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Future Directions for Clinical Psilocybin Research: The Relaxed Symptom Network

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Objective: Recent clinical trials have demonstrated that psilocybin may have strong antidepressant effects, and may be effective in the treatment of depressive disorders when embedded in a psychotherapeutic protocol (psilocybin-assisted psychotherapy; PAP). However, despite promising results, the mechanism(s) that may be responsible for the antidepressant effects of PAP remain contested. Within this article, it is argued that the ‘Network Theory of Mental Disorders’ may be a useful tool for clinical research with psilocybin, and may help elucidate the antidepressant elements of PAP. **Method:** The clinical research using PAP for depressive disorders is briefly summarised, as are the potential mechanisms of PAP. In addition to this, the fundamental tenets of the network theory is presented, with particular reference to depression. In brief, the network theory proposes that depression is an emergent phenomenon, due to strong interactions in a complex dynamic symptom network. **Results:** A model of action based on a symptom network is proposed. It is hypothesised that, if PAP is successful, the connections between symptoms in a network will weaken, thereby rendering the patient less vulnerable to developing/relapsing into depression. It is argued that the application of the network theory may ultimately improve responsiveness and reduce relapse in PAP. Practical guidance in using the network theory for future clinical research with psilocybin is also provided. **Conclusion:** This article presents the primary hypothesis of the authors (The Relaxed Symptom Network), and intends to inform future researchers on how to integrate the network theory with future clinical studies using PAP.

Public Significance Statement

Psilocybin-assisted psychotherapy (PAP) has seen an explosion of interest in the past decade, with preliminary clinical data looking particularly promising for the treatment of depressive disorders. In this article, we highlight that future clinical research conducted with psilocybin would benefit from the application of the network theory, a novel method to classify and diagnose mental health disorders. We argue that the application of the network theory would ultimately improve responsiveness to PAP and reduce the rate of relapse in response to this promising therapeutic modality.

Keywords: psychedelics, network theory, psychopathology, psychotherapy, depression

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“Classic” psychedelics are defined as agonists, or partial agonists, at the 5-HT_{2A} receptor (Nichols, 2016). This broad category of substances includes psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine), lysergic acid diethylamide (LSD), and *N,N*-dimethyltryptamine (DMT). Neuroimaging studies have revealed that ingestion of these substances significantly alters the functional organization of the brain (Carhart-Harris et al., 2012; Girn et al., 2020; Muthukumaraswamy et al., 2013; Petri et al., 2014; Roseman et al., 2014). Moreover, these radical changes in the brain are accompanied by a significantly altered state of consciousness, comprising of changes in mood, perception, and cognition (e.g., Griffiths et al., 2006; Hasler et al., 2004; Liechti et al., 2017; Schmid et al., 2015). In addition to the distinct neurobiological and phenomenological effects of classic psychedelics, recent clinical trials have found extremely large effect sizes when using psilocybin (the psychoactive component in mushrooms from the *Psilocybe* genus) to treat depressive disorders (Agin-Liebess et al., 2020; Carhart-Harris et al., 2016; Carhart-Harris, Bolstridge, et al., 2018; Davis et al., 2020; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Moreover, at the time of writing, clinicaltrials.gov lists 88 registered trials that intend to use psilocybin to treat a variety of mental health disorders, including anorexia nervosa (e.g., NCT04661514), alcohol use disorder (e.g., NCT04410913), and obsessive-compulsive disorder (e.g., NCT03356483). As the field of psychedelic psychiatry develops, it is imperative for researchers and clinicians to deepen their understanding of the clinical action of psychedelics. We therefore aim to highlight how clinicians and researchers may achieve this through the integration of a contemporary practical and statistical tool in the field of clinical psychology, known as the network theory of mental disorders (Borsboom, 2017; hereby, the network theory), into future psychedelic research.

Briefly, the network theory is a novel way to conceptualize mental health disorders. Rather than a diagnostic perspective, where researchers commit to a latent construct (such as depression) causing a manifestation in corresponding symptoms, the network theory uses formal statistical modeling to conceptualize mental disorders as symptom networks (see The Network Theory of Mental Disorders section for an overview). The symptoms within the networks are connected to

each other in varying strengths, which determine an individual’s vulnerability to developing a specific mental health issue (Cramer et al., 2016). The primary hypothesis of this article is that, if psilocybin-assisted psychotherapy (PAP) is successful, the connections between symptoms in a network will weaken, thereby rendering the patient less vulnerable to developing depression. Moreover, this testable hypothesis has important implications for how to maximize the potential of PAP to facilitate the emergence of a network less vulnerable to developing depression (and potentially other disorders).

Leading up to the presentation of the “Relaxed Symptom Network” hypothesis, we point the reader to several meta-analyses that examine the antidepressant potential of PAP. We specifically present evidence of psilocybin for depressive disorders as it is the most thoroughly researched in contemporary psychedelic psychiatry. Second, we provide an overview of the network theory of mental disorders and present our main hypothesis of the article. Finally, we outline the concrete benefits that the network theory will provide when applied to clinical psychedelic research. The benefits of applying the network theory to psychedelic research include the following: (a) gaining deeper insights into patients’ potential to relapse, (b) answering questions regarding the efficacy of PAP to target specific symptoms within a network across patients, and (c) identifying central symptoms in an individual patients’ network, allowing both patients and clinicians to specify an intention for an upcoming therapeutic psychedelic session.

PAP: A Critical Evaluation

Clinical psychedelic research has a tumultuous history and has been marred by prohibition (Nutt & Carhart-Harris, 2021). However, contemporary academia is, once again, comprehensively studying the effects of psychedelics, both on the brain and on specific mental health disorders (Nutt & Carhart-Harris, 2021). PAP is an intervention that is receiving considerable and growing clinical and scientific attention. Psilocybin is the most commonly used “classic” psychedelic in contemporary psychedelic psychiatry due to its tolerability (Rucker et al., 2022) and its relatively short-lived effects (compared to, e.g., LSD). Commonly, a PAP protocol lasts for 6–10 weeks and will involve 1–3 dosing sessions with

psilocybin (Payne et al., 2021). Prior to the dosing session(s), the patient undergoes preparatory therapeutic support. Within this part of the protocol, the patient develops a relationship with the therapist(s) who is/are present for the dosing session. The patient is told what to expect and often sets an “intention” for the upcoming dosing session (Watts & Luoma, 2020). During the session, the patient ingests psilocybin (commonly 25–30 mg as a high dose) in the presence of a therapist(s), who provides guidance and emotional support when needed. However, the patient is encouraged to approach the session introspectively—eye shades are provided, and a curated playlist of music is played in order to accompany or guide the psychedelic experience (Kaelen et al., 2018). Succeeding the psychedelic session, a number of integration sessions are attended, aiming to synthesize any insights from the experience, with the aim of integrating behavioral or cognitive changes that may lead to positive long-term mental health outcomes. While there has been some effort to standardize the therapeutic protocols associated with PAP (Watts & Luoma, 2020), further research is needed to verify the ideal way to deliver this modality.

It is beyond the scope of this article to summarize all of the clinical research that has used PAP to treat depressive disorders. We invite the reader to seek out the following references, which each provide a meta-analysis of PAP for depressive disorders (Goldberg et al., 2020; Vargas et al., 2020), and, more broadly, for PAP for depressive disorders (Galvão-Coelho et al., 2021; Luoma et al., 2020; Romeo et al., 2020). Most recently, Carhart-Harris, Giribaldi, et al. (2021) compared the effects of psilocybin on major depressive disorder versus escitalopram, a conventionally prescribed antidepressant. Although both interventions reduced depression symptoms, the researchers found no significant difference between subjects on the primary measure. However, PAP significantly outperformed escitalopram on all other secondary measures of depression.

The observed effect sizes within the meta-analyses are consistently larger in magnitude than those associated with the use of psychotherapy alone (Cuijpers et al., 2008, 2010), antidepressants (Fournier et al., 2010), or pharmacotherapy and psychotherapy combined (Cuijpers et al., 2014). Due to these large effect sizes, and the potential for PAP to be efficacious for treatment-resistant depression (e.g., Carhart-Harris et al., 2016; Carhart-Harris, Bolstridge, et

al., 2018), PAP may represent a groundbreaking new and effective treatment for depressive disorders. However, it should be highlighted that these effect sizes are computed from within-participant analyses of studies with small sample sizes. It is therefore of the utmost importance to continue to study the effects of PAP in larger sample sizes with effective placebo-control measures (Schenberg, 2021), to elucidate the “true” magnitude of effects of PAP.

The Mechanisms Underlying PAP

Over the past 15 years, there have been a variety of theories that intend to model the effects of “classic” psychedelics such as psilocybin and highlight the primary mechanism(s) at play that are responsible for positive changes in mental health (e.g., Carhart-Harris & Friston, 2019; Flanagan & Nichols, 2018; Hartogssohn, 2016; Hendricks, 2018; Olson, 2018; Vollenweider & Preller, 2020; Watts & Luoma, 2020). Different mechanisms have been proposed to account for the efficacy of PAP. As PAP is an experiential as well as a pharmacological therapeutic intervention, researchers may generate a variety of hypotheses from different explanatory levels of the protocol. Some theories of action may focus on the neurochemical effects of psilocybin (i.e., 5HT_{2A} receptor signaling; glutamate release; stimulation of brain-derived neurotrophic factor; anti-inflammatory effects), while others will focus on the neural effects (i.e., neurogenesis and plasticity; increased connectivity between brain networks). Others still may focus on the phenomenological effects of psilocybin (i.e., insight, mystical experiences, enhanced perception of emotions), and some may even focus on extrapharmacological associated with PAP. While many of the ideas highlighted in each theory are compelling, an integrative review is beyond the scope of this article. However, we would like to emphasize here that PAP is a multilevel therapeutic modality, with a biopsychosocial approach at its core; there are many proposed mechanisms (van Elk & Yaden, 2022) that are hypothetically contributing to PAP’s efficacy in treating depressive disorders (among a panoply of other neuropsychiatric issues). This puts a spotlight on an issue within psychedelic research: Although there are many hypotheses, researchers are still unsure what mechanisms are most relevant for the greatest improvements in mental health in a PAP protocol (Swanson, 2018). It is therefore of the utmost

importance to attempt to improve clinical studies by including measures that provide insight into a patients' clinical development. As all of the clinical studies with psychedelic substances have, to the best of our knowledge, primarily used cross-sectional data via standardized score scales, we argue below that clinical research with psychedelic substances would highly benefit from the application of the network theory. In the next section, we briefly summarize the network theory of psychopathology for readers that are not familiar with its central tenets.

The Network Theory of Mental Disorders

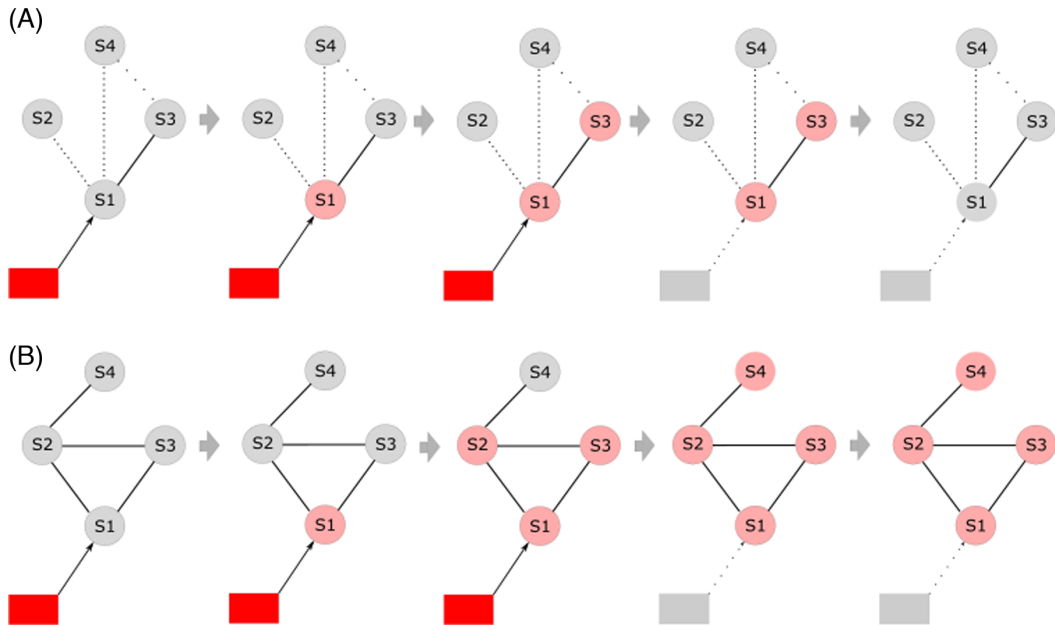
Traditionally, the field of modern psychiatry has taken either a diagnostic or a dimensional perspective on mental disorders (Borsboom, 2008). The diagnostic perspective assumes that there are discrete categories of symptoms, which are defined and caused by an underlying latent construct. For example, within the diagnostic perspective, the symptoms of major depression (e.g., low mood, lack of appetite, etc.) are *caused* by the presence of the underlying mental health disorder labeled depression (similar to the way one “has” or “gets” a cold, one “has” or “gets” depression). The dimensional perspective, on the other hand, somewhat differs in its assumptions; this perspective conceptualizes mental health disorders as occurring on a continuous scale, with more severe symptomatology entailing a more severe *case* of depression. However, both perspectives share the same common view; that the etiology of mental disorders is defined by their specific construct. Whether or not you take a diagnostic or a dimensional perspective, you believe that the symptomatology of depression *is defined and caused by the presence of the disease construct depression*. These perspectives within psychiatry have been considered problematic both from a theoretical and a psychometric perspective (Borsboom, 2008, 2017; Kendler et al., 2011). Despite this, these “latent construct” approaches remain hugely influential in the field of psychiatry. For example, Insel and Cuthbert (2015) argued that the etiology/causal mechanisms of mental disorders reside in the brain. This reductionist approach, that mental disorders are equivalent to “brain circuit disorders,” is yet to yield a reliable biomarker of depression.

The network approach, however, proposes an alternative causal account of psychopathology.

Here, symptoms are causally connected to each other, and mutually reinforce each other, through psychological, biological, and societal mechanisms (Borsboom, 2017). It is unique from the traditional approach because there is no underlying construct, or reducibility, of depression. Instead, depression *is* the very network of symptoms (e.g., behaviors, states, emotions, and social relationships) associated with it. To identify the network, this approach applies formal modeling techniques to self-report data collected from patients, which permits researchers to “see” an individual’s or a group’s manifestation of a psychopathology as a web of interconnected clusters of symptoms.

Within a symptom network of, for example, depression, if enough symptoms are active, then the psychopathology of depression emerges. When two symptoms frequently co-occur in the self-report data, they are said to be “strongly connected” (see below for concrete example). In other words, when one symptom is active, it is highly likely that the other is also active. In cases where networks are made up primarily of strong connections between symptoms (Figure 1B), the network behaves in such a way that symptoms causally and persistently activate each other (e.g., insomnia may be strongly connected to not leaving the house). It is therefore highly likely that the psychopathology of depression will emerge, and remain, as these strong symptom connections facilitate a self-sustaining feedback loop. What must be stressed here is that, rather than symptoms of depression being caused by the presence of said disease, *it is the way that these symptoms are causally connected in a network which defines the pathogenesis and etiology of depression*.

While the network theory is a relatively new methodological approach to the classification of psychopathology, it has been successfully applied to a variety of psychopathologies including major depression (Boschloo et al., 2016; Cramer et al., 2016; Fried et al., 2016; van Borkulo et al., 2015), substance abuse (Rhemtulla et al., 2016), and anxiety disorders (Beard et al., 2016; Heeren & McNally, 2016). The network theory is also gaining increasing empirical support (Fried et al., 2017), as the approach has identified network characteristics that may preclude the emergence of depressive episodes (van de Leemput et al., 2014; Wichers et al., 2016), has been able to demonstrate how major depression can manifest and maintain itself (Cramer et al., 2016), and parsimoniously

Figure 1*A Schematic Illustration of the Emergence of Major Depression Due to Strong Network Connectivity*

Note. Two simple networks differ only in terms of their network connectivity and are affected by the same external event (red box). The network is composed of nodes (i.e., symptoms such as S1) and connections between the symptoms. A full gray line signifies a strong connection between two symptoms, a dashed line signifies a weak connection, and an absence of one signifies no connection between symptoms. Top (A): A symptom network with weak intersymptom connections results in the activation of only two symptoms following a stressful external event. Bottom (B): A symptom network with strong symptom connectivity results in the continued activation of a cluster of symptoms in response to an external event, which then leads to the emergence of depression.

explains the existence of high rates of comorbidity in specific mental health disorders (Cramer et al., 2010). An empirical example of the network theory being applied to major depression can be found in Cramer et al. (2016). Within their article, the researchers characterized major depression as a complex dynamic system. When networks exhibited strong connections between symptoms, the individual was particularly vulnerable to developing major depression. However, when symptom networks were comprised of weak connections, the individual would be less vulnerable to developing depression.

For a comprehensive introduction to the network theory, we refer the interested reader to Borsboom (2017), where four axiomatic principles that comprise the theoretical backbone of the network theory's approach to the conceptualization of mental disorders are laid out.

To allow the reader to become more familiar with the pathogenesis of depression in light of the

network theory, we use the following example (as exemplified in Figure 1). Here, two depression network structures are compared when undergoing a stressful external event (red box external to network). The network is composed of symptoms of depression signified as nodes (such as S1) and connections between the symptoms. A full line signifies a strong connection between two symptoms, a dashed line signifies a weak connection, and an absence of one signifies no connection between symptoms. Figure 1A denotes a weakly connected network (less connections, with weaker connections between symptoms), while Figure 1B denotes a strongly connected network.

In the first two columns of both figures, an external event, typically a stressor, causes the activation of a symptom (S1 turns from gray to red). For example, hearing from your boss that your contract will not be extended can be a major stressor, which results in sleeping problems as you ponder the consequences of this decision at night. S3 is also

activated in Figure 1A, as a result of a strong connection between the two symptoms (e.g., sleeping problems in turn cause heightened irritability the next day). Removal of the external event (in the fourth column, as the square box turns from red to gray) leads to a reduced symptom activation over time. Weak connections between symptoms in this particular network imply the absence of feedback loops that lead to the perpetuation of symptom activation. As a result, the network returns to a healthy state in the fifth column. However, in Figure 1B, the connections between symptoms are stronger. As a result, more symptoms are activated in response to the stressor than in Figure 1A (as demonstrated in the third and fourth column). For instance, hearing that you lost your job causes sleeping problems, but also irritability, ruminative thought patterns, and loss of self-worth. Due to more widespread symptom activation, and strong connections between inactive and active symptoms, the complete network is activated, instantiating a global *self-sustaining feedback loop*. As the external stressor is removed, the network does not return to its previous state, as the feedback loops facilitate the perpetual activation of symptoms. This leads to the emergence and maintenance of depression, despite the absence of a stressor.

While this is a somewhat simplistic example of the emergence of depression, the above illustrates how an individual may become “stuck” in a depressive episode; the strength of connections between symptoms will indicate the vulnerability of a patient to develop a depressive episode (Cramer et al., 2016). Strong connections in a psychopathology network will both facilitate the emergence of depression due to minor perturbations of a system (i.e., mild stressors in the environment) and keep that individual in the throes of a depressive episode.

Primary Hypothesis: The Relaxed Symptom Network

Relating the network theory back to clinical research with psychedelics, an interesting parallel between the two approaches is that they both represent a paradigmatic shift within the field of psychiatry (Fried et al., 2017; Nutt et al., 2020). The network theory aims to move away from a latent model of psychopathology and acknowledges that mental health issues occur in a nuanced fashion with biological,

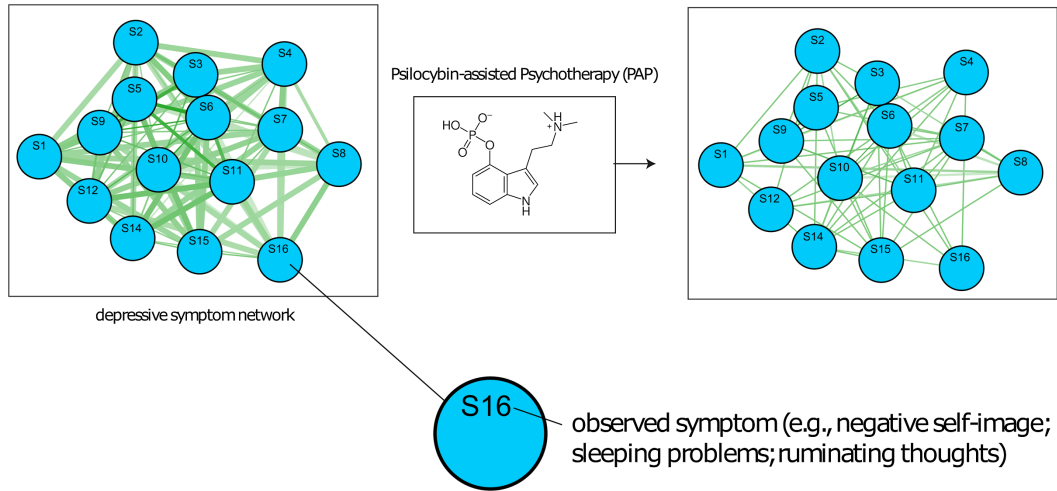
psychological, and environmental factors that all contribute to the proliferation of a disorder. Clinical psychedelic research has made a similar suggestion for the field of psychiatry; the pharmacological action of psychedelics (*bio*) has psychological and phenomenological consequences (*psycho*) which leaves a window of opportunity for patients to develop new adaptive patterns of behavior and thought and bolster a deeper sense of connection with the world around them (*social*; Carhart-Harris, Erritzoe, et al., 2018). It therefore seems fruitful to integrate these two approaches, as their focus is on initiating greater change in the field of psychiatry.

To integrate these two approaches, as a starting point, we know that PAP may be effective at reducing depressive symptomatology. However, patients have the potential to relapse back into a depressive episode after several months. For example, despite a large reduction in depressive symptoms in the sample, three out of nine patients that were responsive to PAP for treatment-resistant depression relapsed back into a depressive episode 6 months posttreatment (Carhart-Harris, Bolstridge, et al., 2018). Further to this, researchers and clinicians do not understand why some individuals are unresponsive to psychedelic therapy.

We therefore bring forward our primary hypothesis in regard to the application of the network theory within psychedelic research: *If the PAP protocol is effective, the connections between symptoms in a patient's depression network ought to weaken*. That is, as the patient progresses through the PAP protocol, the connections between symptoms in a network will reduce, ultimately leading to the patient becoming less vulnerable to developing a depressive episode later on. Metaphorically, the network of depressive symptoms is like a spider's web in which the individual is “stuck.” If the connections in the web weaken, the web becomes easier to escape. By this logic, patients more likely to relapse would not have “weakened the web” sufficiently during the PAP protocol, possibly requiring additional sessions or postintervention monitoring to ensure that old symptom networks do not easily “reconnect” (see Figure 2).

The primary hypothesis—that the symptom network will *relax* as a result of effective PAP treatment—is supported by other popular models regarding the effects of psychedelics, as well as predictive processing models of depression (e.g.,

Figure 2
Schematic of the Relaxed Symptom Network



Note. On the left is a highly connected symptom network. This leads an individual being vulnerable to develop a depressive episode. The administration of psilocybin in a psychotherapeutic context (i.e., psilocybin-assisted psychotherapy [PAP]) may result in the weakening of connections in a symptom network, if PAP is successful.

Badcock et al., 2017; Kube et al., 2020). For example, the REBUS model (relaxed beliefs under psychedelics; Carhart-Harris & Friston, 2019) posits that psychedelics serve to *relax* prior beliefs. When a collection of these prior beliefs forms a maladaptive generative model of the world, individuals may become “stuck” in a depressive episode. Through this disinhibition, psychedelics therefore allow patients to shift from a maladaptive model to a healthier one, as these top-down depressive beliefs have less influence on the generation of conscious experience. This framework is also broadly consistent with the Accept, Connect, Embody model (Watts & Luoma, 2020), which proposes psychological flexibility as a key therapeutic mechanism. The “relaxed priors” may engender an acute period of psychological flexibility and hence a relaxed symptom network, providing a window for deep psychological change.

Practical Applications of the Network Theory in Clinical Psychedelic Research

In order to provide an application of the network theory, we present real-world examples of how to generate psychopathology networks and further explore their utility in solving practical

issues within clinical psychedelic research. A summary of the benefits of applying the network theory to clinical psychedelic research can be found in Table 1. Two prevailing types of networks can be generated when applying the network theory to psychopathology, personalized

Table 1
Benefits of Applying the Network Theory to Clinical Psychedelic Research

Type of network computed	Advantage of application
Personalized symptom networks	Identification of central symptoms for each patient may generate empirically derived intentions to take into the psychedelic session.
Cross-sectional networks	Answer questions regarding efficacy of PAP to target specific symptom interactions in networks across patients.
Personalized networks	Network connectivity strength may provide insights into the likelihood of relapse for specific patients and may allow clinicians to modulate the intensity/frequency of PAP protocols more effectively.

Note. PAP = psilocybin-assisted psychotherapy.

symptom networks, and cross-sectional networks (Fried & Cramer, 2017). *Cross-sectional networks* are used to elucidate differences at a group level to identify central symptoms. For example, Santos et al. (2018) used a cross-sectional approach to investigate the relationships between depressive symptoms in low-income mothers and found a number of stable symptom associations, such as concentration difficulties being associated to feeling disliked and feeling lonely to sleep disturbance. Cross-sectional networks may be useful in clinical psychedelic research for three primary reasons. First, they can be used to directly test the specific hypothesis that the connections between symptoms in a depression network will weaken as a function of successful PAP. This hypothesis can be empirically evaluated using the network comparison test (van Borkulo et al., 2022). Second, cross-sectional networks may allow researchers to ask exploratory questions regarding the effects of psilocybin on specific symptoms at the group level. For example, do psilocybin sessions affect the connectivity between specific symptoms? Are there specific relationships between symptoms that have been diminished at the group level? These are pertinent questions in the field of psychedelic research. Third, application of these cross-sectional networks may allow researchers to draw more specific conclusions about the effects of PAP versus placebo or another means of mental health treatment. To contextualize this, as mentioned on p. 6, a recent study found that PAP did not significantly outperform a conventional antidepressant on the primary outcome measure of depression, yet PAP was significantly more effective on all other secondary outcome measures of depression (Carhart-Harris, Giribaldi, et al., 2021). We argue that the generation of cross-sectional networks may remedy the issues that come hand in hand with measuring depression on standardized scale scores, by allowing researchers to more easily evaluate the difference between groups on the basis of variables such as network connectivity.

Personalized symptom networks (Epskamp et al., 2018) are generated using the experience sampling method (aan het Rot et al., 2012; Myin-Germeys et al., 2009). Using this method, patients repeatedly report symptoms (e.g., five times per day for 2 weeks), which generate time-series data that can be used to map the intraindividual dynamics of the psychopathology, and create a personalized symptom network. These

specific types of networks are useful within clinical psychedelic research for two primary reasons. First, personalized symptom networks can provide insights into the effectiveness of the psychedelic session on an intraindividual basis. As mentioned above, we hypothesize that successful psilocybin therapy will decrease the overall connectivity of an individual's personalized depression symptom network. By generating personalized symptom networks, both before and after the psychedelic session, we expect to observe diminished connectivity in the symptom network postpsychedelic session. Future researchers may therefore also use personalized symptom networks (specifically the intraindividual network connectivity) to gain insight into the susceptibility of a patient to relapse into another depressive episode (Cramer et al., 2016; van Borkulo et al., 2015). This insight can be used to tailor the intensity/frequency of psychotherapeutic protocols specifically to that patient's needs. For example, if a patient still has a strongly connected network following a psychedelic session, we may predict that this patient is more likely to relapse into another depressive episode, and warrants closer psychotherapeutic attention, or even another psychedelic session, in order to further diminish the connections between symptoms.

Second, personalized symptom networks can provide insights into which symptoms are most central for an individual. Researchers may use centrality measures as a proxy for the importance of that symptom in depression. Examples of centrality measures include degree centrality, defined by the number of direct connections that one symptom possesses with other nodes in the network (Freeman, 1978), and closeness centrality, quantified by the inverse of the sum of distances of a node of interest and other symptoms in the network (Costantini et al., 2015). These centrality measures in turn can provide insights as to what specific symptoms need to be addressed in the psilocybin session. Personalized symptom networks are also more "robust" to false associations between symptoms, allowing researchers to conclude more reliably that specific symptoms play a central role in the perpetuation of the specific psychopathology (for debate about the use of centrality measures, see Bringmann et al., 2019; Hallquist et al., 2021). By generating a personalized symptom network and identifying central symptoms in a depressive disorder within

individuals prior to the psychedelic experience, clinicians can then attempt to target underlying problems that may connect to central symptoms during therapy (e.g., feelings of worthlessness). This may also help in guiding clinicians and patients to set an intention that draws attention toward a central symptom during the psychedelic session, potentially making it more amenable to change and thus increasing the chances that the patient “breaks” the depressive symptom network (Watts & Luoma, 2020).

One final point to highlight is the advantageous nature of time-series data over data collected through standardized score scales such as the Beck Depression Inventory (BDI) or the Quick Inventory of Depressive Symptomatology (QIDS) at discrete time points. Again, in the clinical trial of Carhart-Harris, Giribaldi, et al. (2021), one of the issues here is that the conclusions were drawn on the basis of depression symptoms sampled at a discrete time point. However, if time-series data were collected, for example, through a mobile application, researchers may have been able to gain a deeper insight into the specific fluctuations of symptomatology and more conclusively drawn differences between the two samples. The application of data collection through digital means has recently been highlighted as a tool that may push psychedelic research forward (Carhart-Harris, Wagner, et al., 2021). We may argue here that, as symptom networks are relatively easy to compute using time-series data, the collection of this type of data may serve to both gain a deeper insight into the pathogenesis of depressive disorders for individual patients, while also allowing researchers to move away from the issues that plague standardized scale scores to categorize and measure mental health.

Limitations

While we are hopeful about the application of the network theory to future psychedelic research, we must also highlight some pertinent issues around the network theory, and our model, for future researchers to consider. First, much of the research that has been conducted with the network approach has based the network structure solely on symptoms extracted from the Diagnostic and Statistical Manual of Mental Disorders (*DSM*) or International Classification of Diseases (*ICD*). To allow a

network model to be more specific, researchers may also consider including nodes that have some causal relevance in the pathology of mental disorders, such as beliefs, behaviors, or psychophysiological measures (Jones et al., 2017). By including these other variables within a network, the network model of psychopathology may have more explanatory power. For example, researchers may include variables in an exemplary network that are antithetical to depressive symptoms, such as positive mood or high self-esteem. From this, the relative strength between these variables could be computed before and after PAP; if some depressive symptoms are strongly connected to these variables post-PAP, then this corresponding network may be less vulnerable to the emergence of depression.

Second, we highlight that our model of PAP action is specifically related to major depression and the use of psilocybin. We acknowledge here that PAP is currently being evaluated as a transdiagnostic therapeutic modality. Different subtypes of mental disorders will most likely have different topological organizations of symptoms, thus making the generalization of applications, such as symptom centrality, more complicated (Contreras et al., 2019). We therefore argue that our hypothesis can be applied to a variety of mental health issues, and the application of the network theory may benefit psychedelic psychiatry as a whole.

Conclusion

This article highlights the current clinical work using PAP to treat depressive disorders. We argue that the network theory is a valuable statistical tool for clinical psychedelic researchers in the future for a number of reasons. First, network connectivity may be computed for each patient, thereby providing an insight into specifically tailoring the intensity/frequency of psychedelic dosing during a PAP protocol; if a patient’s network connectivity remains strong succeeding a psychedelic session, clinicians may pay more attention to this patient in case of relapse. Second, by computing cross-sectional networks, future researchers may discover whether PAP exerts its effectiveness on specific symptoms within depressive disorders, thereby gaining a deeper insight into the psychological changes induced by PAP. Third, prior to the dosing session,

personalized symptom networks may be computed, thereby allowing clinicians to potentially identify central symptoms within an individual's network, which may glean an insight into the most therapeutically beneficial intention for an upcoming psychedelic session. And finally, tracking symptom networks could also be used to test theories regarding therapeutic mechanisms.

As there is a strong convergence between both the network theory and psychedelic psychiatry—through the fact that they seek to view mental health issues through a biopsychosocial lens—we hope to have actively encouraged a new paradigm of research that integrates the two approaches.

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