2022

A network approach to depression symptomology in acute ketamine treatment

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

A NETWORK APPROACH TO DEPRESSION SYMPTOMOLOGY IN ACUTE KETAMINE TREATMENT

by

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B.S., University of California, San Diego, 2016

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2022

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ACKNOWLEDGMENTS

The completion of this study could not have been done without my entire support system. I would not have been able to learn so, so much without every one of you!

First, I would like to thank my advisor, Dr. Pedrelli, for her unwavering support and mentorship through the ups-and-downs of working through writer's block, the IRB responses, and so much more. I would also like to thank my master's advisor, Dr. McKnight, who has supported me through my entire time at Boston University. I would not have made it through without his guidance.

I would also like to thank Dr. Curtiss for his guidance with learning R and network analysis. I appreciate him answering my many questions and always being willing to help. Thank you to all the members of the DCRP, particularly Dr. Cusin, Julianne Origlio, Aava Jahan, and Radhika Shah.

I am also very grateful for the support and many lectures I received from Georg Hahn and Santiago Romero-Brufau. Both of you encouraged me and helped me push through the last steps!

Finally, many thanks to Mauna Dasari and Jake Zwart. Your understanding and support through all of my over-stressing was greatly appreciated.

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ABSTRACT

Background: Major depression is a pervasive condition that affects every aspect of a patient's life, and many patients are unable to find symptom alleviation with the current available medications. Ketamine has recently shown promise as a rapid-acting antidepressant, yet its mechanisms are not yet well-understood.

Objective: We sought to understand the change in depression symptom interrelationships, with particular interest in sleep, in the context of ketamine treatment in depression by completing a network analysis.

Methods: 97 patients with treatment-resistant depression were given ketamine over six treatments, and symptoms were examined via the Quick Inventory of Depressive Symptomology (QIDS-SR-16). Two networks were constructed: one prior to the first treatment, and one prior to the sixth treatment. Each symptom of the inventory formed a node, and partial correlations were used to construct the edges of the network. Centrality indices and network structure was then evaluated and compared.

Results: Centrality indices measured were unstable, limiting assertions to node strength, but global network structure was revealed to be changed between the networks.

Conclusion: The data suggests that ketamine may affect the interrelationships between depressive symptoms, by impacting some symptoms more than others.

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INTRODUCTION

Major depressive disorder (MDD) is a widespread condition that profoundly affects every aspect of a patient's life. Patients struggle with a multitude of symptoms, including reduced concentration, weight change, and thoughts of death among others (American Psychiatric Association [APA], 2013). The etiology behind depression has yet to be fully elucidated, leading there to be varied mechanisms of treatment proposed. Although many patients find relief with selective serotonin reuptake inhibitors (SSRIs) and other medications, 30% of MDD sufferers do not respond to these treatments (Voineskos et al., 2020). In this form of treatment resistant depression (TRD), ketamine has become a promising new option for patients. The mechanisms of action of ketamine reveal interactions with different compounds, with some particularly related to sleep, raising the question of whether ketamine's antidepressant effects are occurring through the mechanism of alleviation of sleep disorders, which are common among patients with MDD (Schmitt et al., 2016). By taking a network approach, one can further understand the interconnected role of sleep with other MDD symptoms in those undergoing ketamine treatment, and possibly further discern which patients may respond better to treatment.

A. Depression: A Pervasive Medical Condition

In 2019, roughly 280 million people globally suffered from depression, and those numbers have only been rising (Searing, 2022). Within the United States alone in 2020, 21 million suffered from a major depressive episode, defined as a period of at least 2 weeks where a patient exhibits depressed mood or anhedonia, along with at least four of

the other major depression symptoms (Searing, 2022; APA, 2013). These other symptoms include significant change in appetite/weight, sleep disturbance, psychomotor shifts, low energy, inability to concentrate, and thoughts of death (APA, 2013). Each of these symptoms are not seen in every MDD patient, as depression has many diverse clinical presentations, which may allude to varied underlying biological mechanisms (Clark et al., 2017).

B. Depression's Neurobiological Basis

Monoamine Oxidase Enzyme Theory

The prevailing hypothesis for the last few decades has been related to monoamine oxidase enzyme (MAO) metabolism. MAO is known to metabolize different neurotransmitters and reduce their availability to neurons (Pitsillou et al., 2019). There are two isoenzymes, MAO-A and MAO-B, which vary in their primary locations, with MAO-A found in gastrointestinal tract, hepatic, and brain tissue and MAO-B found in blood platelets and more specifically with dopaminergic neurons in the brain (Finberg & Rabey, 2016). MAO-A is of particular interest in depression treatment research, as MAO-A exhibits a greater affinity for norepinephrine (NE) and serotonin (5-hydroxytryptamine, 5-HT) (Thase, 2012). NE has been found to have an important role in motivation and cognition, while 5-HT is key in emotional processing and responses (Moret & Briley, 2011; Cowen & Browning, 2015). These neurotransmitters are considered vital in healthy functioning and are thought to be deficient after MAO

processes them (Pitsillou et al., 2019). Thus, treatments for depression have focused on targeting MAO.

While MAO-A has been shown to be elevated during major depressive episodes, it is also important in the metabolism of many other enzymes (Meyer et al., 2006). Consequently, targeting this mechanism are often associated with many unintended side-effects, leading to a reduction in their individual use and more specific targeting of norepinephrine and serotonin metabolism (Finberg & Rabey, 2016).

Norepinephrine & Serotonin in Depression

Norepinephrine plays a significant role in the limbic system, which includes the hippocampus, hypothalamus, and the amygdala. These structures are relevant to a wide variety of functions, including memory, autonomic system activity, emotional responses, and other executive functions (Drevets et al., 2002). Changes in these functions can directly bring about depression symptoms, and impact social interaction, indirectly contributing to depression (Moret & Briley, 2011). Further, altered metabolism of NE has been found among depressed patients via postmortem neural tissue, as compared with healthy individuals (Valdizán et al., 2010; Klimek et al., 1997). Additionally, when NE is depleted in MDD-remitted patients, abrupt recurrence of symptoms is observed, while depletion in healthy individuals was not correlated with any change in mood. Thus, clearly NE plays a role in depression symptoms, but likely not alone (Moret & Briley, 2011).

Serotonin has long been considered important in MDD, as it has a role in nearly all human behaviors, and in much of the central nervous system. There are many types of

serotonin receptors, each affecting behavior in a different way (Berger et al., 2009). Characterizing its numerous functions is beyond the scope of this study, though the receptors are known to be a focus for depression treatments. Selective serotonin reuptake inhibitors (SSRIs) target these receptors and have been the primary form of treatment for depression for the last decades, though many patients do not find success with them (Cowen & Browning, 2015).

Recent research has shown that both NE and 5-HT may not be the only factors in depression, but possibly contributors to onset of symptoms. While acute decline in the amount of available NE or 5-HT has not been observed to induce a depressive episode in healthy individuals, it has been associated with MDD symptoms returning in remitted patients (Hamon & Blier, 2013; Cowen & Browning, 2015). Thus, NE dysregulation alone may not be sufficient to cause depression.

Glutamate & Gamma-Aminobutyric Acid in Depression

Within the brain, glutamate is the major excitatory neurotransmitter, while gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter. Glutamate plays a significant role in neural plasticity, which is the ability of neural tissues to change and organize (Pitsillou et al., 2019). Neuroplasticity can function to strengthen brain circuits at the bases of depressive symptom behavior, but it can also be used to reorganize them (Albert, 2019). Severity of MDD symptoms has also been directly correlated with plasma glutamate (Mitani et al., 2006). As for GABA, it is also implicated in a variety of functions, particularly related to stress, and has been found to be reduced in cortical neural tissue of MDD patients (Duman et al., 2019). Both glutamate and GABA can have

a myriad of deleterious effects to patient wellbeing, if not in the proper concentration in the appropriate area (Zhou & Danbolt, 2014).

The N-methyl-D-aspartate (NMDA) receptor is a key glutamate receptor that GABA is known to regulate. This receptor plays a large role in glutamate's ability to affect memory formation and neuroplasticity. Though, GABA itself is also affected by glutamate and NMDA interactions (Kantamneni, 2015). Although new agents utilizing NMDA receptors in-part show rapid efficacy as antidepressants, current research is now shifting away from the NMDA hypothesis as a sole biological basis behind depression, as NMDA-specific antagonists have not been effective in symptom reduction alone (Duman et al., 2019; Newport, et al., 2015).

New Direction in Depression Research

Although MAO inhibitors and SSRIs have been involved in depression treatment for much of the century, they have not shown success in many MDD patients. Patients with TRD may have tried various MAO inhibitors, SSRIs, and other treatment options without symptom alleviation (Schmitt et al., 2016). One newer direction in depression research involves another compound directly involved in neuroplasticity: brain-derived neurotrophic factor (BDNF). It is regulated by multiple factors, including by 5-HT, among others. BDNF is concentrated in different parts of the brain, including in the amygdala, prefrontal cortex, and hippocampus (Schmitt et al., 2016). These areas are particularly important in emotional regulation, memory formation and storage, and sleep, and further BDNF is key in plasticity in neuronal health and helping individuals to adapt to varied situations (Schmitt et al., 2016; Sen et al., 2008). BDNF is now also being

considered as a marker for mood and antidepressant response. In Sen et al., it was found that BDNF levels are markedly low in patients suffering from MDD, and then increased after treatment with antidepressants (2008). Though, to consider possible other mechanisms, BDNF has also been found to be decreased in many other conditions, including other psychiatric conditions (Sen et al., 2008). This may allude to a possible common pathophysiology, meaning it may not be a sole factor. Regardless, BDNF appears to be a crucial player in depression, as BDNF infusions in two established depression rat models directly led to a rapid antidepressant response (Shirayama et al., 2002).

C. Ketamine as an Antidepressant

Ketamine is currently a promising new treatment for depression, as it associated with a rapid reduction in suicidal thought and alleviation of overall depression (Serafini et al., 2014). Although ketamine has been used as an anesthetic for decades, its mechanism of action as an antidepressant is still under study (Serafini et al., 2014).

There are two enantiomers of ketamine: R-ketamine and S-ketamine. Both have been examined for the treatment of depression, with R-ketamine showing greater potency as an antidepressant. Infusions include a racemic mixture (Yang et al., 2015). From the monoaminergic perspective, R-ketamine has been found to have a dose-dependent release relationship with 5-HT in the prefrontal cortex (Ago et al., 2019). Though, when a 5-HT depletion study was completed in conjunction with R-ketamine in a mouse model, the antidepressant effects are not significantly changed (Zhang et al., 2018). This suggests

that, although 5-HT may be related to the antidepressant effects of ketamine, it is not the sole factor.

As for the GABAergic and glutamatergic involvement in the mechanism of action of ketamine, there are several different postulations due to the complicated nature of these neurotransmitters. The principal theory is the disinhibition hypothesis – subanesthetic doses of ketamine block the normally tonically-active NMDA receptors on GABA interneurons, which regulate glutamate release (Duman, 2018; Kohtala, 2021). The antagonization of these receptors removes the inhibition, thus causing a release of glutamate, and allowing excitation to occur (Duman, 2018). This may lead to several downstream processes that may result in the alleviation of depression, particularly through increasing the available amount of BDNF. There are a few theories as to how this may occur, including through ketamine interacting with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors directly or upstream, or via increasing BDNF translation from direct NMDA interaction on the postsynaptic neuron (Kohtala, 2021). It is also possible that multiple of these interactions are occurring, allowing for further increase in BDNF (Duman, 2018). Evidence has shown that BDNF has a clear role in ketamine as a fast-acting antidepressant in a BDNF-knockout mouse model, as antidepressant effects were not observed as compared to BDNF-normal controls (Autry et al., 2011). Further studies of BDNF signaling function downstream have also been completed in mouse models, and shown importance in the relief of depression symptoms (Fukuda et al., 2016; Hasegawa et al., 2019).

It is also possible that ketamine may function at several points in these mechanisms, possibly leading to longer-term buildup of other compounds or changes in the overall neurocircuitry. Many of these networks are also involved in sleep disturbance, supporting the proposed connection between ketamine and sleep (Kohtala, 2021).

D. Sleep Disorder in Depression

Sleep disturbance is reported in the majority of MDD patients, whether it be early, mid, or late insomnia, hypersomnia, or both (Geoffrey et al., 2018). Through polysomnography studies, it has been shown that MDD patients experience lessened slow-wave sleep and rapid-eye movement (REM) sleep, more discontinuous sleep, and increased sleep onset latency (Hein et al., 2017). These characteristics are also seen among those with primary insomnia, furthering the concept of a possible overlap or common disease pathway between the two (Hein et al., 2017). This brings forward ideas concerning one affecting the other.

For centuries, depression was canonically considered a cause of insomnia, though this relationship has been reconsidered in recent years. A possible bi-directional relationship has been the subject of study, though this has been difficult to study due to many antidepressants affecting sleep (Benca & Peterson, 2008; Riemann et al., 2019). Though, leveraging the fact that many antidepressants reduce REM sleep, studies have been able to show that the extent of REM suppression may serve as a predictor for better response to treatment (Riemann et al., 2019). Further, treatment of insomnia via cognitive behavioral therapy for insomnia (CBT-I) has been shown to reduce depressive symptoms in patients with insomnia and subclinical levels of depression (Riemann et al., 2019).

This clinically exhibits a connection between the two in terms of treatment - treatment of sleep disturbance may lead to better MDD outcomes.

While sleep may play a role in antidepressant response through several pathways, most studies in this area have focused on examining the role of BDNF. Mechanisms are not understood, but BDNF has been correlated with increased slow-wave activity, which is important in synaptic strength (Duncan et al., 2013). Additionally, MDD patients have been shown to display circadian abnormalities, with altered cortisol release, and consequently shifted circadian rhythm (Gold et al., 1986; Schmitt et al., 2016).

Interestingly, sleep deprivation has also shown promise in causing symptom abatement, possibly by leading to increases in serum BDNF and reduced depression severity scores (Giese et al., 2014). However, this alleviation has been shown to be short-lived. Upon patients returning to sleep, depression symptoms have been shown to reappear (Schmitt et al., 2016).

E. Ketamine, Sleep, & Depression

A few hypotheses have been proposed of how ketamine may affect sleep, and then depression. Ketamine may effect sleep via the previously mentioned mechanisms of BDNF, and also via circadian systems and shifted encoding systems. Consistently, in MDD or bipolar disorder patients receiving ketamine, those whose sleep behaviors improved were shown to have increased BDNF levels relative to those whose sleep did not significantly change (Wang et al., 2021). This finding suggests that ketamine may contribute to a direct shift of BDNF signaling, and that improved sleep may play a role in treatment.

For sleep more directly, ketamine has been found to directly impact circadian gene expression in a dose-dependent fashion (Bellet et al., 2011). These altered protein concentrations may contribute to altered sleep pressure dynamics, increased neuroplasticity, slow-wave activity, generally higher quality sleep, and shifted circadian rhythm (Bellet et al., 2011; Kohtala, 2021). These can also contribute to mood improvement, leading to a reduction in depressive symptoms (Kohtala, 2021).

Rantamäki and Kohtala proposed the hypothesis of encoding, consolidation, and renormalization in depression (ENCORE-D), which combines these different theories of plasticity into one model (2020). It is thought that depression networks are shifted from regular neurocircuitry, leading to the varied symptoms. With ketamine treatment, there may be an opportunity to change these circuits via changing how information is encoded into the brain. This may further allow a return to a non-depressive network, and alleviation of MDD symptoms (Rantamaki & Kohtala, 2020).

Putting these findings together, ketamine has demonstrated a robust antidepressant response and an effect on MDD patients' sleep. Nonetheless, the connection is not yet mechanistically well-elucidated. Most studies on the effectiveness of ketamine have examined depressive symptoms together and have not focused on single items. However, depressive symptoms do not occur in a vacuum - each symptom may play a role in another symptom. Thus, it is essential to better understand the interrelated nature of these symptoms in relation to ketamine treatment.

F. Network Approach to Ketamine Treatment in MDD

Traditional latent model theory asserts that one underlying factor affects a variety of other factors, but network theory introduces the concept that symptoms are dynamically affecting each other to form a psychological condition. Moreover, network theory hypothesizes the existence of symptoms that are more central and exert the greatest impact upon the rest of the network. Theoretically, treatments targeting more central symptoms may have the highest effect on disrupting existing depression networks (Castro et al., 2019).

By using the network approach in the context of ketamine treatment, one can characterize the correlative nature of depression symptoms and ascertain which symptoms may be most affected by ketamine treatment and their possible shift after receiving treatment (Castro et al., 2019).

SPECIFIC AIMS

Recent research has underscored the rapid-acting role of ketamine in depression treatment, while looking at the reduction of depressive symptoms together or each symptom independently. There is a dearth of literature related to how each symptom relates to another in the treatment context, and this study aimed to better characterize these relationships over the course of acute ketamine treatment, with focus on the relationship between ketamine and sleep symptoms.

By leveraging a network approach, we sought to analyze which symptoms may play a more crucial role in the networks. Given the relationship between depression and sleep disturbance, we hypothesized that sleep-related elements would form highly central nodes in both the pre-treatment and post-treatment networks. Further, we also hypothesized that the post-treatment network would exhibit a varied network structure due to the posited targeting of ketamine on sleep processes.

METHODS

A. Participant Selection

Participants included patients receiving intravenous and/or intranasal ketamine treatment at the Massachusetts General Hospital Ketamine Clinic between October 2018 and April 2021. Each patient was diagnosed with depression by a psychiatrist according to the DSM-IV and must have attempted at least two other antidepressant medications without relief. Exclusionary criteria included active substance use disorder, past or current psychosis, or any other major medical illness that may interfere or contraindicate ketamine treatment. Each patient must have received six doses of ketamine and completed the QIDS-SR-16 questionnaire before their first and sixth treatment. For additional details about the study procedure, please refer to Sakurai, et al. (2020).

B. Administration of Ketamine

Patients were overseen by a psychiatrist, anesthesiologist, and a nurse. Patients were either given intravenous ketamine or intranasal racemic ketamine. For the intravenous ketamine, all patients had a first visit ketamine dosage of 0.5 mg/kg administered over 40 minutes, though further administration's dosages were adjusted by the staff psychiatrist according to patient response. This dose may have been adjusted up to 1.2 mg/kg, still administered over 40 minutes. For the intranasal ketamine, patients had a first visit ketamine dosage of 50 mg with adjustment up to 200 mg according to patient response. All patients were given ketamine twice a week over three weeks, for a total of

six treatments (Sakurai et al., 2020). Other medications were not changed over the course of ketamine treatment.

During administration, blood pressure, nausea, and anxiety/dissociative symptoms were monitored by the staff and treated intravenously. Any clinically significant increases in blood pressure were treated with labetalol (beta-blocker). Nausea was treated with either or both ondansetron (antiemitic) and prochlorperazine (antiemitic with sedative properties), while anxiety and dissociative side-effects were treated with 1mg of lorazepam (sedative) (Sakurai et al., 2020).

C. Administration of QIDS-SR-16

The QIDS-SR-16 questionnaire was administered to patients prior to receiving every ketamine treatment in order to evaluate patient depressive symptoms. For this study, the QIDS-SR-16 data from prior to the first ketamine infusion is considered pre-treatment data and QIDS-SR-16 data from prior to the sixth ketamine infusion is considered post-treatment data. The QIDS-SR-16 is considered a valid self-report measure of depression and includes 16 questions inquiring about their state during the previous seven days (Lamoureux et al., 2010). Each question is valued 0 to 3, with 3 reflecting the highest severity. As mentioned, the first four questions of the QIDS-SR-16 inquire about sleep quality: falling asleep, sleep continuity in the night, early rising, and hypersomnia. Further questions inquire about sadness, concentration, self-esteem, suicidal ideation, motivation, energy level, and psychomotor slowing and agitation.

Additionally, the survey includes two sets of questions relating to appetite (decreased or increased) and weight (over two weeks; decreased or increased). These questions were discarded from the final model, as is reviewed in the Discussion.

D. Method of Analysis

A network approach was employed to investigate the interrelated nature between the various depression symptoms prior and at the end of acute ketamine treatment. The method for this analysis was described in more detail by Curtiss et al. (2018; 2021).

The R package *qgraph* was used to estimate the networks using partial correlations between the depression symptoms (i.e. the nodes) as measured by the QIDS-SR-16. Each item of the QIDS-16 was assigned a node in the network, apart from the appetite and weight paired questions. These four questions were removed from the final analysis due to their highly-correlated nature leading to a non-positive-definite matrix, and the current methodology for use of compound questions is beyond the scope of this study. All of the nodes' correlations were found using *cor_auto*, which provided polychoric correlation matrices. The correlations exhibited the relationship between two nodes while removing any effects from other nodes.

The relationships were then represented by undirected lines (i.e. edges) that were created using *pcor*. The partial correlation network allows visualization of the correlations, any collinearity, or mediator variables. They may also allow for exploration of causative relationships, if no variables are considered latent. Additionally, these partial correlation networks may allow one to discern a latent variable (Epskamp et al., 2017). The partial correlation networks are displayed, and then the graphical LASSO (glasso)

method was also completed to limit the amount of possible spurious relationships and allow for deeper analysis. The glasso algorithm was used with the polychoric correlation matrix in combination with an Extended Bayesian Information Criterion (EBIC) parameter gamma (Epskamp et al., 2017). The gamma value is often between 0 and 0.5 with a higher value signifying a more strict network, with less allowance for explorative relationships. A gamma value of 0.25 was selected for this study, due to it providing a middle-ground between allowing more spurious edges at 0 and possibly losing relationships at 0.5 (Hevey et al., 2018). The Goldbricker algorithm, as present in the R package *networktools*, was also applied to check for collinearity and be aware of redundant nodes (Curtiss et al., 2018).

Centrality indices are often thought to produce targetable elements of the network, with most central nodes being considered the most key to the network (van Borkulo et al., 2017). Strength centrality is the total of the edge weights summed, without regard for direction of correlation, while expected influence (EI) takes into account direction of correlation (or whether a node may reduce activation across the network, or vice versa). EI is considered a better measure when negative edges are present in a network, as described by Robinaugh et al. (2016). One-step EI (EI-1) indicates the node's role with respect to its adjacent neighbors (directly connected), while two-step EI (EI-2) provides information concerning the node's role in the broader network by accounting for the node's second-step connectivity (Robinaugh et al., 2016).

Additionally, the *NetworkComparisonTest* package was run in order to have a more quantitative assessment of the differences across the networks before and after

treatment. The network invariance test was run to see the overall edge differences, while the global strength test was completed to see the density or level of connectivity. Also from this package, the edge invariance test was completed to investigate the specific changes between edges. The network comparison test has not been validated for use with polychoric correlations, so this analysis must be considered with caution (van Borkulo et al., 2017).

Finally, network stability was examined via a bootstrapping permutation test from the package *bootnet*. where the correlation stability is found through repeated removal of cases. The stability of the network is designated by a stability coefficient (CS), which is defined as the maximum proportion of cases that can be removed while maintaining a 0.7 centrality with at least 95% of samples (Epskamp et al., 2017). The CS ranges between 0 and 1, with 0.25 indicating acceptable stability and 0.5 signifying moderate stability. This acts as a form of determining the replicability of the data to see significance and interpret as a true difference (Epskamp et al., 2017).

RESULTS

A. Participant Description

Table 1 displays the demographic data for the 97 study participants analyzed. The average age of patients was 43.79 years (SD = 17.71), with a range of 17 to 79 years. A larger percentage of women (56%) than men (44%) were analyzed for the study, and the majority of participants identified as White (92%).

Characteristic	Patients, 97 total
Mean age in years ± SD (range)	43.79 ± 17.71 (17-79)
Female sex (% of total) Male sex (% of total)	54 (56%) 43 (44%)
White (%) White - Hispanic (%) Asian (%) Other (%)	89 (92%) 3 (3%)* 3 (3%) 2 (2%)

Table 1. Participant Characteristics. The baseline demographic characteristics are described, including the average age, percentage of each sex, and ethnicity. *Note*. SD= Standard Deviation. Sex was recorded, but not gender identity. *Note*. Hispanic identity status provided by 54 out of total 97 patients.

B. Network Approach

Raw correlations were computed for both pre-treatment and post-treatment QIDS-SR-16 data groups (see Table 2 and Table 3). Most items were positively correlated, but there were a few negative correlations throughout both sets, which are further discussed through network structure.

Pre-Treatment Network

The pre-treatment networks are presented in Figure 1 and Figure 2, with the latter being glasso-regularized. The most central nodes to the networks were sadness and concentration, with EI-1 values of 1.95 and 1.03 and EI-2 values of 2.21 and 2.03, each respectively (see Figure 3). Both nodes showed the highest level of influence on their immediate adjacent nodes and their second-step nodes. As observed in the networks, sadness exhibited a strong association with thoughts of death/suicide, general interest, and energy level. Concentration was most notably associated with self-esteem, restlessness, and psychomotor slowing.

As for the sleep disturbance questions, their centrality within the network varied. Sleep during the night had an EI-1 of 1.03, the third highest EI-1, but also had an EI-2 of 0.56, the second lowest. This indicates that sleep continuity has relatively strong adjacent node connectivity, but a reduced overall role in the network. The node also displayed a strong positive relationship with early rising, which alone had an EI-1 of 0.03, the second lowest, and an EI-2 of 1.72, which was the fifth highest EI-2. Early rising additionally showed the strongest negative relationship with hypersomnia. Over-sleeping had the lowest EI-1 and EI-2 values of -0.09 and 0.41 respectively, and a moderately strong,

positive relationship with energy level. Lastly, falling asleep had an EI-1 of 0.68 and an EI-2 of 0.94, the third lowest, and only demonstrated moderate relationships with concentration and restlessness. Apart from sleep continuity in EI-1, the sleep-related questions generally had low EI values relative to the other elements and showed relationships with each other in terms of centrality. The overall influence of the sleep items appears to be low, with their interrelationships leading to increased immediate neighbor influence. As observed in the network, the sleep questions (apart from falling asleep) form a cluster with varied correlations, while the rest of the network appears diffuse.

	s.1	*s.2*	*s.3*	*s.4*	*sad*	*con*	*slf*	*si*	*int*	*eng*	*slw*
s.1											
s.2	0.202										
s.3	0.230	0.504***									
s.4	-0.162	-0.295*	-0.532***								
sad	0.230	-0.032	0.457**	-0.036							
con	0.362**	0.257*	0.284*	-0.160	0.407***						
slf	0.273*	-0.023	0.164	0.010	0.517***	0.490***					
si	0.228	0.090	0.094	0.040	0.638***	0.314*	0.282*				
int	0.263*	-0.063	0.159	0.032	0.615***	0.308**	0.359**	0.376**			
eng	0.195	-0.198	0.006	0.346**	0.544***	0.396***	0.384**	0.299**	0.469***		
slw	0.224	0.143	0.130	0.056	0.392**	0.458***	0.397**	0.316**	0.349**	0.454***	
rst	0.367**	0.229	0.289*	-0.010	0.304*	0.477***	0.279*	0.246*	0.092	0.176	0.202

Table 2. Pre-Treatment Correlations. The pre-treatment QIDS-SR-16 interitem correlations are shown with varied significance levels. *Note*. s.1 = falling asleep; s.2 = sleep continuity through the night; s.3 = early rising; s.4= over-sleeping; sad = sadness; con = concentration; slf = self-esteem; si = suicidal thought; int = motivation/interest levels; eng = energy; slw = psychomotor slowing; rst = psychomotor restlessness. $p < 0.05$ * ; $p < 0.01$ ** ; $p < 0.001$ *** .

	s.1	*s.2*	*s.3*	*s.4*	*sad*	*con*	*slf*	*si*	*int*	*eng*	*slw*
s.1											
s.2	0.406**										
s.3	0.215	0.471***									
s.4	0.035	-0.330*	-0.324**								
sad	0.304**	0.140	0.301*	0.059							
con	0.126	0.094	0.212	-0.135	0.448***						
slf	0.278*	0.085	0.244	0.093	0.690***	0.525***					
si	0.254*	0.183	0.141	0.117	0.722***	0.461***	0.517***				
int	0.284**	0.099	0.240	0.260*	0.528***	0.519***	0.440***	0.464***			
eng	0.236*	0.045	0.252	0.296*	0.558***	0.625***	0.461***	0.471***	0.815***		
slw	0.148	0.232	0.424***	-0.286*	0.542***	0.726***	0.456***	0.482***	0.425***	0.592***	
rst	0.323**	0.330*	0.497***	-0.163	0.345**	0.324*	0.299*	0.340*	0.258*	0.270*	0.298*

Table 3. Post-Treatment Correlations. The post-treatment QIDS-SR-16 interitem correlations are shown with varied significance levels. *Note*. s.1 = falling asleep; s.2 = sleep continuity through the night; s.3 = early rising; s.4= over-sleeping; sad = sadness; con = concentration; slf = self-esteem; si = suicidal thought; int = motivation/interest levels; eng = energy; slw = psychomotor slowing; rst = psychomotor restlessness. $p < 0.05$ * ; $p < 0.01$ ** ; $p < 0.001$ *** .

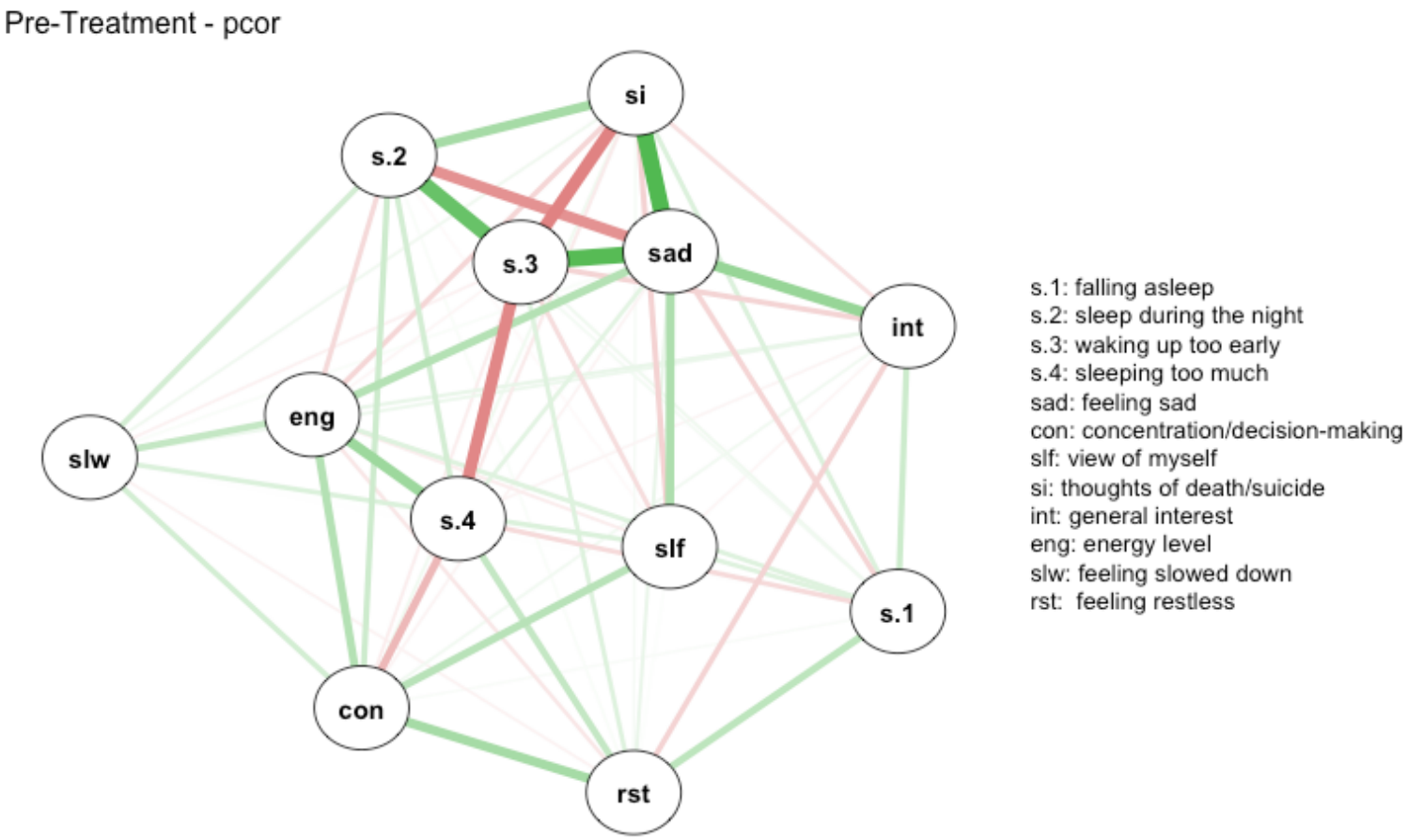

Figure 1. Pre-treatment Network with Partial Correlations. The nodes are shown in circles, with the edges indicated by the lines connecting the nodes. The green edges indicate a positive correlation, while the red edges show a negative correlation. The thickness of each line represents the magnitude of the correlation.

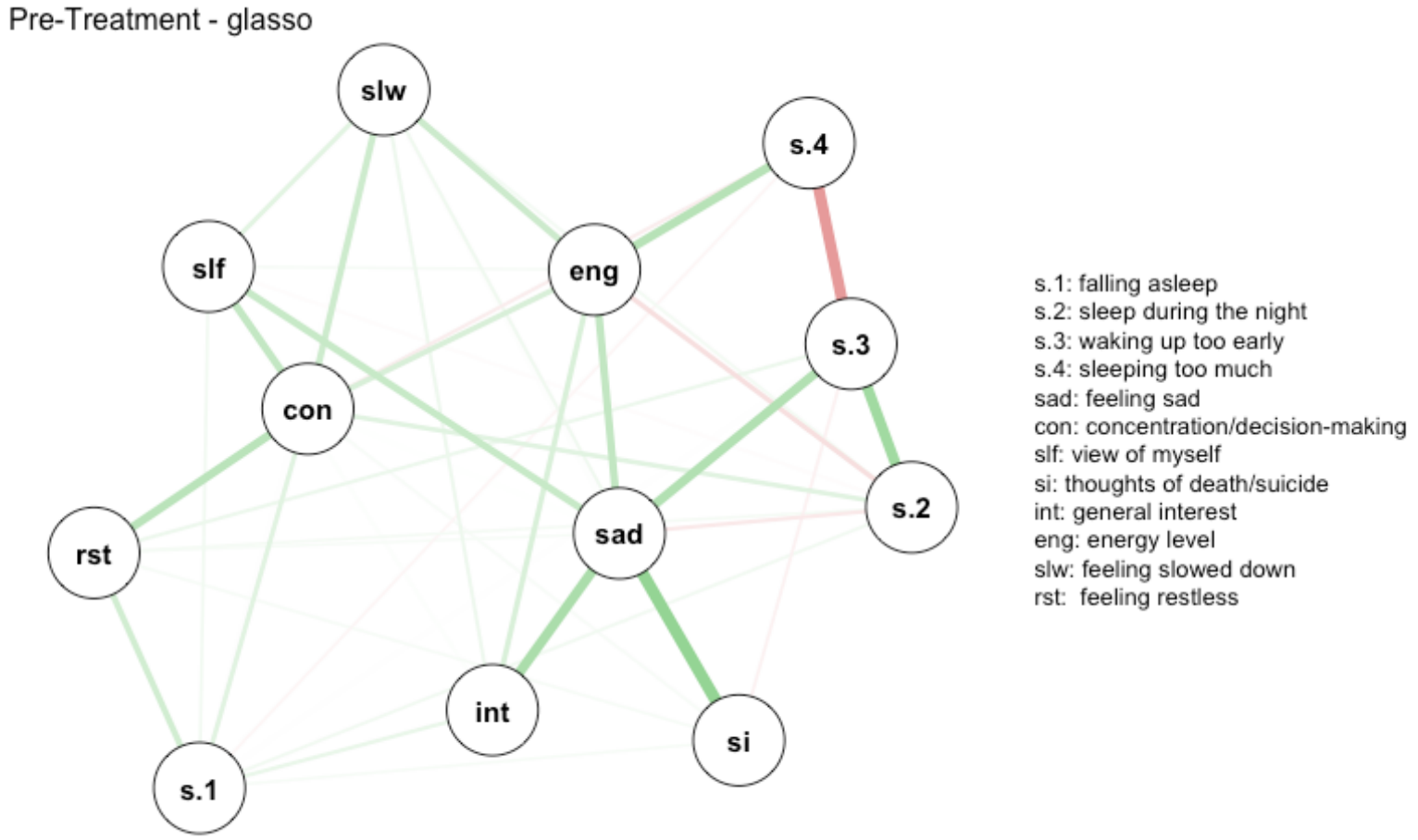

Figure 2. Pre-treatment Network with Glasso Regularization. The nodes are shown in circles, with the edges indicated by the lines connecting the nodes. The green edges indicate a positive correlation, while the red edges show a negative correlation. The thickness of each line represents the magnitude of the correlation.

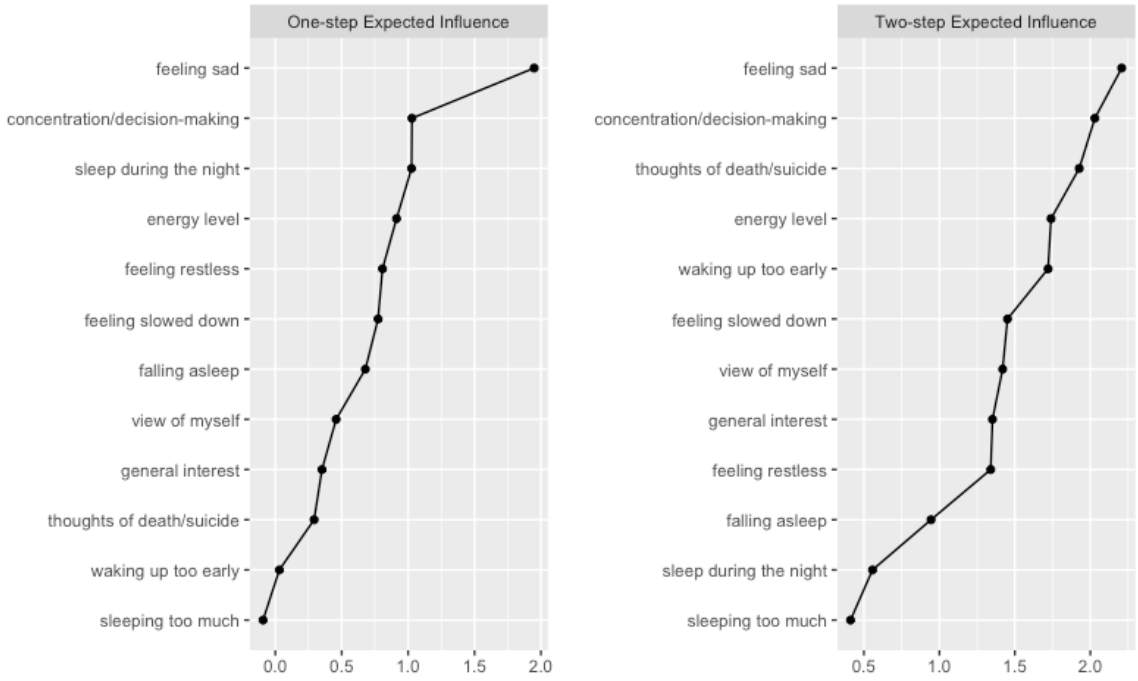

Figure 3. Pre-treatment Expected Influence Values. The 1-step expected influence and 2-step expected influence values are graphed as raw scores for the pre-treatment partial correlation network.

Post-Treatment Network

The post-treatment networks are presented in Figure 4 and Figure 5. With visual inspection, there appear to be clusters of symptoms formed between interest and energy level, psychomotor slowing and concentration, and view of self, suicidal thought, and sadness. Within the post-treatment network, the most central node was energy level in terms of immediate centrality, with an EI-1 of 1.74 (see Figure 6). The node also evidenced the second highest EI-2, with a value of 2.40, and the strongest association in the post-treatment network with level of interest. Thoughts of death formed the second most central node in the network and showed the strongest connectivity to sadness (the second strongest relationship in the network) and view of myself. The EI-1 for thoughts of death was 1.08, and the EI-2 was 1.57, which was fifth-highest relative to the other nodes. Both nodes exhibited high centrality in the network and independent relationships from each other.

Sleep questions again did not form the most central nodes in the network. All sleep items were in the bottom half of EI-1 values, with sleeping too much having the lowest value in both EI-1 and EI-2 (-0.29 and 0.27, respectively). The EI-2 data placed the other sleep disturbance questions as the three lowest questions in terms of connectivity. This suggested that sleep played a relatively small role with the other elements in the network, both with neighboring nodes and with broader connectivity.

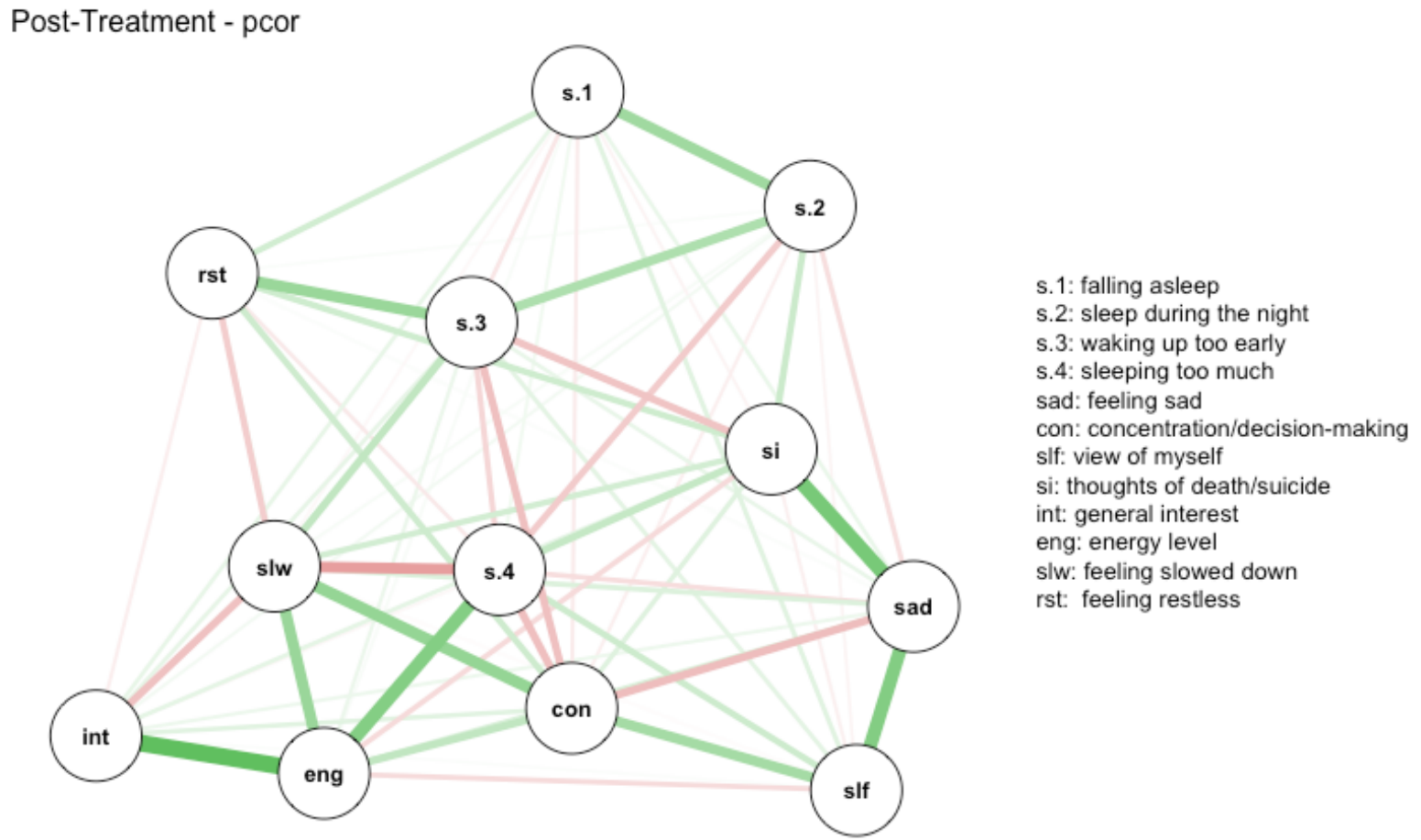

Figure 4. Post-treatment Network with Partial Correlations. The nodes are shown in circles, with the edges indicated by the lines connecting the nodes. The green edges indicate a positive correlation, while the red edges show a negative correlation. The thickness of each line represents the magnitude of the correlation.

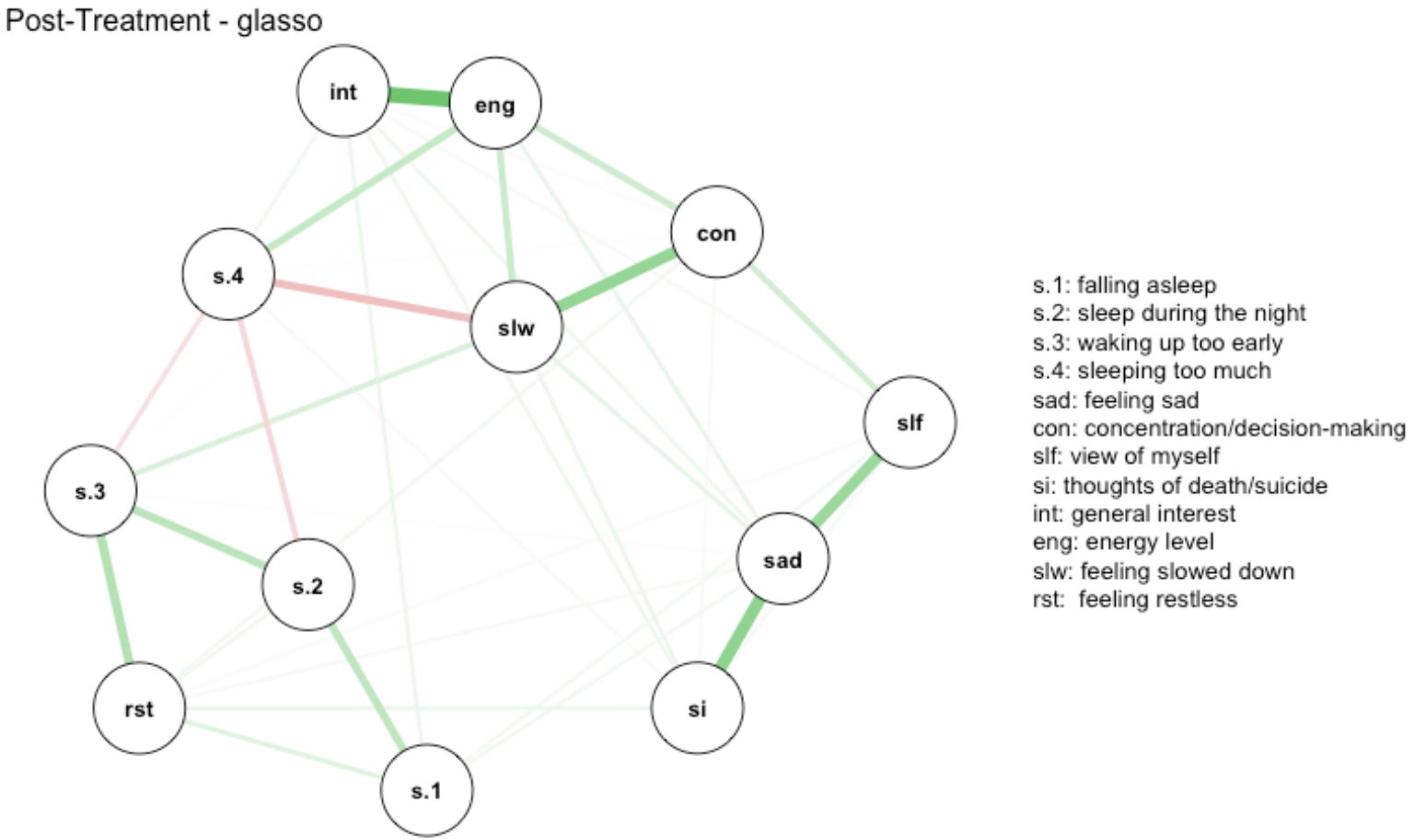

Figure 5. Post-treatment Network with Glasso Regularization. The nodes are shown in circles, with the edges indicated by the lines connecting the nodes. The green edges indicate a positive correlation, while the red edges show a negative correlation. The thickness of each line represents the magnitude of the correlation.

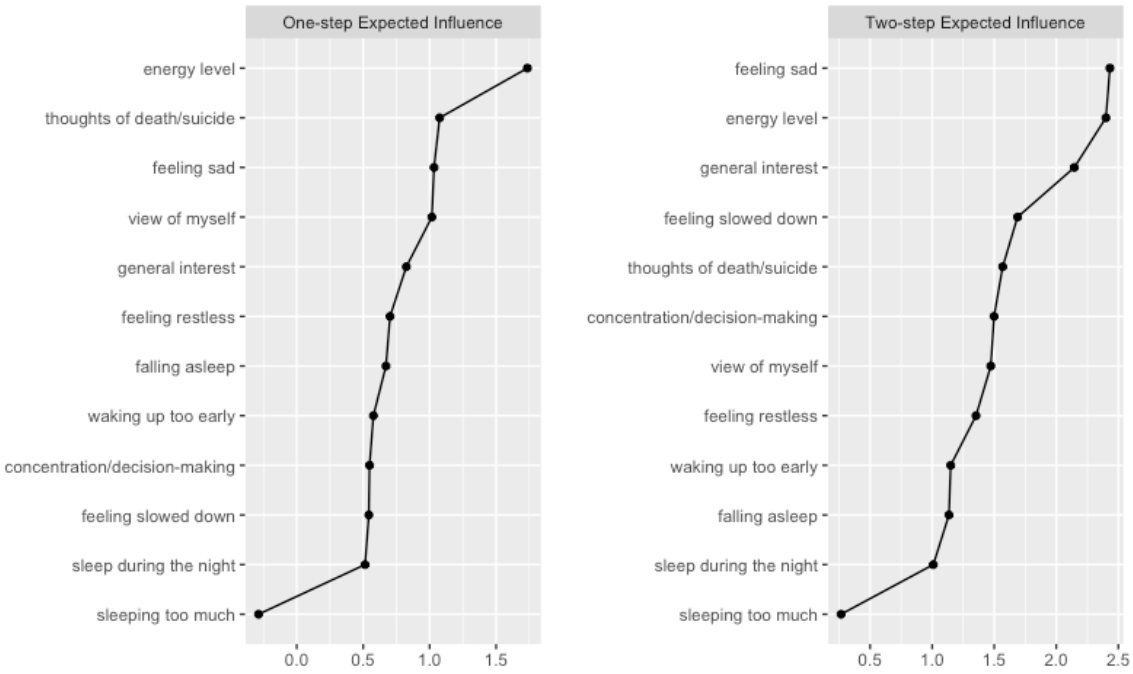

Figure 6. Post-treatment Expected Influence Values. The 1-step expected influence and 2-step expected influence values are graphed as raw scores for the post-treatment partial correlation network.

Network Comparison

The network comparison test was first completed to compare the overall differences in structure between the networks. The network invariance test examined the null hypothesis of all edges being equal, and it returned that the networks were significantly different ($p = .03$). This suggests that the pre-treatment network structure was overall changed from the post-treatment network in edge connections. The level of connectivity was then examined by the global strength invariance test. The null hypothesis was retained, meaning no overall differences in network density were exhibited ($p = .12$).

Each edge was then specifically analyzed to see any significant alteration in connectivity in the pre-treatment versus the post-treatment networks. Results indicated a noteworthy change in the edge between general interest and energy level ($p < 0.01$). The edges were relatively weakly correlated in the pre-treatment network, but became the strongest association in the post-treatment network. The other substantial variations in edge strength were related to the sleep items. The edge between waking up too early and feeling slowed down significantly shifted ($p = .04$). In the pre-treatment network, the two showed a small, insignificant correlation, but that shifted with the post-treatment network where a moderate positive correlation emerged. The relationship between feeling slowed down also considerably changed with over-sleeping ($p < 0.01$). The pre-treatment network revealed a weak, insignificant correlation, while the post-treatment network showed a moderate negative correlation. Lastly, results also exhibited a meaningful shift in the edge between early rising and restlessness ($p = .01$). Both networks displayed a

noteworthy positive correlation, though the relationship appears to have grown stronger in the post-treatment network.

Network Stability

Each network's stability was then examined with case removal. In the pre-treatment network stability analysis, the edge stability was determined to be acceptable (CS (cor = 0.7) = 0.36), while the strength centrality stability evidenced poor stability (CS (cor = 0.7) = 0.20). The pre-treatment network correlation stabilities for edge and strength centralities are graphically represented in Figure 7 and Figure 8, respectively. In the post-treatment stability analysis, the edge stability was also acceptable (CS (cor = 0.7) = 0.44), which was increased from the pre-treatment network. The strength centrality stability indicated weak stability (CS (cor = 0.7) = 0.13). These are displayed graphically in Figure 9 and Figure 10. The edge stability analyses show some level of stability, but the strength centrality revealed instability and less significance.

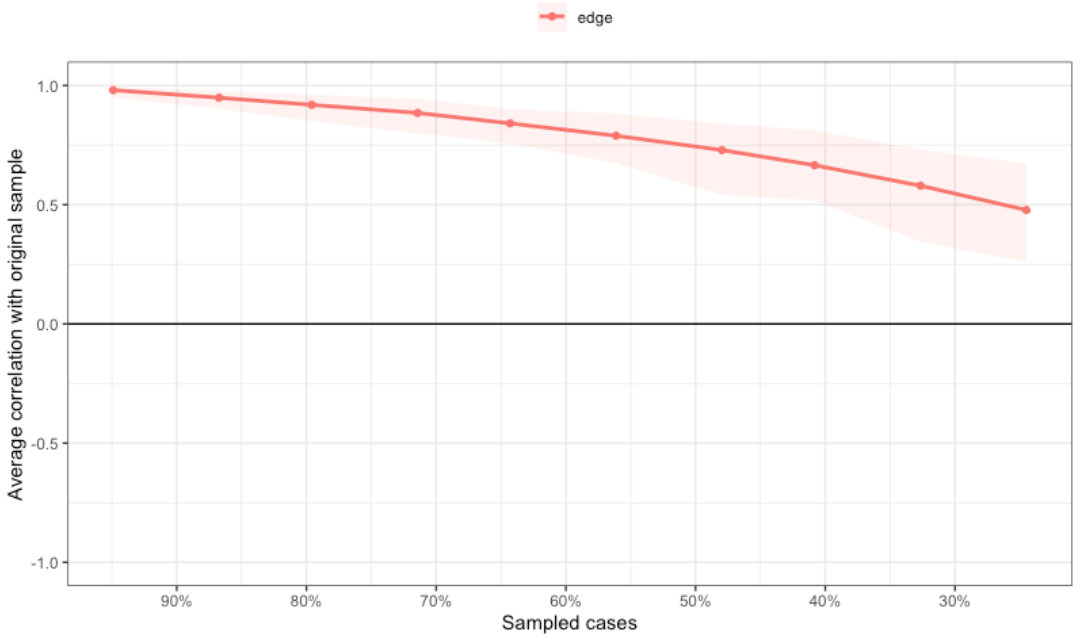

Figure 7. Pre-Treatment Bootstrap Edge Stability Analysis. Case-removal bootstrapping was completed to determine the stability of the pre-treatment pcor network. With the removal of more cases from the sample, the average correlation diminished. The red shading indicates the confidence level.

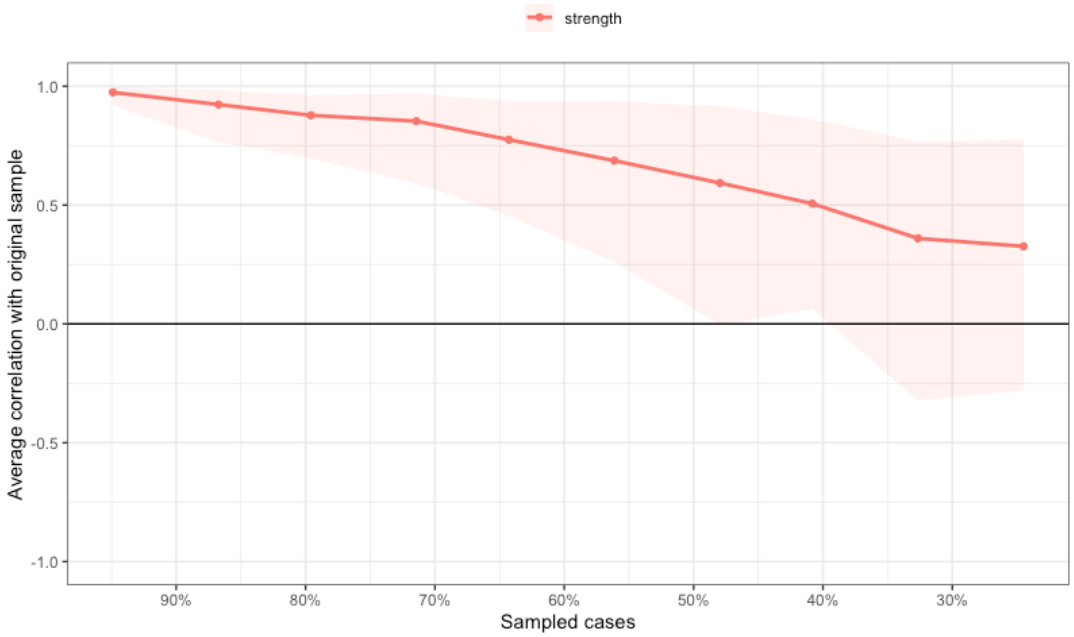

Figure 8. Pre-Treatment Bootstrap Strength Centrality Stability Analysis. Case-removal bootstrapping was completed to determine the stability of the pre-treatment pcor network. With the removal of more cases from the sample, the average correlation diminished. The red shading indicates the confidence level.

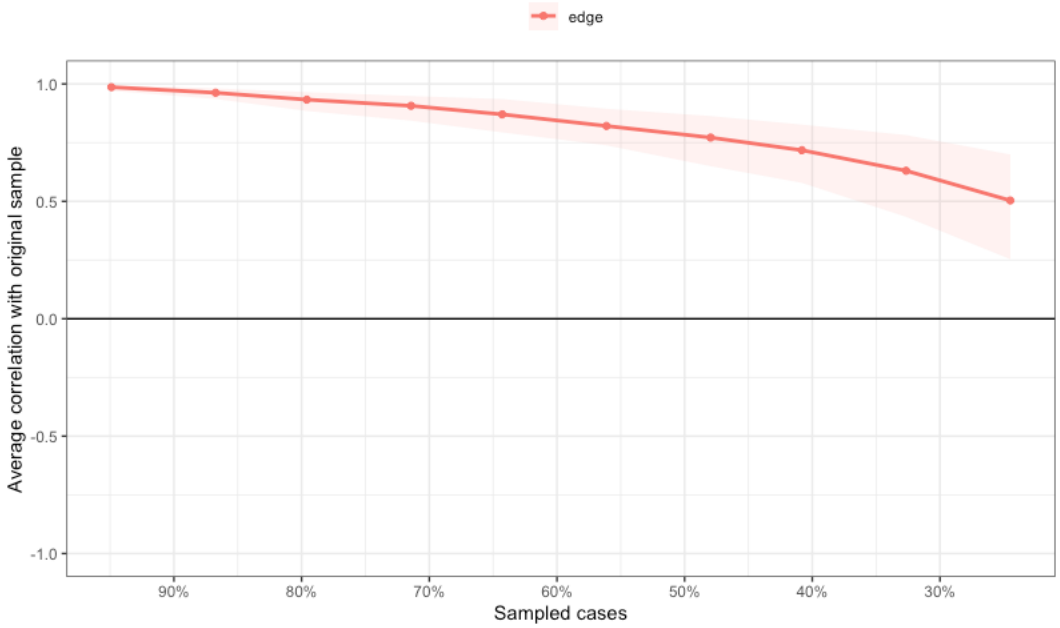

Figure 9. Post-Treatment Bootstrap Edge Stability Analysis. Case-removal bootstrapping was completed to determine the stability of the pre-treatment pcor network. With the removal of more cases from the sample, the average correlation diminished. The red shading indicates the confidence level.

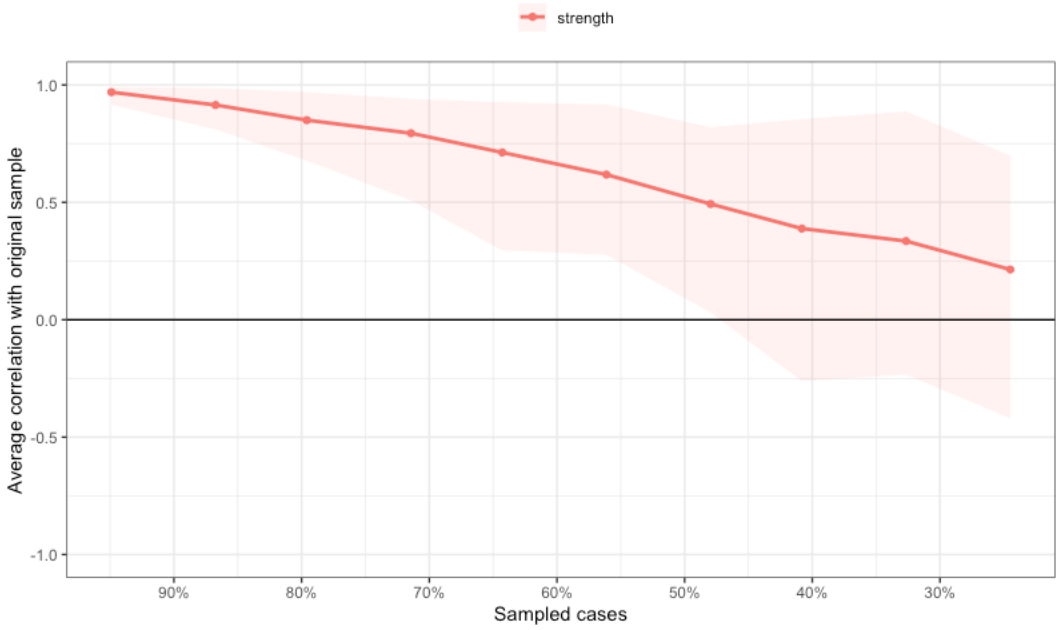

Figure 10. Post-Treatment Bootstrap Strength Centrality Stability Analysis. Case-removal bootstrapping was completed to determine the stability of the pre-treatment pcor network. With the removal of more cases from the sample, the average correlation diminished. The red shading indicates the confidence level.

DISCUSSION

In this study, we performed a network analysis in the context of acute ketamine treatment for depression, specifically analyzing the relationship between different symptoms of depression before and after acute ketamine treatment. Our major findings were related to global network structure; the interrelationships between depression symptoms changed before and after treatment. This suggests that ketamine may not equally impact each symptom, or at least disrupts the symptom associations present prior to treatment, and establishes new connections after treatment. Some of these connections found to be altered were related to sleep, which aligns with our initial hypothesis: there may be a link between sleep, depression, and ketamine. We then more specifically examined correlations between symptoms looking for changes in the network.

Findings in the context of existing literature

General interest and energy level were weakly correlated prior to ketamine treatment but became significantly correlated in the post-treatment network. This is in line with the study by Saligan, Luckenbaugh, Slonena, et al. where ketamine exhibited a strong anti-fatigue effect in bipolar depression (2016). This was demonstrated after controlling for other depressive symptoms, suggesting that ketamine may impact fatigue symptoms more directly. With that, patients may feel a transformation in energy, and further mental energy, possibly leading to changes in interest levels. It is also possible that other energy level was more influenced by other factors prior to treatment, but, with the alleviation of those factors through treatment, the association between energy and

interest levels became clearer. Visually, one can see sadness playing a part between interest and energy level in the pre-treatment network, but its relationship has nearly disappeared in the post-treatment network. This may be due to motivation differences – pre-treatment, sadness played a role in one's energy, while post-treatment, the association was more related to whether patients had energy to engage in activities. Conversely, ketamine may directly impact interest-related symptoms more straightforwardly, producing a renewed sense of energy.

Other elements found to have a different relationship before and after treatment were related to sleep. On visual inspection, the pre-treatment network seems to display a moderate clustering of the sleep items, but that grouping's correlations seem weaker in the post-treatment network. This is compatible with the existing literature, as Fried, Epskamp, Nesse, et al. also observed a cluster of sleep symptoms across depressed outpatients (2016). This is also consistent with our hypothesis that ketamine treatment may affect a patient's sleep symptoms. As shown in Figure 11, restlessness appears to be more positively correlated with waking up too early, which is also more positively associated with feeling slowed down, which itself is negatively correlated with over-sleeping. Sleep may alleviate psychomotor slowing, with restlessness being additionally explained by high energy levels preventing sleep. Yet, it is perplexing that energy was not observed to be largely correlated across the sleep items. Another variable may be consistently impacting the sleep items in both networks. Further, one may be able to consider fatigue in relation to psychomotor slowing. As mentioned, ketamine is associated with anti-fatigue effects, which may also be represented in the model via

psychomotor slowing (Saligan et al., 2016). However, if we associate psychomotor slowing with fatigue, one must consider energy level as well. We would expect a consistent strong correlation between psychomotor slowing and energy level, which was not observed. This speaks to the need for specific definitions/questionnaires, or more qualitative assessment in order to further understand each symptom.

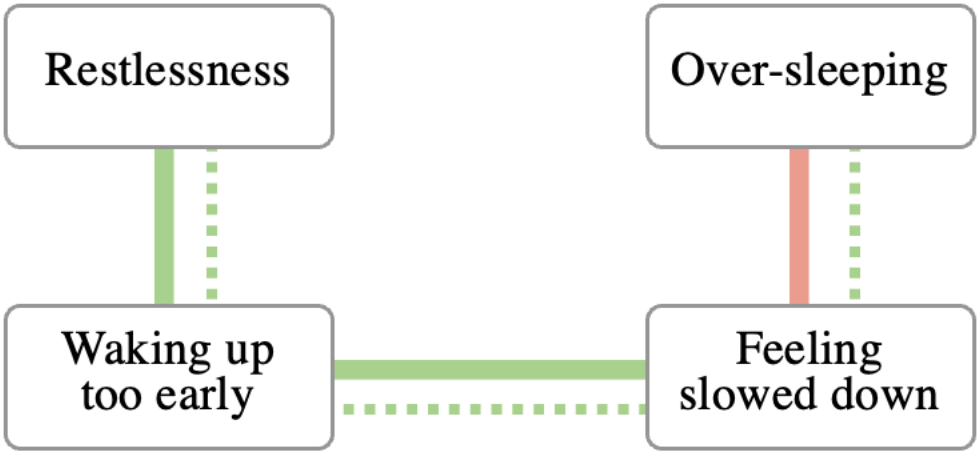

Figure 11. Sleep Symptom Relationship Changes Between Networks. Pre-treatment network edges are represented with the dashed lines, while the post-treatment network edges are shown in solid lines. Green lines indicate a positive correlation and red lines indicate a negative correlation. Thickness of lines is not proportional to correlation. We can see that, in the post-treatment network, feeling slowed down becomes negatively correlated with over-sleeping.

Although the networks showed alteration in the mentioned edges, the measures of network density did not show a meaningful difference. The level of connectivity was not appreciably altered between the two networks, which could indicate that the network connectivity was similar. However, as pointed out in van Borkulo et al., it is also possible that there was a considerable change in which symptoms became relevant in the post-treatment condition (2017). The latter may lead to an insignificant global strength test if

half of the edges were non-zero in one network, but became zero (or nearly) in the second network, with the opposite occurrence across the other half of edges (van Borkulo et al., 2017). This may provide a varied network without an overall density difference. Curiously, our findings conflicted with another psychiatric network analysis by Beard, Millner, and Forgeard et al., where depression symptom correlations increased over the course of inpatient treatment for personality, anxiety, mood, and other psychotic disorders (2016). However, the patient sample had a wider set of diagnoses and were undergoing a larger variety of treatments.

Strengths & Limitations

To our knowledge, this is the first study to assess changes in the structure of the correlation network between depression symptoms over the course of ketamine treatment. Nonetheless, particular limitations merit discussion.

First, we could not analyze centrality metrics due to low stability during the bootstrapping process. Stability issues are often seen within network analyses due to low power, particularly in situations with low sample size relative to the number of nodes, as is likely in our analysis. With an increase in sample size or reduced numbers of parameters, one may be able to make more substantial determinations. Additionally, if the edge weights are truly similar, the bootstrap network approach may not be able to appropriately adjust. The ranking of the nodes' centrality will appear to change with each sampling permutation, leading to lower network stability (Epskamp & Fried, 2018).

A common approach in network analysis in the literature is to calculate centrality metrics with the goal of identifying the most central symptom, in the hope that targeting

those symptoms can better improve overall patient well-being. Although this thinking predominated network analysis literature, this approach has recently been called into question. In Spiller, Levi, and Neria et al., two complementary analyses yielded apparently conflicting results: expected influence was the only centrality metric that successfully predicted variation in overall network structure, but that was not observed with node-dropping analyses (2020). That diminishes the long-standing hypothesis of centrality as a clinically relevant tool. Additionally, a node that is found to be highly central may inadvertently be indicative of the study selection criteria. For example, inpatient inclusion for depression studies may directly lead to thoughts of suicide being a more central node, as that may have been hospital admission criteria. Centrality may also not be as important if the symptom itself is an outcome measure. As another example, if the appetite and weight questions were retained, one's appetite being increased and having reduced energy levels may directly lead to weight gain, meaning it would become an outcome measure. Thus, targeting weight gain as a symptom would not alleviate the network in a direct manner, regardless of its high centrality.

Along the same thread, pathological relationships may differ specifically across patients with depression. As discussed, the clinical presentation of depression is often heterogeneous – some patients may experience some symptoms but not others, and that may or may not change with treatment. Patients may also have varied concurrent medications and comorbid conditions, which were both not recorded in our preliminary study, so we cannot assess whether ketamine may have varied antidepressant effect with

other drugs. These sources of variance in the sample can make more in-depth interpretation challenging.

In addition, the sample included all patients who completed the six-ketamine treatment protocol with a QIDS-SR-16 for each infusion, though a patient's treatment response to ketamine was not incorporated. Those who did not experience alleviation of depression symptoms were included alongside those who did, which may skew the results when understanding ketamine as an antidepressant. Not all antidepressants will work for all types of depression or all patients, and separation of non-responders, possibly by QIDS-SR-16 total reduction or change scores, may lead to different network outcomes. Comparison of depression symptom networks between non-responders and responders may also reveal predictor elements.

Due to the timing of each QIDS-SR-16 administration, network differences may have not been as pronounced. Ketamine's effects are short-lived, and the questionnaires were provided to each patient prior to each treatment (Sakurai, et al. 2020). The pre-treatment condition was prior to any ketamine administration, but the post-treatment network was derived from the QIDS-SR-16 administered prior to the sixth ketamine treatment and may be more alike to the pre-treatment network due to patient's symptoms returning. If post-treatment questionnaires were, instead, dispensed the day after the sixth ketamine treatment, the revealed network may be more accurate to the antidepressant effects of ketamine.

Lastly, the COVID-19 pandemic may have played a role across our study, with the date range of collected data encompassing both pre-pandemic and pandemic-onset

time periods. The COVID-19 pandemic may have created a varied subset of symptoms than patients otherwise may not have had, which may have skewed patients towards particular symptoms. Without controlling for the pandemic, it becomes difficult to generalize the ketamine treatment data when depression may have become more heterogenous (Santomauro et al., 2021).

Next Steps

Future work should address these limitations by having more specific selection criteria to be able to make more certain assertions. In part, to remedy this situation, development of the Diagnostic and Statistical Manual of Mental Disorders (DSM; i.e. the accepted classification criteria for psychiatric conditions) to a greater extent to include more subtypes of depression may be helpful. Expanding on that, the QIDS-SR-16 also included weight and appetite elements, which were discarded for the present study for their opposing nature in correlations. Though, in Fried, Epskamp, and Nesse et al., strong correlations were seen between sleep symptoms and weight/appetite elements, which formed a separate cluster (2016). With further consideration of the network method applied in that study, it may be revealing to apply that method to this population to more profoundly explore sleep and appetite across the ketamine treatment variable. Additionally, if sleep were to be more profoundly investigated, integration of chronotypes (i.e. one's natural sleep behaviors in relation to time of day) into sleep metrics may further elucidate the role of circadian rhythm in depression and mood, specifically through ketamine treatment.

CONCLUSION

The study sought to explore network structure in patients undergoing ketamine treatment for clinical depression, in order to understand if sleep disturbance symptoms were more significant to the network, and if the relationships between symptoms were changed. Our results could not speak to individual significance of symptoms to each network, but the data suggested that the interactions between the symptoms are changed. More analysis is necessary to understand symptom clustering. These insights may contribute to further understanding ketamine response predictors in depression.

REFERENCES

Ago, Y., Tanabe, W., Higuchi, M., Tsukada, S., Tanaka, T., Yamaguchi, T., Igarashi, H., Yokoyama, R., Seiriki, K., Kasai, A., Nakazawa, T., Nakagawa, S., Hashimoto, K., & Hashimoto, H. (2019). (R)-Ketamine Induces a Greater Increase in Prefrontal 5-HT Release Than (S)-Ketamine and Ketamine Metabolites via an AMPA Receptor-Independent Mechanism. *The International Journal of Neuropsychopharmacology*, *22*(10), 665–674. https://doi.org/10.1093/ijnp/pyz041

Albert, P. R. (2019). Adult neuroplasticity: A new "cure" for major depression? *Journal of Psychiatry & Neuroscience : JPN*, *44*(3), 147–150. https://doi.org/10.1503/jpn.190072

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.).https://doi.org/10.1176/appi.books.9780890425596

Autry, A. E., Adachi, M., Nosyreva, E., Na, E. S., Los, M. F., Cheng, P., Kavalali, E. T., & Monteggia, L. M. (2011). NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature*, *475*(7354), 91–95. https://doi.org/10.1038/nature10130

Beard, C., Millner, A. J., Forgeard, M. J. C., Fried, E. I., Hsu, K. J., Treadway, M., Leonard, C. V., Kertz, S., & Björgvinsson, T. (2016). Network Analysis of Depression and Anxiety Symptom Relations in a Psychiatric Sample. *Psychological Medicine*, *46*(16), 3359–3369. https://doi.org/10.1017/S0033291716002300

Bellet, M. M., Vawter, M. P., Bunney, B. G., Bunney, W. E., & Sassone-Corsi, P. (2011). Ketamine Influences CLOCK:BMAL1 Function Leading to Altered Circadian Gene Expression. *PLOS ONE*, *6*(8), e23982. https://doi.org/10.1371/journal.pone.0023982

Benca, R. M., & Peterson, M. J. (2008). Insomnia and depression. *Sleep Medicine*, *9*, S3–S9. https://doi.org/10.1016/S1389-9457(08)70010-8

Berger, M., Gray, J. A., & Roth, B. L. (2009). The Expanded Biology of Serotonin. *Annual Review of Medicine*, *60*, 355–366. https://doi.org/10.1146/annurev.med.60.042307.110802

Clark, L. A., Cuthbert, B., Lewis-Fernández, R., Narrow, W. E., & Reed, G. M. (2017). Three Approaches to Understanding and Classifying Mental Disorder: ICD-11, DSM-5, and the National Institute of Mental Health's Research Domain Criteria (RDoC). *Psychological Science in the Public Interest*, *18*(2), 72–145. https://doi.org/10.1177/1529100617727266

Cowen, P. J., & Browning, M. (2015). What has serotonin to do with depression? *World Psychiatry*, *14*(2), 158–160. https://doi.org/10.1002/wps.20229

Curtiss, J. E., Wallace, B., Fisher, L. B., Nyer, M., Jain, F., Cusin, C., & Pedrelli, P. (2021). Change processes in cognitive behavioral therapy and motivational interviewing for depression and heavy alcohol use: A network approach. *Journal of Affective Disorders Reports*, *3*, 100040. https://doi.org/10.1016/j.jadr.2020.100040

Curtiss, J., Ito, M., Takebayashi, Y., & Hofmann, S. G. (2018). Longitudinal Network Stability of the Functional Impairment of Anxiety and Depression. *Clinical Psychological Science*, *6*(3), 325–334. https://doi.org/10.1177/2167702617745640

Drevets, W. C., Bogers, W., & Raichle, M. E. (2002). Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *12*(6), 527–544. https://doi.org/10.1016/s0924-977x(02)00102-5

Duman, R. S. (2018). Ketamine and rapid-acting antidepressants: A new era in the battle against depression and suicide. *F1000Research*, *7*, F1000 Faculty Rev-659. https://doi.org/10.12688/f1000research.14344.1

Duman, R. S., Sanacora, G., & Krystal, J. H. (2019). Altered Connectivity in Depression: GABA and Glutamate Neurotransmitter Deficits and Reversal by Novel Treatments. *Neuron*, *102*(1), 75–90. https://doi.org/10.1016/j.neuron.2019.03.013

Duncan, W. C., Sarasso, S., Ferrarelli, F., Selter, J., Riedner, B. A., Hejazi, N. S., Yuan, P., Brutsche, N., Manji, H. K., Tononi, G., & Zarate, C. A. (2013). Concomitant BDNF and sleep slow wave changes indicate ketamine-induced plasticity in major depressive disorder. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, *16*(2), 301–311. https://doi.org/10.1017/S1461145712000545

Epskamp, S., & Fried, E. I. (2018). A tutorial on regularized partial correlation networks. *Psychological Methods*, *23*(4), 617–634. https://doi.org/10.1037/met0000167

Epskamp, S., Rhemtulla, M., & Borsboom, D. (2017). Generalized Network Psychometrics: Combining Network and Latent Variable Models. *Psychometrika*, *82*(4), 904–927. https://doi.org/10.1007/s11336-017-9557-x

Finberg, J. P. M., & Rabey, J. M. (2016). Inhibitors of MAO-A and MAO-B in Psychiatry and Neurology. *Frontiers in Pharmacology*, *7*. https://www.frontiersin.org/article/10.3389/fphar.2016.00340

Fried, E. I., Epskamp, S., Nesse, R. M., Tuerlinckx, F., & Borsboom, D. (2016). What are "good" depression symptoms? Comparing the centrality of DSM and non-DSM

symptoms of depression in a network analysis. *Journal of Affective Disorders*, *189*, 314–320. https://doi.org/10.1016/j.jad.2015.09.005

Fukuda, M., Takatori, A., Nakamura, Y., Suganami, A., Hoshino, T., Tamura, Y., & Nakagawara, A. (2016). Effects of novel small compounds targeting TrkB on neuronal cell survival and depression-like behavior. *Neurochemistry International*, *97*, 42–48. https://doi.org/10.1016/j.neuint.2016.04.017

GBD Results Tool | GHDx. (n.d.). Retrieved March 21, 2022, from https://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/d780dffbe8a381b25e1416884959e88b

Geoffroy, P. A., Hoertel, N., Etain, B., Bellivier, F., Delorme, R., Limosin, F., & Peyre, H. (2018). Insomnia and hypersomnia in major depressive episode: Prevalence, sociodemographic characteristics and psychiatric comorbidity in a population-based study. *Journal of Affective Disorders*, *226*, 132–141. https://doi.org/10.1016/j.jad.2017.09.032

Giese, M., Beck, J., Brand, S., Muheim, F., Hemmeter, U., Hatzinger, M., Holsboer-Trachsler, E., & Eckert, A. (2014). Fast BDNF serum level increase and diurnal BDNF oscillations are associated with therapeutic response after partial sleep deprivation. *Journal of Psychiatric Research*, *59*, 1–7. https://doi.org/10.1016/j.jpsychires.2014.09.005

Gold, P. W., Loriaux, D. L., Roy, A., Kling, M. A., Calabrese, J. R., Kellner, C. H., Nieman, L. K., Post, R. M., Pickar, D., & Gallucci, W. (1986). Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease. Pathophysiologic and diagnostic implications. *The New England Journal of Medicine*, *314*(21), 1329–1335. https://doi.org/10.1056/NEJM198605223142101

Hamon, M., & Blier, P. (2013). Monoamine neurocircuitry in depression and strategies for new treatments. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *45*, 54–63. https://doi.org/10.1016/j.pnpbp.2013.04.009

Hasegawa, Y., Zhu, X., & Kamiya, A. (n.d.). NV-5138 as a fast-acting antidepressant via direct activation of mTORC1 signaling. *The Journal of Clinical Investigation*, *129*(6), 2207–2209. https://doi.org/10.1172/JCI129702

Hein, M., Lanquart, J.-P., Loas, G., Hubain, P., & Linkowski, P. (2017). Similar polysomnographic pattern in primary insomnia and major depression with objective insomnia: A sign of common pathophysiology? *BMC Psychiatry*, *17*(1), 273. https://doi.org/10.1186/s12888-017-1438-4

Kantamneni, S. (2015). Cross-talk and regulation between glutamate and GABAB receptors. *Frontiers in Cellular Neuroscience*, *9*. https://www.frontiersin.org/article/10.3389/fncel.2015.00135

Klimek, V., Stockmeier, C., Overholser, J., Meltzer, H. Y., Kalka, S., Dilley, G., & Ordway, G. A. (1997). Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *17*(21), 8451–8458.

Kohtala, S. (2021). Ketamine—50 years in use: From anesthesia to rapid antidepressant effects and neurobiological mechanisms. *Pharmacological Reports*, *73*(2), 323–345. https://doi.org/10.1007/s43440-021-00232-4

Lamoureux, B. E., Linardatos, E., Fresco, D. M., Bartko, D., Logue, E., & Milo, L. (2010). Using the QIDS-SR16 to identify major depressive disorder in primary care medical patients. *Behavior Therapy*, *41*(3), 423–431. https://doi.org/10.1016/j.beth.2009.12.002

Meyer, J. H., Ginovart, N., Boovariwala, A., Sagrati, S., Hussey, D., Garcia, A., Young, T., Praschak-Rieder, N., Wilson, A. A., & Houle, S. (2006). Elevated monoamine oxidase a levels in the brain: An explanation for the monoamine imbalance of major depression. *Archives of General Psychiatry*, *63*(11), 1209–1216. https://doi.org/10.1001/archpsyc.63.11.1209

Mitani, H., Shirayama, Y., Yamada, T., Maeda, K., Ashby, C. R., & Kawahara, R. (2006). Correlation between plasma levels of glutamate, alanine and serine with severity of depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *30*(6), 1155–1158. https://doi.org/10.1016/j.pnpbp.2006.03.036

Moret, C., & Briley, M. (2011). The importance of norepinephrine in depression. *Neuropsychiatric Disease and Treatment*, *7*(Suppl 1), 9–13. https://doi.org/10.2147/NDT.S19619

Newport, D. J., Carpenter, L. L., McDonald, W. M., Potash, J. B., Tohen, M., Nemeroff, C. B., & APA Council of Research Task Force on Novel Biomarkers and Treatments. (2015). Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression. *The American Journal of Psychiatry*, *172*(10), 950–966. https://doi.org/10.1176/appi.ajp.2015.15040465

Pitsillou, E., Bresnehan, S. M., Kagarakis, E. A., Wijoyo, S. J., Liang, J., Hung, A., & Karagiannis, T. C. (2020). The cellular and molecular basis of major depressive disorder: Towards a unified model for understanding clinical depression. *Molecular Biology Reports*, *47*(1), 753–770. https://doi.org/10.1007/s11033-019-05129-3

Rantamäki, T., & Kohtala, S. (2020). Encoding, Consolidation, and Renormalization in Depression: Synaptic Homeostasis, Plasticity, and Sleep Integrate Rapid Antidepressant Effects. *Pharmacological Reviews*, *72*, 439–465. https://doi.org/10.1124/pr.119.018697

Riemann, D., Krone, L. B., Wulff, K., & Nissen, C. (2020). Sleep, insomnia, and depression. *Neuropsychopharmacology*, *45*(1), 74–89. https://doi.org/10.1038/s41386-019-0411-y

Robinaugh, D. J., Millner, A. J., & McNally, R. J. (2016). Identifying highly influential nodes in the complicated grief network. *Journal of Abnormal Psychology*, *125*(6), 747–757. https://doi.org/10.1037/abn0000181

Sakurai, H., Jain, F., Foster, S., Pedrelli, P., Mischoulon, D., Fava, M., & Cusin, C. (2020). Long-term outcome in outpatients with depression treated with acute and maintenance intravenous ketamine: A retrospective chart review. *Journal of Affective Disorders*, *276*, 660–666. https://doi.org/10.1016/j.jad.2020.07.089

Saligan, L. N., Luckenbaugh, D. A., Slonena, E. E., Machado-Vieira, R., & Zarate, C. A. (2016). An assessment of the anti-fatigue effects of ketamine from a double-blind, placebo-controlled, crossover study in bipolar disorder. *Journal of Affective Disorders*, *194*, 115–119. https://doi.org/10.1016/j.jad.2016.01.009

Santomauro, D. F., Herrera, A. M. M., Shadid, J., Zheng, P., Ashbaugh, C., Pigott, D. M., Abbafati, C., Adolph, C., Amlag, J. O., Aravkin, A. Y., Bang-Jensen, B. L., Bertolacci, G. J., Bloom, S. S., Castellano, R., Castro, E., Chakrabarti, S., Chattopadhyay, J., Cogen, R. M., Collins, J. K., … Ferrari, A. J. (2021). Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *The Lancet*, *398*(10312), 1700–1712. https://doi.org/10.1016/S0140-6736(21)02143-7

Schmitt, K., Holsboer-Trachsler, E., & Eckert, A. (2016). BDNF in sleep, insomnia, and sleep deprivation. *Annals of Medicine*, *48*(1–2), 42–51. https://doi.org/10.3109/07853890.2015.1131327

Searing, L. (2022, February 25). *Depression affects about 280 million people worldwide*. The Washington Post. Retrieved March 21, 2022, from https://www.washingtonpost.com/health/2022/02/27/depression-worldwide/

Sen, S., Duman, R., & Sanacora, G. (2008). Serum Brain-Derived Neurotrophic Factor, Depression, and Antidepressant Medications: Meta-Analyses and Implications. *Biological Psychiatry*, *64*(6), 527–532. https://doi.org/10.1016/j.biopsych.2008.05.005

Serafini, G., Howland, R. H., Rovedi, F., Girardi, P., & Amore, M. (2014). The role of ketamine in treatment-resistant depression: A systematic review. *Current Neuropharmacology*, *12*(5), 444–461. https://doi.org/10.2174/1570159X12666140619204251

Shirayama, Y., Chen, A. C.-H., Nakagawa, S., Russell, D. S., & Duman, R. S. (2002). Brain-Derived Neurotrophic Factor Produces Antidepressant Effects in Behavioral Models of Depression. *The Journal of Neuroscience*, *22*(8), 3251–3261. https://doi.org/10.1523/JNEUROSCI.22-08-03251.2002

Spiller, T. R., Levi, O., Neria, Y., Suarez-Jimenez, B., Bar-Haim, Y., & Lazarov, A. (2020). On the validity of the centrality hypothesis in cross-sectional between-subject networks of psychopathology. *BMC Medicine*, *18*(1), 297. https://doi.org/10.1186/s12916-020-01740-5

Substance Abuse and Mental Health Services Administration. (2016). *DSM-5 Changes: Implications for Child Serious Emotional Disturbance*. Substance Abuse and Mental Health Services Administration (US). http://www.ncbi.nlm.nih.gov/books/NBK519708/

Thase, M. E. (2012). The Role of Monoamine Oxidase Inhibitors in Depression Treatment Guidelines. *The Journal of Clinical Psychiatry*, *73*(suppl 1), 18690. https://doi.org/10.4088/JCP.11096su1c.02

Valdizán, E. M., Díez-Alarcia, R., González-Maeso, J., Pilar-Cuéllar, F., García-Sevilla, J. A., Meana, J. J., & Pazos, A. (2010). A_2-Adrenoceptor functionality in postmortem frontal cortex of depressed suicide victims. *Biological Psychiatry*, *68*(9), 869–872. https://doi.org/10.1016/j.biopsych.2010.07.023

van Borkulo, C., van Bork, R., Boschloo, L., Kossakowski, J., Tio, P., Schoevers, R., Borsboom, D., & Waldorp, L. (2017). *Comparing network structures on three aspects: A permutation test (pre-print version; published version available through link below)*.

Voineskos, D., Daskalakis, Z. J., & Blumberger, D. M. (2020). Management of Treatment-Resistant Depression: Challenges and Strategies . *Neuropsychiatric Disease and Treatment*, *16*, 221–234. https://doi.org/10.2147/NDT.S198774

Wang, M., Zhang, B., Zhou, Y., Wang, C., Zheng, W., Liu, W., Zhan, Y., Lan, X., & Ning, Y. (2021). Sleep improvement is associated with the antidepressant efficacy of repeated-dose ketamine and serum BDNF levels: A post-hoc analysis. *Pharmacological Reports: PR*, *73*(2), 594–603. https://doi.org/10.1007/s43440-020-00203-1

Yang, C., Shirayama, Y., Zhang, J. -c, Ren, Q., Yao, W., Ma, M., Dong, C., & Hashimoto, K. (2015). R-ketamine: A rapid-onset and sustained antidepressant without psychotomimetic side effects. *Translational Psychiatry*, *5*(9), e632–e632. https://doi.org/10.1038/tp.2015.136

Zhang, K., Dong, C., Fujita, Y., Fujita, A., & Hashimoto, K. (2018). 5-Hydroxytryptamine-Independent Antidepressant Actions of (R)-Ketamine in a Chronic Social Defeat Stress Model. *The International Journal of Neuropsychopharmacology*, *21*(2), 157–163. https://doi.org/10.1093/ijnp/pyx100

Zhou, Y., & Danbolt, N. C. (2014). Glutamate as a neurotransmitter in the healthy brain. *Journal of Neural Transmission*, *121*(8), 799–817. https://doi.org/10.1007/s00702-014-1180-8

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