This indicates that existential concerns were overall related to worse psychopathology. Generally, the network appears to be stable as indicated by the generally narrow confidence intervals of the edge weights (Figure S1 in the Supplementary materials). The strongest cross-domain edge was between recognition of psychiatric disorder and anxiety (weight= .28), in which stronger recognition of psychiatric disorder was related to worse anxiety. This edge was significantly different from 9 other edges (Figure S2 in the Supplementary materials). Existential concerns were most strongly related to depressive and anxiety symptoms whereas psychosis was related to identity. The edge matrix for the network can be viewed in Table S3 and results of stability checks can be viewed in Figures S1-S4 in the Supplementary materials.

Table 2. Demographic and clinical characteristics of participants.

Characteristics	Whole sample (N= 996)
Age (years), mean (SD)	34.8 (14.0)
Gender, women, No. (%)	548 (55)
Completed education ^a , No. (%)	
Low	99 (9.9)
Middle	311 (31.2)
High	585 (58.7)
Unknown	1 (0.1)
DSM diagnostic category ^b , No. (%)	
Schizophrenia spectrum and other psychotic disorders	139 (14.0)
Depressive disorder	125 (12.6)
Anxiety disorder	49 (4.9)
Obsessive-compulsive and related disorders	218 (21.9)
Misophonia	356 (35.7)
Bipolar disorder	33 (3.31)
Other disorders	76 (7.6)
Comorbidity, No. (%)	260 (26.1)
Medication use, No. (%)	
Antidepressants	247 (24.8)
Antipsychotics	126 (12.7)
Benzodiazepines	27 (2.7)
Psychostimulants	9 (0.9)
Mood stabilizers	8 (0.8)
Other (non-psychotropic) ^c	165 (16.6)
None	414 (41.6)

Note: SD= standard deviation, DSM= Diagnostic and Statistical Manual of Mental Disorders, NOS= not otherwise specified.

^a Based on Verhage⁵⁷: low (1 through 4: less than or equal to primary education or low-level secondary education), middle (5: average-level secondary education), high (6 and 7: high-level secondary education or university degree).

^b Diagnostic category is only for the primary diagnosis. Specific diagnoses can be viewed in Table S1 in the Supplementary Materials.

^cOther medication includes: anti-inflammatory, anti-histamines, anti-epilepsy, contraceptives, cholesterol medication, corticosteroids, dopamine-agonists, and various supplements.

Anxiety had the highest EI overall, meaning that it had the highest cumulative influence in the network as determined by the summed weight of its edges, and the existential factor with the highest EI was autonomy with identity as a close second. Autonomy and identity were significantly different from 4 other nodes, but were not significantly different from each other (Figure S3 in the Supplementary Materials). EI is highly stable with a CS coefficient of 0.75, meaning that 75% of the data could be dropped and retain a correlation of 0.7 with the original dataset with 95% certainty. Furthermore, EI was not significantly correlated with infrequency of endorsement

($r = -.07, p = .88$), mean ($r = .64, p = .12$), variance ($r = .59, p = .16$), or standard deviation ($r = .63, p = .13$) of nodes, indicating the EI was not influenced by variable properties.

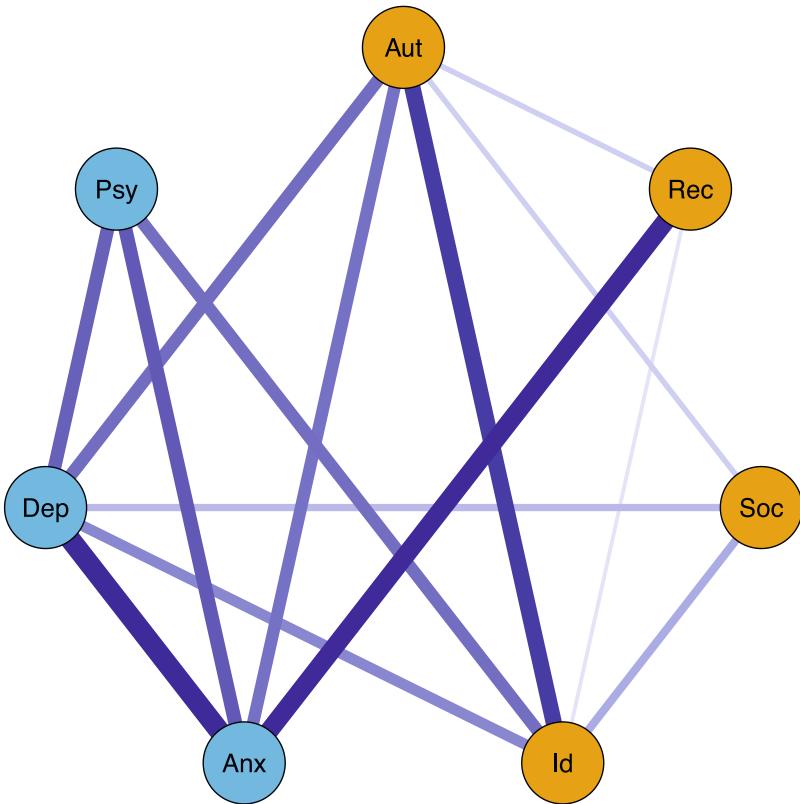


Figure 1. Transdiagnostic networks of existential concerns and psychopathological symptoms. Nodes represent the variables included in the network and edges indicate an association between two nodes. Blue edges represent positive associations whereas red edges represent negative associations, and thickness of an edge represents the strength of association between two nodes. The color of each node indicates to which overarching domain it belongs: existential concerns (yellow) and symptoms (blue).

Abbreviations: Anx = Anxiety symptoms, Aut = Autonomy, Dep = Depressive symptoms, Id = Identity, Psy = (Subclinical) psychotic symptoms, Rec = Recognition of psychiatric disorder, Soc = Social

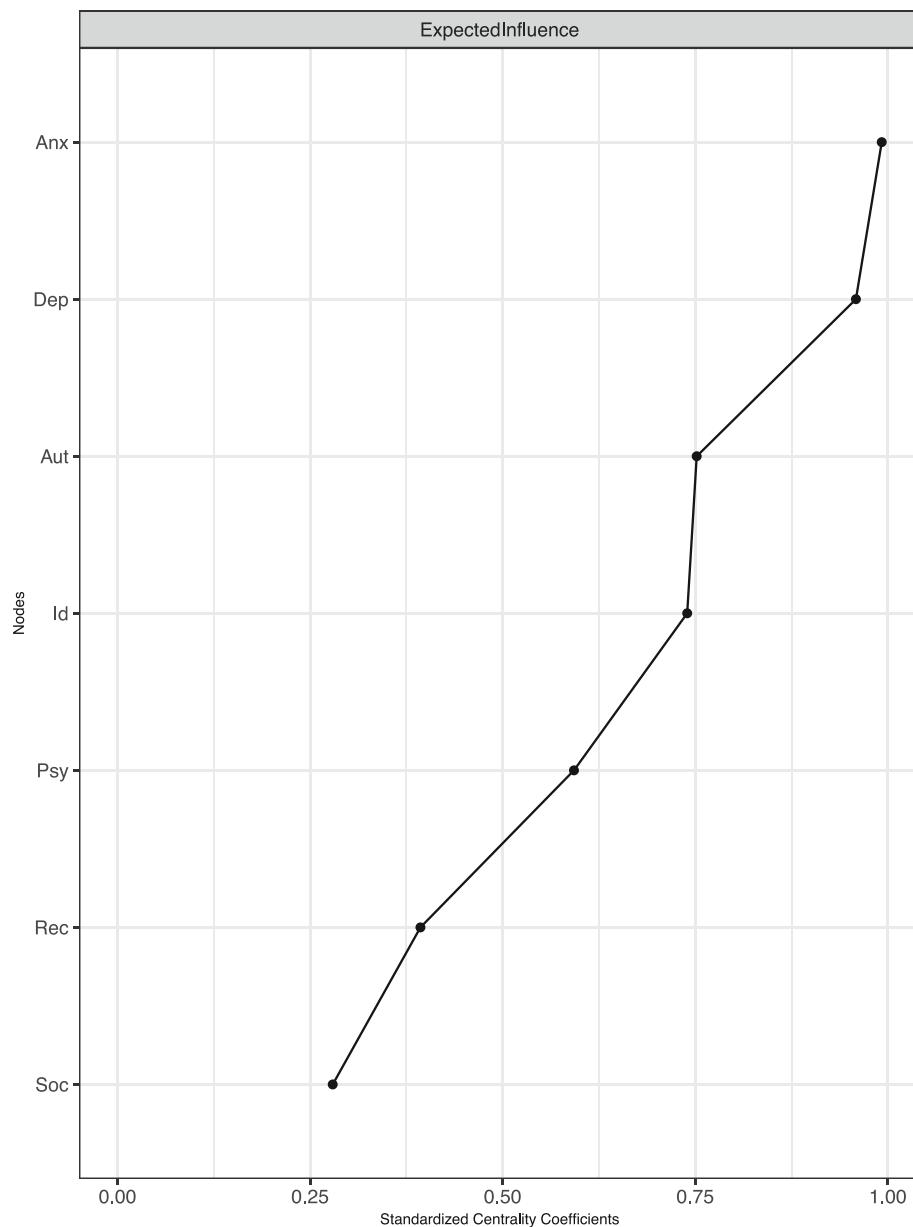


Figure 2. Centrality plots of expected influence. The nodes are denoted on the y-axis and the standardized centrality coefficients are denoted on the x-axis. Higher z-scores indicate higher centrality.

Abbreviations: Anx = Anxiety symptoms, Aut= Autonomy, Dep= Depressive symptoms, Id= Identity, Psy= (Subclinical) psychotic symptoms, Rec= Recognition of psychiatric disorder, Soc= Social

Effects of covariates can also be viewed in Table S3. Across all networks, diagnosis had the most relationships with the existential concerns and symptoms. Diagnosis had the strongest relationship with recognition of psychiatric disorder and depressive symptoms.

The control network without misophonia ($n= 640$) resulted in 13 non-zero edges, 100% of which were positive. The control network also appears to be stable as indicated by the narrow confidence intervals of the edge weights (Figure S7 in the Supplementary materials). The edges of the main and control network were strongly correlated ($r= .96, p< .001$). 91% of the edges in the control network were replicated in the main network and 86% of the edges in the main network were replicated in the control network. The edge between recognition of psychiatric disorder and anxiety as the strongest (weight= .32) was replicated, which was significantly different from 9 other edges (Figure S8 in the Supplementary materials). Autonomy and identity also had the highest EI out of the existential concerns, which were significantly different from 3 other nodes, but were not significantly different from each other (Figure S9 in the Supplementary materials), and the overall EI is significantly correlated between the main and control networks ($r= .98, p< .001$). EI demonstrated high stability (CS coefficient= .75). The control network, centrality plots, and stability and difference tests can be viewed in the Supplementary Materials (Figures S5-S10).

Discussion

This study for the first time investigated existential concerns and symptoms in patients with various psychiatric disorders from a transdiagnostic perspective using network analysis. In a large naturalistic cohort, we found that worse symptom severity was related to worse existential concerns and that autonomy and identity were highly influential nodes in the network. The findings highlight the importance of including existential concerns in psychiatric research.

Overall, we found that existential concerns were mostly related to anxiety and depressive symptoms. This is in line with previous existential works in which existential concerns are an integral part of psychiatric suffering and especially deeply intertwined with anxiety and depression^{3,58}. The literature on the general population and patients with cancer also shows a clear relation between existential concerns and negative emotional states, such as anxiety and depression e.g.,^{59,60-62}. Some consider anxiety and depression to be existential states in and of themselves and numerous existential philosophers and psychiatrists (e.g., Paul Tillich⁶³, Viktor Frankl⁶⁴, Irvin Yalom³, and Martin Heidegger⁶⁵, among others) have posited that psychopathology is a reaction to or extension of existential concerns. For instance, anxiety can manifest when one confronts existential concerns, such as death e.g.,⁶³, or depression can be

an outcome of a sense of meaninglessness e.g.,⁶⁶. Over time, these experiences of anxiety or depression can become pathological and pathologized⁶⁷. However, not all psychopathology results from existential concerns. Experiencing a chronic illness, including a psychiatric disorder, can make one more acutely aware of existential concerns as one grapples with what it means to live with a disorder, though^{3,13}.

The strongest cross-domain relationship was between recognition of psychiatric disorder and anxiety symptoms. This could potentially reflect the “insight paradox,” in which increased insight can have positive effects, such as better clinical and psychosocial outcomes, while also having negative effects, such as decreased well-being and depression⁶⁸⁻⁷⁰. Shame and self-stigma can be related to insight⁷¹, and studies have shown relationships between shame, self-stigma, and anxiety symptoms^{72,73}. As observed in the clinic, recognition could increase also anxiety as patients realize the severity of their situation and the uncertainty of their trajectory and outcomes, especially if they have a family history of mental illness—an observation that merits further investigation. Additionally, psychopathology can cause suffering beyond symptomatology due to negative effects, such as impaired functioning, losses in several life domains, and thwarted motivations⁷¹. For instance, one can perceive oneself as worthless for being depressed or worry about potential consequences of having a disorder⁷⁴. Suffering due to psychopathology can be considered transdiagnostic and related to negative mood and anxious apprehension⁷¹. Altogether, this finding further supports the importance of targeting not only symptoms but the behaviors, thoughts, and outcomes in response to the symptoms and their meaning to the patient.

Autonomy and identity had the highest expected influence and were nodes that most strongly related to all other existential concerns and symptoms, except for (subclinical) psychotic and anxiety symptoms, respectively. Autonomy can be described as the capacity of an individual that enables them to live a meaningful life of their own making¹⁸ and is considered a basic psychological need to function effectively and for well-being⁷⁵. Compromised autonomy, including perceived lack of control and avolition, can be related to depression and negative affect^{76,77}. Additionally, a possible relation is seen between autonomy and mental disorders, in which autonomy can be differently affected in mental disorders according to the underlying psychopathology¹⁸.

As found in previous literature, many individuals with psychiatric disorders struggle with a loss of self and identity^{13,14}. Identity disturbance has been associated with numerous psychiatric disorders^{78,79} and could be considered a transdiagnostic construct. It has also been shown to be specifically related to depression severity

⁸⁰ and psychosis or psychotic-like experiences ^{81,82}. Bergamin, Luigjes, Kiverstein, Bockting, Denys ¹⁸ posit that in depression and psychosis, a loss of autonomy relates more to an affected sense of identity and motivations. Interestingly, autonomy and identity were the most strongly related of all other existential concerns. Supporting autonomy and positive identity formation may therefore be areas for intervention. For instance, self-stigma can thwart both autonomy and identity ^{18,71} and could be a potential mechanism to intervene on.

Whether existential concerns overlap with, lead to or arise from psychopathology, addressing these concerns in psychiatric research and practice is important ³⁶, especially because many patients find that symptom-reduction alone is insufficient as treatment outcome ^{30,31}. Addressing existential concerns may sometimes fall out of the scope or capacity of conventional care. Existential psychotherapy, which was conceptualized by Irvin Yalom through a psychodynamic model ^{3,83}, and social prescribing are examples of supplementary or alternative interventions that address existential and social needs e.g., ^{3,84}. Third-wave therapies, such as Acceptance and Commitment therapy (ACT), and the emerging process-based therapies and approaches are also turning their attention to more existential themes. Recovery-oriented frameworks and interventions may also prove fruitful, such as the CHIME model, which focuses on empowerment and meaning in life ⁸⁵. It could also be possible to address existential concerns in standard psychotherapy by targeting underlying psychological constructs (e.g., self-efficacy for autonomy) ¹⁸. Existential concerns should be treated as part of the lived experience and not pathologized, however. Peer support workers can in this case be instrumental in aiding existential recovery ⁸⁶. Further research is necessary to differentiate between general existential concerns and psychopathology to avoid overtreatment and give opportunity for personal growth ⁶⁷.

The main strengths of the study pertain to the naturalistic and transdiagnostic nature of the sample and instruments and the relatively large sample size. Our results were stable, and we included some demographic and clinical characteristics as covariates to limit confounding effects. Furthermore, we performed sensitivity and control analyses to check for the effect of misophonia and variable properties on our main findings, lending support to the validity of our results.

Nonetheless, the results of this study should be interpreted with a number of limitations. First, the cross-sectional design prevents any directional or causal interpretations of relationships and decreases robust interpretation of centrality as it does not always translate to mechanisms of change nor can we ascertain directionality of influence ⁵⁴. However, cross-sectional networks have exploratory

value and may be useful to investigate the co-occurrence of symptoms or other clinical factors and generate hypotheses^{87,88}. Furthermore, existential concerns were not derived from questionnaires specifically measuring existential concerns, which may reduce validity of the items included in this network. The Across study was also not specifically designed to investigate existential themes, meaning that our operationalization of these themes is not thorough and that not all potential existential themes are included in this study. As a result, our hypotheses and analyses of these themes remained exploratory. Sum scores of symptom questionnaires were also used, which can lead to a loss of information about relationships between individual items. This was done to reduce the number of nodes in the network due to the exploratory nature of this study.

Additionally, sample bias may have played a role, such that those with worse psychopathology were less likely to participate. The overrepresentation of misophonia in the sample could be a reflection of this, but we conducted a sensitivity analysis for this. Lastly, while the sample size was relatively large, the diagnostic categories were not large enough to compare individual diagnosis networks. Support for the transdiagnostic nature of our findings is therefore less robust. We did however include diagnosis as a covariate in the network in order to control for potential diagnostic effects. Lastly, we were not able to take into account the potential impact of somatic diseases and conditions, such as cancer, which have been shown to affect existential concerns. As psychiatric disorders and somatic diseases regularly co-occur, it is necessary for future research on existential concerns and psychopathology to include somatic diseases as a potential factor.

Overall, the findings of this study further support the importance of including existential concerns in psychiatric research. While there is evidence that individuals with psychiatric disorders grapple with existential concerns, further research is needed to investigate the interplay of existential concerns and dimensions of psychopathology, especially with dynamic and longitudinal designs to determine directionality of relationships and more robustly elucidate potential treatment targets.

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References

1. Koole SL, Greenberg J, Pyszcynski T. Introducing Science to the Psychology of the Soul: Experimental Existential Psychology. *Curr Dir Psychol Sci.* 2006;15(5):212-216.
2. Koole SL. Existential psychology. *The Corsini Encyclopedia of Psychology.* 2010:1-2.
3. Yalom ID. *Existential psychotherapy.* New York: Basic Books; 1980.
4. de Haan S. The existential dimension in psychiatry: an enactive framework. *Mental Health, Religion & Culture.* 2017;20(6):528-535.
5. Greenberg J, Koole SL, Pyszcynski TA. *Handbook of experimental existential psychology.* Guilford Press; 2004.
6. Damsgaard JB, Overgaard CL, Birkelund R. Personal recovery and depression, taking existential and social aspects into account: A struggle with institutional structures, loneliness and identity. *Int J Soc Psychiatry.* 2021;67(1):7-14.
7. Huguelet P. The Contribution of Existential Phenomenology in the Recovery-Oriented Care of Patients with Severe Mental Disorders. *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine.* 2014;39(4):346-367.
8. Wagner LC, King M. Existential needs of people with psychotic disorders in Pôrto Alegre, Brazil. *Br J Psychiatry.* 2005;186(2):141-145.
9. Søberg AIB, Kjørven Haug SH, Danbolt LJ, Lien L, Sørensen T. Existential themes in the treatment of people at suicide risk. Understandings and practices of specialist healthcare professionals. *Mental Health, Religion & Culture.* 2018;21(6):588-600.
10. Iverach L, Menzies RG, Menzies RE. Death anxiety and its role in psychopathology: Reviewing the status of a transdiagnostic construct. *Clin Psychol Rev.* 2014;34(7):580-593.
11. Yager J. Addressing Suffering in Patients With Psychiatric Disorders. *J Nerv Ment Dis.* 2021;209(9):615-621.
12. Herron SJ, Sani F. Understanding the typical presentation of emptiness: a study of lived-experience. *Journal of Mental Health.* 2022;31(2):188-195.
13. Kaite CP, Karanikola M, Merkouris A, Papathanassoglou EDE. "An Ongoing Struggle With the Self and Illness": A Meta-Synthesis of the Studies of the Lived Experience of Severe Mental Illness. *Arch Psychiatr Nurs.* 2015;29(6):458-473.
14. Wisdom JP, Bruce K, Auzeen Saedi G, Weis T, Green CA. 'Stealing Me from Myself': Identity and Recovery in Personal Accounts of Mental Illness. *Aust N Z J Psychiatry.* 2008;42(6):489-495.
15. Persike M, Seiffge-Krenke I, Cok F, et al. Emerging Adults' Psychopathology in Seven Countries: The Impact of Identity-Related Risk Factors. *Emerging Adulthood.* 2020;8(3):179-194.
16. Hill RM, Pettit JW. The Role of Autonomy Needs in Suicidal Ideation: Integrating the Interpersonal-Psychological Theory of Suicide and Self-Determination Theory. *Archives of Suicide Research.* 2013;17(3):288-301.
17. van Bergen DD, Saharso S. Suicidality of young ethnic minority women with an immigrant background: The role of autonomy. *European Journal of Women's Studies.* 2016;23(3):297-311.
18. Bergamin J, Luigjes J, Kiverstein J, Bockting CL, Denys D. Defining Autonomy in Psychiatry. *Frontiers in Psychiatry.* 2022;13.
19. Chou K-L, Liang K, Sareen J. The association between social isolation and DSM-IV mood, anxiety, and substance use disorders: wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *The Journal of clinical psychiatry.* 2011;72(11):0-0.
20. Leigh-Hunt N, Baggaley D, Bash K, et al. An overview of systematic reviews on the public health consequences of social isolation and loneliness. *Public Health.* 2017;152:157-171.
21. Ryan RM, Deci EL. Autonomy Is No Illusion: Self-Determination Theory and the Empirical Study of Authenticity, Awareness, and Will. In: *Handbook of Experimental Existential Psychology.* New York, NY, US: Guilford Press; 2004:449-479.
22. Pinel EC, Long AE, Murdoch EQ, Helm P. A prisoner of one's own mind: Identifying and understanding existential isolation. *Pers Individ Dif.* 2017;105:54-63.
23. Saeri AK, Cruwys T, Barlow FK, Stronge S, Sibley CG. Social connectedness improves public mental health: Investigating bidirectional relationships in the New Zealand attitudes and values survey. *Aust N Z J Psychiatry.* 2018;52(4):365-374.

24. Chawla S, Menzies RE, Menzies RG. Existential concerns in OCD with aggressive and sexual obsessions. *Journal of Obsessive-Compulsive and Related Disorders*. 2022;32:100710.
25. Kretschmer M, Storm L. The relationships of the five existential concerns with depression and existential thinking. *Int J Existence Psychol Psychother*. 2018;7:20.
26. Quek TC, Ho CS, Choo CC, Nguyen LH, Tran BX, Ho RC. Misophonia in Singaporean Psychiatric Patients: A Cross-Sectional Study. *Int J Environ Res Public Health*. 2018;15(7):1410.
27. Nestadt G, Samuels J, Riddle MA, et al. The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study. *Psychol Med*. 2001;31(3):481-487.
28. Wilson RS, Yung AR, Morrison AP. Comorbidity rates of depression and anxiety in first episode psychosis: A systematic review and meta-analysis. *Schizophr Res*. 2020;216:322-329.
29. Hanssen M, Peeters F, Krabbendam L, Radstake S, Verdoux H, Van Os J. How psychotic are individuals with non-psychotic disorders? *Soc Psychiatry Psychiatr Epidemiol*. 2003;38(3):149-154.
30. Binder P-E, Holgersen H, Nielsen GHs. What is a “good outcome” in psychotherapy? A qualitative exploration of former patients’ point of view. *Psychotherapy Research*. 2010;20(3):285-294.
31. Zimmerman M, McGlinchey JB, Posternak MA, Friedman M, Attiullah N, Boerescu D. How Should Remission From Depression Be Defined? The Depressed Patient’s Perspective. *Am J Psychiatry*. 2006;163(1):148-150.
32. Kogstad RE, Ekeland TJ, Hummelvoll JK. In defence of a humanistic approach to mental health care: recovery processes investigated with the help of clients’ narratives on turning points and processes of gradual change. *J Psychiatr Ment Health Nurs*. 2011;18(6):479-486.
33. Koslander T, da Silva AB, Roxberg Å. Existential and spiritual needs in mental health care: An ethical and holistic perspective. *J Holist Nurs*. 2009;27(1):34-42.
34. Ulland D, DeMarinis V. Understanding and working with existential information in a Norwegian adolescent psychiatry context: a need and a challenge. *Mental Health, Religion & Culture*. 2014;17(6):582-593.
35. van Os J, Guloksuz S, Vijn TW, Hafkenscheid A, Delespaul P. The evidence-based group-level symptom-reduction model as the organizing principle for mental health care: time for change? *World Psychiatry*. 2019;18(1):88-96.
36. Moore LJ, Goldner-Vukov M. The existential way to recovery. *Psychiatria danubina*. 2009;21(4):453-462.
37. Borsboom D, Cramer AO. Network analysis: an integrative approach to the structure of psychopathology. *Annu Rev Clin Psychol*. 2013;9:91-121.
38. Nieman DH, Chavez-Baldini U, Vulink NC, et al. Protocol Across study: longitudinal transdiagnostic cognitive functioning, psychiatric symptoms, and biological parameters in patients with a psychiatric disorder. *BMC Psychiatry*. 2020;20(1):212.
39. Nieman DH, Vulink NC, Chavez-Baldini U, Verweij K, Denys D. Psychiatric Dimensions Questionnaire. <https://osf.io/6s48a/>. Published 2021. Accessed.
40. Lecomte T, Corbière M, Laisné F. Investigating self-esteem in individuals with schizophrenia: relevance of the Self-Esteem Rating Scale-Short Form. *Psychiatry Res*. 2006;143(1):99-108.
41. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50-55.
42. Maier W, Buller R, Philipp M, Heuser I. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. *J Affect Disord*. 1988;14(1):61-68.
43. Rush AJ, Giles DE, Schlessier MA, Fulton CL, Weissenburger J, Burns C. The inventory for depressive symptomatology (IDS): preliminary findings. *Psychiatry Res*. 1986;18(1):65-87.
44. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The inventory of depressive symptomatology (IDS): psychometric properties. *Psychol Med*. 1996;26(3):477-486.
45. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573-583.
46. Bech P. *Clinical psychometrics*. John Wiley & Sons; 2012.
47. Bech P. Measuring states of anxiety with clinician-rated and patient-rated scales. *Different views of anxiety disorders Rijeka, New York, Shanghai: InTech*. 2011;4(2):169-184.
48. Ising HK, Veling W, Loewy RL, et al. The validity of the 16-item version of the Prodromal Questionnaire (PQ-16) to screen for ultra high risk of developing psychosis in the general help-seeking population. *Schizophr Bull*. 2012;38(6):1288-1296.

49. Golino H, Christensen A, Moulder R. EGAnet: Exploratory Graph Analysis: A framework for estimating the number of dimensions in multivariate data using network psychometrics. *R package version 0.9*. 2020;2.
50. R: A Language and Environment for Statistical Computing [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2020.
51. Haslbeck JMB, Waldorp LJ. mgm: Estimating Time-Varying Mixed Graphical Models in High-Dimensional Data. *J Stat Softw*. 2020;93(8):1 - 46.
52. Epskamp S, Cramer AO, Waldorp LJ, Schmittmann VD, Borsboom D. qgraph: Network visualizations of relationships in psychometric data. *J Stat Softw*. 2012;48(4):1-18.
53. Robinaugh DJ, Millner AJ, McNally RJ. Identifying highly influential nodes in the complicated grief network. *J Abnorm Psychol*. 2016;125(6):747-757.
54. Spiller TR, Levi O, Neria Y, Suarez-Jimenez B, Bar-Haim Y, Lazarov A. On the validity of the centrality hypothesis in cross-sectional between-subject networks of psychopathology. *BMC Med*. 2020;18(1):297.
55. Terluin B, de Boer MR, de Vet HCW. Differences in Connection Strength between Mental Symptoms Might Be Explained by Differences in Variance: Reanalysis of Network Data Did Not Confirm Staging. *PLoS One*. 2016;11(11):e0155205.
56. Epskamp S, Borsboom D, Fried EI. Estimating psychological networks and their accuracy: A tutorial paper. *Behav Res Methods*. 2018;50(1):195-212.
57. Verhage F. *Intelligentie en leeftijd: Onderzoek bij Nederlanders van twaalf tot zeventenzeventig jaar*. van Gorcum; 1964.
58. Bygstad-Landro M, Giske T. Risking existence: The experience and handling of depression. *J Clin Nurs*. 2018;27(3-4):e514-e522.
59. Chen W, Chen Y, Xiao H. Existential Distress in Cancer Patients: A Concept Analysis. *Cancer Nurs*. 2022;45(2):E471-E486.
60. Vehling S, Kissane DW. Existential distress in cancer: Alleviating suffering from fundamental loss and change. *Psychooncology*. 2018;27(11):2525-2530.
61. Mascaro N, Rosen DH. Existential meaning's role in the enhancement of hope and prevention of depressive symptoms. *J Pers*. 2005;73(4):985-1014.
62. Berman SL, Weems CF, Stickle TR. Existential Anxiety in Adolescents: Prevalence, Structure, Association with Psychological Symptoms and Identity Development. *J Youth Adolesc*. 2006;35(3):285-292.
63. Tillich P. *The courage to be*. New Haven: Yale University Press; 1952.
64. Frankl VE. *Man's search for meaning*. Simon and Schuster; 1985.
65. Heidegger M. *Sein und Zeit [Being and time]*. Tübingen, Germany: Max Niemeyer; 1977.
66. Frankl V. *On the theory and therapy of mental disorders: An introduction to logotherapy and existential analysis*. Routledge; 2005.
67. Nieman DH. *Prevention in mental health care: Time for a new approach*. Routledge; 2016.
68. Lysaker PH, Roe D, Yanos PT. Toward Understanding the Insight Paradox: Internalized Stigma Moderates the Association Between Insight and Social Functioning, Hope, and Self-esteem Among People with Schizophrenia Spectrum Disorders. *Schizophr Bull*. 2006;33(1):192-199.
69. Gonzalez VM. Recognition of Mental Illness and Suicidality Among Individuals With Serious Mental Illness. *J Nerv Ment Dis*. 2008;196(10):727-734.
70. Sorgaard KW, Nivison M, Hansen V, Øiesvold T. Acknowledging illness and treatment needs in first-time admitted psychiatric patients. *Eur Psychiatry*. 2011;26(7):446-451.
71. Buchman-Wildbaum T, Váradi E, Schmelowszky Á, Griffiths MD, Demetrovics Z, Urbán R. The paradoxical role of insight in mental illness: The experience of stigma and shame in schizophrenia, mood disorders, and anxiety disorders. *Arch Psychiatr Nurs*. 2020;34(6):449-457.
72. Szentágotai-Tátar A, Nechita D-M, Miu AC. Shame in Anxiety and Obsessive-Compulsive Disorders. *Current Psychiatry Reports*. 2020;22(4):16.
73. Busby Grant J, Bruce CP, Batterham PJ. Predictors of personal, perceived and self-stigma towards anxiety and depression. *Epidemiol Psychiatr Sci*. 2016;25(3):247-254.
74. Hanson B, Young MA. Why Depressive Symptoms Cause Distress: The Clients' Perspective. *J Clin Psychol*. 2012;68(7):860-874.

75. Deci EL, Ryan RM. The "what" and "why" of goal pursuits: Human needs and the self-determination of behavior. *Psychol Inq.* 2000;11(4):227-268.
76. Vansteenkiste M, Lens W, Soenens B, Luyckx K. Autonomy and Relatedness among Chinese Sojourners and Applicants: Conflictual or Independent Predictors of Well-Being and Adjustment? *Motivation and Emotion.* 2006;30(4):273-282.
77. Rouse PC, Turner PJF, Siddall AG, Schmid J, Standage M, Bilzon JLJ. The interplay between psychological need satisfaction and psychological need frustration within a work context: A variable and person-oriented approach. *Motivation and Emotion.* 2020;44(2):175-189.
78. Kaufman EA, Cundiff JM, Crowell SE. The Development, Factor Structure, and Validation of the Self-concept and Identity Measure (SCIM): A Self-Report Assessment of Clinical Identity Disturbance. *Journal of Psychopathology and Behavioral Assessment.* 2015;37(1):122-133.
79. Neacsu AD, Herr NR, Fang CM, Rodriguez MA, Rosenthal MZ. Identity Disturbance and Problems With Emotion Regulation Are Related Constructs Across Diagnoses. *J Clin Psychol.* 2015;71(4):346-361.
80. Sokol Y, Eisenheim E. The relationship between continuous identity disturbances, negative mood, and suicidal ideation. *The primary care companion for CNS disorders.* 2016;18(1):26150.
81. Cicero DC. Self-concept clarity and psychopathology. In: *Self-concept clarity.* Springer; 2017:219-242.
82. Cowan HR, Mittal VA, McAdams DP. Narrative identity in the psychosis spectrum: A systematic review and developmental model. *Clin Psychol Rev.* 2021;88:102067.
83. Shannon J. Deconstructing an Existential form of Therapy: A Review. *Romanian Journal of Counseling/Jurnalul Român de Consiliere* vol. 2019;5(1).
84. South J, Higgins TJ, Woodall J, White SM. Can social prescribing provide the missing link? *Primary Health Care Research & Development.* 2008;9(4):310-318.
85. Van Weeghel J, van Zelst C, Boertien D, Hasson-Ohayon I. Conceptualizations, assessments, and implications of personal recovery in mental illness: A scoping review of systematic reviews and meta-analyses. *Psychiatric rehabilitation journal.* 2019;42(2):169.
86. Rob Whitley PD, Robert E. Drake MD, Ph.D., Recovery: A Dimensional Approach. *Psychiatr Serv.* 2010;61(12):1248-1250.
87. Bos FM, Snippe E, de Vos S, et al. Can We Jump from Cross-Sectional to Dynamic? Interpretations of Networks Implications for the Network Perspective in Psychiatry. *Psychother Psychosom.* 2017;86(3):175-177.
88. von Klipstein L, Borsboom D, Arntz A. The exploratory value of cross-sectional partial correlation networks: Predicting relationships between change trajectories in borderline personality disorder. *PLoS One.* 2021;16(7):e0254496.

Supplementary Materials

Table S1. Specific diagnoses per diagnostic category

Diagnosis	n
Schizophrenia spectrum and other psychotic disorders (n= 139)	
Schizophrenia, Paranoid Type	39
Schizophrenia, Catatonic Type	1
Schizophrenia, Disorganized Type	5
Schizophrenia or Psychotic Disorder NOS	47
Brief Psychotic Episode	4
Schizophreniform Disorder	13
Schizoaffective Disorder	27
Delusional Disorder	3
Depressive disorders (n= 125)	
Major Depressive Disorder, Recurrent	56
Major Depressive Disorder, Single Episode	38
Dysthymic Disorder	8
Cyclothymic Disorder	1
Depressive Disorder NOS	22
Anxiety disorders (n= 49)	
Generalized Anxiety Disorder	9
Panic Disorder	11
Social Anxiety/Phobia	6
Posttraumatic Stress Disorder	16
Specific Phobia	3
Anxiety Disorder NOS	4
Obsessive-compulsive and related disorders (n= 218)	
Body Dysmorphic Disorder	31
Skin Picking (Excoriation Disorder)	13
Trichotillomania	15
Obsessive-Compulsive Disorder	159
Misophonia (Impulse control disorder NOS)	
Misophonia	356
Bipolar disorders (n= 33)	
Bipolar I Disorder	14
Bipolar II Disorder	15
Bipolar Disorder NOS	4
Other disorders (n= 76)	
Substance Use Disorders	16
Neurodevelopmental Disorders	32
Eating Disorders	5
Impulse Control Disorders	8

Table S1. (continued)

Diagnosis	n
Sleep Disorders	2
Paraphilic Disorders	1
Gender Dysphoria	1
Dissociative Disorder	1
Conduct Disorder	2
Personality Disorders	6
Adjustment disorder	2

Note: Misophonia is not an official DSM diagnosis.

Table S2. Variable scores: Mean (SD), range

Measure	All participants (N=996)	Schizophrenia/psychotic disorders (n=139)	Depressive disorders (n=125)	Anxiety disorders (n= 49)	OCD spectrum (n= 218)	Misophonia (n= 356)	Bipolar (n= 33)	Other (n= 76)	Kruskal-Wallis Test statistic
Autonomy	3.58 (1.8), 0-8	3.03 (1.7), 0-7	4.71 (1.5), 0.33-7.67	4.07 (1.8), 1-8	4.13 (1.8), 0-8	2.81 (1.6), 0-6.67	3.93 (1.8), 0.33-8	4.29 (1.6), 0.67-7.33	H(6)= 164.31***
Recognition of psychiatric disorder	3.88 (2.2), 0-8	3.05 (2.1), 0-8	4.81 (2.0), 0-8	4.34 (2.1), 0-8	4.91 (2.0), 0-8	3.18 (2), 0-8	3.85 (2.1), 0-7.5	3.89 (2.2), 0-7.5	H(6)= 131.76***
Identity	1.98 (1.7), 0-6	1.79 (1.1), 0-5.5	2.08 (1.1), 0.5-5.5	1.7 (1.2), 0-5.5	1.79 (1.1), 0-6	1.57 (0.9), 0-6	1.76 (1.3), 0-6	2.09 (1.2), 0-6	H(6)= 101.65***
Social	1.77 (1.0), 0-6	1.71 (1.7), 0-7	3.06 (1.7), 0-7	2.4 (2.0), 0-7	2.19 (1.7), 0-7	1.45 (1.4), 0-6.5	2.08 (2.0), 0-6.5	2.31 (1.5), 0-6.5	H(6)= 30.45***
Anxiety symptoms	5.98 (4.9), 0-20	4.14 (4.4), 0-20	8.85 (5.1), 0-20	8.76 (4.9), 1-18	7.41 (5.0), 0-20	4.2 (3.8), 0-18	6.21 (4.9), 0-17	7.01 (5.1), 0-18	H(6)= 149.35***
Depression symptoms	10.98 (7.0), 0-37	10.4 (6.3), 0-29	18.05 (7.0), 2-37	12.49 (6.7), 2-31	11.45 (6.5), 0-36	7.49 (5.2), 0-28	12.85 (7.0), 2-27	13.62 (6.7), 0-29	H(6)= 217.34***
(Subclinical) psychotic symptoms	5.58 (5.6), 0-33	7.1 (7.2), 0-33	7.1 (6.6), 0-29	7.1 (5.2), 0-21	5.13 (5.6), 0-31	4.23 (4), 0-22	5.85 (4.6), 0-20	6.76 (6.1), 0-32	H(6)= 39.50***

Note: Significance codes are * P≤ 0.05, **P ≤ 0.01, ***P ≤ 0.00

Table S3. Edge weights matrix

	Aut	Rec	Soc	Id	Anx	Dep	Psy	Age	Gen	Diag	Med
Aut	0										
Rec	.069	0									
Soc	.069	0	0								
Id	.246	.04	.113	0							
Anx	.182	.284	0	0	0						
Dep	.187	0	.098	.157	.317	0					
Psy	0	0	0	.184	.209	.2	0				
Age	0	0	0	0	0	0	.05	0			
Gen	0	0	0	0	0	0	0	0	0		
Diag	.091	.126	0	.063	0	.261	.147	.215	.283	0	
Med	0	.144	0	0	0	0	0	0	0	.587	0

Abbreviations: Anx = Anxiety symptoms, Aut= Autonomy, Dep= Depressive symptoms, Id= Identity, Psy= (Subclinical) psychotic symptoms, Rec= Recognition of psychiatric disorder, Soc= Social

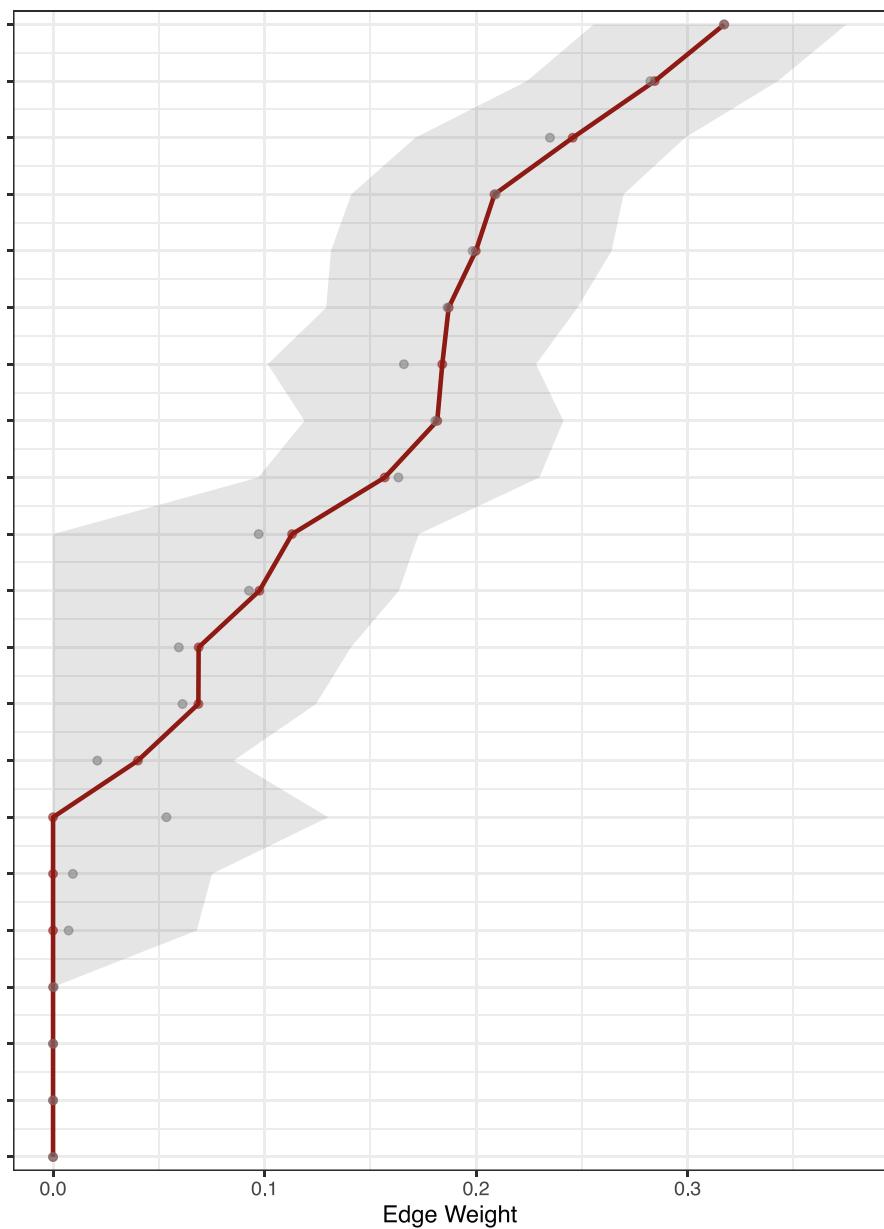
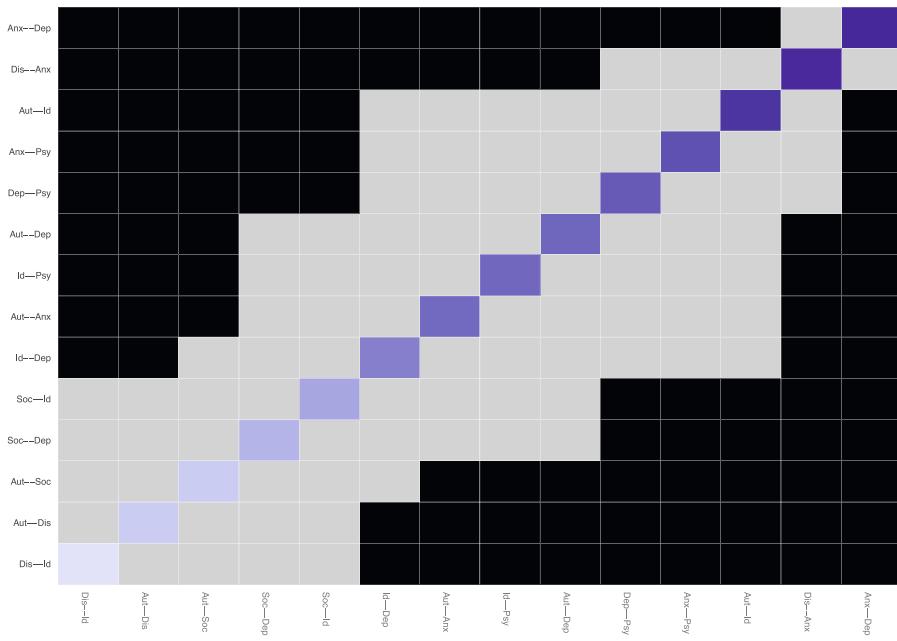
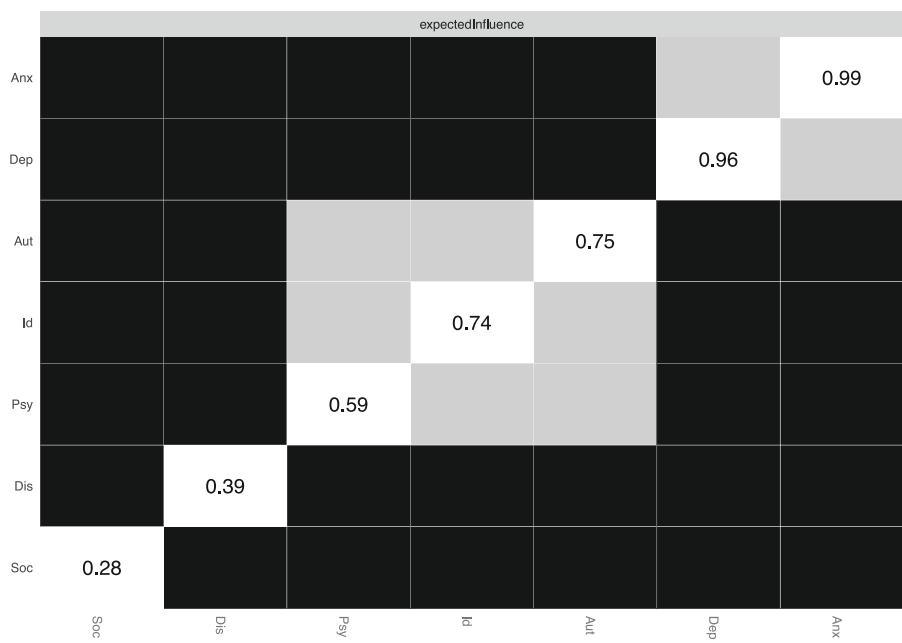


Figure S1. Edge weight confidence intervals

The x-axis shows the weight of the edge. The edges from the original network are shown in red and are arranged from most negative to most positive along the y-axis. The grey area represents confidence intervals based on the bootstrapped networks.

**Figure S2.** Difference tests of edges

Rows and columns represent the different edges in the network, with edges ordered from most negative weight (left, bottom) to most positive (right, top). Black boxes indicate that two edges differ from each other at the $\alpha = 0.05$ level.

**Figure S3.** Difference tests of centralities

Rows and columns represent the nodes in the network. Black boxes represent significant differences at the $\alpha = 0.05$ level.

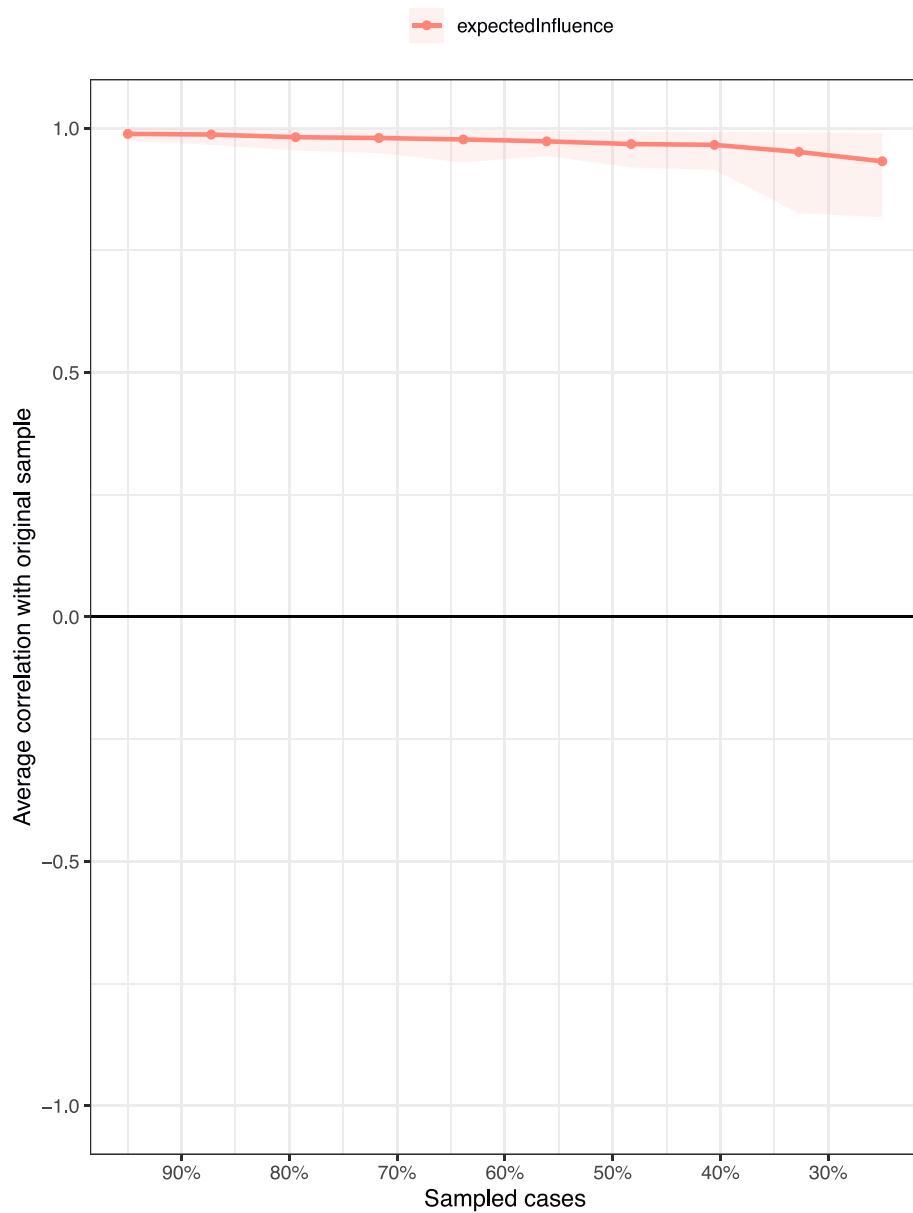


Figure S4. Stability of the centrality measures

The x-axis shows the percentage of patients that was dropped. The y-axis shows the correlation of the centralities after dropping to the original centralities. The shaded areas indicate the 95% confidence interval.

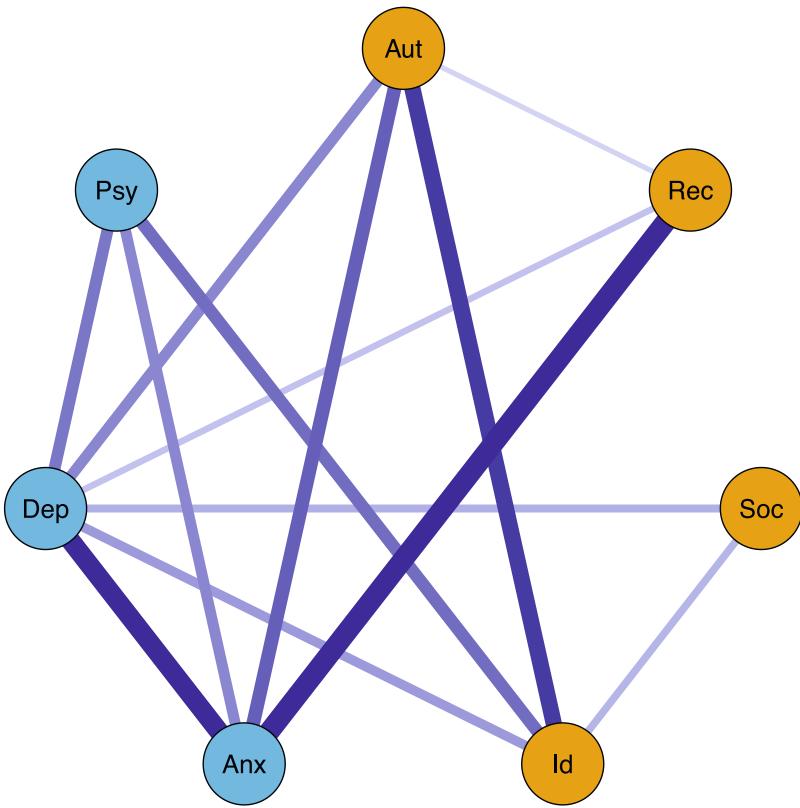


Figure S5. Transdiagnostic control network without misophonia of existential concerns and psychopathological symptoms.

Nodes represent the variables included in the network and edges indicate an association between two nodes. Blue edges represent positive associations whereas red edges represent negative associations, and thickness of an edge represents the strength of association between two nodes. The color of each node indicates to which overarching domain it belongs: existential concerns (yellow) and symptoms (blue). Abbreviations: Anx = Anxiety symptoms, Aut= Autonomy, Dep= Depressive symptoms, Id= Identity, Psy= (Subclinical) psychotic symptoms, Rec= Recognition of psychiatric disorder, Soc= Social

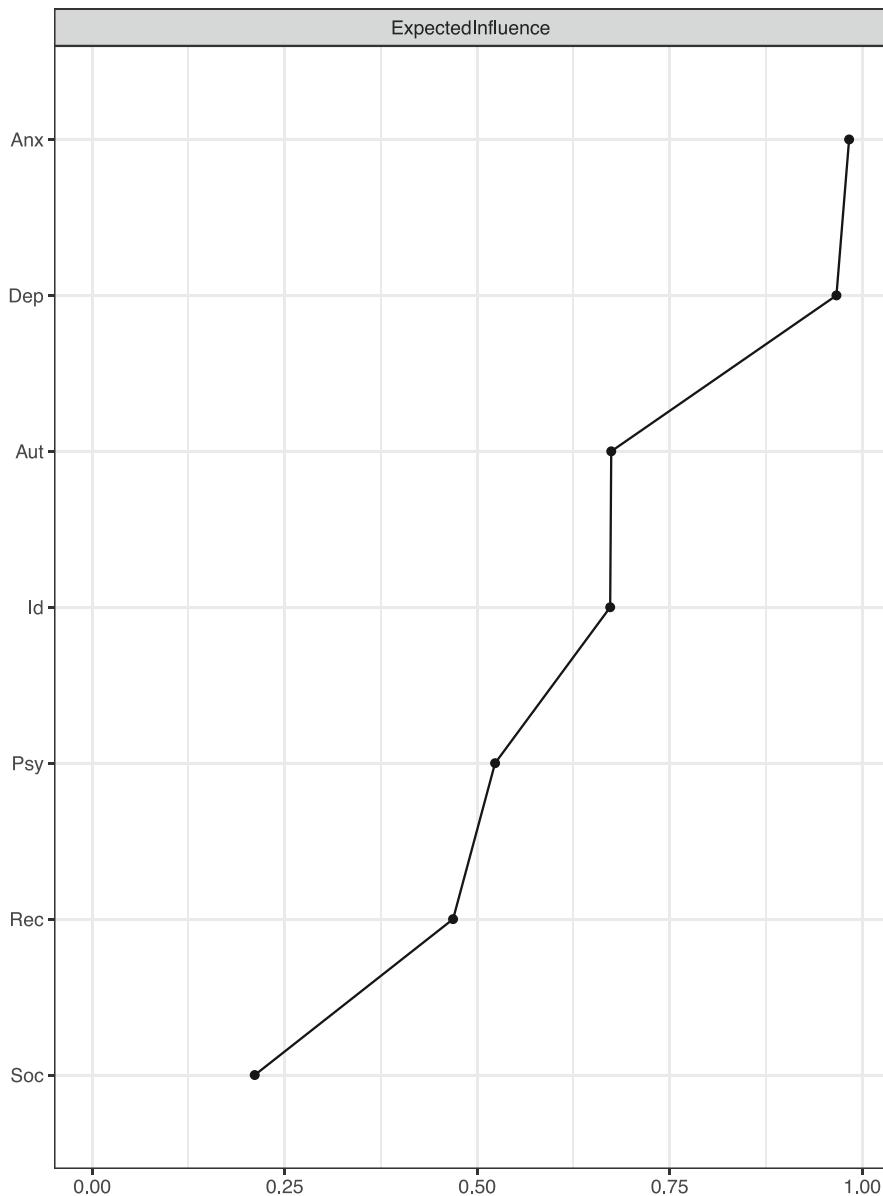


Figure S6. Centrality plots for control network without misophonia.

The nodes are denoted on the y-axis and the standardized centrality coefficients are denoted on the x-axis. Higher z-scores indicate higher centrality.

Abbreviations: Anx = Anxiety symptoms, Aut= Autonomy, Dep= Depressive symptoms, Id= Identity, Psy= (Subclinical) psychotic symptoms, Rec= Recognition of psychiatric disorder, Soc= Social

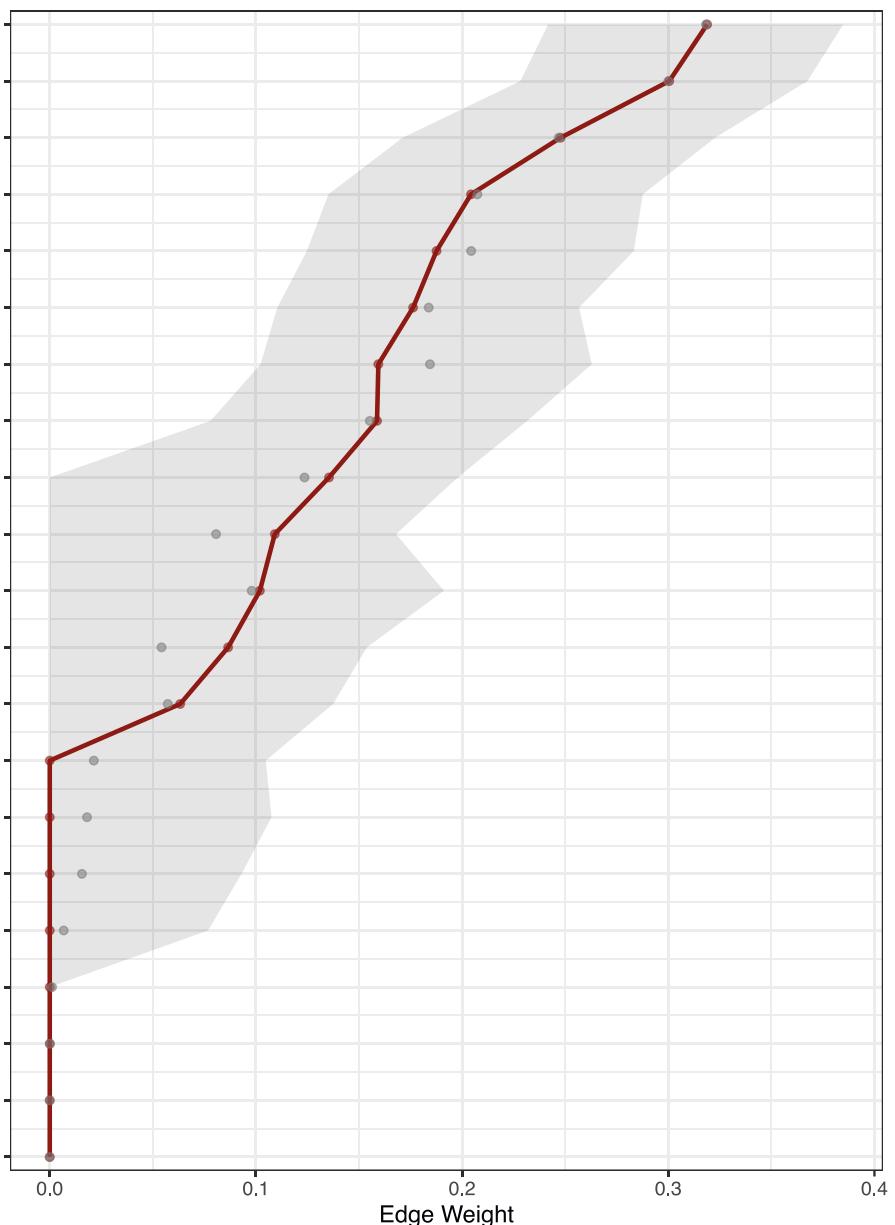
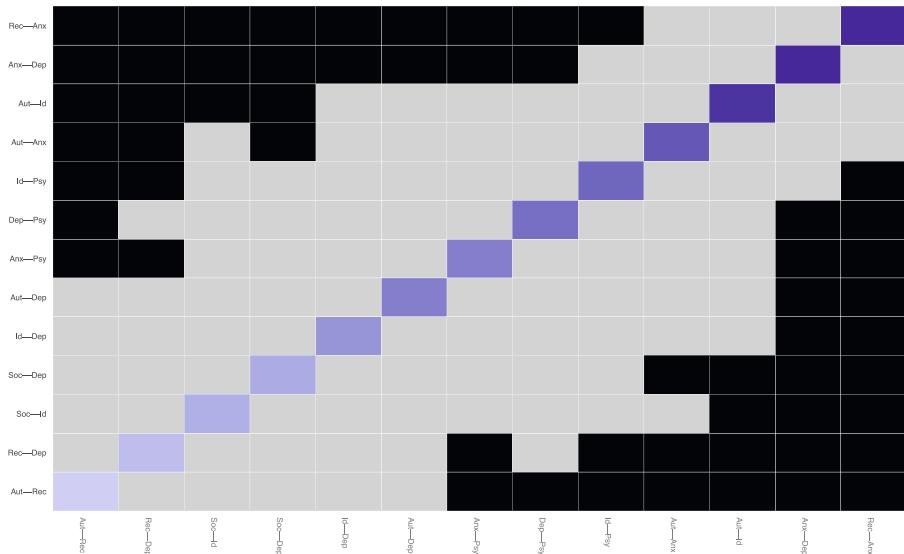
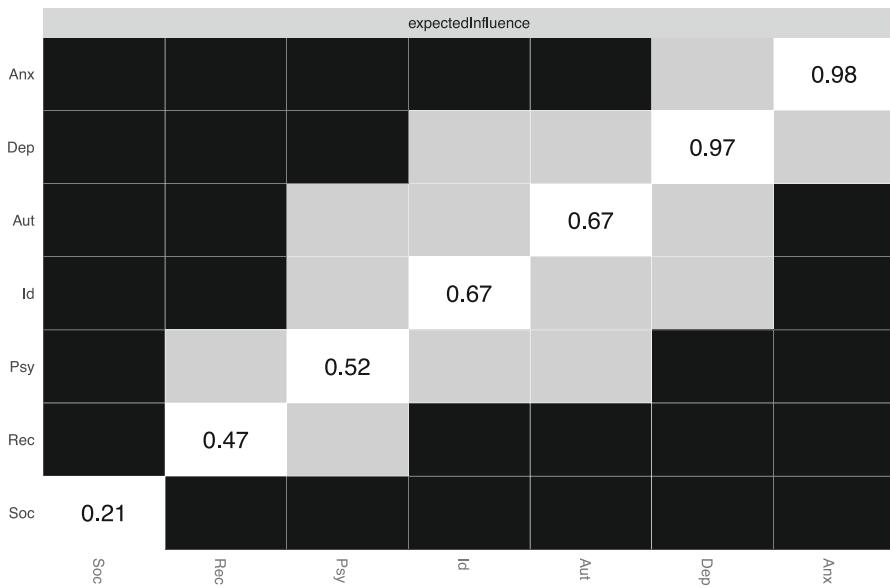


Figure S7. Edge weight confidence intervals for control network without misophonia. The x-axis shows the strength of the edge. The edges from the original network are shown in red and are arranged from most negative to most positive along the y-axis. The grey area represents confidence intervals based on the bootstrapped networks.

**Figure S8.** Difference tests of edges for control network without misophonia

Rows and columns represent the different edges in the network, with edges ordered from most negative weight (left, bottom) to most positive (right, top). Black boxes indicate that two edges differ from each other at the $\alpha = 0.05$ level.

**Figure S9.** Difference tests of centralities for control network without misophonia

Rows and columns represent the nodes in the network. Black boxes represent significant differences at the $\alpha = 0.05$ level.

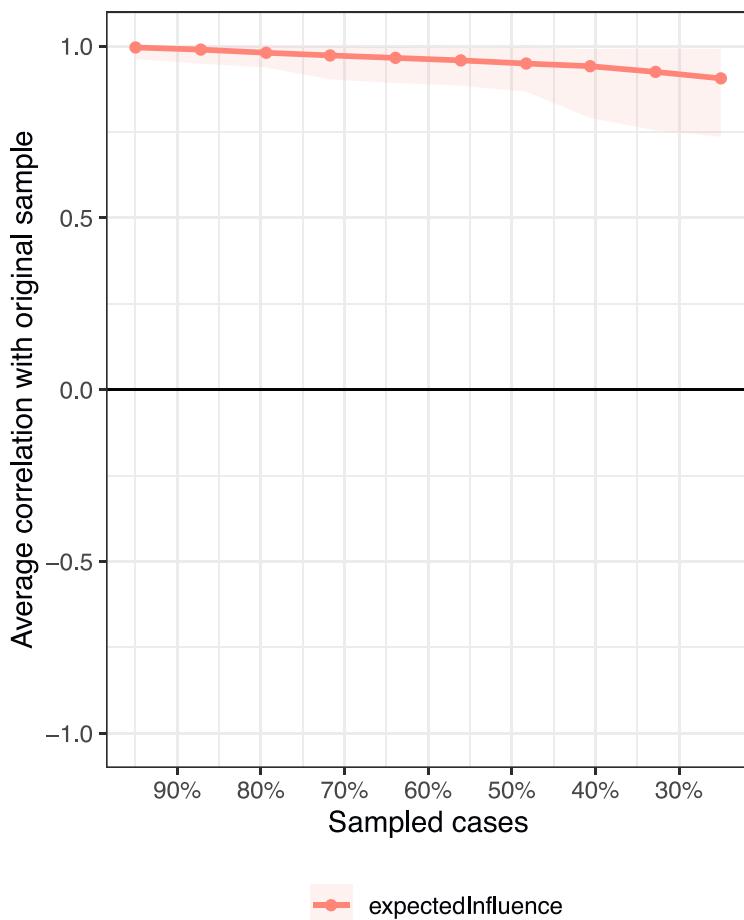


Figure S10. Stability of the centrality measures for control network without misophonia

The x-axis shows the percentage of patients that was dropped. The y-axis shows the correlation of the centralities after dropping to the original centralities. The shaded areas indicate the 95% confidence interval.



7

General Discussion

This thesis investigated the relationships between psychopathological symptoms, cognitive function, and psychological factors, such as self-esteem and existential concerns, using the transdiagnostic and network approaches. The aim was to gain insight into dimension- or symptom-level rather than diagnostic-level relationships and elucidate potential transdiagnostic processes. Progress in psychiatric research has been hindered by the focus on disorder-specific, symptom-focused designs, and the over-reliance on the *DSM* for research and treatment has reduced complex experiences into a set of criteria and forced many individuals into boxes that may not wholly capture their situation. Rather than handling psychopathology as complex, multifactorial, and dynamic, it siloed distress into static categories. Moving from the top-down diagnostic model to a bottom-up dimensional model that is engendered by the transdiagnostic and network approaches is therefore a step that could open the road to further progress in psychiatry. Furthermore, including and investigating non-symptom dimensions in psychiatric research is necessary for more comprehensive understanding of psychopathology and can more closely align with the lived experience, needs, and wants of individuals with psychiatric disorders.

As such, we examined research questions on 1) the relationship between cognitive function and psychopathology and neurobiology, respectively, 2) the interplay of various symptoms dimensions, and 3) the role of psychological and existential factors in psychopathology. Throughout this thesis, we also explored the use of the transdiagnostic and network approaches as methodologies for addressing these research questions and potentially advancing psychiatric research.

In this chapter, the main findings of this thesis are summarized and considered in perspectives surrounding the paradigm shift as well as the limitations. This chapter also discusses the implications of these findings for psychiatric research and clinical practice and potential directions for future research.

Main findings

This thesis is the product of the Across study, an ongoing department-wide research project based on the transdiagnostic approach. Since its inception, the overarching aim of the Across study was to use data-driven bottom-up approaches to investigate the relationships between cognitive function, psychopathological symptoms, and biological parameters in a transdiagnostic, naturalistic sample of patients with various psychiatric disorders. This meant substantial collaboration to administer cognitive tests, a battery of self-report questionnaires on a variety of symptom dimensions and other factors of interest, such as substance use, and collecting blood and hair samples as well as EEG recordings. As a result, we assembled a diverse

database, providing us with a myriad of research opportunities, although we were limited in analysis-ready biological data.

Transdiagnostic networks

The transdiagnostic and network approaches provide an opportunity to loosen the iron grip that the current paradigm has had on the way we conceptualize, research, diagnose, and treat psychopathology. When I first set out with my research ideas a couple of years ago, there was a dearth of studies on transdiagnostic networks. Most transdiagnostic studies also focused on diagnoses or symptom dimensions within one or two diagnostic categories or spectra, and there were not yet recommendations and guidelines for conducting transdiagnostic research. Network analysis methods were also being further developed to accommodate a wider range of research designs and are still in the process of being advanced and improved. The first studies using either approach were published about two decades ago, but especially in the last five years, those initial pebbles burgeoned into an avalanche of literature^{1,2}.

However, many previous network and transdiagnostic studies were still largely based on *DSM* criteria, perpetuating some of the issues that they are supposed to remedy, as focusing purely on symptom networks without including non-symptom dimensions can also lead to reductionism³⁻⁵. In Chapters 3, 5, and 6, we estimated transdiagnostic networks, contributing to the sparse literature using these two complimentary approaches. We used a transdiagnostic sample of patients with various psychiatric disorders as well as instruments on various symptom and non-symptom domains. In both these aspects, our transdiagnostic designs crossed at least two spectra of diagnostic categories.

We found that while symptoms certainly had a prominent role in the networks, other dimensions, such as cognitive function or existential concerns, were also important. Symptoms do not exist or operate in a vacuum, and we can miss out on the intricate processes of psychopathology without other dimensions. Additionally, the symptom reduction model does not wholly capture what patients with psychiatric disorders want out of treatment⁶, so ignoring factors they do find important when conducting research or developing and administering treatment would be negligent at best and unjust at worst.

We also found that cross-dimension relationships were common across networks. For example, individual symptoms from anxious, depressive, and psychotic dimensions interacted with each other. While symptoms might cluster in particular patterns, cross-dimension relationships suggests that there are not hard boundaries

between symptom dimensions⁷. Therefore, any boundaries between symptom clusters are relative. With a network perspective, such clustering is formed in a bottom-up manner through causal interactions between symptoms rather than due to a latent entity or common cause⁸. It is therefore possible for symptoms from different dimensions to all relate to each other to varying extents within one space⁷. If symptoms give rise to psychopathology through their interaction and could therefore be considered as constituting a disorder and boundaries between symptom clusters are relative, then it could be implied that boundaries between categorical diagnoses are also relative, or fuzzy as has been posited before.

As an aim of this thesis was to explore how the transdiagnostic and network approaches can contribute to research, it is necessary to reflect on how useful they can be. Especially with the increased popularity of both approaches, they might sometimes be utilized indiscriminately, and being critical about their uses is necessary. One aspect that I particularly valued was the 'agnostic' nature of network analyses of not having to specify predictor and outcome variables as this can give more room for investigating relationships in different directions, especially if using a more exploratory approach. For example, most previous studies researched self-esteem as a predictor, but we found that it was an important outcome in our network.

Another advantage of the network approach is that it allows us to investigate various interrelations between a number of variables within one model. This can be useful for both global and local inspection, meaning that we can both get an overview of the structure of the network, such as clusters or density, and zoom in on specific edges, or relationships, and central nodes. As a result, network analyses produce many results, which can be exciting but overwhelming if going in with an exploratory approach. Deciding a priori on whether you will focus on global or local inspection and proper use of stability checks can help with determining focus, however, and reporting guidelines are of importance here.

Additionally, being able to focus on individual items when possible led to interesting results and supports the idea that symptoms should not be used interchangeably as they can have differential effects. However, transdiagnostic networks can quickly become limited by sample size if wanting to estimate networks with many nodes, especially of individual symptoms rather than sum-scores of symptom dimensions, and conduct comparative analyses between diagnostic categories to determine the transdiagnostic nature of findings. This is not an issue specific only to network analyses, but it can be limiting if the purpose is to test for transdiagnostic relationships and zoom in on item-level processes.

A potential difficulty for both the transdiagnostic and network approaches is finding appropriate instruments to use. Considering that most instruments are developed with a latent class perspective, such that the individual items are meant to measure a latent concept, it might not always be appropriate to use individual items from a scale. Additionally, many instruments measuring symptom dimensions are based on *DSM* criteria or are developed with a specific diagnostic category. For instance, an item from our subclinical psychosis questionnaire that asks about whether or not one hears things that others do not is meant to screen for a possible auditory hallucinatory experience, but may be misinterpreted by those with misophonia as a hypervigilance to sounds. However, especially with an increase in different network methodologies and growing efforts to create transdiagnostic instruments, more data types can be robustly handled with transdiagnostic network analyses. Although mostly used in an exploratory manner in this thesis to generate hypotheses, these approaches can also be used for testing specific hypotheses and confirmatory manner.

Overall, I found that the transdiagnostic and network approaches can lead to interesting findings and can be feasible and appropriate for a range of research questions. As a researcher, the ability to see the various manners in which variables interact with each other is exciting, and I think both approaches are well-suited for the complex nature of psychopathology. The network approach brings dynamicity into psychopathology, breathing life into it and emphasizing its potential for change. The transdiagnostic approach can further open up the possibilities for including factors that go beyond symptoms or diagnostic categories, potentially leading to new insights on processes underlying psychopathology. Together, they can be expanded into complex systems by including many levels of analysis from genetics to social systems, which can help to shed light on the web of interactions between different dimensions that are relevant to psychiatry. Strides are being made in this direction, situating psychopathology not only in the person but in their environment. While there is still room for improvement in developing guidelines for designing, analyzing, and reporting transdiagnostic and network research in order to produce more robust findings and build an empirical base of support, these approaches still have much to offer.

To illustrate how a transdiagnostic network approach could be applied clinically, we could imagine a hypothetical patient. Sofia is a woman in her late 20s presenting at the general psychiatric clinic of the hospital with numerous fears and anxieties, fatigue, feeling on edge, and difficulty caring for herself. She experiences recurring feelings of social rejection and anxiety in social situations, which makes it difficult to develop and maintain relationships. She often feels as if people are out to get her, and she does not engage in any activities outside of work and has no social life. She

struggles with attention and memory issues, which affect her work, and lead to low self-esteem. Finally, she reports feeling depressed almost every day, as if she does not know herself, and that her life has little meaning. Sofia was diagnosed with moderate to severe Generalized Anxiety Disorder (GAD) and comorbid Social Anxiety Disorder (SAD). Although her paranoid thoughts about people being out to get her and her depressed mood are having a significant impact on her well-being, she does not meet the diagnostic criteria for a mood or psychotic spectrum disorder, and these complaints are not reflected in her diagnosis.

With a transdiagnostic network approach, we would be able to see how these different symptom dimensions impact each other as well as other areas of her life, such as relationships and sense of meaning, rather than solely focusing on her GAD and SAD symptoms. In current practice, formulating a case conceptualization or diagnosis includes hypotheses and observations on personality factors, as well as development and maintenance factors, and potential relationships between them. If we were to estimate a network for her, however, we could examine and test numerous relationships at the same time, allowing us to get an overall view while simultaneously enabling us to zoom in on particular patterns. One variable may have numerous relationships with other variables. For example, her elevated anxiety may be associated with both paranoia and fatigue. Or her lack of personal activities may be related to both her depressed mood and the lack of meaning in her life. We could also see cascading effects, such as low self-esteem being associated with rejection sensitivity and in turn with difficulties with relationships. We might even discover that a certain variable exerts a particularly strong influence on other variables in the network and plays a central role as a root cause of her distress. Perhaps her low self-esteem is the shared trigger that activates her social anxiety, depressed mood, and paranoid thoughts. A central variable like that could then become a treatment target that could unravel the vicious interplay of symptom and non-symptom dimensions that gives rise to her distress. With such information, we could therefore get an idea of how transdiagnostic symptoms and non-symptom dimensions that may have otherwise been neglected interact, the processes underlying her condition that more comprehensively reflect her experience, and points of intervention that could lead to improvements in symptomology, functioning, and general well-being.

Cognitive function

In Chapters 3 and 4, we investigated cognitive function in psychiatric disorders. Previous research has demonstrated cognitive dysfunction to be associated with various psychiatric disorders⁹⁻¹¹ and may therefore be considered a central transdiagnostic dimension of psychopathology¹². While the association between

cognitive dysfunction and psychiatric disorders is well established, the exact nature of its role in psychopathology and relationship with both symptom and non-symptom dimensions are not as well established. Furthermore, most studies on cognitive function focus on specific disorders, and we may therefore miss patterns of co-occurring symptom and non-symptom dimensions that may interact with cognitive function but might not be taken into account because they fall outside of diagnostic boundaries.

We observed two interesting findings that lend support for a dimension-level rather than a diagnostic-level investigation of cognitive function. First, we found that symptoms and cognitive domains exhibited differential relationships in Chapter 3, in which symptoms tended to have fairly uniform relationships with cognitive domains (e.g., more depressive symptoms tended to be related to worse cognitive function) whereas cognitive domains had more varying relationship with symptoms (e.g., verbal memory was better in relation to more obsessive-compulsive symptoms but worse in relation to more subclinical psychotic symptoms). Second, we found that brain oscillations predicted functioning of individual cognitive domains but not diagnoses in Chapter 4. Investigating cognitive function within diagnostic categories may therefore lead to a loss of information on specific relationships between cognitive domains and both symptom and non-symptom dimensions, information that can be captured with a transdiagnostic approach. Additionally, the findings from Chapter 4 supports the idea that it may be more fruitful to research biomarkers for transdiagnostic dimensions rather than disorders. This also brings into question whether any previously found biomarkers for diagnostic categories were actually measuring an underlying dimension. The heterogeneity within diagnoses can lead to inconclusive results, especially if the effect of comorbidity is not taken into account.

Our findings further demonstrated that cognitive function and psychopathological symptoms are distinct yet interrelated dimensions. Research tends to examine cognitive function and emotional processes separately, but there has been an increase in attention to the relationship between emotional factors and cognitive function in psychopathology. While general thought has been that cognitive dysfunction, especially executive dysfunction, acts as a risk factor leading to psychopathology^{10,13,14}, the relationship is likely more reciprocal in nature^{15,16}. For instance, performance on cognitive tests can be affected by psychological factors, such as motivation, anhedonia, self-confidence, and self-efficacy¹². A recent network analysis further demonstrated that self-efficacy and self-esteem were related to attentional control¹⁷, and in our own network from Chapter 3, anhedonia was one of the nodes with the strongest overall negative association with functioning of various cognitive domains.

Another perspective on the relationship between cognitive function and symptoms is the hot and cold model, which describes a cycle of cold, or emotion-independent, cognitive deficits (e.g., executive function) that facilitate hot, or emotion-dependent cognitive biases (e.g., negative attributional styles), which in turn exacerbates cold cognitive deficits, eventually giving rise to psychopathology^{18,19}. With Sofia's network, for instance, we could potentially find out that her depressed mood arises from attention control deficits that deter her from disengaging from rumination, which further depletes her attentional control and impacts her work performance. Given the interplay between cognitive function and emotional or motivational factors, integrating the two is essential to elucidate potential points of preventing or disrupting psychopathological processes. Including social and environmental factors in future research would further contextualize processes between cognitive function and psychopathology as both are deeply affected by the world around us.

Despite the intricate relationship between cognitive function and symptoms, they are nonetheless somewhat independent as demonstrated by the clustering in Chapter 3 and the persistence of deficits in some cognitive domains after symptom remission²⁰⁻²³. The latter is consistent with the idea that cognitive function has both state and trait components²⁴. It remains therefore necessary to investigate which cognitive domains represent state effects that may be more impacted by symptoms and hot cognition and which domains may be trait effects and exhibit more stability. Such a research question could be feasibly researched with a transdiagnostic temporal network and could inform which treatments are effective depending on the cognitive domain that is affected. However, while cognitive function is comprised of numerous domains, they still impact each other, and as we move towards a complex systems approach, investigating the impact of psychopathology on the interplay between cognitive domains, or connectivity of underlying neurological substrates, and vice versa is an important next step.

To conclude, both studies from Chapters 3 and 4 support the need to investigate cognitive function in addition to and separately from psychopathological symptoms and do so in a transdiagnostic manner rather than within specific disorders. With a transdiagnostic and network approach, we were able to determine how individual cognitive domains relate to each other, brain oscillations, symptoms, and other psychological dimensions in ways that do not adhere to diagnostic categories. Cognitive dysfunction has serious consequences for everyday functioning and quality of life and have been shown to sometimes persist after symptom remission²⁰⁻²³, implying that difficulties with daily functioning and diminished quality of life also often persist. While treatment for affective symptoms may improve functioning in some cognitive domains, the persistence of deficits in certain domains point to a need for also specifically treating cognitive deficits. Consequently, it has been

suggested to include cognitive remission as a treatment outcome²⁵. Outcomes from cognitive remediation trials suggest that they can be effective in not only improving cognitive function but also symptoms and psychosocial functioning²⁶, supporting the integral nature of cognitive function in psychopathology.

Psychopathological symptoms

In Chapters 3, 5, and 6, we explored the relationships between different symptom dimensions. One of the main findings that emerged from these chapters was that depressive and anxious symptoms were often central in the different networks, meaning that they had the strongest relationships with other nodes, symptom and non-symptom, and suggesting that they play an important role in psychopathology. Anxiety and depressive disorders are globally the most common psychiatric disorders²⁷, which would put anxious and depressive symptoms as highly prevalent primary symptoms. Furthermore, depressive and anxious symptoms commonly occur with a variety of disorders, and may denote greater severity of psychopathology²⁸⁻³². For instance, an affective pathway has been implicated in psychosis^{33,34}, and high levels of depression and anxiety are associated with substance use disorders³⁵. This central role could be partially explained by the high prevalence of these symptoms and by the fact that they are among the symptoms most often included in research studies, especially in our studies which mostly included patients with internalizing disorders. Depressive and anxious symptoms are nonetheless pertinent dimensions and may be central for other reason.

The central role of depressive and anxious symptoms might reflect a shared underlying emotion dysregulation mechanism that can impact other symptoms or dimensions of functioning or well-being. Depressive and anxious symptoms, or affective symptoms more broadly, are closely connected with high negative affectivity³⁶, which a recent transdiagnostic systematic review found was a common marker for psychopathology³⁷. High negative affectivity by itself may not be solely responsible for psychopathology, however, as experiencing negative affect can be appropriate and healthy given certain circumstances. Instead, it may be the way in which individuals process or deal with emotions that leads to or maintains psychopathology. This is consistent with core emotional dysregulation that is prevalent across many disorders³⁸. For example, experiential avoidance, the unwillingness to experience unpleasant internal stimuli, such as emotions and bodily sensations³⁹, has been implicated in many disorders⁴⁰ while also often shown as specifically related to depressive⁴¹ and anxious symptoms⁴² and may be a relevant factor in the relationship between high negative affectivity and psychopathology. Usually, individuals will avoid these internal experiences in various ways which can

have detrimental effects in the long-term. For instance, suppression of emotions and an inability to accept emotional distress are closely linked to anhedonia^{43,44}, a core depressive symptom and a transdiagnostic factor related to the severity of many other symptom dimensions⁴⁵. Experiential avoidance is also linked to lower sense of meaning in life and inauthenticity^{46,47}, having a potential impact on existential concerns.

Affective symptoms can also arise in response to living with a psychiatric disorder, regardless of diagnosis, which may additionally explain their central transdiagnostic presence in our networks. Studies on comorbidity demonstrate that affective symptoms can manifest after the onset of the non-affective disorder^{28,48}. Factors that many individuals with psychiatric disorders grapple with, such as difficulties with daily activities and relationships, not being able to pursue personal goals or fully participate in society, and uncertainty around prognosis can heighten negative emotions. Our goals, roles in society, and interpersonal relationships can be deeply tied to our identity and sense of meaning and belonging⁴⁹⁻⁵¹ and can therefore, hold existential value for many. As such, it can be imagined that not being able to thrive in those areas of life could potentially cause existential distress and induce negative self-beliefs, such as self-stigma, which are related to anxious and depressive symptoms⁵²⁻⁵⁴. It could easily be imagined that the affective symptoms of our patient, Sofia, who experienced depressed mood, could have arisen in this way because of the impact mental illness has had on her life. It may be that as she started experiencing increasingly severe anxious symptoms, she decreased her personal activities and socializing. Her impaired memory and attention also affect her performance at work. Eventually she starts to feel that she is not living a fulfilling life and letting herself as well as others down and becomes depressed.

In sum, our findings suggest that depressive and anxious symptoms are transdiagnostic dimensions that can play numerous roles in psychopathology, whether as primary symptoms, maintenance factors for other symptoms, as a result of living with a psychiatric disorder or as a complex interplay of these factors. In light of the central role of anxious and depressive symptoms, transdiagnostic interventions that address underlying factors, such as learning to sit with negative emotions and difficulties in daily life rather than trying to get rid of or “fix” symptoms, may have multiple benefits for individuals with psychiatric disorders. Accepting the challenges arising from psychopathology and other personal difficulties and recognizing and acting on one’s personal values and goals could counter experiential avoidance and lead to an improved sense of meaning, which may subsequently reduce symptoms and promote an enhanced quality of life while still potentially experiencing symptoms. Acceptance and Commitment Therapy (ACT) and recovery-

oriented practices both focus on improving quality of life and functioning as well as empowering individuals to pursue personal goals and values^{51,55} and may therefore be suitable interventions for those struggling with depressive or anxious symptoms. Such interventions also move away from symptom-reduction models and are transdiagnostic in nature, which align with current paradigm shifts.

Psychological dimensions

A variety of psychological dimensions were included and investigated in this thesis, two of which we will focus on in this section. In Chapters 3 and 5, we found self-esteem, or self-view, to be a prominent psychological dimension. Disturbances in the sense of self are an integral part of psychopathology, whether they be excessive negative self-beliefs or an incohesive self-concept⁵⁶. As a facet of self-belief, self-esteem has long been implicated in the development and maintenance of psychopathology^{57,58}, and recent network analyses in clinical samples also found self-esteem to be a central node^{59,60}, which align with our findings.

Given that the way we view ourselves can have a great impact how we perceive, interpret, and interact with our experiences and the world around us (and vice versa), it is no surprise that we found self-esteem to be closely connected to psychopathology. In general, self-beliefs (e.g., self-esteem and self-efficacy), are related to various aspects of psychopathology, including symptom severity, psychosocial functioning, and treatment progress⁶¹. Self-stigma is a self-belief that may be of particular relevance for individuals with psychiatric disorders as mental illness tends to be viewed negatively in society and is intimately linked to self-esteem^{54,62}. As part of the “why try” effect, self-stigma and the deleterious effect on self-esteem may prevent individuals with psychiatric disorders from pursuing goals⁶². This effect may also explain how affective symptoms can arise living with a psychiatric disorder as discussed in the previous section.

In Chapter 6, we explored existential concerns and found that they are related to various symptom dimensions, especially depressive and anxious symptoms. Existential concerns have been defined in numerous ways but collectively regard fundamental concepts that are rooted in the experiences of existing and our evaluation of them, such as meaning, belonging, and identity, that most everyone has contended with at some point or another⁶³⁻⁶⁵. In general, existential concerns can have an extensive influence on human behavior, regardless of whether we are explicitly conscious of them or not⁶⁵. We found numerous relationships between individual domains of existential concerns and symptom dimensions, but psychopathology itself could be considered an inherently existential experience^{64,66}. As such, an existential perspective of psychopathology can situate the struggles and suffering

of individuals with psychiatric disorders as part of the human existence, which is also in line with a more humanistic⁶⁷ as well as a dimensional approach that departs from a healthy versus ill perspective. In a symptom-reduction model, existential concerns may be brushed aside, which can ultimately be detrimental for recovery if we are to consider the significant impact they can have on psychopathology.

Self-esteem can also have existential consequences, such that those with lower self-esteem tend to struggle more with existential concerns as they experience existence as futile and daunting⁶⁸. For instance, Terror Management Theory posits that self-esteem is necessary for keeping existential terror at bay, especially when concerning mortality and death, which can be fostered by meeting socio-cultural standards⁶⁹. Additionally, self-esteem has also been shown to be related to autonomy⁷⁰, personal and social identity⁷¹, and social connectedness⁷². One could then argue that self-esteem, and self-beliefs in general, has an existential component to them as they pertain to the stance we take on ourselves. Therefore, self-esteem, and positive self-beliefs in general, may be a necessary component for adequately handling existential concerns in a way that leads to growth rather than distress and can be considered part of the existential dimension of recovery^{51,73}. Sofia's network could elucidate that low self-esteem contributes to her decreased sense of identity and meaning through her lack of social and personal activities.

Altogether, we found self-esteem and existential concerns to be linked to psychopathology, and with a transdiagnostic network approach, we were able to demonstrate the various relationships between symptom dimensions and self-esteem and existential concerns, respectively. The importance of self-esteem in psychopathology is well-established, which our findings further reinforce its status as a transdiagnostic factor. Additionally, our findings support the need for addressing existential concerns in psychiatric research and practice. The existential dimension should be an integral part of recovery-oriented practices^{51,73,74} and could be addressed through interventions, such as ACT⁷⁵. While self-esteem could be addressed through conventional treatments, such as Cognitive-Behavioral Therapy (CBT)⁷⁶, low self-esteem, or the deleterious effects thereof, could also be improved through other interventions, such as psychosocial rehabilitation or self-compassion interventions, which helps protect against low self-esteem⁷⁷ and can reduce self-stigma⁷⁸. Additionally, different aspects of recovery can lead to increases in both self-esteem and the existential dimension and likewise lead to improvements in other areas. For instance, attaining employment and improved social networks can contribute to existential recovery and self-esteem and vice versa⁵¹. Ultimately, going beyond symptom reduction and addressing factors, such as existential concerns, may lead to a more holistic recovery.

General Implications

Throughout this thesis, we found that different symptom dimensions often interacted in ways that do not adhere to diagnostic categories, implying that boundaries between them are more relative than distinct. In light of this, this further supports the need to rethink the assumption that diagnoses are distinct entities, both in clinical practice and in research. Although diagnostic classification systems, such as the *DSM*, will remain in use for the foreseeable future, clinicians and researchers can already incorporate transdiagnostic thinking into case conceptualize or treatment planning even if still having to use the *DSM* for practical purposes. This should also be emphasized during training, which could over time soften the reification of diagnoses. In line with this, our findings support that dimension-level rather than diagnostic-level analyses could be more fruitful. This is especially relevant for investigating biomarkers, which we found predicted the transdiagnostic dimension of cognitive function instead of diagnoses.

We also found that while symptom dimensions played an important role in the networks, non-symptom dimensions were also prominent. This further supports the necessity of a more multifactorial or holistic conceptualization of psychopathology and interventions. Symptom-reduction strategies should accordingly be accompanied by more general rehabilitation, such as those focused on cognitive function or psychosocial well-being, and recovery-oriented interventions that also address the existential dimension. As a higher-order need, addressing existential concerns may seem out of reach for conventional mental health care institutions, but ignoring the existential dimension could cause great harm as it can represent a core process in psychopathology. Developing and improving collaboration between different services and interventions is therefore crucial. For instance, Sofia, our hypothetical patient, may want to reduce her symptoms and cognitive deficits, develop better self-care practices and eating habits, and improve her relationships and access to hobbies or personal activities. A collaboration between a mental health institution, community-based rehabilitation center, and primary care services would then be necessary for her to attain her goals in an accessible manner.

Lastly, researchers need to remain cautious with what they claim to be transdiagnostic. Transdiagnostic research attempts to find shared dimensions and processes across disorders, and while current categorical diagnoses may not accurately or wholly reflect the nature of psychopathology, differences between psychiatric conditions can still exist. For instance, cognitive dysfunction may reflect different mechanisms: attention deficits may be due to depletion because of constant hypervigilance in some or due to lack of effort in others. Attention deficits

may be transdiagnostic, but pooling groups without follow-up comparisons may obscure these mechanistic differences. For transdiagnostic research to be more robust, investigating the direction and strength of effects is necessary.

Strengths and limitations

A main strength of this thesis is that we had instruments on symptom dimensions and a transdiagnostic sample of patients with psychiatric disorders that cut across numerous diagnostic spectra. This increases generalizability of results across disorders from different categories. Additionally, we included dimensions besides core symptoms to more comprehensively capture the complexity of psychopathology, which our findings support are necessary to include. Our sample was also naturalistic as we included patients regardless of treatment type or trajectory and who had comorbid disorders, which better reflects clinical reality, especially that of a tertiary care institution.

The findings of this thesis need to be interpreted in light of the following limitations. While the Across study has a reasonably large sample size for cross-sectional studies, larger sample sizes are necessary to further compare between diagnoses to determine if certain relationships and processes are actually transdiagnostic and hold across diagnoses. As advised by the transdiagnostic research guidelines, TRANSD¹, studies should perform comparative analyses to demonstrate if the transdiagnostic approach is more robust than a specific diagnostic approach. We made an attempt to compare or control for diagnostic effects through jackknife sampling and including diagnosis as a confounder as a first step in this direction, but we acknowledge that we cannot robustly claim our results to be transdiagnostic. Moreover, the percentage of the sample that participated in the follow-up measurement was small, which limited any longitudinal or two-wave analyses. Therefore, most of the studies in this thesis had a cross-sectional design, which precludes any conclusions regarding temporal direction.

Additionally, we had no to limited measures for symptom dimensions from externalizing or thought disorder spectra, respectively, and some symptom questionnaires used skip-logic, meaning they were not truly dimensional in nature and led to smaller data availability. This may limit the generalizability and comprehensiveness of our results as the research design focuses mostly on dimensions from the internalizing spectrum. Furthermore, fluency in Dutch was an inclusion criterion and there was a lack of proper ethnicity measure to include as demographic variable, making it difficult to generalize to non-Dutch populations. Participants were also able to participate at any point of their treatment trajectory.

While this reflects a naturalistic design, treatment effects might confound findings. Throughout the studies, we examined and controlled for medication use or presence of treatment when possible to mitigate some of these confounding effects.

Future direction

While the transdiagnostic and network approaches have gained considerable popularity, there is still plenty of room for advancement as we are entering a new phase in transdiagnostic and network research. A majority of previous studies have been exploratory in design, and it is necessary to move from hypothesis generation to hypothesis testing. This would consist of conducting confirmatory network analysis to test specific hypotheses and replicate exploratory findings and iterative testing and fine-tuning of models and theories². Ideally, such investigations would involve research designs that allow for longitudinal between- and within-subject analyses^{2,79}. Cross-sectional findings can provide useful information, but longitudinal designs are necessary to give insight into the temporal nature of relationships. For instance, time-series designs could give insight into the temporal properties of individual dimensions as well as the interactions between dimensions and the contexts in which these occur.

Psychiatric research is also moving towards a complex dynamical systems and multilevel ecosocial approaches as there an increased recognition for the need to better contextualize and situate psychopathology within larger systems⁸⁰ as even individual-level factors may not be as individual as once thought. For instance, emotion regulation may be considered an individual process but can certainly be impacted by interpersonal situations⁸¹. Such multilevel designs could potentially be accommodated by the transdiagnostic and network approaches. In the pursuit of moving towards a complex dynamical systems approach, however, researchers must also ensure to not overburden participants in an attempt to capture an increasingly diverse set of data. The challenge will be not only in deciding which data to include and developing methods to properly handle them, but also how to feasibly measure these data and make research participation accessible.

Furthermore, use of networks within a clinical setting needs to be further explored^{79,82}. For instance, it needs to be investigated further if centrality metrics do translate into treatment targets. As a tool for personalized treatment, clinicians could also use idiographic networks to ascertain symptom dynamics and contextual characteristics thereof, which can guide treatment processes. For patients themselves, they could be used as a way to gain more insight as well as more fully include them in the treatment process, which could combat feeling powerless, confused or out of control

about their symptoms, and create motivation for change. Personalized networks need not to be limited to symptom networks, however. In this sense, further inclusion of existential and recovery-oriented concepts should also be pursued, especially with a focus on the patient perspective and what they find important. Because these concepts can be highly personal, it would be necessary to research the existential dimension with both nomothetic and idiographic designs.

Moreover, if we want to more robustly explore and examine transdiagnostic dimensions, developing and testing instruments that depart from or expand upon core *DSM* criteria is necessary. Taking into consideration the experiences and needs of patients when developing such instruments is also of utmost importance and should therefore be included in the process from the start. Developing appropriate instruments would also aid in moving from exploratory to confirmatory testing.

Lastly, the findings of this thesis demonstrated the importance of different dimensions and factors in psychopathology. While there has been a call to mind biological reductionism, we must also be careful with psychosocial or symptom reductionism⁸³. Including biological measures and dimensions in transdiagnostic networks is therefore necessary. Networks are increasingly incorporating biological measures, such as inflammatory markers⁸⁴ and polygenic risk scores⁸⁵, and producing stable results, supporting this possibility. Future studies using Across biological data could accomplish this when such data are ready and available for use.

Altogether, a holistic, methodological pluralist approach is necessary for psychiatric research as one approach or method may not be applicable to all situations. While some psychiatric dimensions might be continuous and transdiagnostic, other dimensions or forms of psychopathology might be more categorical. The network, transdiagnostic, and categorical diagnostic approaches are tools with different uses and combining different perspectives will likely be most fruitful for finding valid empirically-based yet clinically-useful results.

General conclusion

Paradigm shifts ask us to take a moment to examine the way we think and operate. The *DSM* and accompanying diagnostic paradigm allowed for a shared language, better standardization of diagnosing and treatment selection, and led to initial advancements in understanding psychopathology. Over time, however, it became an “epistemic prison”⁸⁶ and those advancements slowed, leading to a stagnation in psychiatric research and calls for change. In answer to this call for change, the transdiagnostic and network approaches emerged in the hopes of tackling the

flawed assumptions about psychopathology that became entrenched in psychiatric research, such as diagnoses representing discrete entities and the common cause model. The findings of this thesis demonstrate that the transdiagnostic and network approaches can give new insights into relationships between dimensions, some of which do not receive as much attention as they should, that may stimulate us to view things in way that departs from the status quo. There is still a way to go for the transdiagnostic and network approaches to fully deliver on the radical paradigm shifts they promise while being clinically useful in everyday practice for both clinicians and patients, but as these approaches are increasingly fine-tuned, they could lead to clinically-relevant findings and meaningful progress. This thesis also supports the need for going beyond the symptom-reduction model and harnessing existential and recovery-oriented frameworks. Both frameworks can addressing fundamental concepts that are largely inherent to the human experience, regardless of diagnosis. In this way, paradigm shifts ask us to not only create innovative methods but to also look back on ways of thinking we may have forgotten or ignored. Together, the transdiagnostic and network approaches along with going beyond symptom reduction in research and treatment can foster a more comprehensive understanding of psychopathology that can inform treatment practices.

References

1. Fusar-Poli P, Solmi M, Brondino N, et al. Transdiagnostic psychiatry: a systematic review. *World Psychiatry*. 2019;18(2):192-207.
2. Robinaugh DJ, Hoekstra RHA, Toner ER, Borsboom D. The network approach to psychopathology: a review of the literature 2008–2018 and an agenda for future research. *Psychol Med*. 2020;50(3):353-366.
3. Guloksuz S, Pries LK, van Os J. Application of network methods for understanding mental disorders: pitfalls and promise. *Psychol Med*. 2017;47(16):2743-2752.
4. Fried EI, Cramer AOJ. Moving Forward: Challenges and Directions for Psychopathological Network Theory and Methodology. *Perspect Psychol Sci*. 2017;12(6):999-1020.
5. Köhne AC. The relationalist turn in understanding mental disorders: From essentialism to embracing dynamic and complex relations. *Philos Psychiatr Psychol*. 2020;27(2):119-140.
6. Chui H, Chong ESK, Atzil-Slonim D, et al. Beyond symptom reduction: Development and validation of the Complementary Measure of Psychotherapy Outcome (COMPO). *J Couns Psychol*. 2021;68(5):550-561.
7. Wichers M, Schreuder MJ, Goekoop R, Groen RN. Can we predict the direction of sudden shifts in symptoms? Transdiagnostic implications from a complex systems perspective on psychopathology. *Psychol Med*. 2019;49(3):380-387.
8. Borsboom D. A network theory of mental disorders. *World Psychiatry*. 2017;16(1):5-13.
9. East-Richard C, R-Mercier A, Nadeau D, Cellard C. Transdiagnostic neurocognitive deficits in psychiatry: A review of meta-analyses. *Canadian Psychology/Psychologie canadienne*. 2019.
10. McTeague LM, Goodkind MS, Etkin A. Transdiagnostic impairment of cognitive control in mental illness. *J Psychiatr Res*. 2016;83:37-46.
11. Millan MJ, Agid Y, Brüne M, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov*. 2012;11(2):141.
12. Abramovitch A, Short T, Schweiger A. The C Factor: Cognitive dysfunction as a transdiagnostic dimension in psychopathology. *Clin Psychol Rev*. 2021;86:102007.
13. Snyder HR, Miyake A, Hankin BL. Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. *Front Psychol*. 2015;6:328.
14. Goschke T. Dysfunctions of decision-making and cognitive control as transdiagnostic mechanisms of mental disorders: advances, gaps, and needs in current research. *Int J Methods Psychiatr Res*. 2014;23(S1):41-57.
15. Zainal NH, Newman MG. Depression and executive functioning bidirectionally impair one another across 9 years: Evidence from within-person latent change and cross-lagged models. *Eur Psychiatry*. 2021;64(1):e43.
16. Romer AL, Pizzagalli DA. Is executive dysfunction a risk marker or consequence of psychopathology? A test of executive function as a prospective predictor and outcome of general psychopathology in the adolescent brain cognitive development study®. *Dev Cogn Neurosci*. 2021;51:100994.
17. Pulopulos MM, Hoorelbeke K, Vandenbroucke S, Van Durme K, Hooley JM, De Raedt R. The interplay between self-esteem, expectancy, cognitive control, rumination, and the experience of stress: A network analysis. *Current Psychology*. 2022.
18. Ahern E, Bockting CL, Semkovska M. A Hot-Cold Cognitive Model of Depression: integrating the Neuropsychological Approach Into the Cognitive Theory Framework. *Clinical Psychology in Europe*. 2019;1:e34396.
19. Roiser JP, Sahakian BJ. Hot and cold cognition in depression. *CNS spectrums*. 2013;18(3):139-149.
20. Semkovska M, Quinlivan L, O'Grady T, et al. Cognitive function following a major depressive episode: a systematic review and meta-analysis. *The Lancet Psychiatry*. 2019;6(10):851-861.
21. Gonda X, Pompili M, Serafini G, Carvalho AF, Rihmer Z, Dome P. The role of cognitive dysfunction in the symptoms and remission from depression. *Annals of General Psychiatry*. 2015;14(1):27.

22. Brissos S, Dias VV, Balanzá-Martinez V, Carita AI, Figueira ML. Symptomatic remission in schizophrenia patients: Relationship with social functioning, quality of life, and neurocognitive performance. *Schizophr Res.* 2011;129(2):133-136.
23. Rao NP, Reddy YCJ, Kumar KJ, Kandavel T, Chandrashekhar CR. Are neuropsychological deficits trait markers in OCD? *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(6):1574-1579.
24. Bernhardt M, Klauke S, Schröder A. Longitudinal course of cognitive function across treatment in patients with MDD: A meta-analysis. *J Affect Disord.* 2019;249:52-62.
25. Bortolato B, Miskowiak KW, Köhler CA, et al. Cognitive remission: a novel objective for the treatment of major depression? *BMC Med.* 2016;14(1):9.
26. Kim EJ, Bahk Y-C, Oh H, Lee W-H, Lee J-S, Choi K-H. Current Status of Cognitive Remediation for Psychiatric Disorders: A Review. *Frontiers in Psychiatry.* 2018;9.
27. Dattani S, Ritchie H, Roser M. Mental Health. In: Our World in Data; 2021.
28. Coentre R, Talina MC, Góis C, Figueira ML. Depressive symptoms and suicidal behavior after first-episode psychosis: A comprehensive systematic review. *Psychiatry Res.* 2017;253:240-248.
29. Wilson RS, Yung AR, Morrison AP. Comorbidity rates of depression and anxiety in first episode psychosis: A systematic review and meta-analysis. *Schizophr Res.* 2020;216:322-329.
30. Nestadt G, Samuels J, Riddle MA, et al. The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study. *Psychol Med.* 2001;31(3):481-487.
31. Spoorthy MS, Chakrabarti S, Grover S. Comorbidity of bipolar and anxiety disorders: An overview of trends in research. *World J Psychiatry.* 2019;9(1):7-29.
32. Quarantini LC, Torres AR, Sampaio AS, et al. Comorbid major depression in obsessive-compulsive disorder patients. *Compr Psychiatr.* 2011;52(4):386-393.
33. Hartley S, Barrowclough C, Haddock G. Anxiety and depression in psychosis: a systematic review of associations with positive psychotic symptoms. *Acta Psychiatr Scand.* 2013;128(5):327-346.
34. Myin-Germeys I, van Os J. Stress-reactivity in psychosis: Evidence for an affective pathway to psychosis. *Clin Psychol Rev.* 2007;27(4):409-424.
35. Mohamed II, Ahmad HEK, Hassaan SH, Hassan SM. Assessment of anxiety and depression among substance use disorder patients: a case-control study. *Middle East Current Psychiatry.* 2020;27(1):22.
36. Stanton K, Watson D. Positive and Negative Affective Dysfunction in Psychopathology. *Soc Personal Psychol Compass.* 2014;8(9):555-567.
37. Lynch SJ, Sunderland M, Newton NC, Chapman C. A systematic review of transdiagnostic risk and protective factors for general and specific psychopathology in young people. *Clin Psychol Rev.* 2021;87:102036.
38. Cludius B, Mennin D, Ehring T. Emotion regulation as a transdiagnostic process. *Emotion.* 2020;20(1):37.
39. Hayes SC, Strosahl K, Wilson KG, et al. Measuring experiential avoidance: A preliminary test of a working model. *The Psychological Record.* 2004;54(4):553-578.
40. Malicki S, Ostaszewski P. Experiential avoidance as a functional dimension of a transdiagnostic approach to psychopathology. *Postępy Psychiatrii i Neurologii.* 2014;23(2):61-71.
41. Browning ME, Van Kirk NP, Krompinger JW. Examining depression symptoms within OCD: the role of experiential avoidance. *Behav Cogn Psychother.* 2022;50(4):367-380.
42. Kelso KC, Kashdan TB, İmamoğlu A, Ashraf A. Meaning in life buffers the impact of experiential avoidance on anxiety. *Journal of Contextual Behavioral Science.* 2020;16:192-198.
43. Kashdan TB, Zvolensky MJ, McLeish AC. Anxiety sensitivity and affect regulatory strategies: Individual and interactive risk factors for anxiety-related symptoms. *J Anxiety Disord.* 2008;22(3):429-440.
44. Beblo T, Fernando S, Klocke S, Griepenstroh J, Aschenbrenner S, Driessen M. Increased suppression of negative and positive emotions in major depression. *J Affect Disord.* 2012;141(2):474-479.
45. Guineau MG, Ikani N, Rinck M, et al. Anhedonia as a transdiagnostic symptom across psychological disorders: a network approach. *Psychol Med.* 2022;1-12.

46. Kashdan TB, Barrios V, Forsyth JP, Steger MF. Experiential avoidance as a generalized psychological vulnerability: Comparisons with coping and emotion regulation strategies. *Behav Res Ther.* 2006;44(9):1301-1320.
47. Yela JR, Crego A, Gómez-Martínez MÁ, Jiménez L. Self-compassion, meaning in life, and experiential avoidance explain the relationship between meditation and positive mental health outcomes. *J Clin Psychol.* 2020;76(9):1631-1652.
48. Tibi I, van Oppen P, van Balkom AJLM, et al. The long-term association of OCD and depression and its moderators: A four-year follow up study in a large clinical sample. *Eur Psychiatry.* 2017;44:76-82.
49. Bouguettaya A, Jaeger T, Moulding R. Yet You May See the Meaning of Within: The Role of Identity Concerns and the Self in Psychopathology. In: Menzies RG, Menzies RE, Dingle GA, eds. *Existential Concerns and Cognitive-Behavioral Procedures: An Integrative Approach to Mental Health.* Cham: Springer International Publishing; 2022:167-183.
50. Haslam SA, Jetten J, Postmes T, Haslam C. Social identity, health and well-being: An emerging agenda for applied psychology. *Applied Psychology.* 2009;58(1):1-23.
51. Winsper C, Crawford-Docherty A, Weich S, Fenton S-J, Singh SP. How do recovery-oriented interventions contribute to personal mental health recovery? A systematic review and logic model. *Clin Psychol Rev.* 2020;76:101815.
52. Szentágotai-Tátar A, Nechita D-M, Miu AC. Shame in Anxiety and Obsessive-Compulsive Disorders. *Current Psychiatry Reports.* 2020;22(4):16.
53. Kim S, Thibodeau R, Jorgensen RS. Shame, guilt, and depressive symptoms: a meta-analytic review. *Psychol Bull.* 2011;137(1):68.
54. Dubreucq J, Plasse J, Franck N. Self-stigma in Serious Mental Illness: A Systematic Review of Frequency, Correlates, and Consequences. *Schizophr Bull.* 2021;47(5):1261-1287.
55. Gaudiano BA, Davis CH, Epstein-Lubow G, Johnson JE, Mueser KT, Miller IW. Acceptance and Commitment Therapy for Inpatients with Psychosis (the REACH Study): Protocol for Treatment Development and Pilot Testing. *Healthcare.* 2017;5(2):23.
56. Kyrios M, Nelson B, Ahern C, Fuchs T, Parnas J. The self in psychopathology. *Psychopathology.* 2015;48(5):275.
57. Zeigler-Hill V. The Connections Between Self-Esteem and Psychopathology. *J Contemp Psychother.* 2011;41(3):157-164.
58. Kresznerits S, Rózsa S, Perczel-Forintos D. A transdiagnostic model of low self-esteem: pathway analysis in a heterogeneous clinical sample. *Behav Cogn Psychother.* 2022;50(2):171-186.
59. Barbalat G, Plasse J, Gauthier E, et al. The central role of self-esteem in the quality of life of patients with mental disorders. *Sci Rep.* 2022;12(1):7852.
60. Monteleone AM, Cascino G. A systematic review of network analysis studies in eating disorders: Is time to broaden the core psychopathology to non specific symptoms. *European Eating Disorders Review.* 2021;29(4):531-547.
61. Seow TXF, Rouault M, Gillan CM, Fleming SM. How Local and Global Metacognition Shape Mental Health. *Biol Psychiatry.* 2021;90(7):436-446.
62. Corrigan PW, Larson JE, Rüschen N. Self-stigma and the "why try" effect: impact on life goals and evidence-based practices. *World Psychiatry.* 2009;8(2):75-81.
63. Yalom ID. *Existential psychotherapy.* New York: Basic Books; 1980.
64. Moore LJ, Goldner-Vukov M. The existential way to recovery. *Psychiatria danubina.* 2009;21(4):453-462.
65. Koole SL, Greenberg J, Pyszcynski T. Introducing Science to the Psychology of the Soul: Experimental Existential Psychology. *Curr Dir Psychol Sci.* 2006;15(5):212-216.
66. de Haan S. The existential dimension in psychiatry: an enactive framework. *Mental Health, Religion & Culture.* 2017;20(6):528-535.
67. Kogstad RE, Ekeland TJ, Hummelvoll JK. In defence of a humanistic approach to mental health care: recovery processes investigated with the help of clients' narratives on turning points and processes of gradual change. *J Psychiatr Ment Health Nurs.* 2011;18(6):479-486.
68. Pyszcynski T, Kesebir P. An existential perspective on the need for self-esteem. In: *Self-esteem.* Psychology Press; 2013:124-144.

69. Greenberg J, Solomon S, Pyszczynski T. Terror Management Theory of Self-Esteem and Cultural Worldviews: Empirical Assessments and Conceptual Refinements. In: Zanna MP, ed. *Advances in Experimental Social Psychology*. Vol 29. Academic Press; 1997:61-139.
70. Heppner WL, Kernis MH, Nezlek JB, Foster J, Lakey CE, Goldman BM. Within-Person Relationships Among Daily Self-Esteem, Need Satisfaction, and Authenticity. *Psychological Science*. 2008;19(11):1140-1145.
71. Stets JE, Burke PJ. Self-Esteem and Identities. *Sociological Perspectives*. 2014;57(4):409-433.
72. Fatima M, Niazi S, Ghayas S. Relationship between self-esteem and social anxiety: Role of social connectedness as a mediator. *Pakistan journal of social and clinical psychology*. 2017;15(2):12-17.
73. Rob Whitley PD, Robert E. Drake MD, Ph.D., Recovery: A Dimensional Approach. *Psychiatr Serv*. 2010;61(12):1248-1250.
74. Huguelet P. The Contribution of Existential Phenomenology in the Recovery-Oriented Care of Patients with Severe Mental Disorders. *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine*. 2014;39(4):346-367.
75. Ciarrochi J, Hayes L, Quinlen G, Sahdra B, Ferrari M, Yap K. Letting Go, Creating Meaning: The Role of Acceptance and Commitment Therapy in Helping People Confront Existential Concerns and Lead a Vital Life. In: Menzies RG, Menzies RE, Dingle GA, eds. *Existential Concerns and Cognitive-Behavioral Procedures: An Integrative Approach to Mental Health*. Cham: Springer International Publishing; 2022:283-302.
76. Kolubinski DC, Frings D, Nikčević AV, Lawrence JA, Spada MM. A systematic review and meta-analysis of CBT interventions based on the Fennell model of low self-esteem. *Psychiatry Res*. 2018;267:296-305.
77. Marshall SL, Parker PD, Ciarrochi J, Sahdra B, Jackson CJ, Heaven PCL. Self-compassion protects against the negative effects of low self-esteem: A longitudinal study in a large adolescent sample. *Pers Individ Dif*. 2015;74:116-121.
78. Wong CCY, Knee CR, Neighbors C, Zvolensky MJ. Hacking Stigma by Loving Yourself: a Mediated-Moderation Model of Self-Compassion and Stigma. *Mindfulness*. 2019;10(3):415-433.
79. McNally RJ. Network Analysis of Psychopathology: Controversies and Challenges. *Annu Rev Clin Psychol*. 2021;17(1):31-53.
80. Kirmayer LJ, Crafa D. What kind of science for psychiatry? *Front Hum Neurosci*. 2014;8.
81. Dixon-Gordon KL, Bernecker SL, Christensen K. Recent innovations in the field of interpersonal emotion regulation. *Current Opinion in Psychology*. 2015;3:36-42.
82. Kroese R, van der Veen DC, Servaas MN, et al. Personalized Feedback on Symptom Dynamics of Psychopathology: A Proof-of-Principle Study. *J Pers Oriented Res*. 2017;3(1):1-10.
83. Nephew BC, Febo M, Santos HP. Neither biological nor symptomatology reductionism: A call for integration in psychopathology research. *Behav Brain Sci*. 2019;42:e17.
84. Fried EI, von Stockert S, Haslbeck JMB, Lamers F, Schoevers RA, Penninx BWJH. Using network analysis to examine links between individual depressive symptoms, inflammatory markers, and covariates. *Psychol Med*. 2020;50(16):2682-2690.
85. Garcia-Mondragon L, Konac D, Newbury JB, et al. Role of polygenic and environmental factors in the co-occurrence of depression and psychosis symptoms: a network analysis. *Translational Psychiatry*. 2022;12(1):259.
86. Hyman SE. The diagnosis of mental disorders: the problem of reification. *Annu Rev Clin Psychol*. 2010;6:155-179.



A

Appendices

Summary

Dutch summary / Nederlandse samenvatting

Author Contributions

PhD portfolio

List of publications

Curriculum Vitae

Acknowledgements

Summary

The nature of psychopathology is and has been an important question in psychiatry. Over the last couple of decades, an increasingly critical eye has been cast upon the current system of conceptualizing, researching, and treating psychopathology. With the widespread and systematic use of psychiatric diagnostic classification systems, such as the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, came the assumption that psychopathology can be categorized into distinct categorical latent classes, which have become reified. With the increased recognition of the shortcomings and accompanying issues of such a categorical classification and overreliance of the *DSM*, calls for a paradigm shift ensued. As an attempt to remedy current shortcomings, the transdiagnostic and network approaches emerged.

We began in **Chapter 1** with an overview of the current paradigm in psychiatry and the accompanying assumptions and shortcomings. The limitations of the symptom-reduction model derived from the prevailing paradigm were also brought into the foreground. We then introduced the transdiagnostic and network approaches, discussed the current status thereof, and considered gaps in research. Furthermore, we touched on approaches that go beyond the symptom reduction model, such as the recovery-oriented framework and inclusion of the existential dimension. Lastly, we presented the aims and outline of this thesis.

In **Chapter 2**, we described the protocol of the Across study, which provided a basis and starting blocks for my thesis. The background, rationale, and methodology of the study are discussed. The overall objective of the Across study is to elucidate relationships among cognitive function, psychopathological symptoms, and biomarkers.

Next, in **Chapter 3**, we investigated the relationships between psychopathological symptom and cognitive domains with a cross-sectional partial correlation network model in a transdiagnostic sample of patients with psychiatric disorders. We generally found that increased symptom severity was associated with worse cognitive functioning, and that depression, anxiety, verbal memory, and visual attention played a central role in this network. Furthermore, we found that cognitive functioning and psychopathology are distinct but related dimensions, which interact in a transdiagnostic manner. Our results also suggest that future studies should focus on symptom-specific interactions with cognitive domains rather than investigating cognitive functioning within specific diagnostic categories.

We then explored in **Chapter 4** the transdiagnostic relationship between resting-state EEG activity and cognitive function using random forest regression. We identified

resting-state EEG features associated with episodic memory and associative learning, information processing speed, and attentional set-shifting and executive function but not with diagnosis, suggesting that EEG activity in psychiatric disorders may be related to cognitive dysfunction. There were also no differences in cognitive function between diagnostic categories nor any associations between cognitive function and symptom dimensions. This approach may shed light on the neurobiological basis and clinical relevance of cognitive dysfunction across psychiatric disorders.

Furthermore, we investigated in **Chapter 5** the longitudinal two-wave relationships between individual psychopathological symptoms using a cross-lagged panel network analysis in a transdiagnostic sample of patients with various psychiatric disorders. We found that more suicidal ideation predicting more negative self-view and that self-view was a highly predictable node, suggesting that it may be an important transdiagnostic outcome variable. The results of our study could lead to new insights into how individual symptoms impact each other over time and further elucidate which symptoms may play a central role in psychiatric illness to inform future treatments. Additionally, our findings further illustrate the importance of symptom-level rather than diagnostic-level research in understanding psychopathology.

Lastly, in **Chapter 6**, we explored cross-sectional relationships between existential concerns and psychopathological symptom domains in a transdiagnostic sample of patients with various psychiatric disorders using mixed graphical modeling. We found that existential concerns were related to more severe symptomology and that autonomy and identity were the most central existential variables in the network. The results therefore further support the role of existential concerns in psychopathology and advocate to address existential concerns in clinical practice and research on top of symptom reduction.

We end the thesis with **Chapter 7**, in which we discuss the general use of the transdiagnostic and network approaches in this thesis as well as findings relating to three overarching dimensions: cognitive function, psychopathological symptoms, and psychological factors (i.e., self-esteem and existential concerns). We situate the findings within the perspectives of the paradigm shift and discuss the research and clinical implications. Furthermore, we reflect on the strengths and limitations of the studies, the general implications, and potential directions for future research.

In conclusion, this thesis demonstrates that the transdiagnostic and network approaches can be useful and valuable for gaining insights into relationships between different dimensions of psychopathology. However, both approaches require more rigorous testing to build a solid empirical base and be applied clinically. Furthermore,

this thesis demonstrates the necessity of going beyond the symptom-reduction model and addressing non-symptom factors, such as cognitive function and existential concerns, in addition to symptoms, which could be accomplished through recovery-oriented frameworks. Altogether, the transdiagnostic and network approaches can continue drive the paradigm shift that departs from current perspectives of psychopathology as distinct categories as well as the common cause and symptom-reduction models, which may lead to a more comprehensive understanding of psychopathology and better inform research as well as clinical practice.

Dutch summary / Nederlandse samenvatting

De aard van psychopathologie was en is een belangrijk vraagstuk in de psychiatrie. In de afgelopen decennia is er een steeds kritischere blik geworpen op het huidige systeem van conceptualiseren, onderzoeken en behandelen van psychopathologie. Het wijdverbreide en systematische gebruik van psychiatrische diagnostische classificatiesystemen, zoals de *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, bracht de aanname met zich mee dat psychopathologie kan worden gecategoriseerd in verschillende categorische latente klassen, die verwezenlijkt zijn geworden. Met de toenemende erkenning van de tekortkomingen en de bijbehorende problemen van een dergelijke categorische classificatie en het overmatige gebruik van de DSM, volgde de roep om een paradigmaverschuiving.

We begonnen in **Hoofdstuk 1** met een overzicht van het huidige paradigma in de psychiatrie en de daarbij horende aannames en tekortkomingen. Ook werden de beperkingen van het symptoomreductiemodel, afgeleid van het huidige paradigma, naar de voorgrond gebracht. Vervolgens hebben we de transdiagnostische en netwerkbenaderingen geïntroduceerd, de huidige status daarvan en hiaten in het onderzoek besproken. Verder benoemden we kort benaderingen die verder gaan dan het symptoomreductiemodel, zoals het herstelondersteunende kader en de inclusie van de existentiële dimensie. Ten slotte hebben we de doelstellingen en de opzet van dit proefschrift gepresenteerd.

In **Hoofdstuk 2** hebben we het protocol van de Across studie beschreven, dat de basis en startblokken voor mijn proefschrift heeft opgeleverd. De achtergrond, redenering en methodologie van het onderzoek worden besproken. Het algemene doel van de Across studie is meer inzicht te krijgen in de relaties tussen cognitieve functies, psychopathologische symptomen en biomarkers.

Vervolgens onderzochten we in **Hoofdstuk 3** de relaties tussen psychopathologische symptomen en cognitieve domeinen met een cross-sectioneel partieel correlatienetwerkmodel in een transdiagnostische steekproef van patiënten met psychiatrische stoornissen. Over het algemeen vonden we dat ernstigere symptomen geassocieerd waren met slechter cognitief functioneren, en dat depressie, angst, verbaal geheugen en visuele aandacht een centrale rol speelden in dit netwerk. Verder vonden we dat cognitief functioneren en psychopathologie verschillende maar gerelateerde dimensies zijn, die elkaar en andere domeinen op een transdiagnostische manier beïnvloedden. Onze resultaten suggereren ook dat toekomstige studies zich zouden moeten richten op symptoom-specifieke interacties met cognitieve domeinen in plaats van cognitief functioneren binnen specifieke diagnostische categorieën te onderzoeken.

We onderzochten daarna in **Hoofdstuk 4** de transdiagnostische relatie tussen EEG-activiteit in rust en cognitieve functie met random forest regressie. We identificeerden EEG-kenmerken die verband houden met episodisch geheugen en associatief leren, informatieverwerkingsnelheid, en aandachtshift en executieve functie, maar niet met diagnose, wat suggereert dat EEG-activiteit bij psychiatrische stoornissen verband kunnen houden met cognitieve disfunctie. Er waren ook geen verschillen in cognitief functioneren tussen diagnostische categorieën, noch associaties tussen cognitief functioneren en symptoomdimensies. Deze benadering kan licht werpen op de neurobiologische basis en klinische relevantie van cognitieve stoornissen bij psychiatrische stoornissen.

Verder hebben we in **Hoofdstuk 5** de longitudinale relaties tussen individuele psychopathologische symptomen op twee meetmomenten onderzocht middels een cross-lagged panel netwerkanalyse in een transdiagnostische steekproef van patiënten met verschillende psychiatrische stoornissen. We ontdekten dat meer zelfmoordgedachten een negatiever zelfbeeld voorspelden en dat zelfbeeld een zeer voorspelbaar node was, wat suggereert dat het een belangrijke transdiagnostische uitkomstvariabele kan zijn. De resultaten van onze studie kunnen tot nieuwe inzichten leiden in hoe individuele symptomen elkaar beïnvloeden in de loop van de tijd en verder verduidelijken welke symptomen een centrale rol kunnen spelen bij psychiatrische aandoeningen om richting te geven aan de ontwikkeling van toekomstige behandelingen. Bovendien illustreren onze bevindingen verder het belang van onderzoek op symptoomniveau in plaats van op diagnostisch niveau voor het begrijpen van psychopathologie.

Tot slot, in **Hoofdstuk 6**, hebben we cross-sectionele relaties tussen existentiële problemen en psychopathologische symptoomdomeinen onderzocht in een transdiagnostische steekproef van patiënten met verschillende psychiatrische stoornissen met mixed graphical modellen. We ontdekten dat existentiële zorgen gerelateerd waren aan ernstigere symptomen en dat autonomie en identiteit de meest centrale existentiële variabelen in het netwerk waren. De resultaten ondersteunen daarom verder de rol van existentiële zorgen in psychopathologie en pleiten voor het aanpakken van existentiële zorgen in de klinische praktijk en onderzoek naast symptoomvermindering.

We eindigen het proefschrift met **Hoofdstuk 7**, waarin we het algemene gebruik van de transdiagnostische en netwerkbenaderingen in dit proefschrift bespreken, evenals bevindingen met betrekking tot drie overkoepelende dimensies: cognitief functioneren, psychopathologische symptomen en psychologische factoren (d.w.z. zelfvertrouwen en existentiële zorgen). We situeren de bevindingen binnen de

perspectieven van de paradigmaverschuiving en bespreken het onderzoek en de klinische implicaties. Verder reflecteren we op de sterke punten en beperkingen van de studies, de algemene implicaties en mogelijke richtingen voor toekomstig onderzoek.

Concluderend laat dit proefschrift zien dat de transdiagnostische en netwerkbenaderingen nuttig en waardevol kunnen zijn voor het verkrijgen van inzicht in relaties tussen verschillende dimensies van psychopathologie. Beide benaderingen vereisen echter meer rigoureuze tests om een solide empirische basis op te bouwen en klinisch te worden toegepast. Daarnaast demonstreert dit proefschrift de noodzaak om verder te gaan dan het symptoomreductiemodel en om niet-symptoomfactoren aan te pakken, zoals cognitieve functie en existentiële problemen, naast symptomen, wat zou kunnen worden bereikt door herstelondersteunende kaders. Al met al kunnen de transdiagnostische en netwerkbenaderingen de paradigmaverschuiving voortzetten die de huidige perspectieven van psychopathologie als afzonderlijke categorieën, evenals de common cause en symptoomreductie modellen, verwerpt. Dit kan leiden tot een beter begrip van psychopathologie en beter geïnformeerd onderzoeks- en klinische praktijk.

Author Contributions

Chapter 2: Protocol Across study: Longitudinal transdiagnostic cognitive functioning, psychiatric symptoms, and biological parameters in patients with a psychiatric disorder

Nieman, Vulink, & Denys: Conceptualization, Supervision, Resources, Funding acquisition. Lok, Smit, van Wingen, de Koning, Verweij, and Mocking: Methodology, Writing - Review & Editing. Bockting: Writing - Review & Editing. Nieman, Vulink, and Chavez-Baldini: Writing - Original Draft, Project administration.

Chapter 3: The relationship between cognitive functioning and psychopathology in patients with psychiatric disorders: A transdiagnostic network analysis

Chavez-Baldini: Data Curation, Writing - Original Draft, Project administration. Keestra: Formal analysis, Writing - Original Draft, Visualization. Nieman, Vulink & Denys: Conceptualization, Writing - Original Draft, Supervision, Resources, Funding acquisition. Lok, Mocking, de Koning, Sutterland: Writing - Review & Editing, Methodology. Bockting, Rooijen, Smit, Verweij, van Wingen, Wigman: Writing - Review & Editing.

Chapter 4: Resting-state brain oscillations predict cognitive function in psychiatric disorders: A transdiagnostic machine learning approach

Sargent: Conceptualization, Formal analysis, Writing - Original Draft. Master, Lok, Sutterland: Writing - Review & Editing. Verweij, Vulink, Denys: Writing - Review & Editing, Project administration. Chavez-Baldini: Data curation, Formal analysis, Writing - Review & Editing, Project administration. Smit & Nieman: Supervision, Methodology.

Chapter 5: The interplay between psychopathological symptoms: Transdiagnostic cross-lagged panel network model

Chavez-Baldini: Conceptualization, Formal analysis, Data Curation, Writing - Original Draft, Project administration. Verweij: Writing - Review & Editing, Project administration. Lok, Sutterland, Bockting, de Beurs, van Rooijen & van Wingen: Writing - Review & Editing. Across Consortium: Methodology, Investigation, Resources. Denys: Supervision, Funding acquisition, Writing - Review & Editing. Nieman & Vulink: Supervision, Writing - Original Draft, Project administration.

Chapter 6: Existential concerns in psychiatry: A transdiagnostic network analysis

Chavez-Baldini: Conceptualization, Formal analysis, Data Curation, Writing - Original Draft, Project administration. Verweij: Writing - Review & Editing, Project administration. Bergamin, Luigjes, & Mocking: Writing - Review & Editing. Across Consortium: Methodology, Investigation, Resources. Denys: Supervision, Funding acquisition, Writing - Review & Editing. Nieman & Vulink: Supervision, Writing - Original Draft, Project administration.

PhD portfolio

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PhD period: January 2019 until November 2022

Promotor: Prof. dr. D.A.J.P. Denys

Co-promotors: dr. D.H. Nieman, dr. N.C.C. Vulink

Courses

General courses

AMC World of Science

BROK ('Basiscursus Regelgeving Klinisch Onderzoek')

Research Data Management

Peer to Peer Group Coaching

Correct Citation

Dutch Language Course

Zoeken voor een CAT

Project Management

Specific courses

Castor EDC Workshop and Webinars

Didactical Skills Training

Seminars, workshops and master classes

Amsterdam Workshop- Diagnosis with Utility: Building Blocks and Tools for a New Era

Studenten begeleiden op afstand (HvA Training)

Data Science Day (UvA Data Science Center)

Presentations

Oral presentation: Transdiagnostic Network Analysis, Department of Psychiatry Research Meeting, Amsterdam, 2019

Poster: The relationship between cognitive functioning and psychopathology in patients with psychiatric disorders: A transdiagnostic network analysis, 28th EPA European Congress of Psychiatry, Virtual, 2020

Oral presentation: Bridging neurobiological measures and clinical phenomenology: a transdiagnostic approach, Department of Psychiatry Research Meeting, Amsterdam, 2020

Poster: The interplay between psychopathological symptoms: A transdiagnostic cross-lagged panel network model, 21st WPA World Congress of Psychiatry, Cartagena, 2021

Poster: Investigating the biological pathway between urbanicity and psychiatric disorders: A research proposal, 34th ECNP Congress, Lisbon, 2021

Poster: Existential factors in psychiatry: A transdiagnostic network approach, 22nd WPA World Congress of Psychiatry, Bangkok, 2022

(Inter)national conferences

28th EPA European Congress of Psychiatry, Virtual, 2020
33rd ECNP Congress, Virtual, 2020
21st WPA World Congress of Psychiatry, Cartagena, 2021
34th ECNP Congress, Lisbon, 2021
30th EPA Congress, Budapest, 2022
22nd WPA World Congress of Psychiatry, Bangkok, 2022

Teaching

Supervising - Master Thesis

Busra Ayasli - *The relationship between negative self-esteem, social anxiety, and alcohol use*, Master thesis Clinical Psychology, VU, 2019

Chanel Bansema - *Biomarkers in misophonia: An ERP study*, Master thesis Clinical Neuropsychology, VU, 2019

Saloua El Hadrati - *The relationship between trauma, psychotic experiences, and working memory*, Master thesis Clinical Psychology, VU, 2019

Niklas Strüwe - *Presence of Alcohol (Ab)use in psychiatric patients and the effects on memory*, Master Thesis Clinical Psychology, VU, 2019

Hadassa Thio - *Transdiagnostic assessment of the relations between depression symptoms subtypes and verbal memory functioning among a large group of psychiatric patients*, Master thesis Clinical Neuropsychology, UvA, 2019

Yeliz Ünsal - *Focusing on neurocognitive functioning in MDD: investigating the associations between MDD, neurocognitive functioning and psychosocial functioning*, Master thesis Clinical Neuropsychology, VU, 2019

Sarah Amhaini - *The relationship between bullying, self-esteem, and alcohol use*, Master thesis Clinical Psychology, VU, 2020

Ashyka Chabile - *Misophonia: Psychopathological and cognitive symptoms comparison*, Master thesis Clinical Neuropsychology, UvA, 2020

Sharoma Gokkoel - *The relationship between cannabis use, psychotic symptoms, and memory*, Master thesis Clinical Psychology, VU, 2020

Rachel Jansen - *Area-level socioeconomic status functions as a predictor for cognitive flexibility in patients with psychiatric disorders*, Master thesis Clinical Neuropsychology, Leiden University, 2020

Appendices

Ruqaiya Jhagroe - *The relationship between alcohol use, depressive symptoms, and attention/alertness*, Master thesis Clinical Psychology, VU, 2020

Niloofar Khorrami - *The relationship between psychotic features and memory: a longitudinal study*, Master thesis Clinical Neuropsychology, VU, 2020

Ildiko Walther - *The relationship between subclinical psychotic symptoms and obsessive-compulsive symptoms on attention: A transdiagnostic study*, Master thesis Clinical Psychology, VU, 2020

Hanae Douhri - *The relationship between cannabis use, psychotic experiences, self-esteem, and psychosocial function*, Master thesis Clinical Psychology, VU, 2021

Adinda Janse - *Neuroscientific network analysis of executive functions and resting-state EEG oscillations in patients with a psychiatric disorder*, Master thesis Clinical Neuropsychology, Leiden University, 2021

Valerie Kemp - *The relationship between substance use, planning, and psychosocial function*, Master thesis Clinical Psychology, VU, 2021

Nilay Kilic - *The relationship between gender, obsessive-compulsive symptoms, and self-esteem*, Master thesis Clinical Psychology, VU, 2021

Yanna Loogman - *Psychotic symptoms and executive functions: what is the influence of anxiety and mood complaints*, Master thesis Clinical Psychology, VU, 2021

Maartje Overhaus - *Can microstates be considered as vulnerability biomarkers for psychotic disorders?*, Research project Research Master Brain and Cognition, UvA, 2021

Quinten Schotten - *The relationship between transdiagnostic factors and psychosocial functioning*, Master thesis Clinical Psychology, VU, 2021

Cheryl Sumter - *The relationship between cognitive function, psychotic symptoms, and anhedonia*, Master thesis Clinical Psychology, VU, 2021

Marianne Tip - *The association between social anxiety and daily functioning with alcohol use as a moderator*, Master thesis Clinical Psychology, VU, 2021

Noortje van de Graaf - *Moderation of depressive symptoms and anhedonia in the relationship between trauma and cognitive function*, Master thesis Research Master Brain and Cognition, UvA, 2021

Senné Walraven - *P3 in patients with misophonia and psychiatric disorders with and without hallucinations: An ERP study*, Master thesis Research Master Brain and Cognition, UvA, 2021

Margot de Wijze - *Differences between misophonia and obsessive-compulsive disorder in cognitive function*, Master thesis Clinical Neuropsychology, Leiden University, 2021

Isa Gent - *Anxiety and executive functioning in psychiatric patients: a transdiagnostic approach*, Master thesis Clinical Psychology, VU, 2022

Willemijn van der Burg-Gros - *Relationship of psychosocial functioning with depressive symptoms, psychotic symptoms and cognitive functioning in a transdiagnostic sample of mental health patients*, Master thesis Clinical Neuropsychology, VU, 2022

Fatima Sacirovic - *Relationship between alcohol use, executive functioning and daily functioning in psychiatric patients*, Master thesis Clinical Neuropsychology, VU, 2022

Vivian Wendt - *This is odd: Investigating event related potentials using the oddball paradigm*, Master thesis Clinical Neuropsychology, Leiden University, 2022

Supervising - Other

Nyssah Hernandez - 3rd Year Internship & Training Manual: Adequaat en Consequente te Werk te Gaan, Capstone Project, Applied Psychology, HvA, 2019 & 2020

Fanny Jagers - 3rd Year Internship, Applied Psychology, HvA, 2019

Safae Moussa - 3rd Year Internship & Workbook: Leren Omgaan met een Cognitief Probleem, Capstone Project, Applied Psychology, HvA, 2019 & 2020

Fleur Smit - 3rd Year Internship, Applied Psychology, HvA, 2020

Nina Thenadey - 3rd Year Internship, Applied Psychology, HvA, 2021

Melanie Tito - 3rd Year Internship, Applied Psychology, HvA, 2021

List of publications

Peer reviewed - in this thesis

Chavez-Baldini, U., Verweij, K., de Beurs, D., Bockting, C., Lok, A., Sutterland, A. L., . . . Nieman, D. (2022). The interplay between psychopathological symptoms: Transdiagnostic cross-lagged panel network model. *BJPsych Open*, 8(4), e116. doi:10.1192/bjo.2022.516

Chavez-Baldini, U., Nieman, D. H., Keestra, A., Lok, A., Mocking, R. J. T., de Koning, P., . . . Denys, D. (2021). The relationship between cognitive functioning and psychopathology in patients with psychiatric disorders: A transdiagnostic network analysis. *Psychological Medicine*, 1-10. doi:10.1017/S0033291721001781

Sargent, K., **Chavez-Baldini, U.**, Master, S. L., Verweij, K. J. H., Lok, A., Sutterland, A. L., . . . Nieman, D. H. (2021). Resting-state brain oscillations predict cognitive function in psychiatric disorders: A transdiagnostic machine learning approach. *NeuroImage: Clinical*, 30, 102617. doi:<https://doi.org/10.1016/j.nicl.2021.102617>

Nieman, D. H., **Chavez-Baldini, U.**, Vulink, N. C., Smit, D. J. A., van Wingen, G., de Koning, P., . . . Denys, D. (2020). Protocol Across study: Longitudinal transdiagnostic cognitive functioning, psychiatric symptoms, and biological parameters in patients with a psychiatric disorder. *BMC Psychiatry*, 20(1), 212. doi:10.1186/s12888-020-02624-x

Peer reviewed - not in this thesis

Chavez-Baldini, U., Wichers, M., Reininghaus, U., Wigman, J. T. W., Genetic, R., & Outcome of Psychosis, I. (2020). Expressive suppression in psychosis: The association with social context. *PLoS One*, 15(3), e0230102. doi:10.1371/journal.pone.0230102

Reininghaus, U., Böhnke, J. R., **Chavez-Baldini, U.**, Gibbons, R., Ivleva, E., Clementz, B. A., . . . Tamminga, C. A. (2019). Transdiagnostic dimensions of psychosis in the bipolar-schizophrenia network on intermediate phenotypes (b-snip). *World Psychiatry*, 18(1), 67-76. doi:<https://doi.org/10.1002/wps.20607>

Klippe, A., Myin-Germeys, I., **Chavez-Baldini, U.**, Preacher, K. J., Kempton, M., Valmaggia, L., . . . Hubbard, K. (2017). Modeling the interplay between psychological processes and adverse, stressful contexts and experiences in pathways to psychosis: An experience sampling study. *Schizophrenia Bulletin*, 43(2), 302-315.

Under review - in this thesis

Chavez-Baldini, U., Verweij, K. J. H., Bergamin, J., Luigjes, J., Mocking, R. J. T., Denys, D., Nieman, D. H., & Vulink, N. C. Existential concerns in psychiatry: A transdiagnostic network analysis.

Other

Travel Grant for 28th EPA European Congress of Psychiatry

Curriculum Vitae

UnYoung Gabriela Chavez-Baldini was born on the 5th of October, 1992 in Honduras. She was raised mostly in Latin America in her early years and then raised in Florida, USA for most of her life. After gaining an interest in social phenomena and psychology in high school, she attended Florida State University from 2011 to 2014 where she completed a double-major degree in psychology and sociology (*summa cum laude*). It was during the bachelor that she became interested in research, especially on social and clinical psychology, and became involved in research activities as a research assistant and lab manager.

Pursuing this interest in research, she took a big leap across the ocean and attended the research master program at Maastricht University where she earned her degree in Cognitive and Clinical Neuroscience with a specialization in Psychopathology in 2017 (*cum laude*). During the master's program, she engaged in research activities as a research assistant at the Department of Psychiatry and Psychology in Maastricht and later as an intern at the Interdisciplinary Center Psychopathology and Emotion Regulation at the University Medical Center Groningen.

During her master's program and research activities, she learned about the trans-diagnostic approach, which she viewed as an exciting and promising part of the paradigm shift in psychiatry, and wished to apply this approach in her own research. This led her to applying for the research coordinator position of the Across study as an opportunity to further expand her knowledge of this approach, which eventually turned into a PhD position. During the PhD, she had the opportunity to investigate the new perspectives of recent paradigm shifts.

Currently she is living in Utrecht and exploring different opportunities with the hope of getting involved in social psychiatry and community-based or client-oriented research that focuses on the lived experiences of individuals with mental disorders.

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