Future Directions for Clinical Psychedelic Research: The Relaxed Symptom Network

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Abstract

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 (psychedelic-assisted psychotherapy; PAP). There are now dozens of registered and ongoing clinical trials that intend to test for the efficacy of psilocybin within a psychotherapeutic protocol. Despite promising results, the mechanism(s) that may be responsible for the antidepressant effects of PAP are still hotly contested. In this paper, we provide a broad overview of the recent clinical work conducted with psychedelics on depressive disorders, and summarise several theories of action of PAP. Extending on the state of the field, we argue that the ‘Network Theory of Mental Disorders’ is a useful tool for clinical research with psychedelics. We hypothesise that, if PAP is successful, the connections between symptoms in a network will weaken, thereby rendering the patient less vulnerable to developing or relapsing into depression. We argue that application of the Network Theory may (a) provide deeper insights into the effects of PAP on specific symptom interactions, both on an interindividual and intraindividual basis, (b) generate fruitful hypotheses for the clinical action of PAP, and (c) provide a pre-emptive tool for making the most of ‘intentions’ preceding and during psychedelic experiences. These findings we hope will ultimately improve responsiveness and reduce relapse in response to this promising therapy.

Keywords: Psychedelics, Network Theory, Psychopathology, Psychotherapy, Depression
Future Directions for Clinical Psychedelic Research: Application of the Network Theory

‘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 organisation of the brain (Girn et al., 2020; Muthukumaraswamy et al., 2013; Carhart-Harris et al., 2012; Roseman et al., 2014; Petri 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 naturally-occurring psychedelic mushrooms) to treat depressive disorders (Grob et al., 2011; Ross et al., 2016; Griffiths et al., 2016; Carhart-Harris et al., 2016; 2018; Agin-Liebes et al., 2020; Davis et al., 2020). Moreover, at the time of writing, clinicaltrials.gov lists 99 registered trials that intend to use psychedelics 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.
The network theory aims to reconceptualise mental health disorders as symptom networks, rather than as a latent construct (such as depression) causing a constellation of symptoms (see ‘The Network Theory…’ 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 paper is that, if psychedelic-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 maximise the potential of PAP to support the emergence of a network robust to depression and potentially other disorders.

Leading up to the presentation of the ‘Relaxed Symptom Network’ hypothesis, we begin with an overview of the growing evidence that examines the antidepressant potential of PAP. We specifically present evidence of psychedelics for depressive disorders as it is the most thoroughly researched in contemporary psychedelic psychiatry. However, while much of the literature focuses on the use of psilocybin, we acknowledge that there are transdiagnostic elements at play when it comes to PAP. Therefore, we argue that the application of the network theory may benefit clinical psychedelic research as a whole, but, for the sake of simplicity, we focus specifically on depressive disorders. Second, we present several recent theoretical papers that attempt to underpin how psilocybin, and other classic psychedelics, may exert their therapeutic effects. The aim of this section is to provide a broad overview into the psychological and neurobiological changes that may be responsible for a psychedelic’s antidepressant effects. Third, we provide an overview of the network theory of mental disorders, and outline our hypothesis regarding the action of PAP on the psychopathology network. 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: 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.

**What is Psychedelic-Assisted Psychotherapy?**

Clinical psychedelic research has a tumultuous history, and has been marred by prohibition (Nutt & Carhart-Harris, 2021). However, contemporary academia is re-opening itself up to the study of psychedelics, both on the brain and on mental health (Nutt & Carhart-Harris, 2021). Psychedelic-assisted psychotherapy (PAP) is an intervention that is receiving considerable and growing clinical and scientific attention. Commonly, a PAP protocol lasts for six to ten weeks, and will involve one to three dosing sessions with a psychedelic (Payne et al., 2021). The most common psychedelic used in Western psychedelic science is psilocybin, which we will hereby refer to. 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) that 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 25-30mg as a high dose) in the presence of a therapist(s), who provides guidance and emotional support when needed. However, the patients are 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 provided,
aiming to synthesise any insights from the experience, with the aim of integrating behavioural or cognitive changes that may lead to positive long-term mental health outcomes. While there has been some effort to standardise the therapeutic protocols associated with PAP (Watts & Luoma, 2020), further research is needed to verify the ideal way to deliver psychedelic therapy.

It is beyond the scope of this review to summarise 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; Romeo et al., 2020; Luoma et al., 2020; Galvão-Coelho et al., 2021). While the observed effect sizes within these meta-analyses are consistently larger in magnitude than those associated with the use of psychotherapy alone (Cuijpers et al., 2008; Cuijpers et al., 2010), antidepressants (Fournier et al., 2010), or pharmacotherapy and psychotherapy combined (Cuijpers et al., 2014), it should be highlighted that these effect sizes in clinical psychedelic trials may be overestimated due to low sample sizes, or due to a lack of robust placebo-controls. It is therefore of the utmost importance to replicate these findings in larger sample sizes with robust placebo-control measures. Furthermore, it is pertinent to highlight that all of the summarised studies use cross-sectional data to evaluate the effectiveness of PAP on depressive symptoms. While this is a conventional method, we argue that time-series data may be a more appropriate and informative style of sampling when evaluating the efficacy of PAP (see our recommendations below).

How Does PAP Work?

Over the past fifteen 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. Within this section of the paper,
we summarise three theories of psychedelic action. These three have been chosen as they are based on different areas of study - psychotherapy (ACE model), psychology (Awe Model), and cognitive neuroscience (REBUS model) - with the clinical efficacy of PAP hinging on distinct – though related - mechanisms in each theory. While many of the ideas highlighted in each theory are compelling and receive partial empirical support, we also argue here that the mechanism(s) of action at play during PAP remain contested. We also acknowledge there are many alternative models accounting for the efficacy of PAP (e.g. Flanagan & Nichols, 2018; Hartogsohn, 2016; Olson, 2018; Vollenweider & Preller, 2020). However, a full review of these would be beyond the scope of the paper.

**The Accept-Connect-Embody Model**

Watts & Luoma (2020) recently theorised the accept, connect, embody (ACE) model to highlight that psilocybin may increase psychological flexibility, which may be the underlying psychotherapeutic mechanism underpinning its effectiveness in treating depressive disorders. The researchers highlight that acceptance and commitment therapy (ACT) primarily focuses on enhancing psychological flexibility, defined as “the ability to contact the present moment more fully as a conscious human being, and to change or persist in behaviour when doing so serves valued ends” (Hayes et al., 2006, p.7). However, there are still many patients that do not yield enhanced psychological flexibility, and therefore are unresponsive to ACT (A-Tjak et al., 2015). The researchers argue that the psilocybin dosing session may provide another route that facilitates the enhancement of psychological flexibility. The authors argue that the process of PAP requires the patient to ‘let-go’ and become open to the psychedelic experience, which would allow maximal therapeutic benefit. This opening up, in combination with the altered states that are commonplace during a psychedelic experience, such as the mystical-type experience
(Griffiths et al., 2011), ego dissolution (Nour et al., 2016), and emotional breakthrough (Roseman et al., 2019), facilitate the enhancement of psychological flexibility within the patient. The ACE model proposes that the enhancement of psychological flexibility is one of the primary underlying mechanisms that underpin PAPs efficacy for treating neuropsychiatric disorders such as major depression.

**The Awe Model**

Hendricks (2018) focuses on the psychological changes that are encountered in a psychedelic experience as a catalyst of the positive effects of PAP. The crux of the argument is that the emotion of ‘awe’ is the psychological mechanism responsible for mystical-type experiences during the psychedelic state, which translates into improvements in clinical outcomes. Awe is defined as an emotion “in the upper reaches of pleasure and on the boundary of fear” (Keltner & Haidt, 2003, p.297), and is elicited in response to two key appraisals: vastness and accommodation. The concept of vastness refers to stimuli that are represented as larger than the self, both in a physical context (e.g., shaking ground or loud sounds), and a social context (e.g., markers of social status such as fame). The concept of accommodation refers to the process of integrating a novel experience through the adjustment of psychological structures. Hendricks (2018) goes on to argue that a hallmark of the psychedelic state, the mystical-type experience, may be characterised by feelings of awe. This is supported by the fact that the mystical experience questionnaire (Barrett, Johnson & Griffiths, 2015) explicitly intends to measure ‘Sense of awe or awesomeness’, as well as ‘Experience of amazement’. Moreover, the questionnaire attempts to quantify the degree in which the sense of self becomes smaller, relating to the concept of vastness (e.g., ‘Experience of the fusion of your personal self into a larger whole’). As the intensity of these mystical-type experiences that occur within a psychedelic
dosing session have been correlated with positive clinical outcomes (Yaden & Griffiths, 2020), Hendricks (2018) argues that the fundamental emotion of awe during the psychedelic experience (vastness) may serve as the catalyst that instantiates a plethora of long-term effects such as positive affect, increased well-being, and an enhanced sense of connection (thus referring to the concept of accommodation).

**REBUS Model**

The relaxed beliefs under psychedelics (REBUS) model hypothesises that the pharmacological action of psychedelics – 5-HT2A receptor agonism – is responsible for the majority of the effects of psychedelics (Carhart-Harris & Friston, 2019). Within the context of hierarchical predictive processing (an explanatory framework that posits the brain as a predictive machine), the authors report that 5-HT2A receptors are densely expressed on deep pyramidal neurons (located at higher hierarchical levels of the brain), which are hypothesised to encode prior beliefs (Bastos et al., 2012). Agonism at the 5-HT2A receptors will cause a disinhibiting effect on the top-down processing of sensory information in the brain. That is, during normal waking states of consciousness, these deep pyramidal cells will inhibit sensory information that may not concord with existing prior beliefs, thereby minimising a state of surprise. However, during the psychedelic state, agonism at the 5-HT2A receptor will result in disinhibition of this neurocognitive mechanism. This disinhibition reduces the certainty of these prior beliefs, thereby rendering the brain more sensitive to incoming sensory information, as less phenomena are ‘explained away’ by the brain’s generative model. Thus, psychedelics serve to ‘relax’ prior beliefs. This is a pertinent mechanism, especially in the context of PAP, as the predictive processing literature on depressive disorders has implicated that overconfidence in depressive prior beliefs may be responsible for the facilitation and perpetuation of a depressive generative
model (e.g., Clark et al., 2018; Edwards et al., 2012; Kube et al., 2020). As 5-HT_{2A} receptor agonists, psychedelics may downweigh the felt confidence in these depressive beliefs, thereby facilitating a shift from a maladaptive generative model to a representation of the world that is aligned with positive mental health. Thus, according to the REBUS model, the neuropharmacological mechanism of 5-HT_{2A} receptor agonism will translate into the disinhibition of sensory information, thereby potentially leading to a shift in one’s model of self and world.

**Interim Summary**

As mentioned, this is a non-exhaustive list of theories of psychedelic action in the context of PAP. However, it highlights that PAP is a multi-faceted psychotherapeutic protocol, consisting of preparatory and integration phases, as well as the dosing session itself. Therefore, there are many proposed mechanisms that are hypothetically responsible for PAP’s efficacy in treating depressive disorders (amongst a panoply of other neuropsychiatric issues). Moreover, as PAP is a multidimensional (or experiential) therapeutic modality, researchers may generate a variety of hypotheses from different explanatory levels of the protocol. As illustrated above, researchers may focus on the biological action of psychedelics (e.g., REBUS model), the psychotherapeutic protocol (e.g., ACE model), or the phenomenology of the psychedelic experience itself (e.g., awe model) to underpin its therapeutic effects. This puts a spotlight on an issue within psychedelic research: although there are many hypotheses, researchers are still unsure what mechanisms are most responsible 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 the most 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 standardised-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 therefore aim to summarise the network theory of psychopathology. The network theory will then be contextualised within clinical psychedelic research, highlighting our specific hypotheses regarding the changes in a psychopathology network as a function of PAP, as well as the potential benefits of using the network theory within future studies.

**The Network Theory of Mental Disorders**

The network approach proposes to explain psychopathology as an emergent property based on a dynamic complex network of interacting symptoms (Figure 1). These symptoms (or nodes) are causally connected to each other through psychological, biological, and societal mechanisms (Borsboom, 2017). In cases of strong connections, the causal interplay between symptoms will create a self-sustaining feedback loop, facilitating the emergence of a mental disorder (Borsboom & Cramer, 2013). The network approach to psychopathology employs statistical techniques that aim to map the dynamic structure of symptom networks in 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 and McNally, 2016). The network theory is 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 explains the existence of high rates of comorbidity in specific mental health disorders (Cramer et al., 2010). For a comprehensive introduction to the network theory, see Borsboom (2017).
Figure 1

A schematic illustration of the emergence of major depression due to strong network connectivity. 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 grey 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 inter-symptom 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.

We exemplify how the network theory is applied to account for major depression in Figure 1. Here, two network structures are compared when undergoing a stressful external event (red box external to network). The network is composed of symptoms 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 grey 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 grey) leads to a reduced symptom activation over time. Weak connections between symptoms in this particular network infer 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 a mental health disorder, 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, we know that PAP may be effective at reducing depressive symptomatology. However, some individual patients may relapse back into a depressive episode after several months. For example, despite a large reduction in depressive symptoms in the patient sample, three out of nine patients that were responsive to PAP treatment for TRD relapsed back into a depressive episode 6-months post treatment (Carhart-Harris et al., 2018a). As-of-yet, 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 patients’ 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. Thus, in cases of relapse, it may be that the patients who are least responsive to PAP, have smaller changes in the connection strength of the psychopathology network. We therefore argue that the application of the network theory within clinical psychedelic research would allow clinicians and researchers to gain deeper insights into the unfolding experience of patients, rather than the current model of sampling symptomatology at discrete time points.
This primary hypothesis - that the symptom network will relax as a result of effective PAP treatment - builds on previous models regarding the effects of psychedelics. As mentioned above, the REBUS model 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. Parallel to this, when an individual’s symptom network is strongly connected, it is likely that an individual will become ‘stuck’ in a depressive episode (Cramer et al., 2016). This framework is also broadly consistent with the ACE 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.

Drawing on existing theoretical accounts, we therefore argue that successful PAP will allow a patient to become ‘unstuck’, and develop remission from a depressive episode, which ought to translate into a weaker connected symptom network (see Figure 2). In the next section we outline 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.

**Practical Applications of the Network Theory in Clinical Psychedelic Research**

Two prevailing types of networks can be generated when applying the network theory to psychopathology; personalised symptom networks, and cross-sectional networks (Fried and Cramer 2017). *Cross-sectional networks* are used to elucidate differences at a group-level to
Figure 2: Schematic of the relaxed symptom network. On the left is a highly connected symptom network. This leads an individual being vulnerable to develop a depressive episode. The administration of a psychedelic in a psychotherapeutic context (e.g., psilocybin-assisted psychotherapy; PAP) may result in the weakening of connections in a symptom network, if PAP is successful.

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 two 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 tested using the network comparison test (van Borkulo et al., 2017).

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
### Table 1

**Benefits of Applying the Network Theory to Clinical Psychedelic Research**

<table>
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<tr>
<th>Type of Network Computed</th>
<th>Advantage of Application</th>
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<tbody>
<tr>
<td>Personalised Symptom Networks</td>
<td>Identification of central symptoms for each patient may generate empirically derived intentions to take into the psychedelic session.</td>
</tr>
<tr>
<td>Cross-Sectional Networks</td>
<td>Answer questions regarding efficacy of PAP to target specific symptom interactions in networks across patients.</td>
</tr>
<tr>
<td>Personalised Networks</td>
<td>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.</td>
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</table>

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 effect of PAP vs. placebo or another means of mental health treatment. To contextualise this, a recent study found that PAP did not significantly outperform a conventional antidepressant on the primary outcome measure of depression, yet PAP significantly differed on other secondary outcome measures of depression (Carhart-Harris et al., 2021a). We argue that the generation of cross-sectional networks may remedy the issues that come hand-in-hand with measuring depression on standardised scale scores, by allowing researchers to more easily evaluate the difference between groups on the basis of variables such as network connectivity.
Personalised 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 two weeks), which generates time series data that can be used to map the intraindividual dynamics of the psychopathology, and create a personalised symptom network. These specific types of networks are useful within clinical psychedelic research for two primary reasons. First, personalised symptom networks can provide insights into the effectiveness of the psychedelic session on an intraindividual basis. As mentioned above, we hypothesise that successful psilocybin therapy will decrease the overall connectivity of an individual’s personalised depression symptom network. By generating personalised symptom networks, both before and after the psychedelic session, we expect to observe diminished connectivity in the symptom network post psychedelic session. Future researchers may therefore also use personalised symptom networks (specifically the intraindividual network connectivity) to gain insight into the susceptibility of a patient to relapse into another depressive episode (van Borkulo et al., 2015; Cramer et al., 2016). 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 post 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, personalised 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. Personalised 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., 2019).

By generating a personalised 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 towards 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 and Luoma, 2020).

One final point to highlight is the advantageous nature of time-series data over data collected through standardised score scales such as the Beck's Depression Inventory (BDI) or the Quick Inventory of Depressive Symptomatology (QIDS) at discrete time points. Again, contextualising this within the most recent and comprehensive clinical psychedelic trial, Carhart-Harris et al. (2021a) compared the efficacy of PAP against a conventional antidepressant (escitalopram). PAP failed to significantly outperform escitalopram on the primary outcome measure (QIDS), yet significantly outperformed escitalopram on all secondary measures (e.g. BDI). One of the issues here is that these 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 et al., 2021b). This, coupled with the fact that psychopathology networks are relatively easy to compute, may therefore allow researchers to move away from the issues that plague standardised scale scores to categorise and measure mental health.

**Conclusion**

This paper highlights the current clinical work using PAP to treat depressive disorders, and outlines three theories of how PAP exerts its therapeutic effects. 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, personalised 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.
One final thought, and an interesting parallel between psychedelic research and the field of network models in clinical psychology, is that they both seek to revolutionise 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 a similar flavour, and aims to harness a biopsychosocial approach as its core; 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 behaviour and thought, and bolster a deeper sense of connection with the world around them (social; Carhart-Harris et al., 2018b). It therefore seems fruitful to marry these two approaches, as their focus is on initiating greater change in the field of psychiatry. We hope that this paper paves the way for further clinical psychedelic research to utilise the network theory, and may pique the interest of future researchers.
References


