Neuroscience and Biobehavioral Reviews 130 (2021) 81–90

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Connecting brain and behavior in clinical neuroscience: A network approach

Tessa F. Blanken [a,*], Joe Bathelt [b], Marie K. Deserno [c], Lily Voge [d], Denny Borsboom [a], Linda Douw [d,e]

[a] Department of Psychological Methods, University of Amsterdam, 1018 WT, Amsterdam, the Netherlands
[b] Royal Holloway, University of London, Department of Psychology, Egham, Surrey, TW20 0EX, United Kingdom
[c] Max Planck Institute for Human Development, 14195, Berlin, Germany
[d] Department of Anatomy and Neurosciences, Amsterdam University Medical Centres, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, 1081 HZ, Amsterdam, the Netherlands
[e] Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusets General Hospital, Boston, MA, 02129, USA

ARTICLE INFO

Keywords:
Brain
Behavior
Network science
Psychopathology
Clinical neuroscience
Graph theory

ABSTRACT

In recent years, there has been an increase in applications of network science in many different fields. In clinical neuroscience and psychopathology, the developments and applications of network science have occurred mostly simultaneously, but without much collaboration between the two fields. The promise of integrating these network applications lies in a united framework to tackle one of the fundamental questions of our time: how to understand the link between brain and behavior. In the current overview, we bridge this gap by introducing conventions in both fields, highlighting similarities, and creating a common language that enables the exploitation of synergies. We provide research examples in autism research, as it accurately represents research lines in both network neuroscience and psychological networks. We integrate brain and behavior not only semantically, but also practically, by showcasing three methodological avenues that allow to combine networks of brain and behavioral data. As such, the current paper offers a stepping stone to further develop multi-modal networks and to integrate brain and behavior.

1. Introduction

If one had to write a one-sentence summary of a century of research into human behavior and the processes that underlie it, a good candidate would be: "it's complicated". Indeed, the complexities encountered at every level of analysis, from the neural underpinnings of cognitive and affective processes to the intricacies of behavior itself, are astounding and we are just beginning to realize the magnitude of the undertaking that (neuro)psychology has ventured on. In the past years, however, we have seen an interesting twist: instead of lamenting complexity as a problem, novel methodologies have leveraged complexity as a strength, and have brought to bear novel insights from the area of network science to shed light on the topic. Two such areas are neuroscience, where network analysis has become a common way of considering the brain, and psychopathology, where the interactions between symptoms are reconceptualized as network structures. But how should we connect such different levels of analysis? Connections between neurons in our brain, interactions between psychological states, and social relations we engage in all form networks, but how should we envisage the relations between networks that exist at such different levels? This question calls for the development of methodologies suited to link network analyses executed at distinct levels of analysis. This paper provides an overview of methodological strategies that can be used to couple network analyses at the brain and behavioral levels, illustrates their application to the case of autism, and discusses open problems and avenues for further development.

2. Networks in neuroscience

2.1. The history of network neuroscience

Neuroscience is a relatively young field of science, stemming from a fusion between physiology, anatomy, molecular biology, developmental biology, cytology, mathematical modeling, and psychology. One goal of

* Corresponding author at: Nieuwe-Achtergracht 129-B, 1018 WS, Amsterdam, the Netherlands.
E-mail address: t.f.blanken@uva.nl (T.F. Blanken).

https://doi.org/10.1016/j.neubiorev.2021.07.027
Received 19 April 2021; Received in revised form 14 July 2021; Accepted 23 July 2021
Available online 26 July 2021

Table 1
Terms and definitions used in brain network and symptom network analysis.

Term	Brain	Behavior
Node	Brain regions can be defined in any modality by • anatomical markers, often taken from a template according to sulcal or gyral pattern • statistical association of brain signals, e.g. independent component analysis (ICA), spatial clustering.T The definition of the brain region can be binary or probabilistic Voxels for MRI modalities with superior spatial resolution Channels/Electrodes/Sensors, particularly for EEG, electrocorticography (ECoG), and near-infrared spectroscopy (NIRS), sometimes for MEG Functional imaging and neurophysiology: Statistical association between signals. In fMRI, the most common measures are correlation, partial correlation, or covariance. In M/EEG, it is coherence, (weighted) phase lag index (wPLI) or other phase based measures, or (amplitude) envelope correlation, to take into account the higher temporal resolution and avoid artifacts due to volume conduction and signal leakage in these methods. Functional networks are almost always individually determined.	Symptoms can be operationalized by • diagnostic nosologies (eg DSM-5, ICD-10) • items or sub-scales from self -report questionnaires (often developed to assess a diagnosis and based on the diagnostic nosologies) • diagnostic interview schedules, such as the SKID-5 and similar instruments • functions of objective behavioral measures (e.g., movement data, sleep registrations, etc.) Experimentally induced responses (e.g., CO^2 challenge in panic disorder, responses to white noise in speech illusions in psychotic disorders)
Link	Diffusion imaging: Microstructural properties of white matter, i.e. fractional anisotropy (FA), radial diffusivity (RD), count of (probability of) streamlines from tractography, often normalized by distance or area size. Diffusion-based networks are almost always individually determined. Anatomical imaging: Correlation or covariance of morphological measurements across participants, correlation of morphological measurements between regions. Structural covariance networks can be determined at both the individual or the group level.	Statistical associations between symptoms: The statistical associations between symptoms can be uncovered cross-sectionally (i.e., by measuring many individuals once) or individually (i.e., by measuring an individual over time). When investigating the statistical association between symptoms in individuals over time, three different networks can be constructed: (i) a temporal network that captures how symptoms influence each other over time; (ii) a contemporaneous network that captures how symptoms are statistically related at each time-point, after taking the temporal effects into account; and in case multiple individuals are measured (iii) a between-subject network can be constructed to reflect the statistical associations between symptoms across individuals. Perceived causal relations: In this approach, links between symptoms are be self-reported, as individuals indicate how they perceive symptoms to affect one another.

neuroscience is to understand how brain features relate to human behavior. Throughout the history of neuroscience and its preceding scientific disciplines, two seemingly opposing views can easily be distinguished, alternating as the ruling doctrine in particular periods of history.

The first view is based on the idea that distinct behaviors are governed by the structure and function of distinguishable brain regions, such that particular brain regions are responsible for particular functions. This localizationist view has been championed by scientists investigating the effects of focal lesions on functioning: Galen, doctor and surgeon to the gladiators that entertained the crowds in ancient Rome, observed how injuries to the head led to loss of cognitive functions. In more recent times, neurosurgeon Wilder Penfield executed 'virtual' lesioning experiments on humans, by temporarily shutting down brain functioning through electrical stimulation in epilepsy patients undergoing awake neurosurgery. This groundbreaking work provided us with the homunculus, a mapping of sensory and motor functions onto the cortex of the brain (Penfield and Boldrey, 1937).

Opposing this rather reductionist account of brain-behavior relationships is the view that it is impossible to localize behavior in particular areas of the brain. Instead, the brain is viewed as a holistic organ that gives rise to behavior in a more unitary manner. An example of such a framework is the idea of 'mass action', proposed by memory investigator Karl Lashley, which holds that memory is distributed throughout the cortex and cannot be localized to particular regions (Lashley, 1931). Lesions leading to memory dysfunction are seen as a proportional effect: the larger the area in the brain that is injured, the more cognitive problems will ensue. Another famous proponent of this view is Charles Sherrington, who attributed the process of waking up and becoming conscious to the brain functioning as an enchanted loom: no single thread can be held accountable for the fabric as a whole (Sherrington, 1951).

Up to the end of the 20th century, these views opposed each other and were difficult if not impossible to reconcile theoretically and experimentally. Since 1998, however, network neuroscience offers a mathematical framework that unites local specialization with global integration through graph theoretical approaches applied to the brain (Watts and Strogatz, 1998). In their seminal work, Watts and Strogatz were the first to convert the central nervous system of the nematode Caenorhabditis elegans to a graph or network, with each of the animal's 302 neurons being a node or vertex, and each axonal connection between those neurons being a link or edge. They then describe two algorithms that capture nodal specialization (clustering coefficient) and global integration (average path length), and propose that the combination of high specialization and integration, the 'small-world' network topology, is optimal for functioning of any complex network, including the brain. Since then, network neuroscientific studies of the human brain have indeed shown that optimal brain functioning is governed by such a network signature (van den Heuvel et al., 2009; Douw et al., 2011), and that behavioral impairments, such as those present in autism spectrum disorder (ASD; see 2.3.), go hand in hand with brain network dysfunction (van den Heuvel and Sporns, 2019; Bassett et al., 2018a).

2.2. Methodology in network neuroscience

Macro-scale brain networks (which are the most often explored type of brain networks in living humans) can be constructed in several ways, based on different data modalities. The nodes in such a network typically represent voxels (see Table 1), or larger brain areas from an atlas. Many different atlases are in use, for instance the 92-region automated anatomical labeling atlas that is based on cytoarchitecture (Tzourio-Mazoyer et al., 2002) and the 246-region brainnetome atlas that is based on connectivity pattern similarity per voxel (Fan et al., 2016). The choice of atlas impacts all subsequent analyses and should not be taken lightly. Several recent papers highlight the particulars of this choice and offer guidance for different research questions (Arslan et al., 2018; Power et al., 2013; Schaefer et al., 2018).

The links in the macro-scale brain network can be established in different ways (see Fig. 1). Early methodologies to investigate the brain network include structural covariance networks, where covariations in cortical thickness of voxels or brain regions across people are quantified (Wright et al., 1999; He et al., 2007). The rationale behind the method is that (changes in) the structural properties of pairs of brain regions may reflect shared underlying processes. Of note, since they take into account individual differences in morphology, structural covariance networks are usually constructed at the group level. More recent techniques do allow for individual network reconstruction, for instance using inter-hemispheric similarity in morphology (Tijms et al., 2012) or by

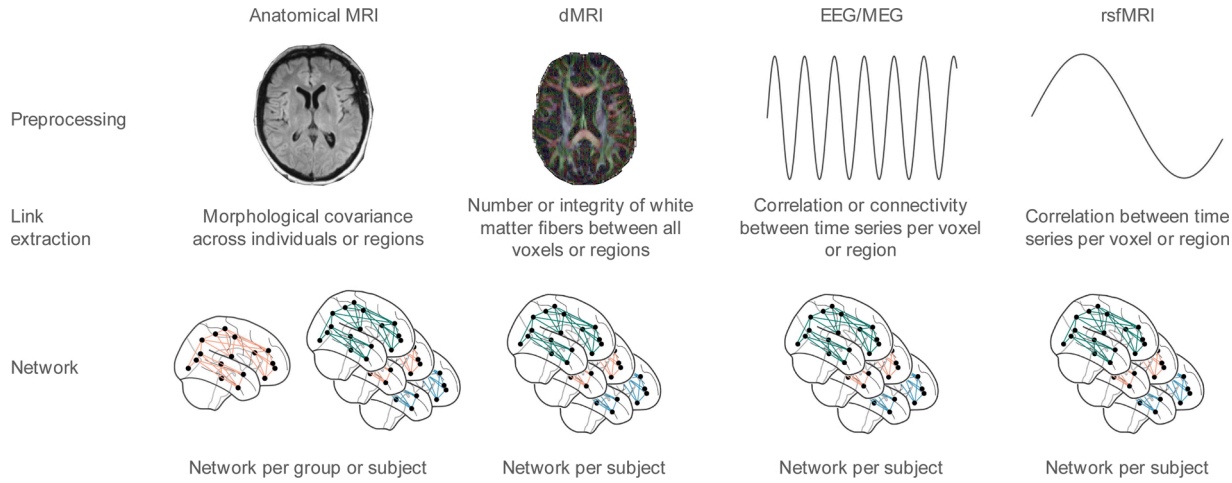

Fig. 1. Methods in networks neuroscience. MRI = magnetic resonance imaging, EEG = electroencephalography, MEG = magnetoencephalography, rsfMRI = resting-state functional MRI. In brain networks, nodes are usually brain regions or voxels. Links are modality-specific: when using anatomical MRI, links are extracted by investigating morphological covariance at the subject or group level. Diffusion MRI allows for estimation of the number or integrity (weight) of structural connections between different voxels or brain regions in individual subjects. Functionally, EEG/MEG/rsfMRI time series per voxel or region can be correlated to define functional links, usually using connectivity measures that take the specific pitfalls of these modalities into account: whereas rsfMRI analysis usually involves (partial) correlation coefficients, EEG/MEG connectivity calculation is susceptible to source conduction (EEG) or field spread (MEG), thus rendering it necessary to account for these artifacts through choice of connectivity measure. This yields a single network per subject.

correlating multiple morphological parameters of two regions within the same person (Seidlitz et al., 2018). Although the idea behind construction of these networks is similar, i.e., structural covariance determines the links across or within subjects, it is important to note that individual structural covariance networks obviously allow for more detailed hypothesis testing than the group level network.

The anatomical connections between nodes can be imaged using diffusion magnetic resonance imaging (dMRI; Hagmann et al., 2007), which picks up on the directionality of diffusion of water molecules depending on how constrained they are by white matter bundles. Reconstruction algorithms (i.e. tractography) then allow one to either deterministically or probabilistically establish the number and/or integrity of fiber bundles between each node in the brain network. Although this method is commonly viewed as the gold standard for anatomical connectivity estimation, it is important to note that tractography always yields merely an estimate of the actual anatomical connectivity between brain regions, and is subject to several methodological pitfalls (Maier-Hein et al., 2017), such as overestimation of fibers, particularly in areas where tracts cross or 'kiss'. Finally, this approach yields an estimated anatomical brain network per scan.

Functional connections are most often assessed per individual using functional MRI (fMRI), either during a task (tfMRI) or more often during a resting-state (rsfMRI; Salvador et al., 2005). The modality indirectly captures brain activity as represented by the blood-oxygenation level dependent (BOLD) response. Although fMRI has high spatial resolution at the level of millimeters, the sampling frequency of activity is low: typically, it is measured every 1–5 seconds. In order to create a network, the time series of activity from each node are correlated, based on the idea that synchronized activity patterns would reflect some sort of functional communication or connectivity. Any temporal dependency could obviously indicate a direct functional connection between two regions, or a common latent source of activity spreading to both regions simultaneously. As such, no causal conclusion on which region is driving the correlation can be drawn from functional connectivity. Although a somewhat stable network can be constructed using only a few hundred timepoints of data (typically 5−10 min of scanning are performed; Van Dijk et al., 2010), recent literature suggests that extended data collection may significantly increase reliability of network estimation through functional connectivity (Noble et al., 2019). The analysis typically yields a brain network per scan.

Individual functional connectivity may also be investigated using neurophysiological techniques such as electroencephalography (EEG; Linkenkaer-Hansen et al., 2001) and/or magnetoencephalography (MEG; Stam, 2004) during the resting-state. Both measure neuronal activity more directly than fMRI, by either capturing the electric or magnetic changes, respectively, induced by postsynaptic currents of large numbers of neurons (n>50,000). The temporal resolution of these techniques is therefore very high, with a sampling frequency above 1000 Hz, but the spatial resolution is more variable per region of the brain and is in the order of centimeters. Again, functional connectivity is established by calculating some sort of synchronization between the resulting time series, although extra care should be taken to mitigate the methodological pitfalls of the techniques, such as volume conduction in EEG and spurious sources and signal leakage in MEG. With these techniques, recording length (i.e., number of samples) is less influential in network reconstruction due to the high sampling rate: approximately 1 min of data already yields relatively stable network topology (Chu et al., 2012). EEG and MEG yield a brain network per recording.

2.3. *Autism as a brain network disorder*

A case in point for the application of a network neuroscience perspective is research on the neural basis of autism spectrum disorder (ASD). ASD is a complex disorder characterized by difficulties with social interaction and communication alongside restricted interests, repetitive behaviors, and sensory hyper- or hypo-sensitivities (American Psychiatric Association, 2013). While there is no generally accepted etiological theory of the disorder, research over the last decades has focused on identifying a neurobiological basis. Traditional neuroimaging methods that were designed to localize differences in the context of lesion studies and a modular view of brain organization failed to identify consistent focal differences in ASD (Maximo et al., 2014). Emblematic of research across complex psychiatric conditions, the focus has since shifted towards characterizing the role of brain network differences in ASD (see Hull et al., 2017 for a review). A consistent finding in the first wave of studies on rsfMRI connectivity was reduced long-range connectivity in ASD, particularly between parietal and frontal areas (Just et al., 2007; Kana et al., 2009). However, other studies also reported increased connectivity (Shih et al., 2011), e.g., between parietal and temporal regions. More recent studies based on

thousands of participants suggest a more complex picture with some stronger and some weaker connections in ASD relative to typical groups (Oldehinkel et al., 2019). Recent years saw a more direct application of network theory to characterize brain connectivity differences in ASD. Rather than just describing patterns of differences, network theory helps to understand the implications of connectivity differences for the network architecture. For instance, differences in functional brain connectivity in ASD have been interpreted as a deviation from the typical small-world architecture (Rudie et al., 2013), a shift in the balance of modularization versus integration (Keown et al., 2017), and a difference in the hub-spoke network hierarchy (Hong et al., 2019). These network accounts suggest that subtle and distributed differences across the network can accumulate in sub-optimal trade-offs in the network architecture (van den Heuvel and Sporns, 2019). Further, the network account suggests that particular areas may be implicated because of their role for supporting an efficient network architecture rather than their function for any specific computation (de Lange et al., 2019). This perspective has led to new hypothesis to explain behavioral features of autism on the basis of brain differences. For instance, Markram and Markram put forward the 'intense world' theory that proposes a mechanism by which the behavioral features of autism may arise from local hyperconnectivity (Markram and Markram, 2010). As this brief summary shows, the addition of a network perspective has enriched brain research and provided a theoretical basis for mechanistic hypotheses to understand this highly complex and heterogeneous condition (Bertolero and Bassett, 2020).

3. Networks in psychopathology research

3.1. History

Reminiscent of the tension between localized and holistic theories of information processing in the human brain, the history of psychopathology research is characterized by a similar tension between reductionist and holistic approaches. In keeping with the original presentation of psychiatry as a medical discipline (Kraepelin and Lange, 1927), mental disorders are often portrayed in terms of a disease analogy (Hyland, 2011). For instance, in current nosologies such as the DSM-5, different mental disorders, psychological disorders, or neurodevelopmental disorders are all accompanied by a specific list of observable symptoms; within a disease analogy, the disorders are thought to underlie, cause, or determine these sets of symptoms that often co-occur in individuals. Thus, an anxiety disorder causes the symptoms of excessive worry and irritability; and a depression disorder causes the symptoms of insomnia, fatigue, and concentration problems. Following this conceptualization, disorders are considered to be underlying causal entities that are ultimately rooted in brain functions. From such a viewpoint, the central aim of psychiatry is to uncover these entities through neuroscientific research (e.g., mental disorders are "brain circuit disorders" that can be treated by "tuning these circuits"; Insel and Cuthbert, 2015, p. 500).

On the other hand, in the history of the field, attention has been repeatedly drawn to the fact that mental disorders crucially involve subjective experience (Jaspers, 1963) and also appear to transcend the physical borders of the human body, in the sense that they involve interactions between human behavior and the physical and cultural environment in which it unfolds (Kendler et al., 2011; Borsboom et al., 2019). For example, symptoms of mental disorders often promote behavior that leads to a change of environment which may itself promote other symptoms (e.g., a lack of human interaction due to social anxiety may lead to withdrawal from social life, which in turn may lead to loneliness and depressed mood; a drug addict may choose to live in the city, which both accommodates the addiction and exposes the individual to a larger set of hazards that may promote further symptomatology). Such observed complexities typically appeal to systems analogies, in which mental disorders are seen as disturbances in the behavioral, cognitive, and affective equilibria that characterizes mental health; these alterations will typically include feedback loops that involve the physical, social, and cultural environment and as such portray psychiatric disorders as extended beyond the body and brain (Borsboom et al., 2019).

Proponents of more holistic approaches note the lack of success in identifying central pathogenic pathways on a purely genetic or neurobiological basis (Kendler, 2012) and point to the importance of transdiagnostic processes that span multiple disorders (Nolen-Hoeksema and Watkins, 2011). Nonetheless, neuroscience is crucially important in developing further understanding of psychopathology and the question therefore is not so much *whether* the brain matters, but rather *how* alternatives to reductionism can be organized into a methodologically operational approach integrating neuroscience with other levels of analysis.

In recent years, it has been proposed that network analysis may offer such methodology towards unraveling the complexity of psychopathology and accommodating the interaction between biological and psychological levels of analysis. In one incarnation of this approach, symptoms themselves are considered to interact in a causal network (Borsboom and Cramer, 2013; McNally, 2021), and disorders are viewed as alternative stable states of the causal system that arise out of these interactions (Borsboom, 2017). In the wake of these theoretical developments, researchers have worked towards developing techniques to estimate these connections between symptoms using the application of network analytic approaches to multivariate data.

3.2. Psychological networks methodology

Psychological networks, like brain networks, consist of nodes and links among them. In psychopathology networks, the nodes typically represent symptoms that can be assessed using self-report questionnaires or diagnostic interviews. It is important to note that the nodes in a psychopathology network thus do not reflect any fixed set of symptoms nor any physically localized entities; nodes represent variables (i.e., functions defined on an outcome space), not things.

In psychopathology networks at least two different types of links can be distinguished. First, and most commonly, links between symptoms can be *estimated* from data and thus reflect statistical associations. Second, links between symptoms can reflect *reported* relations, a method that is known as Perceived Causal Relations (Frewen et al., 2012, 2013).

When the links between symptoms are estimated from data, these can be estimated *over people* using cross-sectional network modeling (e.g., how does 'insomnia' relate to 'concentration problems' across people); or *over time* using temporal network modeling (e.g., how does 'insomnia' relate to 'concentration problems' within one person, over time).

In cross-sectional network modeling (left panel in Fig. 2), a network is estimated *across participants* at a single timepoint and reflects how symptoms co-occur *across people*. There are multiple ways to estimate such relations, and currently it is most common to estimate a Gaussian Graphical Model (GGM; Epskamp et al., 2018d). A GGM can be visualized as a network, where the symptoms are shown as nodes and the links represent the *partial correlations*, indicating how two symptoms co-occur, when taking all the other symptoms in the network into account.

In temporal network modeling (middle panel in Fig. 2), a network is estimated *across timepoints* and at least two networks can be constructed: a *temporal network* reflecting how symptoms predict each other over time in a directed network, and a *contemporaneous network* showing the undirected relations among symptoms at a single measurement occasion, after controlling for the temporal effects and all the other symptoms in the network (Epskamp et al., 2018b). If multiple people are estimated over time, a between-subjects network can be estimated that reflects how the mean-levels of symptoms covary between persons. Note that this is not the same as a cross-sectional network, as the

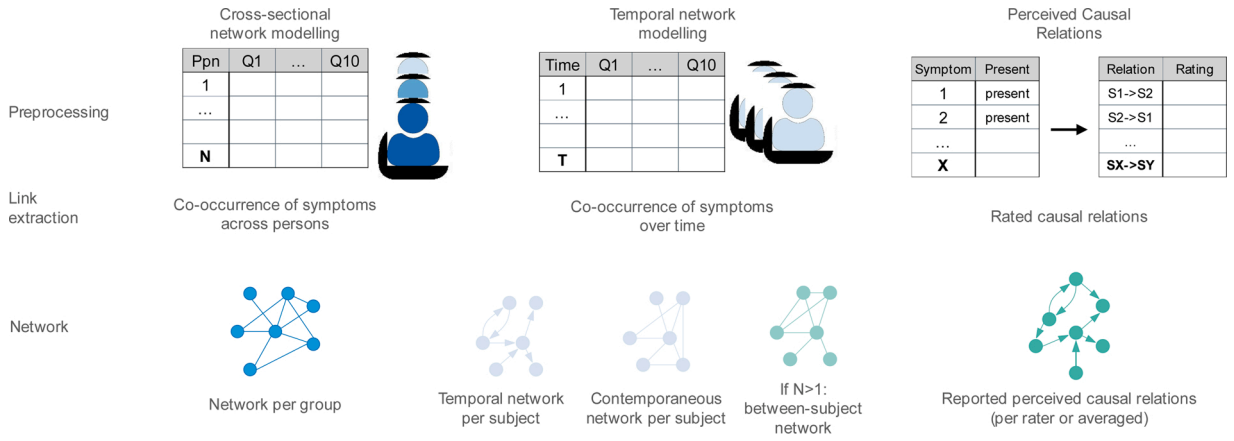

Fig. 2. Methods in psychopathology networks. In psychological networks, nodes usually represent symptoms. Links can be either estimated from data (left and middle panel), or reported (right panel). Cross-sectional network modelling estimates associations between symptoms (the links) across people and yields a single network per group. Temporal network modelling estimates the associations between symptoms over time and yields at least two networks per subject: a temporal network showing the associations over time, and a contemporaneous network including the associations within one time-point, after taking the temporal associations into account. If temporal data is available for multiple subjects, a between-subject network can be estimated. Perceived Causal Relations is a method that links symptoms based on reported relations by a rater (e.g., patient or clinician). This method can yield a network per rater or an averaged network across raters.

cross-sectional network reflects a mix of both within- and between-person effects (see Epskamp et al., 2018d for more details).

When networks are estimated from data there are two important considerations. The first consideration is that of model selection. After the model is estimated, there are different ways to determine whether a link should be included in the network: thresholding, pruning, and regularization. In brief, thresholding and pruning are similar as first a saturated network is estimated (i.e., a network in which all possible edges are included), after which only certain edges are selected (e.g., only significant edges are included). In thresholding the edges that do not meet the criertion are simply omitted, whereas in pruning the model in which these edges are put to zero is then refitted to the data. Alternatively, a network can be estimated using regularization techniques, which shrinks or selects some of the estimated links, see Epskamp and Fried (2018a) for a tutorial on estimating regularized networks.

The second consideration is that of accuracy and stability of the estimated links. When estimating associations from data, there will, inevitably, be some uncertainty around the estimated links. Therefore, it is important to consider how accurate and stable the estimated network parameters are (Borsboom et al., 2018). Over the last years it has become common practice to evaluate this uncertainty using bootstraps (Epskamp et al., 2018c).

While estimating the relations among symptoms from data is the most common way to construct psychopathology networks, there are alternative ways. One method, Perceived Causal Relations (PCR; right panel in Fig. 2), links symptoms based on the self-rated causal relations among symptoms (Frewen et al., 2012). First, the patient or proxy is asked to select an individual set of experienced or relevant symptoms. Then, for each symptom-pair that is present, the participant is asked to what extent the symptoms cause one another. For example, if someone suffers from 'insomnia' and 'concentration problems' they are asked to what extent their insomnia causes their concentration problems, and vice versa, to what extent their concentration problems cause their insomnia. With this (personalized) rating technique, a directed network of the perceived causal relations of a patient can be constructed. Originally, the method was mainly applied in patient samples (Frewen et al., 2012), but more recently it has also been used to investigate the causal relations as they are perceived by expert clinicians in their autistic patients (Deserno et al., 2020).

3.3. Autism as a psychological network disorder

The phenotypic study of autism too has seen recent efforts to apply network theory to characterize symptom profiles and covariance in ASD (Anderson, 2008; Deserno et al., 2017). Traditionally, neurodevelopmental disorders such as ASD have been conceptualized with the – often implicit – assumption that the co-occurrence of its diagnostic features stems from some traceable etiological agent. In recent years, however, the autism field, too, re-evaluated the implications of such causal model being confronted with its theoretical and practical limits. Recent work reconceptualizes the autistic phenotype as the result of multiple interacting cognitive atypicalities instead of a common cause (Happé and Ronald, 2008), and as a common adaptive response to mild but widespread neural atypicalities (Johnson, 2017). To capture the complex developmental interactions implied by these theories, the field has started to integrate statistical representations of dynamic interaction effects on the symptom level. Network analytic tools are now also used to analyze networks of autism characteristics (Deserno et al., 2017), networks of autism and comorbid conditions, such as OCD (Ruzzano et al., 2015) and depression (Van Heijst et al., 2020). Such network representations have opened the door to a field-wide re-evaluation to the question of how adaptive, and potentially amendable, some consequences of atypical development are. One of the first network studies in the field, for example, suggested that sensory interest might funnel the co-occurrence between autism and OCD (Ruzzano et al., 2015). Other network studies concluded that anxiety and insomnia might be important targets to reduce depression in autistic individuals (Montazeri et al., 2020), and that general well-being in autistic adults could be improved by creating opportunities for them to contribute to society, and monitor their social satisfaction (Deserno et al., 2017). Taken together, these examples illustrate that the network paradigm has triggered a growing interest in the field to study the interrelation and dynamic adaptivity of developmental outcomes previously thought to be more or less set in stone (Happé and Frith, 2020).

4. Linking neuroscience and psychology: methodological avenues

While the fields of network neuroscience and network psychometrics are rapidly developing, their synergy is lagging behind. This is striking, as many of the pivotal questions that are being investigated are very much alike. This holds for method development and statistics (e.g., how to best estimate links between nodes) as well as for the substantive questions (e.g., does the brain or symptom network differ for people with autism compared with controls). While researchers in both fields work on the same disorders, as evident from our autism example, and

while most researchers agree that brain *and* behavior are crucial to advance our understanding of disorders such as autism, efforts to link the fields of network neuroscience and network psychometrics are scarce. A general barrier towards such collaboration is that interdisciplinary research, although recognized by many to be essential for science to progress, is only minimally embedded in institutions and funding schemes. Therefore, such research approaches need to overcome many challenges both substantively and practically.

Conceptually, for example, the definition of nodes in a network differs greatly (see Table 1). In network neuroscience, a node refers to some physical entity (e.g., a voxel or brain region), whereas in network psychometrics this is never the case; symptoms are abstract states that are defined on the bases of characteristic patterns of affect, cognition, and behavior, rather than physically localized entities. Such differences also bring about differences in research questions. Whereas network neuroscience is generally concerned with discovering the underlying brain structure or function, such conversion to an 'underlying structure' does not need to be the main goal in network psychometrics. In fact, in network psychometrics it is generally known that the structure itself will depend on the variables that are included. The step of variable selection is thus a pivotal step in network psychometrics, whereas in network neuroscience nodes will always represent the brain.

Very recently, the links between brain and behavior networks have been explored. An opinion paper has posited that multilayer graph theory might be able to bridge the gap between personality traits and brain networks (Brooks et al., 2020). Furthermore, a recent paper uses both symptom and brain data in combination with network analysis to explore the links between specific depression symptoms and brain structure (Hilland et al., 2020). The authors used cortical thickness of five relevant brain regions as brain nodes, and scores on an often-used depression questionnaire as symptom nodes, and looked at their association in 268 participants. Their results unveil several links between specific brain regions and individual symptoms of depression for the first time.

These papers highlight the importance and potential of integrating brain and behavior. Yet, when integrating both fields, statistical challenges may arise concerning sampling issues, data collection, model estimation, and model selection. First, for a model integrating brain and behavior, the data has to be collected along the same dimensions, which is often not the case. For example, brain networks are typically computed at an individual level using *intra* individual data estimated on the basis of anatomical models or functional time series, whereas symptom networks often reflect *inter* individual differences that are estimated on cross-sectional data. In such cases, it is not straightforward how to link the brain and symptom networks. Second, integrating both brain regions and symptoms into a single network requires estimation of an increasing number of parameters compared with estimating a network in only one domain, which necessitates availability of extensive data samples. The nature of these necessary data samples differs as well between brain and psychology networks: while many individuals or many different time points are necessary to estimate a psychological network, additional data limitations in network neuroscience relate to scanning length and availability of advanced machinery. Third, problems may occur in estimating relations among the brain and symptom levels as the effect sizes of these cross-level associations (i.e., associations between brain regions and symptoms) are likely to be much smaller than those within a level (i.e., associations among brain regions or associations among symptoms). Fourth, and relatedly, the ways in which it is decided when to include an association into the network model differs greatly in both fields. In network neuroscience it is relatively common to threshold the estimated associations, whereas in network psychometrics often regularization techniques are used. However, both may be sub-optimal given that the associations differ in size (how to determine a threshold in such a case) and the inter-level associations are likely to be the smallest (and will thus likely be omitted when using regularization techniques).

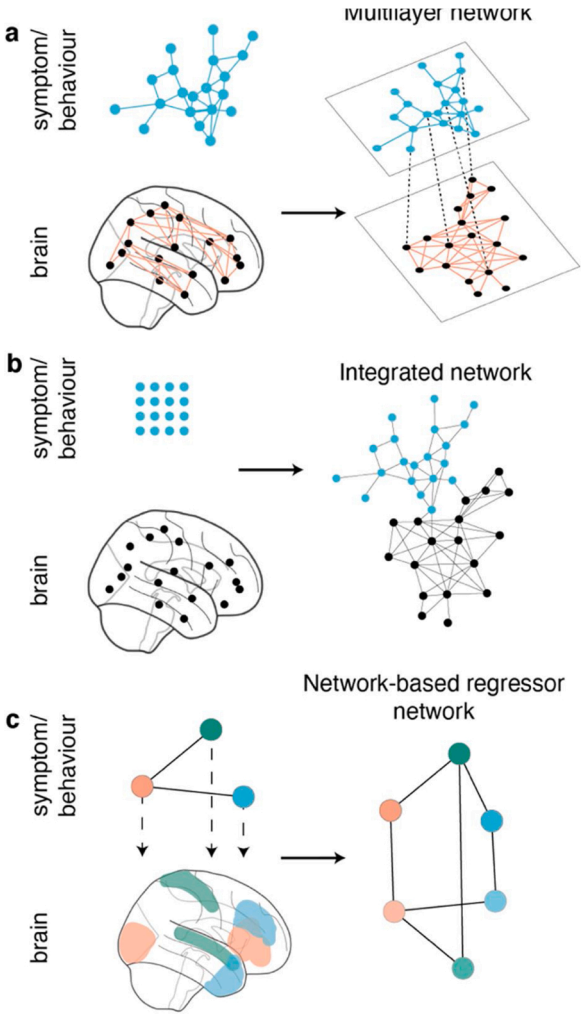

Fig. 3. Overview of the proposed methodological avenues. a) Multilayer networks: the symptom/behavior network and brain network are integrated into a multilayer network that contains within- and between-layer links. b) Integrated networks: nodes from behavioral/symptom measures and brain measures are combined into a single network. c) Network-based regressor network: behavior/symptom networks are used to identify brain correlates of each node in the behavioral/symptom network and are subsequently combined in a single network.

We have explored three ways of uniting the analytical network levels of brain and behavior, schematically presented in Fig. 3. Each of these methodological avenues tackles some of the challenges reported above and may serve as a stepping stone for further multi-modal network development.

4.1. Multilayer networks

4.1.1. Background

The most inclusive way to link brain and symptom networks is incorporating both networks fully into some multilevel data structure. In the past decade, so-called multilayer networks have been described (Mucha et al., 2010), and may be used on brain-symptom networks (Brooks et al., 2020). A multilayer network combines several levels of network behavior in a system, both within and across the different levels or layers. Thereby, it is able to incorporate brain connectivity, symptom connectivity, and the connectivity between the brain and symptom nodes. Importantly, the dynamics of the multilayer network may supersede properties of individual layers in other types of networks (Stegehuis et al., 2016; Cellai et al., 2016).

4.1.2. Method

Constructing a multilayer network involves multiple steps. First, each layer-specific network is constructed (see Fig. 3a). For brain as well as symptom networks, the methodologies described in the earlier sections of this paper can be used. The idea here is that by adhering to current standards within these separate fields, the layer-specific network information is preserved. Then, these networks are connected through interlayer connections, for instance based on covariance of node properties, in order to track whether individual differences go hand in hand across layers. From the behavioral data, we can take subjects' scores on each subscale. From the brain data, average connectivity of each brain region can be used as a fingerprint of that region per subject. The correlation between the two defines interlayer connectivity between each pair of nodes. Ultimately, the layer-specific networks and interlayer connectivities are combined into a supra-adjacency matrix, of which multilayer network properties can be determined.

4.1.3. Interpretation

The resulting multilayer network may be a starting point to explore brain-behavior relationships in a new way. For instance, one may extract cross-level communities using a multilevel clustering algorithm. Communities are clusters of nodes that share more links with each other than with nodes outside these clusters (De Domenico et al., 2015). These communities can highlight important connections in the network, thereby supporting previous results or yet undiscovered findings. The main advantage of using the multilayer approach is that layer-specific network information is kept and included in the calculation of relevant measures.

4.1.4. Limitations

At the same time, many assumptions and choices are part of such multilayer analyses. First, each layer is of course still subject to the shortcomings of that particular network methodology. Secondly, the data used for both networks may differ. Most brain networks are calculated on an individual level, based on time series or individual tractography. On the other hand, psychology networks are usually calculated at the group level. Consequently, the operationalization and interpretation of interlayer connections is particularly difficult. Third, there is a need to limit the number of false positives within and across layers. Particularly for the interlayer connections, the optimal way to do so is unclear. Fourth, multilayer network analysis is impacted by absolute weights per layer and between layers (Mandke et al., 2018), necessitating some sort of weight normalization. Finally, data availability is a major limitation of multilayer network analysis in the context of brain-behavior relationships. Since the multilayer network obviously has even more nodes than brain or symptom networks alone, more data is needed to be able to assume links with a reasonable level of certainty.

4.2. Integrated network modelling

4.2.1. Background

Instead of first estimating a network at the brain and behavioral level separately and then connecting these, it is also possible to estimate a single, integrated network model including both brain and behavior data (e.g., Hilland et al., 2020). This integrated network modelling requires the brain and behavioral metrics to be measured along the same dimension (i.e., over time, or over people). To this end, large cohorts provide unique opportunities to link brain and behavior at a cross-sectional level. These cohorts (e.g., UK biobank) contain both brain and behavioral measures at a large scale, which enable us to relate brain and behavior across people.

4.2.2. Method

The most straightforward case of estimating an integrated network model will be in large cross-sectional datasets. Estimating the integrated network then starts out with assembling a dataset that contains, for each person, the available brain and behavioral metrics (see Fig. 3b). Unlike multilayer networks, these brain and behavioral metrics are included as separate values (nodes) without first estimating the relations among them. Then, similar to estimating a network in each discipline separately, this dataset can be used to estimate the relations among all included values, now containing both brain and behavioral information.

In estimating a network on the collated dataset there are choices to be made regarding the estimation of the relations (e.g., using correlations or partial correlations) and how to select or include links (e.g., use some kind of pruning or regularization). If the sample is sufficiently large, moderation effects could be included to investigate whether specific brain regions may underlie the links between two symptoms (Haslbeck et al., 2019).

4.2.3. Interpretation

By estimating an integrated network model, we can disentangle, at a more fine-grained level, how specific brain regions relate to specific symptoms. Using partial correlations could have the advantage to in addition distinguish direct from indirect relations. Estimating an integrated network model, Hilland et al. (2020) identified direct links between depression symptoms and brain regions, involving predominantly the hippocampus, cingulate, and fusiform gyrus. When moderation effects are estimated, integrated network modelling could detect potential brain regions that may underlie the interaction between two symptoms.

4.2.4. Limitations

While simple and straightforward, a great caveat to this method is that the brain and behavior metrics must be measured in the same dimensions. Given that many psychological networks are estimated on large groups of people (cross-sectional data), whereas many brain networks are individually based, this method might not always be suitable.

4.3. Network-based regressors

4.3.1. Background

One difficulty associated with integrating brain and behavior networks is the potentially large number of links in both networks. Further, most questions in clinical neuroscience focus on symptoms and one may only be interested in the brain measures if they relate to the symptoms. To reduce the number of brain nodes to the ones that are tied to the symptoms, regression approaches are commonly used to identify brain correlates. However, symptom scores may be highly correlated, obscuring the specific brain correlate of particular symptoms. In the context of network psychometrics, the unique variance of each node in the symptom network can be estimated to obtain the brain correlates to correspond specifically to each node.

4.3.2. Method

To obtain the unique variance of a variable, one may simply regress the effect of other variables from each variable and retain the residual. The residual terms can be used as regressors to obtain the neural correlates of the unique variance of each behavioral measure. Next, one can obtain the network structure of the neural correlates, e.g., by calculating the correlation between the regions that best predicted the behavioral measures (see Fig. 3c).

Using this approach, Bathelt et al. (2020) investigated the network structure of autism symptoms at the level of behavior and brain function. At the behavioral level, the results replicate the factor structure of close links between social interaction and communication and weaker links with RRBIs. However, at the level of functional brain correlates, social interaction and RRBIs were more closely linked.

4.3.3. Interpretation

The interpretation of the results from this method is relatively straightforward, because the measures at the neural level reflect the unique variance in the behavioral measures. It may be of particular

interest to identify any mismatch between the networks at each level or to integrate both into a single network to assess potential confluence of nodes.

4.3.4. Limitations

In some cases, there may be no clear neural correlate of a node in the behavioral or symptom network. This may be because of genuine weaker relation at the brain-level or because there is not enough variance in the behavioral or symptom measure once the variance of other nodes has been taken into account. A careful inspection of the structure of the behavior or symptom network is always advisable. If there is reason to assume that there may not be a link with the brain measure for a specific node in the behavior or symptom network, the corresponding node can be omitted from the network-based regressor network.

5. Conclusions and future perspectives

We have laid out the parallel development and incorporation of networks and complexity theory in neuroscience on the one hand, and in psychological science on the other. As these fields have rapidly evolved, both methodologically and conceptually in the past decades, now is the time to invest into merging these insights and develop a brain-behavior network methodology to answer new questions. Coming back to our main example of ASD as a brain and symptom network disorder underlines the promise that multi-level analysis may add to current level-specific insights in terms of etiology, symptomatology and potentially treatment of this disorder. A first multi-level study on ASD, using one of the methodological avenues from this paper, indicates that the (known) overlap between communication and social difficulties in the symptom network is not reflected in the overlap between their functional brain correlates (Bathelt et al., 2020). Knowledge on the multilevel organization of symptoms and brain networks may therefore impact treatment strategies. Treatment of psychiatric disorders may be optimized by better understanding the relationship between brain and behavior (e.g., Graham et al., 2014). For example, pharmacological treatment targets molecular processes in the brain, but it is difficult to understand and predict how behavior may change as a result of it because we lack the essential multilevel knowledge to do so. Even more relevantly, non-pharmacological treatments that directly target the brain, for instance electrical or magnetic stimulation, have been center stage in developing ideas on how interventions at the brain network level may predict individual symptoms in psychiatric disorders (Douw et al., 2020; Fox et al., 2014; Li et al., 2018). A multilevel network view of both symptom and brain network behavior may allow further precision in developing such treatment targets for patients suffering from psychopathology. Coming back to our ASD example, the finding that brain network correlates of behaviorally connected symptoms are more separate (Bathelt et al., 2020), may mean that multimodal treatment targeting different functional networks is necessary, or that behavioral therapy that targets both connected symptoms may be more beneficial. These results highlight the new insights that can be gained from integrating brain and psychometric networks. However, the true potential of these new avenues for understanding ASD and other complex disorders will only become apparent once they are applied more widely and developed further.

We conclude with some thoughts on how to advance this exciting synergy between fields. First, methodological developments within both network neuroscience and psychological network science are and will remain ongoing. Keeping up with these field-specific advances will greatly aid in tailoring any brain-behavior network combination. This obviously necessitates collaboration between experts from both fields, which undoubtedly takes more time and effort than field-specific research. Secondly, sophisticated experiments will become necessary to redeem the promise of brain-behavior networks. This will certainly involve extensive data collection mitigating the previously described variety of requirements that holds for both fields. Moreover, elegant study designs may be able to disentangle the trivial versus synergetic information that the complex combination between brain and behavior networks has to offer. For instance, a combined set of intervention studies targeting the symptom network (e.g., cognitive behavioral therapy for depression), the brain network (e.g., non-invasive brain stimulation), or a combination of both (e.g., stimulation during therapy), could elucidate whether and how these two levels correlate before treatment, and how this might change as a result of manipulation. Also, the utility of computational modeling in validating and expanding empirical work on networks has been essential within physics, and is winning ground in network neuroscience (Bassett et al., 2018b; Levenstein et al., 2020) and psychology (Guest and Martin, 2021). Future endeavors in the field of brain-behavior networks may incorporate such computational modeling in a way that also allows for fine-tuning of cross-field insights. Finally, although network science offers a rich theoretical framework with respect to the structure and dynamics of both brain and behavior networks, the connection between neurophysiological and psychological theories is still largely lacking. Developing this connecting framework will help guide methodological development and empirical exploration of the links between brain and behavior. Very related to this point is the need to keep track of what type of explanation or understanding these analyses are offering. Ideas have been put forward on theory and explanation within network neuroscience (Bertolero and Bassett, 2020) and psychological network science (Borsboom, 2017), but the union between these methods or levels of explanation remains largely unexplored from a philosophical standpoint.

In conclusion, it is still complicated. However, we strongly encourage those tickled by the idea of combining brain and behavior networks to persist and take on this difficult task without getting overwhelmed by these obstacles. There is value in embracing what seem to be overwhelming levels of complexity, making mistakes, and learning as we go.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

This work was supported by a BIAL Foundation grant 284/20 awarded to TF Blanken and an NWO Vidi grant 198.015 awarded to L Douw.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. https://doi.org/10.1176/appi.books.9780890425596

Anderson, G.M., 2008. The potential role for emergence in autism. Autism Res. 1, 18–30.

Arslan, S., Ktena, S.I., Makropoulos, A., Robinson, E.C., Rueckert, D., Parisot, S., 2018. Human brain mapping: a systematic comparison of parcellation methods for the human cerebral cortex. Neuroimage 170 (April), 5–30. https://doi.org/10.1016/j.neuroimage.2017.04.014. Epub 2017 Apr 13. PMID: 28412442.

Bassett, D.S., Xia, C.H., Satterthwaite, T.D., 2018a. Understanding the emergence of neuropsychiatric disorders with network neuroscience. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3 (9), 742–753. https://doi.org/10.1016/j.bpsc.2018.03.015.

Bassett, D.S., Zurn, P., Gold, J.I., 2018b. On the nature and use of models in network neuroscience. Nat. Rev. Neurosci. 19 (9), 566–578. https://doi.org/10.1038/s41583-018-0038-8.

Bathelt, J., Geurts, H.M., Borsboom, D., 2020. More than the sum of its parts: merging network psychometrics and network neuroscience with application in autism. bioRxiv. https://doi.org/10.1101/2020.11.17.386276.

Bertolero, M.A., Bassett, D.S., 2020. On the nature of explanations offered by network science: a perspective from and for practicing neuroscientists. Top. Cogn. Sci. 12 (4), 1272–1293. https://doi.org/10.1111/tops.12504.

Borsboom, D., 2017. A network theory of mental disorders. World Psychiatry 16 (1), 5–13. https://doi.org/10.1002/wps.20375.

Borsboom, D., Cramer, A.O.J., 2013. Network analysis: an integrative approach to the structure of psychopathology. Annu. Rev. Clin. Psychol. 9 (1), 91–121. https://doi.org/10.1146/annurev-clinpsy-050212-185608.

Borsboom, D., Robinaugh, D.J., Group, T.P., Rhemtulla, M., Cramer, A.O., 2018. Robustness and replicability of psychopathology networks. World Psychiatry 17 (2), 143. https://doi.org/10.1002/wps.20375.
Borsboom, D., Cramer, A.O., Kalis, A., 2019. Brain disorders? Not really: why network structures block reductionism in psychopathology research. Behav. Brain Sci. 42, 1–54. https://doi.org/10.1017/S0140525X17002266.
Brooks, D., Hulst, H.E., de Bruin, L., Glas, G., Geurts, J.J.G., Douw, L., 2020. The multilayer network approach in the study of personality neuroscience. Brain Sci. 10 (12), 915. https://doi.org/10.3390/brainsci10120915.
Cellai, D., Dorogovtsev, S.N., Bianconi, G., 2016. Message passing theory for percolation models on multiplex networks with link overlap. Phys. Rev. E 94 (3), 032301. https://doi.org/10.1103/physreve.94.032301.
Chu, C.J., Kramer, M.A., Pathmanathan, J., Bianchi, M.T., Westover, M.B., Wizon, L., Cash, S.S., 2012. Emergence of stable functional networks in long-term human electroencephalography. J. Neurosci. 32 (8), 2703–2713. https://doi.org/10.1523/JNEUROSCI.5669-11.2012.
De Domenico, M., Lancichinetti, A., Arenas, A., Rosvall, M., 2015. Identifying modular flows on multilayer networks reveals highly overlapping organization in interconnected systems. Phys. Rev. X 5 (1), 011027. https://doi.org/10.1103/physrevx.5.011027.
de Lange, S.C., Scholtens, L.H., van den Berg, L.H., Boks, M.P., Bozzali, M., van den Heuvel, M.P., 2019. Shared vulnerability for connectome alterations across psychiatric and neurological brain disorders. Nat. Hum. Behav. 3 (9), 988–998. https://doi.org/10.1038/s41562-019-0659-6.
Deserno, M.K., Borsboom, D., Begeer, S., Geurts, H.M., 2017. Multicausal systems ask for multicausal approaches: a network perspective on subjective well-being in individuals with autism spectrum disorder. Autism 21 (8), 960–971. https://doi.org/10.1177/1362361316660309.
Deserno, M.K., Borsboom, D., Begeer, S., van Bork, R., Hinne, M., Geurts, H.M., 2020. Highways to happiness for autistic adults? Perceived causal relations among clinicians. PLoS One 15 (12), e0243298. https://doi.org/10.1371/journal.pone.0243298.
Douw, L., Schoonheim, M.M., Landi, D., van der Meer, M.L., Geurts, J.J., Reijneveld, J.C., Klein, M., Stam, C.J., 2011. Cognition is related to resting-state small-world network topology: an magnetoencephalographic study. Neuroscience 175, 169–177. https://doi.org/10.1016/j.neuroscience.2010.11.039.
Douw, L., Quaak, M., Fitzsimmons, S.M.D.D., de Wit, S.J., van der Werf, Y.D., van den Heuvel, O.A., Vriend, C., 2020. Static and dynamic network properties of the repetitive transcranial magnetic stimulation target predict changes in emotion regulation in obsessive-compulsive disorder. Brain Stimul. 13 (2), 318–326. https://doi.org/10.1016/j.brs.2019.10.017.
Epskamp, S., Fried, E.I., 2018a. A tutorial on regularized partial correlation networks. Psychol. Methods 23 (4), 617–634. https://doi.org/10.1037/met0000167.
Epskamp, S., van Borkulo, C.D., van der Veen, D.C., Servaas, M.N., Isvoranu, A.M., Riese, H., Cramer, A.O., 2018b. Personalized network modeling in psychopathology: the importance of contemporaneous and temporal connections. Clin. Psychol. Sci. 6 (3), 416–427. https://doi.org/10.1177/2167702617744325.
Epskamp, S., Borsboom, D., Fried, E.I., 2018c. Estimating psychological networks and their accuracy: a tutorial paper. Behav. Res. Methods 50 (1), 195–212. https://doi.org/10.3758/s13428-017-0862-1.
Epskamp, S., Waldorp, L.J., Mõttus, R., Borsboom, D., 2018d. The Gaussian graphical model in cross-sectional and time-series data. Multivariate Behav. Res. 53 (4), 453–480. https://doi.org/10.1080/00273171.2018.1454823.
Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A. R., Fox, P.T., Eickhoff, S.B., Yu, C., Jiang, T., 2016. The human brainnetome atlas: a new brain atlas based on connectional architecture. Cereb. Cortex 26 (8), 3508–3526. https://doi.org/10.1093/cercor/bhw157.
Fox, M.D., Buckner, R.L., Liu, H., Chakravarty, M.M., Lozano, A.M., Pascual-Leone, A., 2014. Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. Proc. Natl. Acad. Sci. 111 (41), E4367–E4375. https://doi.org/10.1073/pnas.1405003111.
Frewen, P.A., Allen, S.L., Lanius, R.A., Neufeld, R.W., 2012. Perceived causal relations: novel methodology for assessing client attributions about causal associations between variables including symptoms and functional impairment. Assessment 19 (4), 480–493. https://doi.org/10.1177/1073191111418297.
Frewen, P.A., Schmittmann, V.D., Bringmann, L.F., Borsboom, D., 2013. Perceived causal relations between anxiety, posttraumatic stress and depression: extension to moderation, mediation, and network analysis. Eur. J. Psychotraumatol. 4, 20656. https://doi.org/10.3402/ejpt.v4i0.20656.
Graham, B.M., Callaghan, B.L., Richardson, R., 2014. Bridging the gap: lessons we have learnt from the merging of psychology and psychiatry for the optimization of treatments for emotional disorders. Behav. Res. Ther. 62, 3–16. https://doi.org/10.1016/j.brat.2014.07.012.
Guest, O., Martin, A.E., 2021. How computational modeling can force theory building in psychological science. Perspect. Psychol. Sci. https://doi.org/10.1177/1745691620970585.
Hagmann, P., Kurant, M., Gigandet, X., Thiran, P., Wedeen, V.J., Meuli, R., Thiran, J.P., 2007. Mapping human whole-brain structural networks with diffusion MRI. PLoS One 2 (7), e597. https://doi.org/10.1371/journal.pone.0000597.
Happé, F., Frith, U., 2020. Annual Research Review: looking back to look forward–changes in the concept of autism and implications for future research. J. Child Psychol. Psychiatry 61 (3), 218–232. https://doi.org/10.1111/jcpp.13176.
Happé, F., Ronald, A., 2008. The 'fractionable autism triad': a review of evidence from behavioural, genetic, cognitive and neural research. Neuropsychol. Rev. 18 (4), 287–304. https://doi.org/10.1007/s11065-008-9076-8.
Haslbeck, J.M.B., Borsboom, D., Waldorp, L.J., 2019. Moderated network models. Multivariate Behav. Res. 1–32. https://doi.org/10.1080/00273171.2019.1677207.
He, Y., Chen, Z.J., Evans, A.C., 2007. Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. Cereb. Cortex 17 (10), 2407–2419. https://doi.org/10.1093/cercor/bhl149.
Hilland, E., Landrø, N.I., Kraft, B., Tamnes, C.K., Fried, E.I., Maglanoc, L.A., Jonassen, R., 2020. Exploring the links between specific depression symptoms and brain structure: a network study. Psychiatry Clin. Neurosci. 74 (3), 220–221. https://doi.org/10.1111/pcn.12969.
Hong, S.-J., de Wael, R.V., Bethlehem, R.A.I., Lariviere, S., Paquola, C., Valk, S.L., Milham, M.P., Martino, A.D., Margulies, D.S., Smallwood, J., Bernhardt, B.C., 2019. Atypical functional connectome hierarchy in autism. Nat. Commun. 10 (1), 1022.
Hull, J.V., Dokovna, L.B., Jacokes, Z.J., Torgerson, C.M., Irimia, A., Horn, J.D.V., 2017. Resting-state functional connectivity in Autism Spectrum Disorders: a review. Front. Psychiatry 7, 205. https://doi.org/10.3389/fpsyt.2016.00205.
Hyland, M.E., 2011. The Origins of Health and Disease, first ed. Cambridge University Press, Cambridge. https://doi.org/10.1017/CBO9780511976216.
Insel, T.R., Cuthbert, B.N., 2015. Brain disorders? Precisely. Science 348, 499–500. https://doi.org/10.1126/science.aab2358.
Jaspers, K., 1963. General Psychopathology. Manchester University Press, Manchester.
Johnson, M.H., 2017. Autism as an adaptive common variant pathway for human brain development. Dev. Cogn. Neurosci. 25, 5–11. https://doi.org/10.1016/j.dcn.2017.02.004.
Just, M.A., Cherkassky, V.L., Keller, T.A., Kana, R.K., Minshew, N.J., 2007. Functional and anatomical cortical underconnectivity in Autism: Evidence from an fMRI Study of an executive function task and corpus callosum morphometry. Cereb. Cortex 17 (4), 951–961. https://doi.org/10.1093/cercor/bhl006.
Kana, R.K., Keller, T.A., Cherkassky, V.L., Minshew, N.J., Just, M.A., 2009. Atypical frontal-posterior synchronization of Theory of Mind regions in autism during mental state attribution. Social Neurosci. 4 (2), 135–152. https://doi.org/10.1080/17470910802198510.
Kendler, K.S., 2012. Levels of explanation in psychiatric and substance use disorders: implications for the development of an etiologically based nosology. Mol. Psychiatry 17, 11–21. https://doi.org/10.1038/mp.2011.70.
Kendler, K.S., Zachar, P., Craver, C., 2011. What kinds of things are psychiatric disorders? Psychol. Med. 41, 1143–1150. https://doi.org/10.1017/S0033291710001844.
Keown, C.L., Datko, M.C., Chen, C.P., Maximo, J.O., Jahedi, A., Müller, R.-A., 2017. Network organization is globally atypical in Autism: A graph theory study of intrinsic functional connectivity. Biol. Psychiatry: Cognit. Neurosci. Neuroimaging 2 (1), 66–75. https://doi.org/10.1016/j.bpsc.2016.07.008.
Kraepelin, E., Lange, J., 1927. Psychiatrie, ninth ed., Vol. I. J. A. Barth, Leipzig.
Lashley, K.S., 1931. Mass action in cerebral function. Science 73 (1888), 245–254. https://doi.org/10.1126/science.73.1888.245.
Levenstein, D., Alvarez, V.A., Amarasingham, A., Azab, H., Gerkin, R.C., Hasenstaub, A., Redish, A.D., 2020. On the Role of Theory and Modeling in Neuroscience. arXiv preprint arXiv:2003.13825.
Li, B.J., Friston, K., Mody, M., Wang, H.N., Lu, H.B., Hu, D.W., 2018. A brain network model for depression: from symptom understanding to disease intervention. CNS Neurosci. Ther. 24 (11), 1004–1019. https://doi.org/10.1111/cns.12998.
Linkenkaer-Hansen, K., Nikouline, V.V., Palva, J.M., Ilmoniemi, R.J., 2001. Long-range temporal correlations and scaling behavior in human brain oscillations. J. Neurosci. 21 (4), 1370–1377. https://doi.org/10.1523/JNEUROSCI.21-04-01370.2001.
Maier-Hein, K.H., Neher, P.F., Houde, J.C., Côté, M.A., Garyfallidis, E., Zhong, J., et al., 2017. The challenge of mapping the human connectome based on diffusion tractography. Nat. Commun. 8 (1), 1349. https://doi.org/10.1038/s41467-017-01285-x.
Mandke, K., Meier, J., Brookes, M.J., O'Dea, R.D., Van Mieghem, P., Stam, C.J., Hillebrand, A., Tewarie, P., 2018. Comparing multilayer brain networks between groups: introducing graph metrics and recommendations. NeuroImage 166, 371–384. https://doi.org/10.1016/j.neuroimage.2017.11.016.
Markram, K., Markram, H., 2010. The intense world theory – a unifying theory of the neurobiology of autism. Front. Hum. Neurosci. 4, 224. https://doi.org/10.3389/fnhum.2010.00224.
Maximo, J.O., Cadena, E.J., Kana, R.K., 2014. The implications of brain connectivity in the neuropsychology of Autism. Neuropsychol. Rev. 24 (1), 16–31. https://doi.org/10.1007/s11065-014-9250-0.
McNally, R.J., 2021. Network analysis of psychopathology: controversies and challenges. Annu. Rev. Clin. Psychol. 17 https://doi.org/10.1146/annurev-clinpsy-081219-092850.
Montazeri, F., de Bildt, A., Dekker, V., Anderson, G.M., 2020. Network analysis of behaviors in the depression and autism realms: inter-relationships and clinical implications. J. Autism Dev. Disord. 50 (5), 1580–1595. https://doi.org/10.1007/s10803-019-03914-4.
Mucha, P.J., Richardson, T., Macon, K., Porter, M.A., Onnela, J.P., 2010. Community structure in time-dependent, multiscale, and multiplex networks. Science 328 (5980), 876–878. https://doi.org/10.1126/science.1184819.
Noble, S., Scheinost, D., Constable, R.T., 2019. A decade of test-retest reliability of functional connectivity: a systematic review and meta-analysis. NeuroImage 203, 116157. https://doi.org/10.1016/j.neuroimage.2019.116157.
Nolen-Hoeksema, S., Watkins, E.R., 2011. A heuristic for developing transdiagnostic models of psychopathology: explaining multifinality and divergent trajectories. Perspect. Psychol. Sci. 6, 589–609. https://doi.org/10.1177/1745691611419672.
Oldehinkel, M., Mennes, M., Marquand, A., Charman, T., Tillmann, J., Ecker, C., Zwiers, M.P., 2019. Altered connectivity between cerebellum, visual, and sensory-motor networks in Autism Spectrum Disorder: results from the EU-AIMS

Longitudinal European Autism Project. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 4 (3), 260–270. https://doi.org/10.1016/j.bpsc.2018.11.010.
Penfield, W., Boldrey, E., 1937. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain 60 (4), 389–443. https://doi.org/10.1093/brain/60.4.389.
Power, J.D., Schlaggar, B.L., Lessov-Schlaggar, C.N., Petersen, S.E., 2013. Evidence for hubs in human functional brain networks. Neuron. 79 (August (4)), 798–813. https://doi.org/10.1016/j.neuron.2013.07.035. PMID: 23972601; PMCID: PMC3838673.
Ruzzano, L., Borsboom, D., Geurts, H.M., 2015. Repetitive behaviors in autism and obsessive–compulsive disorder: new perspectives from a network analysis. J. Autism Dev. Disord. 45 (1), 192–202. https://doi.org/10.1007/s10803-014-2204-9.
Salvador, R., Suckling, J., Coleman, M.R., Pickard, J.D., Menon, D., Bullmore, E., 2005. Neurophysiological architecture of functional magnetic resonance images of human brain. Cereb. Cortex 15 (9), 1332–1342. https://doi.org/10.1093/cercor/bhi016.
Schaefer, A., Kong, R., Gordon, E.M., Laumann, T.O., Zuo, X.N., Holmes, A.J., Eickhoff, S. B., Yeo, B.T.T., 2018. Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. Cereb. Cortex 28 (September (9)), 3095–3114. https://doi.org/10.1093/cercor/bhx179. PMID: 28981612; PMCID: PMC6095216.
Seidlitz, J., Váša, F., Shinn, M., Romero-Garcia, R., Whitaker, K.J., Vértes, P.E., Wagstyl, K., Kirkpatrick Reardon, P., Clasen, L., Liu, S., Messinger, A., Leopold, D.A., Fonagy, P., Dolan, R.J., Jones, P.B., Goodyer, I.M., NSPN Consortium, Raznahan, A., Bullmore, E.T., 2018. Morphometric similarity networks detect microscale cortical organization and predict inter-individual cognitive variation. Neuron 97 (1), 231–247. https://doi.org/10.1016/j.neuron.2017.11.039.
Sherrington, C., 1951. Man on His Nature, second ed. Cambridge University Press, Cambridge.
Shih, P., Keehn, B., Oram, J.K., Leyden, K.M., Keown, C.L., Müller, R.-A., 2011. Functional differentiation of posterior superior temporal sulcus in Autism: a functional connectivity magnetic resonance imaging study. Biol. Psychiatry 70 (3), 270–277. https://doi.org/10.1016/j.biopsych.2011.03.040.
Stam, C.J., 2004. Functional connectivity patterns of human magnetoencephalographic recordings: a 'small-world' network? Neurosci. Lett. 355 (1–2), 25–28. https://doi.org/10.1016/j.neulet.2003.10.063.
Stegehuis, C., van der Hofstad, R., van Leeuwaarden, J., 2016. Epidemic spreading on complex networks with community structures. Sci. Rep. 6, 29748. https://doi.org/10.1038/srep29748.
Tijms, B.M., Seriès, P., Willshaw, D.J., Lawrie, S.M., 2012. Similarity-based extraction of individual networks from gray matter MRI scans. Cereb. Cortex 22 (7), 1530–1541. https://doi.org/10.1093/cercor/bhr221.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15 (1), 273–289. https://doi.org/10.1006/nimg.2001.0978.
van den Heuvel, M.P., Sporns, O., 2019. A cross-disorder connectome landscape of brain dysconnectivity. Nat. Rev. Neurosci. 20 (7), 435–446. https://doi.org/10.1038/s41583-019-0177-6.
Van den Heuvel, M.P., Stam, C.J., Kahn, R.S., Hulshoff Pol, H.E., 2009. Efficiency of functional brain networks and intellectual performance. J. Neurosci. 29 (23), 7619–7624. https://doi.org/10.1523/JNEUROSCI.1443-09.2009.
Van Dijk, K.R., Hedden, T., Venkataraman, A., Evans, K.C., Lazar, S.W., Buckner, R.L., 2010. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. J. Neurophysiol. 103 (1), 297–321. https://doi.org/10.1152/jn.00783.2009.
Van Heijst, B.F., Deserno, M.K., Rhebergen, D., Geurts, H.M., 2020. Autism and depression are connected: a report of two complimentary network studies. Autism 24 (3), 680–692. https://doi.org/10.1177/1362361319872373.
Watts, D.J., Strogatz, S.H., 1998. Collective dynamics of 'small-world' networks. Nature 393 (6684), 440–442. https://doi.org/10.1038/30918.
Wright, I.C., Sharma, T., Ellison, Z.R., McGuire, P.K., Friston, K.J., Brammer, M.J., et al., 1999. Supra-regional brain systems and the neuropathology of schizophrenia. Cereb. Cortex 9 (4), 366–378. https://doi.org/10.1093/cercor/9.4.366.