NETWORK INTERVENTION ANALYSIS INDICATES THAT ROLUPERIDONE ACHIEVES ITS EFFECT ON NEGATIVE SYMPTOMS OF SCHIZOPHRENIA BY SUCCESSFULLY TARGETING AVOLITION

by

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(Under the Direction of GREGORY STRAUSS)

ABSTRACT

Roluperidone has proven efficacious for treating negative symptoms of schizophrenia in phase 2b and phase 3 clinical trials. Using network analysis, we demonstrated that the improvements observed in the phase 2b trial resulted from targeting avolition. The current study aims to replicate these network findings using the phase 3 data. Participants included 496 schizophrenia patients who were randomized to roluperidone 32 mg/day (n =167), 64 mg/day (n = 162), or placebo (n = 167). Negative symptoms were assessed at baseline and weeks 2,4,8, and 12. Network intervention analysis (NIA) evaluated treatment-induced symptom changes over time to identify treatment effects. NIA indicated that the 64 mg/day dose of roluperidone had a direct effect on avolition, suggesting changes in avolition propels treatment effects across the entire negative symptom constellation. These findings replicated the phase 2b findings, indicating roluperidone achieves its effect by influencing the extent to which avolition drives other negative symptoms.

INDEX WORDS: TREATMENT, AVOLITION, RANDOMIZED CLINICAL TRIAL, NETWORK ANALYSIS

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CHAPTER 1

INTRODUCTION

Negative symptoms are a significant predictor of psychosocial functioning and other clinical outcomes in individuals affected by schizophrenia (e.g., recovery, subjective well-being, illness liability) (Fervaha et al., 2014; Piskulic et al., 2012; Strauss et al., 2010, 2012). The notion of negative symptoms encompasses five domains (anhedonia, avolition, and asociality, blunted affect and alogia) (Strauss et al., 2019). The five domains represent independent negative symptoms factors with stability across languages and geographical regions (Ahmed et al., 2019).

Unfortunately, pharmacological treatments evaluated over the past 30 plus years have been largely ineffective and negative symptoms remain a critical unmet need in schizophrenia therapeutics (Fusar-Poli et al., 2015; Galderisi et al., 2018). Roluperidone, a 5-HT_{2A}, $sigma_2$, and α_{1A}-adrenergic receptor antagonist developed specifically to target negative symptoms, has shown efficacy in two very similar clinical trials (Davidson et al., 2017, 2022). Specifically, results from the phase 2b trial indicated that both 32 mg/day (Cohen's d = 0.45) and 64 mg/day (d = 0.57) doses of roluperidone significantly improved negative symptoms from baseline to 12-weeks compared to placebo (Davidson et al., 2017). The phase 3 study replicated these results for the 64 mg/day dose, which demonstrated significantly greater reductions in negative symptoms from baseline to 12 weeks compared to placebo (d = 0.26) (Davidson et al., 2022). In both trials, roluperidone also improved secondary outcomes (e.g., functioning) more so than placebo and was found to be safe and well-tolerated (Davidson et al., 2017, 2022). Furthermore,

in the open-label phase of the trials (6-months in phase 2b or 9-months in phase 3) few patients (<10%) discontinued the treatment due to worsening of psychosis (Rabinowitz et al 2023).

Despite replicated evidence for the efficacy of roluperidone in the treatment of negative symptoms, the path by which roluperidone affects negative symptoms is unclear. One approach to determining how a treatment produces its effects involves the use of network analysis (McNally, 2016, 2021). Classical medical approaches assume that a common pathophysiologic event (e.g. acute ischemia) is responsible for all or most symptomatic manifestations (pain, dyspnea, arrhythmia). Using this logic, when the event(s) underlying the disease pathophysiology are successfully treated, the symptoms underlying the disorder uniformly improve as a result. However, this is probably not the case for psychiatric disorders because these conditions do not have common underlying pathophysiology that cause their various symptoms (Borsboom, 2017). Rather than being effects of a common mechanistic cause, symptoms are thought to cause and maintain each other (i.e., the onset of one symptom engenders subsequent symptoms, which are maintained through continuous activation). Using this approach, constellations of symptoms and their interactions can be illustrated in a network structure where symptoms are represented as nodes, and the relationships between symptoms are represented as edges. However, all symptoms in a network do not necessarily relate to one another or exert equal impact on the overall disease severity (Borsboom, 2017). The degree to which symptoms in a network are interconnected is represented by network density. Networks with strong symptom connections (i.e., highly dense networks) are considered to be self-sustaining, in that the activation of one symptom in the network might lead to the activation of the other symptoms in that network. Research has produced mixed results about the impact of

macroscopic properties (i.e., network density) on treatment response, suggesting that successful treatment can either make symptom networks become more or less dense across time.

From this network approach, one would predict that the successful treatment of a highly "central" (i.e., widely connected) symptom in that network will lead to subsequent reductions in the severity of the other symptoms that have formed causal connections, especially in highly dense networks. Prior studies indicate that network analysis can identify the symptoms with highest "centrality" that may serve as the best treatment targets, as successfully treating the most central symptom(s) will produce global improvement (Hofmann et al., 2016). Understanding how drugs achieve their effects from a network perspective (e.g., whether they reduce global density of connections or impact a highly central symptom that produces cascading improvements on other symptoms) may be relevant for better targeting symptoms across different psychiatric and neurological diagnoses in future drug development.

To inform future drug development to treat negative symptoms of schizophrenia, Strauss et al. (2020) used a network analytic approach to understand how roluperidone achieved its global reduction on negative symptoms using data from the phase 2b trial. Findings indicated that roluperidone did not differ from placebo in its impact on macroscopic properties (e.g., density of the global connection among all negative symptom items). Rather, roluperidone appeared to achieve its effect by impacting the centrality of a single negative symptom domain, avolition (i.e., reductions in the desire for an engagement in goal-directed activities). These results suggest that motivational deficits alone may be the key target, implying that when motivational deficits are successfully treated, they lead to cascading improvements in the other symptom domains. This notion is consistent with the "avolition and Occam's razor" perspective proposed by Foussias and Remmington (2010), which suggested that blunted affect, alogia,

anhedonia, and asociality could be attributed to motivational deficits and the biological processes underlying them. Avolition may therefore be the "core" target in the treatment of negative symptoms (Strauss et al., 2021).

The Current Study

The aim of the current study was to determine whether the network analytic findings of the phase 2b roluperidone trial (Strauss et al., 2020) could be replicated using data from the phase 3 trial. Since efficacy was also demonstrated in the phase 3 trial (Davidson et al., 2022), it was hypothesized that, from a network perspective, roluperidone would achieve its effect by changing the centrality of motivational symptoms. To test this hypothesis, a novel analytic approach termed "network intervention analysis" (NIA) was used. This method was specifically developed to determine the sequential development and order of treatment-induced effects throughout a clinical trial and to identify which effects are directly affected by treatment and which are indirectly affected (Blanken et al., 2019). The method also allows for an estimation of "predictability", which indicates the proportion of variance of a particular symptom that is explained by the other symptoms in the network at each timepoint in the trial. NIA also has the benefit of directly testing causal influence (Bernstein et al., 2023), which was not possible with the centrality measures used in our phase 2b study (Strauss et al., 2020). It was hypothesized that NIA would indicate a direct association (i.e., edge) between core avolition symptom items (PANSS N02, N04) and the treatment node in favor of roluperidone (i.e., a red edge). Support for this hypothesis would suggest that avolition is a key treatment target for improvement in the broader negative symptom constellation.

CHAPTER 2

METHOD

Participants

Analyses included 496 individuals diagnosed with schizophrenia who were recruited from 60 sites in 8 European countries, Israel, and the United States. Participants were recruited from outpatient clinics, psychiatric hospitals, and supervised residential facilities. DSM-5 diagnosis of schizophrenia was confirmed with the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). All patients were symptomatically stable by history and were rated as having moderate to severe negative symptoms for more than six months as expressed by a score of >20 on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) negative symptoms subscale score.

Procedures

Participants deemed eligible for the trial had any psychotropic medications discontinued for at least two days prior to randomization and throughout their study participation. Participants were randomized to roluperidone 32 mg/day, roluperidone 64 mg/day, or placebo in a 1:1:1 ratio No psychotropic medications were allowed during the duration of study participation, except for medications necessary for insomnia or agitation.

Participants were evaluated at baseline and weeks 2, 4, 8, and 12 with the PANSS. The primary outcome was the Marder negative symptom factor: N01: Blunted affect, N02: Emotional withdrawal, N03: Poor rapport, N04: Passive/apathetic social withdrawal, N06: Lack of spontaneity and flow of conversation, G07: Motor retardation, and G16: Active social avoidance

(Marder et al., 1997). Although part of the Marder negative symptom factor, the G16 item was excluded from analyses due to concerns about construct validity. PANSS items that represent avolition are N02: Emotional withdrawal and N04: Passive/apathetic social withdrawal (Strauss et al., 2021). See Davidson et al., 2022 for detailed description of the trial.

Data Analysis

In the current network analysis, nodes represent the PANSS negative symptom items identified above and a treatment allocation variable. Networks were constructed for each assessment timepoint (baseline, week 2, week 4, week 8, and week 12). PANSS negative symptom items were entered into the model as continuous variables, whereas the treatment allocation variable was treated as binary. For ease of interpretation, each roluperidone condition (32 mg/day and 64 mg/day) was compared to placebo in separate network models. The networks comparing 64 mg/day roluperidone to placebo are of particular interest in this study since 64 mg/day was the efficacious dose in the phase 3 trial (Davidson et al., 2022).

Mixed graphical models (MGMs) were computed for each time point using the R package mgm (Haslbeck & Waldorp, 2015). Edges in these models represent pairwise associations among symptoms and control for the effects of all other symptoms included in the model (Epskamp & Fried, 2018). Networks were estimated with all available data for the roluperidone 64 mg/day and placebo conditions at each visit, resulting in variations in sample size for different visits (Baseline N = 329; Week 2 N = 287; Week 4 N = 270; Week 8 N = 244; Week 12 N = 286). Aligning with recommendations, graphical LASSO regularization was performed to reduce spurious edges among nodes (Friedman et al., 2014). Cross-validation with 10 folds was used to select the tuning parameter for regularization. The thickness of the edge depicts the strength of the relationship between the two variables (i.e., thicker edge corresponds

to greater magnitude). Green edges represent positive associations, whereas red edges represent negative associations. Any edge between the treatment variable and another symptom depicts a treatment-specific effect. Red edges between the treatment node and the symptom nodes represent a treatment-specific effect in favor of roluperidone relative to placebo, such that roluperidone was associated with significantly greater reductions in that symptom. Green edges between the treatment node and the symptom nodes indicate a treatment-specific effect in favor of placebo relative to roluperidone, such that placebo was associated with greater reductions in that symptom. Importantly, edges between the treatment node and symptoms nodes only represent differential effects of the treatments, thereby if the two treatments impacted a symptom similarly, the effect is not represented in the network. Therefore, the absence of an edge between the treatment node and a symptom node indicates a lack of a differential treatment effect. For ease of interpretation, layout is similar across networks, so the proximity of nodes in the networks should not be overinterpreted. The relative size of the nodes, as well as the color of the nodes, depict significant differences between treatments in terms of changes in symptom severity from baseline. Larger blue nodes indicate that roluperidone treatment led to greater symptom improvement than placebo treatment. Smaller yellow nodes demonstrate that placebo treatment led to greater symptom improvement than roluperidone treatment. The proportion of the ring surrounding the node that is filled in represents the amount of variance of that symptom that was explained by the other symptoms in the network (i.e., predictability). Specifically, if the ring is completely empty, then the explained variance is 0%, while a completely filled in ring indicates 100% explained variance (Blanken et al., 2019).

In order to assess the accuracy of the edge weight estimates, the resample function from mgm was used, in which 100 bootstrapped samples for each network were conducted. The 5%

and 95% quantiles of the resulting sampling distribution of all the edges were then plotted. Notably, LASSO regularization biases sampling distributions toward zero, resulting in quantiles that may contain zero. Thus, it is recommended to avoid overinterpreting bootstrapped estimates (Blanken et al., 2019).

CHAPTER 3

RESULTS

As depicted in Figure 1, roluperidone did not exert significantly greater effect than placebo at baseline. A weak effect emerged at week 2, where roluperidone exerted a significant effect on N06: lack of spontaneity and flow of conversation (faint red line from treatment node to N06). Stronger effects emerged at weeks 4, 8, and 12 where an avolition item (N02: emotional withdrawal) produced a significantly stronger improvement than placebo (thick red line from treatment node to item N02). At week 8, there was also a significant effect of roluperidone on N04: passive/apathetic social withdrawal and N03: poor rapport, but these did not persist to week 12 like N02: emotional withdrawal. Placebo had greater effect than roluperidone on N01: blunted affect at week 4, N01: blunted affect and G07: motor retardation at week 8, and G07: motor retardation at week 12 (green lines from the treatment node to N01 and G07).

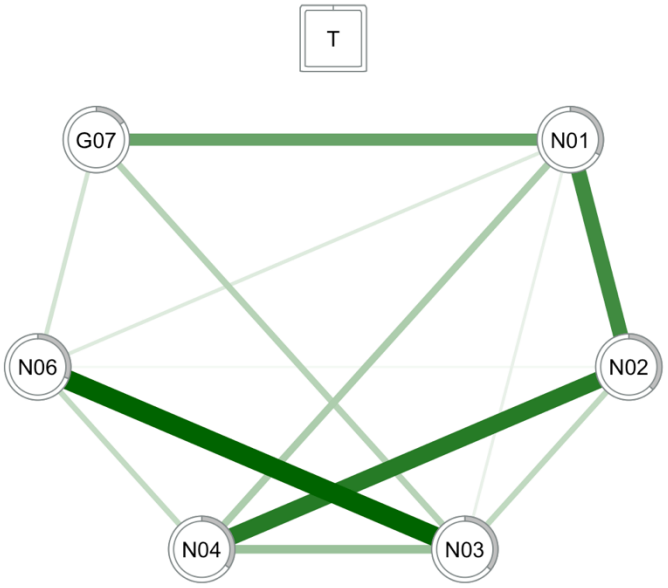
The change in each symptom's predictability (i.e., amount of variance explained by other symptoms) over time was calculated. On average, predictability gradually increased during treatment, from 31% at baseline to 51% at week 12. Each symptom's predictability estimates during treatment are depicted in Figure A5 in the appendix A.

Appendix A also present a plot of centrality estimates for each PANSS item across treatment weeks. Metrics indicate differences in the stability of symptom centrality estimates across time, in that some symptoms had consistent centrality estimates across time points, whereas other symptoms had dynamic centrality estimates over time. At baseline, poor rapport was found to be the most central symptom in the NIA network, but at week 12, emotional

withdrawal was the most central symptom. Notably, across time points, strength centrality estimates for emotional withdrawal increased across time. In the roluperidone-specific network centrality plot, poor rapport was found to be the most central symptom at baseline, but at week 12, passive/apathetic social withdrawal was the most central symptom. Regarding the placebo-specific network centrality plot, passive/apathetic social withdrawal was most central at baseline, whereas at week 12, emotional withdrawal was the most central.

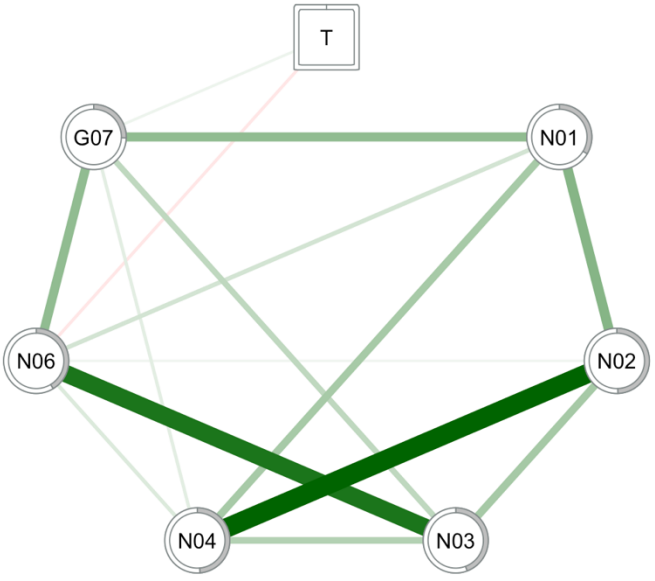
Figures displaying the 5% and 95% quantiles of the sampling distributions and the proportions of estimates with absolute values above zero are included in Appendix A Figures A8-A12. Given that LASSO regularization biases edge weight estimates towards zero, the bootstrapped samples estimates were adequate.

Baseline



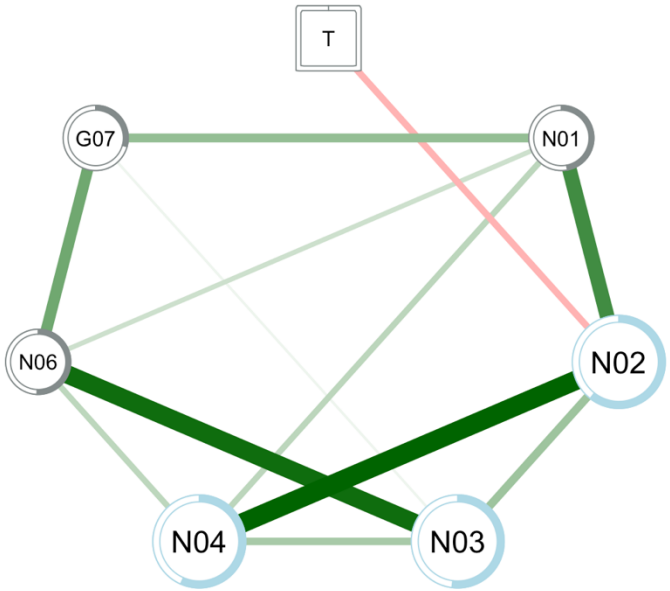
T: Treatment
N01: Blunted Affect
N02: Emotional Withdrawal
N03: Poor Rapport
N04: Passive Withdrawal
N06: No Spontaneity
G07: Motor Retardation

Week 2



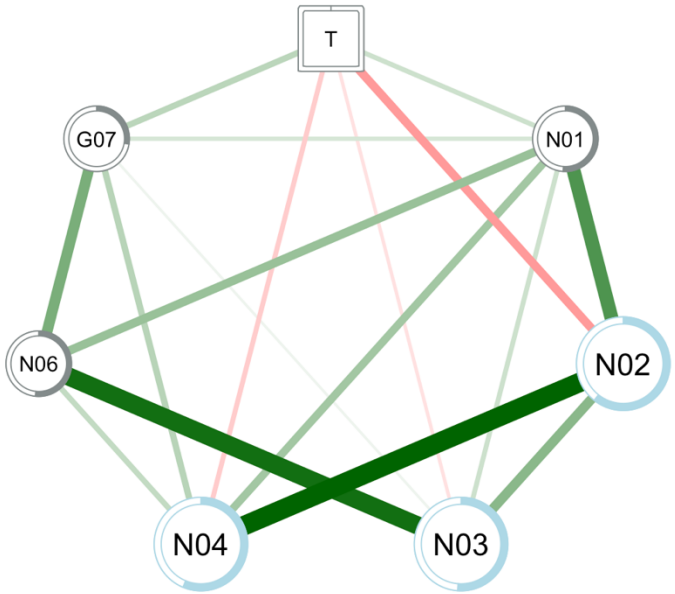
T: Treatment
N01: Blunted Affect
N02: Emotional Withdrawal
N03: Poor Rapport
N04: Passive Withdrawal
N06: No Spontaneity
G07: Motor Retardation

Week 4



T: Treatment
N01: Blunted Affect
N02: Emotional Withdrawal
N03: Poor Rapport
N04: Passive Withdrawal
N06: No Spontaneity
G07: Motor Retardation

Week 8



T: Treatment
N01: Blunted Affect
N02: Emotional Withdrawal
N03: Poor Rapport
N04: Passive Withdrawal
N06: No Spontaneity
G07: Motor Retardation

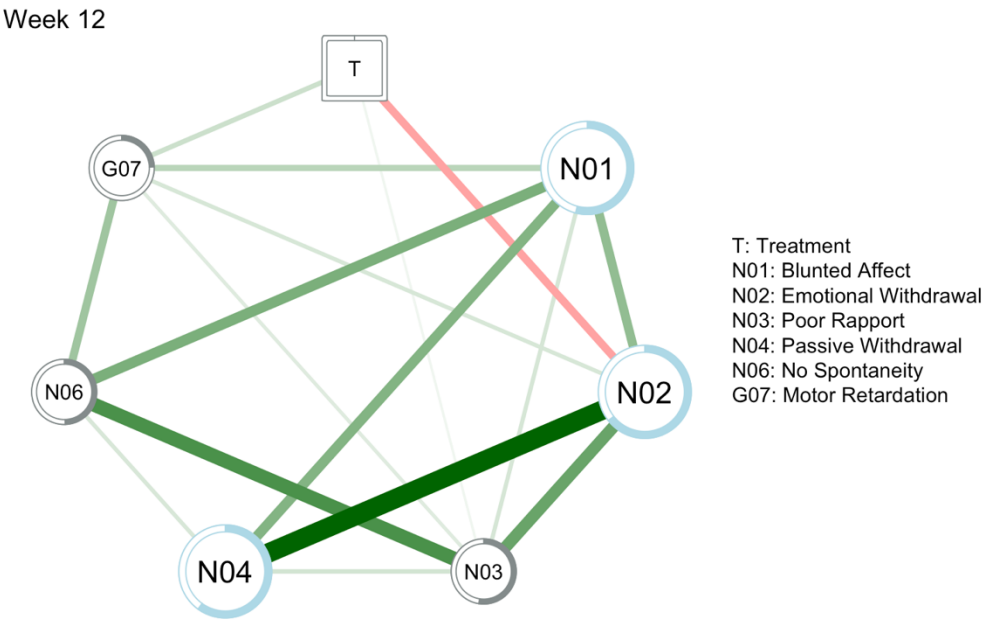


Figure 1. Network Intervention Analysis Effects for Roluperidone 64 mg/day Relative to Placebo

CHAPTER 4

DISCUSSION

The current study evaluated the nature of roluperidone effects on negative symptom by using NIA. Findings of the phase 3 trial indicate that roluperidone produced differential treatment effects on negative symptoms over time. Specifically, roluperidone exerted a consistent treatment effect on emotional withdrawal starting at week 4 that persisted at weeks 8 and 12. There was also an effect of roluperidone on passive/apathetic social withdrawal at week 8 that did not persist to week 12. The reduction in passive/apathetic social withdrawal severity for the roluperidone condition is indicative of an indirect treatment effect, in that the reduction was not directly caused by roluperidone (e.g., absence of an edge between the treatment allocation variable and passive/apathetic social withdrawal). Rather, it appears that the direct effects of roluperidone on emotional withdrawal permeated to other symptoms in the network (e.g., passive/apathetic social withdrawal) through symptom connections. This permeation of treatment effects through emotional withdrawal was also seen on other symptoms at other time points (i.e., poor rapport at weeks 4 and 8, blunted affect at week 12). Notably, the two symptoms without an association with emotional withdrawal, lack of spontaneity and flow of conversation and motor retardation, did not exhibit a significant difference between placebo and roluperidone in changes in severity from baseline. Thus, roluperidone's direct effect on emotional withdrawal and its indirect effects on other symptoms through emotional withdrawal suggests that the mechanism responsible for roluperidone's effectiveness in reducing negative symptom severity may be its direct effect on avolition.

NIA also indicated that the "predictability" of nodes in the network gradually increased over time and this effect was greater for roluperidone than placebo. This suggests that symptom networks become more "self-determined", in that symptoms have a larger influence on one another across time, particularly when successfully treated (Haslbeck & Waldorp, 2018). The increased connectivity between symptoms may enhance global treatment responsiveness. Given that emotional withdrawal also became more highly central within the symptom network across time, successfully augmenting avolition symptoms specifically may be critical for producing global improvement in negative symptoms with roluperidone. These findings are consistent with the "avolition and Occam's razor" theory proposed by Foussias and Remmington (2010), which suggests that avolition is at the heart of the negative symptom construct.

Collectively, these results closely mirror those found in the network analysis of the phase 2b trial by Strauss et al. (2020), in that both studies found that roluperidone exerted its effects through avolition. The consistency of these results across trials is noteworthy, especially considering the use of different negative symptom measures and different network analytic approaches in the studies. These robust findings suggest that roluperidone will likely yield significant improvements in negative symptom severity in a subgroup of individuals with schizophrenia and offer a viable pharmacological treatment option. Furthermore, through its reductions on negative symptom severity, roluperidone may yield significant improvements in other important clinical outcomes (e.g., quality of life, vocational and social functioning, prognosis) as suggested by the long-term results of the phase 3 study (Rabinowitz et al., 2023). Thus, it appears that roluperidone has the potential to greatly improve the lives of individuals diagnosed with schizophrenia, particularly those with significant negative symptoms.

Certain limitations should be considered. First, the PANSS was used to measure negative symptoms. Although a popular instrument that can detect change, the PANSS negative symptom items have some content validity concerns given that its items do not map seamlessly onto current conceptualizations of the 5 NIMH consensus domains (Blanchard et al., 2011). These concerns add challenges to comparisons with the phase 2b network findings (Strauss et al., 2020) that used a 2nd generation rating scale, the Brief Negative Symptom Scale (BNSS: Kirkpatrick et al., 2011), which measures the constructs according to current conceptualizations. Despite its limited scope, the Marder PANSS negative symptom items can be represented in the popular two-factor structure (Khan et al., 2017) that influences even the five factors suggested by current conceptualizations (Ahmed et al., 2022). It is therefore reasonable that its avolition items mimic the influence of the BNSS avolition items in the phase 2b findings. Second, due to the use of LASSO regularization, small treatment effects and weak associations between variables may not have been identified in the current study. Thus, the pathways revealed in the current analyses should be viewed as the most robust trajectories of treatment-specific effects rather than the only possible pathways. Finally, although NIA provides some information on the sequential treatment effects through network construction at each time point, it does not provide information on time-lagged relationships across variables since it solely captures contemporaneous relationships.

Despite these limitations, the results of the current study provide further support for notion that from a network perspective roluperidone achieves its effect on negative symptoms primarily from impacting avolition, which has downstream impact on highly inter-connected symptoms within the broader construct. Importantly, these results were consistent across network analyses of the phase 2b and 3 roluperidone trials, which used different measures and analytic approaches. Thus, there is increasing support for the notion that avolition is at the “core” of the

negative symptom construct and a critical treatment target that can produce downstream effects on the entire symptom constellation when successfully augmented (Foussias & Remmington, 2010; Strauss et al., 2021). Since avolition is also found in other neuropsychiatric diagnoses, findings suggest that roluperidone may also be relevant for treating negative symptoms in disorders other than schizophrenia (Strauss & Cohen, 2017). Furthermore, network density findings suggested that treatment improvements were characterized by increasing strength of density, which is consistent with prior studies indicating that networks that are more tightly coupled are more likely to produce global symptom change (Hoffman et al., 2016).

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APPENDIX A

SUPPLEMENTAL MATERIALS

Macroscopic Properties

Network Density was computed for individual network intervention analysis (NIA) networks at each time point. Density was computed with the formula used by Strauss et al. (2020) and represents the extent at which symptoms in the network are interconnected. The resulting density estimates demonstrate a gradual increase in density across visits, with week 8 having the largest density estimate. NIA networks density estimates at each visit are depicted in Figure A1.

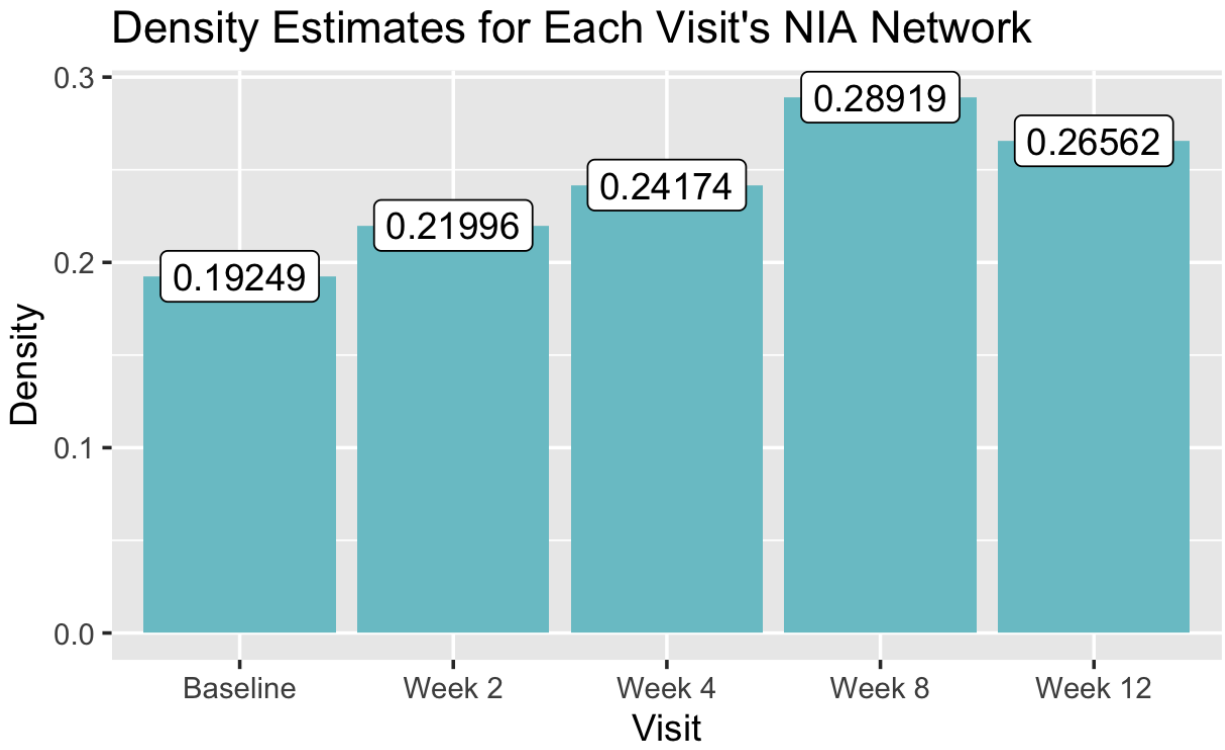

Figure A1. Density Estimates for Each Visit's Network.

Note. NIA = Network Intervention Analysis.

Microscopic Properties

Microscopic properties of each visit's NIA network were computed using the qgraph package in R (Epskamp et al., 2012). Microscopic network properties provide information about individual symptoms included in the network rather than information about the network structure as a whole. Specifically, strength centrality values for the symptoms were estimated and indicate the sum of the edge weights connected to each node (i.e., symptom). Strength centrality provides information on the relative the influence of each symptom within the overall network, with higher values indicating greater influence. Figure A2 depicts the centrality estimates for each symptom across study visits. Further description of these results is included in the manuscript.

To evaluate each condition's microscopic properties, individual networks for each condition at each visit were constructed using the mgm package in R (Haslbeck & Waldorp, 2015). Parameters used to construct the individual condition networks were similar to the parameters used for the NIA networks with the exception of the inclusion of the treatment variable node. Figure A3 depicts the centrality estimates for each symptom across study visits in the placebo condition. Figure A4 depicts the centrality estimates for each symptom across study visits in the roluperidone 64 mg/day condition. Further description of these results is present in the manuscript.

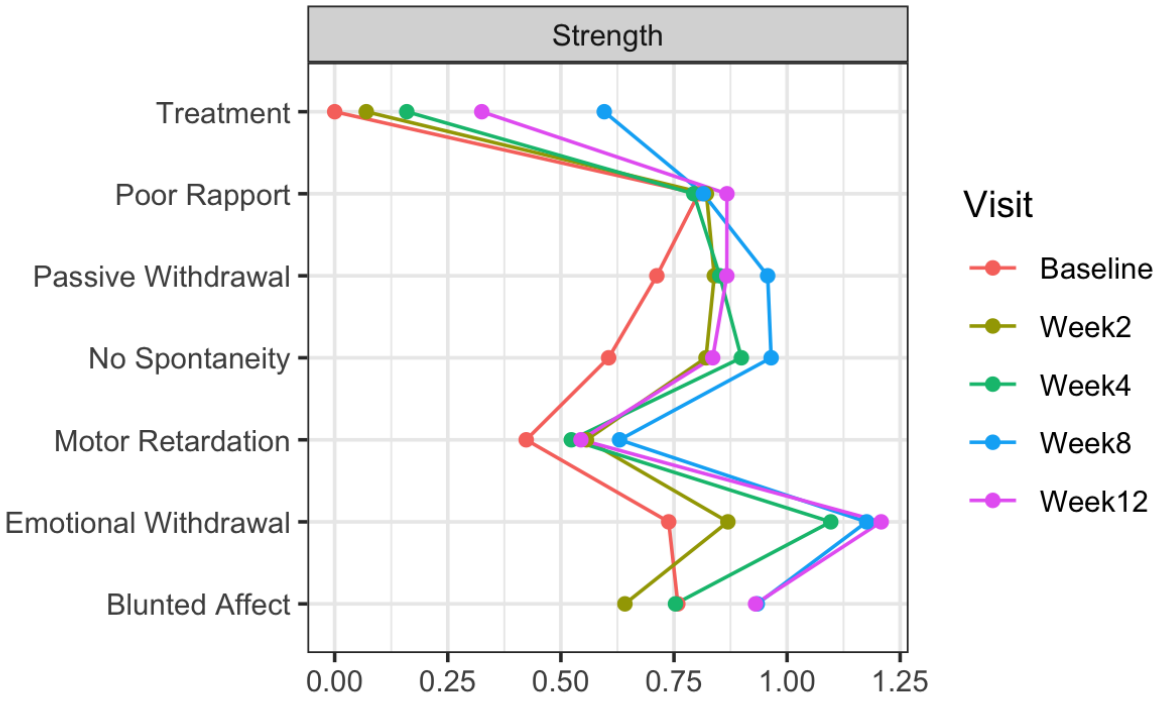

Figure A2. NIA Placebo & Roluperidone 64 mg/day Network Centrality Plots.

Note. NIA = Network Intervention Analysis.

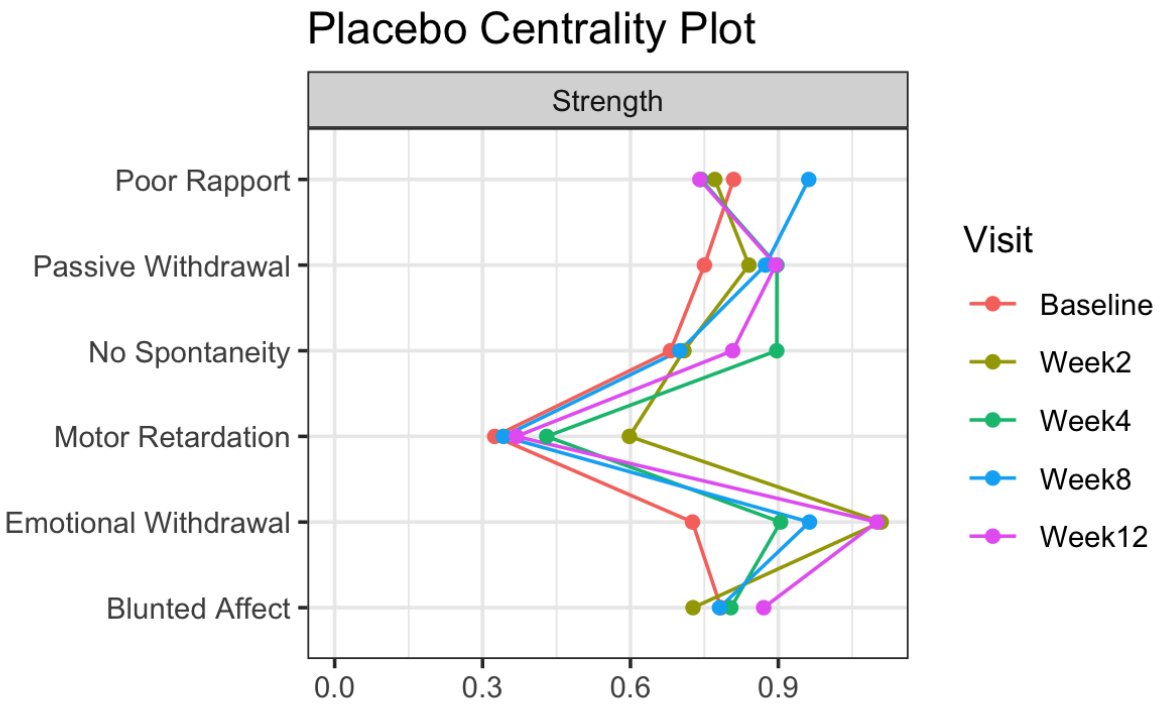

Figure A3. Placebo Network Centrality Plot.

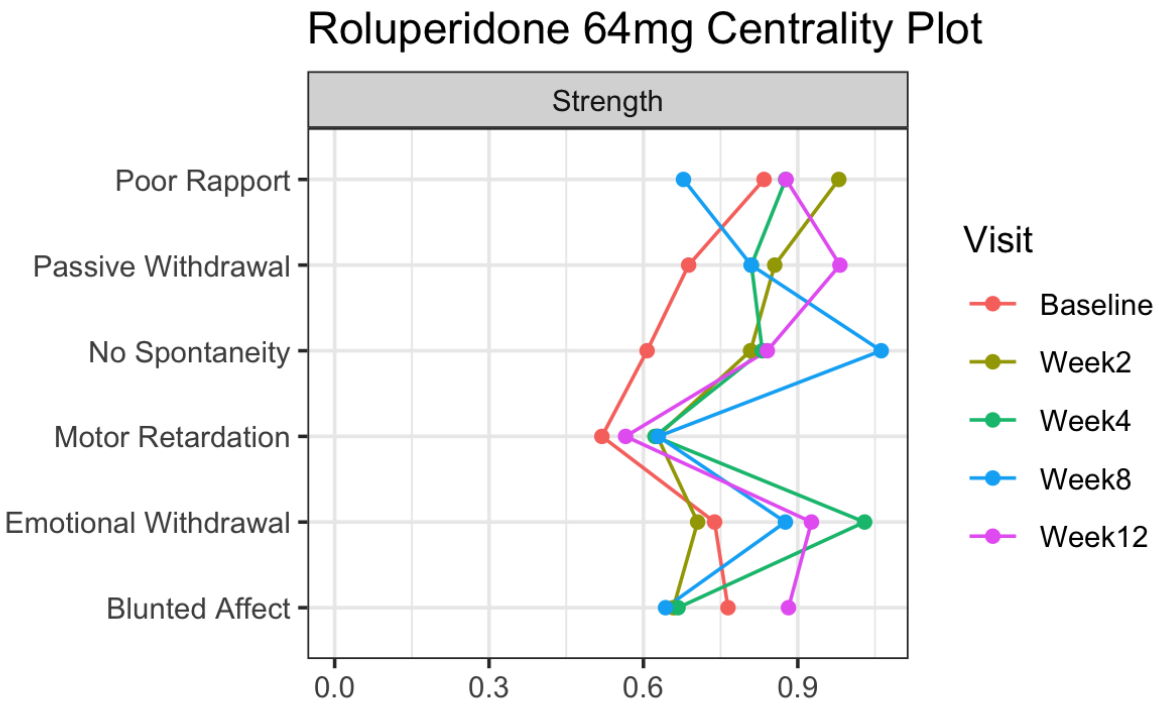

Figure A4. Roluperidone 64 mg/day Network Centrality Plot.

Predictability

Predictability for each symptom were computed for the NIA networks at each time point. Predictability represents the amount of variance of a symptom explained by other symptoms connected to it (Haslbeck & Waldorp, 2018). Figure A5 depicts the predictability of each symptom across the various time points. Predictability of each negative symptom within the NIA increased gradually over time, with the exception of motor retardation, with the greatest increases appearing in emotional withdrawal and Passive/apathetic social withdrawal.

To evaluate symptom predictability in each condition, individual networks for each condition at each visit were constructed using the mgm package in R (Haslbeck & Waldorp, 2015). Parameters used to construct the individual condition networks were similar to the parameters used for the NIA networks with the exception of the inclusion of the treatment variable node. Figure A6 depicts the change in symptom predictability across visits in the placebo condition. These results are similar to the results found in the NIA predictability plot, Figure A5. Figure A7 depicts the change in symptom predictability across study visits in the 64 mg/day roluperidone condition. Based on the figure, there were more fluctuations in symptom predictability across study visits in the roluperidone condition. Overall, however, symptom predictability increased across visits.

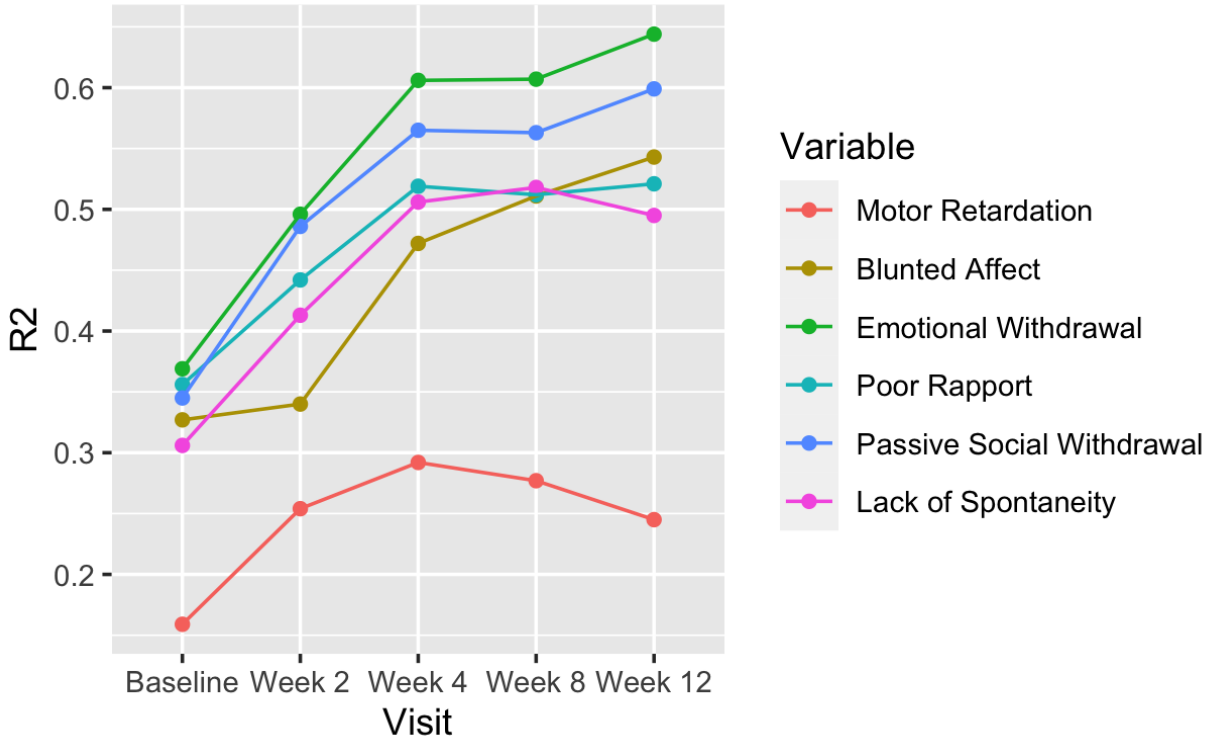

Figure A5. NIA Placebo & Roluperidone 64 mg/day Node Predictability Estimates.

Note. R2 = R^2

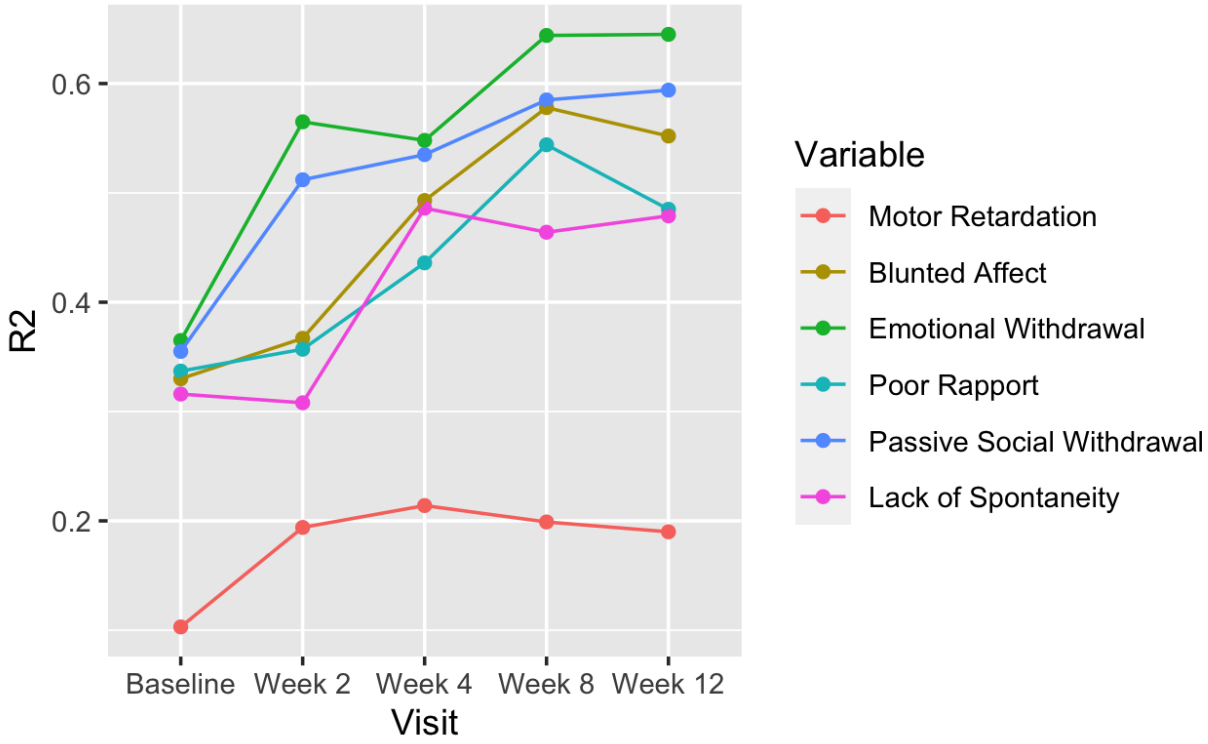

Figure A6. Placebo Network Node Predictability Estimates.

Note. R2 = R^2

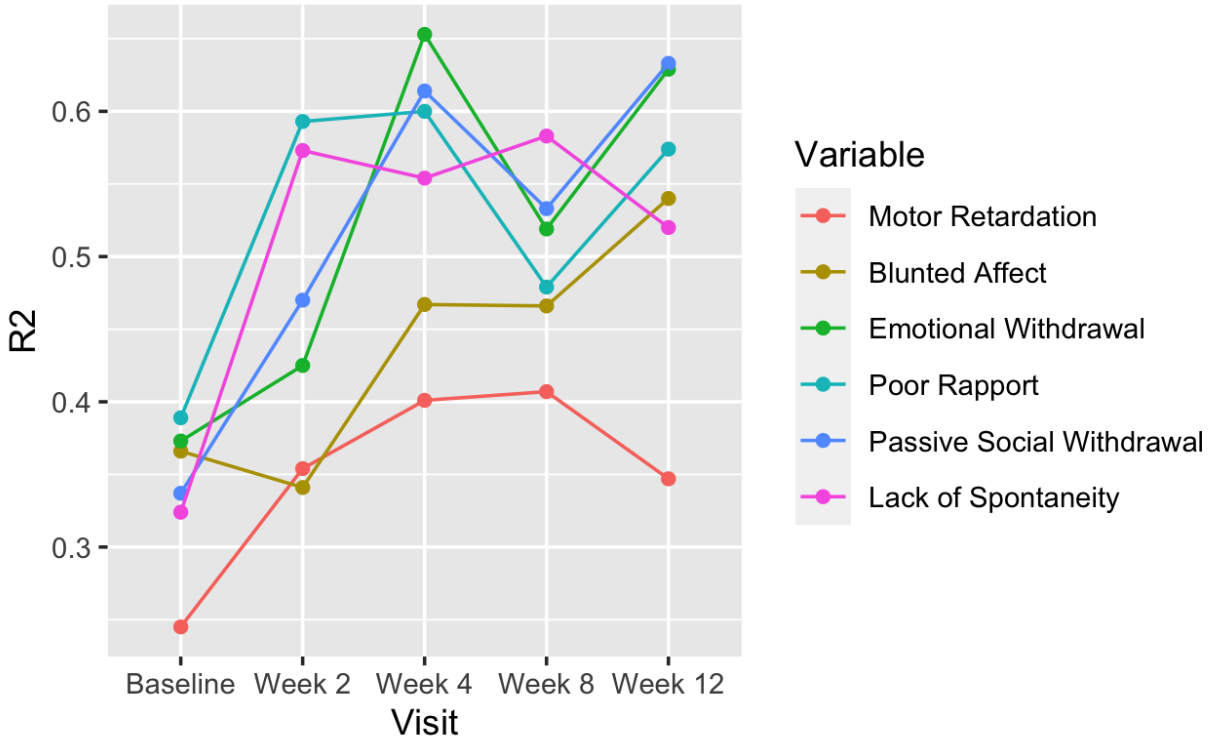

Figure A7. Roluperidone 64 mg/day Network Node Predictability Estimates.

Note. R2 = R^2

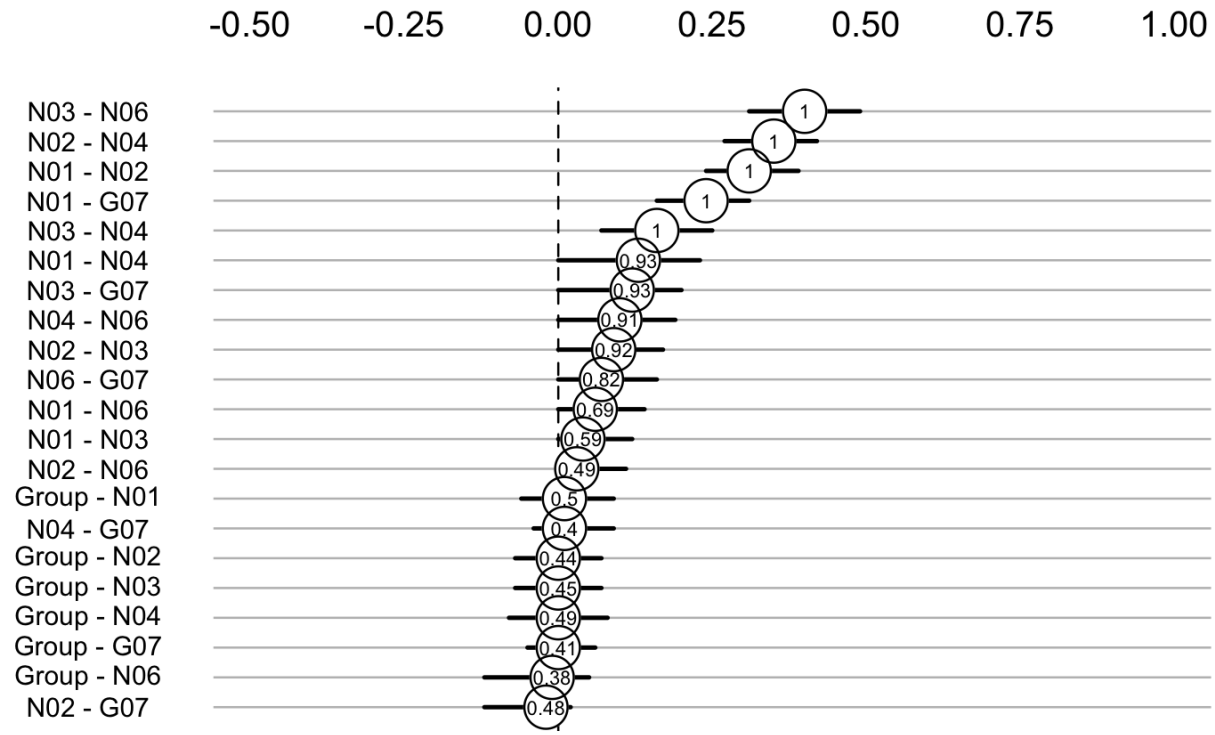

Figure A8. Bootstrapped Sampling Distribution of Edge Weight Estimates at Baseline.

Note. – denotes edges between nodes (e.g., N03 – N06 = Edge between PANSS item N03 and PANSS item N06). PANSS = Positive and Negative Syndrome Scale. N01 = blunted affect. N02 = emotional withdrawal. N03 = Poor rapport. N04 = passive/apathetic social withdrawal. N06 = lack of spontaneity and flow of conversation. G07 = motor retardation. Group = placebo or roluperidone 64 mg/day.

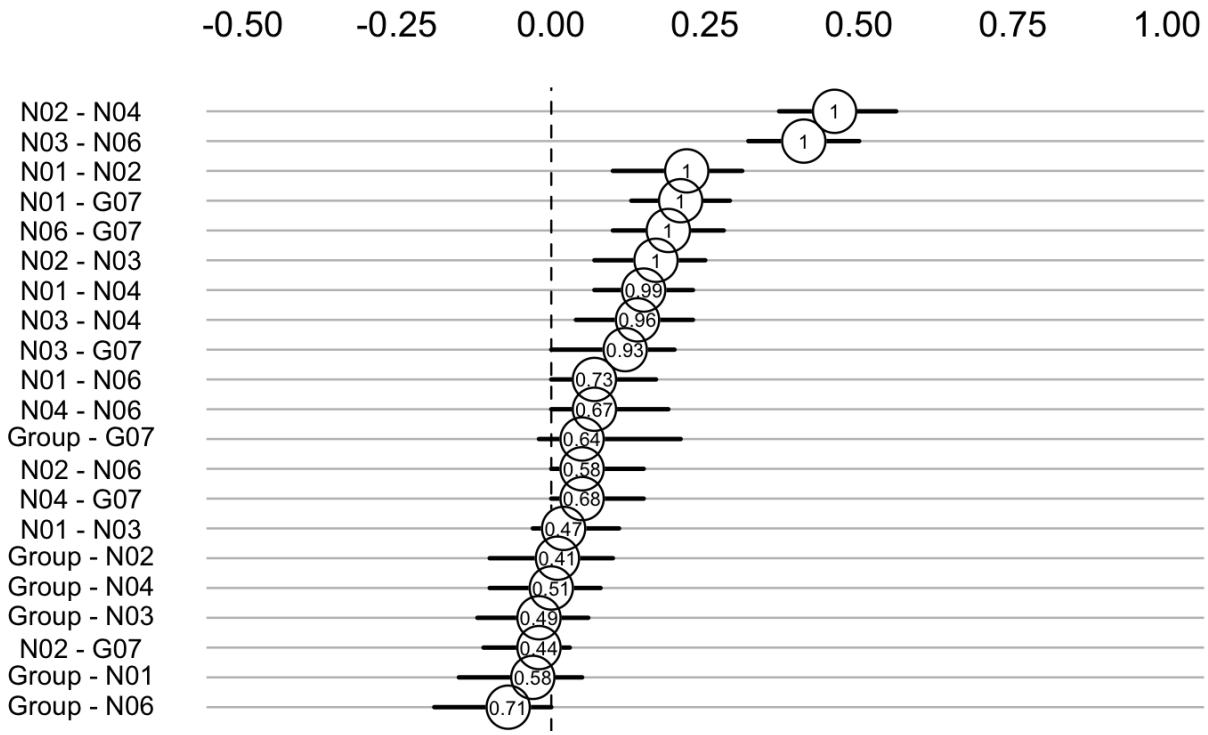

Figure A9. Bootstrapped Sampling Distribution of Edge Weight Estimates at Week 2.

Note. – denotes edges between nodes (e.g., N02 – N04 = Edge between PANSS item N02 and PANSS item N04). PANSS = Positive and Negative Syndrome Scale. N01 = blunted affect. N02 = emotional withdrawal. N03 = Poor rapport. N04 = passive/apathetic social withdrawal. N06 = lack of spontaneity and flow of conversation. G07 = motor retardation. Group = placebo or roluperidone 64 mg/day.

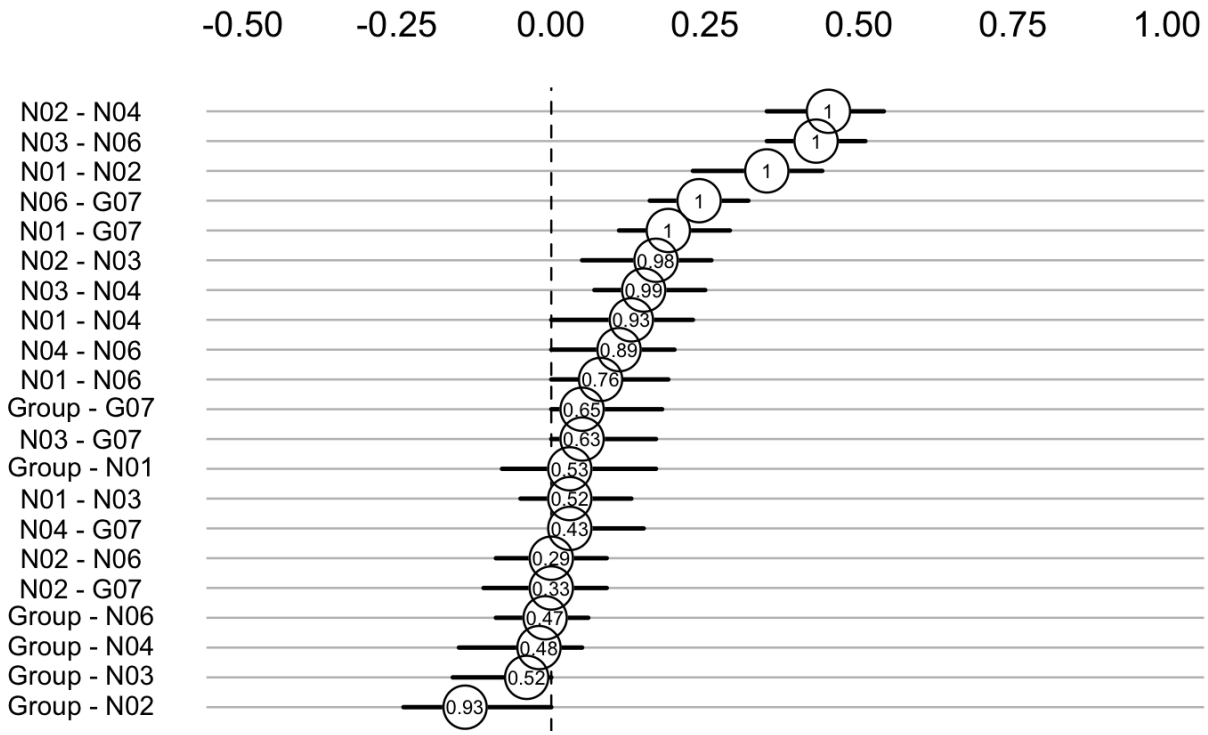

Figure A10. Bootstrapped Sampling Distribution of Edge Weight Estimates at Week 4.

Note. – denotes edges between nodes (e.g., N02 – N04 = Edge between PANSS item N02 and PANSS item N04). PANSS = Positive and Negative Syndrome Scale. N01 = blunted affect. N02 = emotional withdrawal. N03 = Poor rapport. N04 = passive/apathetic social withdrawal. N06 = lack of spontaneity and flow of conversation. G07 = motor retardation. Group = placebo or roluperidone 64 mg/day.

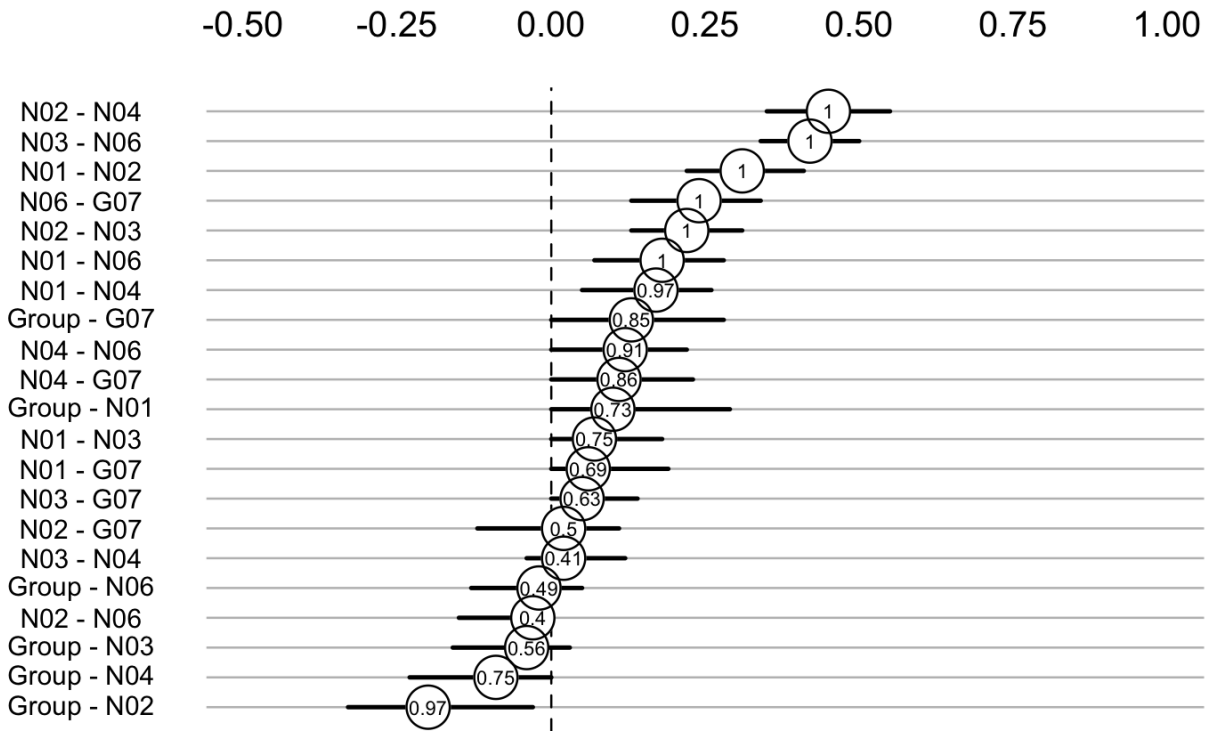

Figure A11. Bootstrapped Sampling Distribution of Edge Weight Estimates at Week 8.

Note. – denotes edges between nodes (e.g., N02 – N04 = Edge between PANSS item N02 and PANSS item N04). PANSS = Positive and Negative Syndrome Scale. N01 = blunted affect. N02 = emotional withdrawal. N03 = Poor rapport. N04 = passive/apathetic social withdrawal. N06 = lack of spontaneity and flow of conversation. G07 = motor retardation. Group = placebo or roluperidone 64 mg/day.

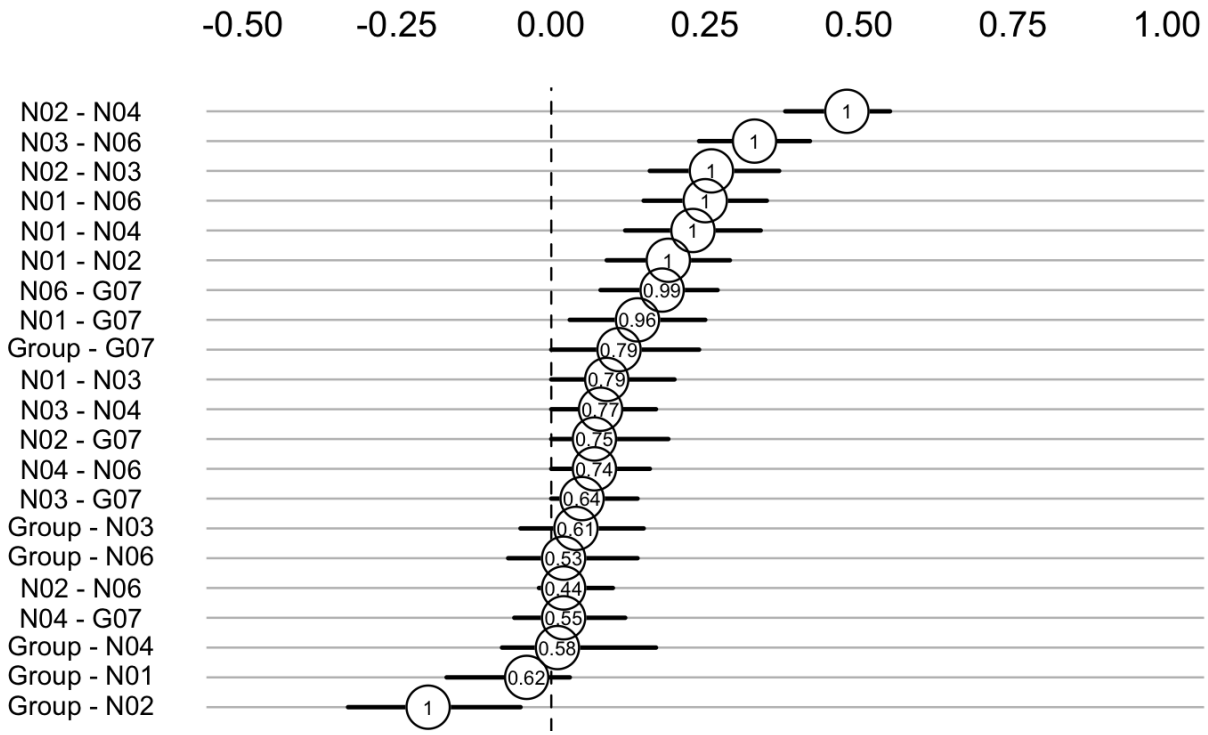

Figure A12. Bootstrapped Sampling Distribution of Edge Weight Estimates at Week 12.

Note. – denotes edges between nodes (e.g., N02 – N04 = Edge between PANSS item N02 and PANSS item N04). PANSS = Positive and Negative Syndrome Scale. N01 = blunted affect. N02 = emotional withdrawal. N03 = Poor rapport. N04 = passive/apathetic social withdrawal. N06 = lack of spontaneity and flow of conversation. G07 = motor retardation. Group = placebo or roluperidone 64 mg/day.