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Integrative Model of Complex Interactions between Cognitive Mechanisms and Symptoms Implicated in Depression

Orientação:

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Integrative model of complex interactions between cognitive mechanisms and symptoms implicated in depression

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Resumo

Esta tese teve como objetivo a constituição de um modelo integrativo complexo da depressão. Os modelos integrativos complexos têm sido considerados cruciais para superar as atuais limitações em torno da falta de estudos que acomodem a complexidade das interações entre fenótipos e endofenótipos da depressão.

A análise de redes tem sido proposta como uma metodologia estatística que permite modelar estas interações complexas entre endofenótipos e fenótipos das perturbações mentais. No entanto, o foco excessivo da teoria das redes psicopatológicas na conectividade global da rede é excessivamente simplista, e não traduz os processos etiopatogénicos das perturbações mentais. Deste modo, a abordagem das redes complexas para as perturbações mentais tem sido prejudicada pela teoria das redes psicopatológicas. Assim, a exploração de propriedades distintas da conectividade, nas redes psicopatológicas é condição necessária para continuar o desenvolvimento da teoria das redes. Por sua vez, o desenvolvimento da teoria das redes psicopatológicas fornecerá uma estrutura consolidada para superar as limitações atuais na investigação sobre depressão e melhorar a precisão e eficácia dos tratamentos.

Os Capítulos I e II concentram-se na estrutura fenotípica da depressão e promovem insights importantes para o desenvolvimento da teoria das redes, através da exploração dos diferentes níveis estruturais da rede. Estes diferentes níveis demonstraram-se capazes de diferenciar estados saudáveis de estados psicopatológicos. E demonstram que o foco na conectividade global da rede é limitador para o estudo das perturbações mentais através da análise de redes.

Por sua vez, o Capítulo III concentrou-se na identificação dos papeis estruturais dos diferentes componentes cognitivos na rede de interações da depressão. Neste capítulo, as estratégias cognitivas de regulação emocional mostraram ter uma função mediadora na

rede entre a depressão e os processos cognitivos. A velocidade de processamento apresentou uma função de ligação entre os processos cognitivos e as estratégias de regulação emocional. Por último, a flexibilidade cognitiva desempenhou um papel crucial na promoção de alterações na conectividade global da rede.

Assim, esta dissertação fornece (1) evidência para a aplicação da abordagem das redes no estudo da depressão; (2) contribui para a teoria das redes identificando propriedades estruturais da rede que são especificas a esta perturbação; (3) e identifica funções específicas para os diferentes constituintes cognitivos da depressão.

Abstract

This thesis aimed to address common problems in depression research by employing a network approach to the study of a complex integrative model. Complex integrative models have been deemed crucial to surpass the current limitations that center around the lack of studies that accommodate the complexity of interactions between phenotypes and endophenotypes of depression.

Network analysis has been viewed as a statistical framework that can model these complex interactions established between endophenotypes and phenotypes of mental disorders. However, the excessive focus of network theory on network connectivity is overly simplistic and does not translate the etiopathogenic processes of mental disorders. The network analysis approach to mental disorders might have been hampered by network theory of mental disorders.

Thus, the exploration of network analysis tools is needed to continue the development of network theory. In turn, development of network theory will provide a consolidated framework to surpass the current limitations in depression research such as treatment precision and efficacy.

Chapters I and II focused on the phenotypic structure of depression and promoted important insights and developments for the network theory, regarding the macro, meso, and micro-level network structure. With network properties having different behaviors on healthy or disordered participants and contributing to the recognition that overall network connectivity might be limiting the study of mental disorders through network analysis.

In turn, in Chapter III focused on the roles of the constituents of an integrative cognitive model of depression. In this Chapter cognitive emotion regulation strategies showed a mediational role in the network. Processing speed had a bridging role demonstrated by its

capacity to connect cognitive processes with cognitive emotion regulation strategies. Cognitive flexibility was associated with alterations in the overall network connectivity. This research provides (1) further support for the application of the network approach in investigating depression; (2) contributing insights to network theory regarding the unique characteristics of network properties in this disorder; (3) delineating the specific functions performed by the suggested cognitive endophenotypes within the network.

Contents

Introduction

Major Depressive Disorder (MDD) is one of the most common disorders, impacting approximately 5% of the adult population (World Health Organization, 2023). Despite this, and although several treatments have been proposed for intervening in MDD (American Psychological Association, 2019), treatments have shown low response rates (Cuijpers et al., 2021) and high recurrence and relapse rates (Richards, 2011). This points to a lack of comprehension about the development and maintenance mechanisms of the disorder (Lemmens et al., 2016). In fact, recent international guidelines, like the Research Domain Criteria (RDoC; Morris et al., 2022) and The Hierarchical Taxonomy of Psychopathology (HiTOP; Conway et al., 2019) propose a perspective focused on the etiopathogenic mechanisms of depression. However, the endophenotypes of MDD remain undefined (Goldstein & Klein, 2014). Various theoretical models have emerged to try to clarify the endophenotype of MDD. These models surface from different scientific fields ranging from neuroscience (Disner et al., 2011) to nutritional and microbiological psychiatry (Du et al., 2020) and to more traditional models from clinical psychology as the cognitive models (LeMoult & Gotlib, 2019).

Due to the promise of cost-effective treatments (Cristea et al., 2015; Edwards et al., 2022; Fodor et al., 2020; Hallion & Ruscio, 2011; Koster et al., 2017) and traditional psychotherapeutic interventions (DeRubeis et al., 2005), the cognitive models seem to be one of the most capable endophenotypic proposals for MDD. Although different cognitive models have been put forward (Beck & Bredemeier, 2016; Disner et al., 2011), there is a substantial overlap between all these proposals. All these cognitive models conceptualize the endophenotype of MDD with three major components, cognitive control, emotion regulation, and cognitive biases (LeMoult & Gotlib, 2019). With studies providing support for a formulation of MDD characterized by cognitive control

impairments (Liu et al., 2023; Schwert et al., 2017; Semkovska et al., 2019), maladaptive emotion regulation strategies (Millgram et al., 2023; Visted et al., 2018), and biases in attention, interpretation, and memory (Everaert, Podina, et al., 2017; LeMoult & Gotlib, 2019).

However, limited progress has been achieved since due to (1) the inability of assessing endophenotypic and phenotypic disorder specificity, (2) the lack of evidence that the endophenotypes effectively constitute depression mechanisms, (3) the continuous study of phenotypes and endophenotypes in isolation, and (4) the association of these endophenotypes with the generic construct of depression.

Endophenotypic Specificity in Major Depressive Disorder

Although there is some evidence that some of the proposed endophenotypes might be more associated with depression than others (Corpas et al., 2023), several of them have been shown to be transdiagnostic (Huang-Pollock et al., 2017; Lavigne et al., 2024; McTeague et al., 2016; Philippot et al., 2023). For example, the study from Corpas et al. (2023) points that, even though worry, meta-cognitive thoughts, and rumination present a certain degree of specificity with generalized anxiety, panic disorder, and depression, all three processes were related with the three disorders. This transdiagnostic nature is also seen in other strategies like suppression and catastrophizing that are present in most anxiety disorders (Garnefski & Kraaij, 2007).

Besides this endophenotypic expression of emotion regulation being transdiagnostic in nature, cognitive control impairment has also been shown to be transversal to several mental disorders (Huang-Pollock et al., 2017; McTeague et al., 2016). With only inhibition of negative material from the working memory to have been shown to be associated with MDD (Gotlib & Joormann, 2010).

This lack of specificity seems to extend to the remaining endophenotypes proposed by the cognitive model, the cognitive biases. Proposed cognitive biases for MDD include memory, attention, and interpretation (LeMoult & Gotlib, 2019) and, although there are studies reporting some degree of specificity for interpretation biases in MDD (Klein et al., 2018), these biases also appear to be non-specific to MDD (Lavigne et al., 2024).

The absence of specificity in diagnosing Major Depressive Disorder (MDD) is problematic because it results in a heterogeneous phenotypic expression of the disorder. Which is more aggravated by the lack of specificity in its defined phenotypic expression (Monroe & Anderson, 2015) and by its polythetic diagnostic scheme (Fried & Nesse, 2014), that leads to 1,497 unique symptom profiles (Østergaard et al., 2011). Due to this heterogenic nature of the disorder, it might be better characterized by the type of interactions established by the endophenotypes and phenotypes of the disorder (Borsboom & Cramer, 2013). Although very few endophenotypes and phenotypes seem to be specific of MDD (Lavigne et al., 2024; McTeague et al., 2016; Philippot et al., 2023), studies show that some endophenotypes are indeed more common in MDD than other disorders (Corpas et al., 2023; Klein et al., 2018). This might mean that, while these endophenotypes might be transdiagnostic, the pattern of interactions established between them might differ from the pattern of interactions in other disorders (Everaert, Grahek, Duyck, et al., 2017; Klein et al., 2014).

It has been pointed out that the study of these endophenotypes in isolation limits our ability to understand the etiopathogenic and maintenance mechanisms due to the interactions that they establish between them (Everaert et al., 2012). For example, both Bernstein et al. (2017) and Hoorelbeke et al. (2016) showed the existence of interactions between a set of cognitive endophenotypes of depression. However, these interactions are

not circumscribed to interactions between the endophenotypes. These endophenotypes also seem to establish differential interactions with MDD phenotypes (Everaert et al., 2014; Everaert, Grahek, & Koster, 2017; Everaert & Joormann, 2019; Vanderlind et al., 2021; Zainal & Newman, 2023b).

Endophenotypic and Phenotypic Interactions in Major Depressive Disorder

As theoretical models suggest (Beck & Bredemeier, 2016; Disner et al., 2011; LeMoult & Gotlib, 2019), the distinct endophenotypes and phenotypes interact with each other. Yet the proposition from these models oversimplifies the complex nature of the interactions these endophenotypes and phenotypes establish. Contradicting studies that show complex interactions between all MDD proposed constituents (Everaert, Grahek, Duyck, et al., 2017; Zainal & Newman, 2023a, 2023b). For example, Everaert, Grahek, Duyck, et al. (2017), have shown that cognitive biases and rumination interact with each other and with depressive symptoms. And Zainal and Newman (2023b; 2023a) also show several interactions between several components of MDD, for example, executive functioning. However, these authors have studied MDD phenotype as a single construct, without considering the specificity of the origin and phenomenology of each of the symptoms (Fried & Nesse, 2015b), as well as the importance of the interactions between them (Fried et al., 2015; Fried & Nesse, 2014).

Problems Studying Major Depressive Disorder as Single Construct

Routinely, MDD is assessed from sum-scores of rating scales, for example, Patient Health Care Questionnaire – 9 (Kroenke et al., 2001), Beck Depression Questionnaire (Beck et al., 1988), or Hamilton Rating Scale for Depression (Hamilton, 1960). However, the usage of a sum-score to assess MDD is problematic (Fried & Nesse, 2015b) because

most of these instruments have a multi-factorial nature without measuring a single underlying construct (Bagby et al., 2004; Shafer, 2006) and with individual symptoms intercorrelated (Cramer, Waldorp, van der Maas, et al., 2010). This led to the suggestion that these rating scales sum-scores carry information about a general psychopathological load (Faravelli, 2004). However, this omits important information since MDD symptoms are not interchangeable indicators of the disorder (Fried & Nesse, 2015a) and are differentially impairing (Fried & Nesse, 2014).

Thus, studying the individual symptoms might produce more relevant information than the usage of the sum-score (Fried, 2015). In fact, specific treatments for MDD seem to be more effective in the presence or absence of specific symptoms (Uher et al., 2014) and symptom patterns of interaction seem to identify the emergence of MDD (Wichers & Groot, 2016). These interactions between symptoms have been suggested has fundamental for understanding the mechanisms associated with its development and the development of comorbidity structures (Borsboom & Cramer, 2013) by allowing the study of specific and differential interactions between endophenotypes and phenotypes (Kossakowski & Cramer, 2017).

Focusing on these interactions, studies have shown that endophenotypes have a specific and differential association with symptoms (Beevers et al., 2019; Everaert & Joormann, 2019; Marchetti et al., 2018). Memory bias, for example, seems to be associated primarily with feelings of incapacity, worthlessness, and pessimism (Marchetti et al., 2018). While repetitive negative thinking seems to be mainly associated with guilt (Everaert & Joormann, 2019) and processing speed with somatic symptoms of MDD (Zainal & Newman, 2023b).

Integrative Models

The development of integrative models that can accommodate these complex interactions between the endophenotypes and phenotypes are needed to understand their role in the maintenance and development of the disorder (Miller & Rockstroh, 2013). In fact, recent meta-analyses (LeMoult & Gotlib, 2019) have emphasized that the specification and validation of integrative models of the structure of interactions among the constituents of these different levels, cognitive, emotional, and symptomatic, represent a critical need. However, developing integrative models that can accommodate the complexity of interactions reported in previous studies (Beevers et al., 2019; Everaert & Joormann, 2019; Hoorelbeke et al., 2016; Hsu et al., 2022; Marchetti et al., 2018; Zainal & Newman, 2023b, 2023a) requires an epistemological shift that might be better addressed with statistical frameworks distinct from those traditionally used to model psychological phenomena (Miller & Rockstroh, 2013).

Network Models

Traditionally, psychological phenomena have been studied through reflective models (Borsboom, 2008). In these models, a reflective latent variable (e.g., depression) leads to changes in its observed indicators (i.e., symptoms). This is known as the common cause hypothesis (Schmittmann et al., 2013), where symptoms covary due to a latent disease. In this perspective, symptoms are viewed as measurements of a mental disorder, and aggregated symptoms assess the person position on the latent variable. Thus, changes in MDD (latent variable) lead to changes in depressive symptoms, and the aggregate of symptoms determines the severity of MDD (person positioning on the latent variable). However, despite several efforts to identify the common cause of MDD little progress has been done (Hasler et al., 2004; Kendler, 2019; Miller, 2010; Miller & Rockstroh, 2013).

Instead, growing evidence challenges this perspective with phenotypes and endophenotypes of MDD displaying a multifactorial etiology composed by biological, psychological, and environmental factors (Kendler, 2012). This suggests that endophenotypes and phenotypes are distinct entities with independent causal influence on one another (Cramer, Waldorp, Van Der Maas, et al., 2010). Then, statistical frameworks that posit this epistemological position and can accommodate the complexity of interactions detected in previous studies are needed.

Network models offer an alternative to this common cause perspective (Bringmann et al., 2022), by conceptualizing mental disorders as causal associations between disorder constituents (Cramer & Borsboom, 2015; Nuijten et al., 2016). In network models' phenotypes and endophenotypes are viewed as nodes and their interactions as edges (Epskamp, Borsboom, et al., 2018). By doing so, these models effectively integrate the complex interactions previous studies identified (Epskamp, Borsboom, et al., 2018). This study of the complex interactions as produced, in recent years, important insights into the nosology and comorbidity structures. Examples of these insights can be seen, for example (Levinson et al., 2017; McElroy et al., 2018; McNally et al., 2017; Yang et al., 2023), in the study of Post-Traumatic Stress Disorder (PTSD) nosology that suggests the removal of the amnesia symptom due to its absence of interactions with the remaining proposed PTSD symptoms (Birkeland & Heir, 2017; McNally et al., 2014; Ross et al., 2018).

In relation to the comorbidity structures, network studies have identified several symptoms that might be responsible for the development of these structures (Castro et al., 2018; Cramer, Waldorp, van der Maas, et al., 2010; Garabiles et al., 2019; Levinson, Brosof, et al., 2018; Price et al., 2019). For example, Garabiles et al. (2019) identified

fatigue as a symptom that might be responsible for the emergence of comorbidity between MDD and generalized anxiety disorder, since it connects both disorders.

In depression the overall strength of the interactions between symptoms was also able to predict the emergence of a MDD episode (van Borkulo et al., 2015; Wichers & Groot, 2016) and several symptoms have been proposed as possible intervention targets due to their importance in the network of interactions (Malgaroli et al., 2021). These insights have been mostly obtained through the exploration of network models at different levels of analysis.

Macro, Meso, and Micro-Level Network Properties

These levels of analysis can be broadly characterized through macro, meso and micro network properties (Vitevitch, 2019). Macro-properties can be defined as metrics that assess the global structure and performance of the networks. These properties include fundamental metrics as the size of the network and other more intricate metrics as connectivity (van Borkulo et al., 2015), average path length (Albert & Barabási, 2002) or global clustering coefficient (Barrat et al., 2004). These global metrics detail different aspects of the network structure that inform us about the network robustness and resilience (Iyer et al., 2013; Liu et al., 2017). For example, a network with high connectivity might be less vulnerable to attacks due to having more redundant edges connecting the nodes. This redundancy might maintain the network performance even when edges or nodes are removed.

Meso properties of the network in turn characterize the structural organization of substructures constituted by sets of nodes (Vitevitch, 2019). These meso-properties are normally identified from the community structure of a network and network motifs (Alon, 2007; Fortunato & Hric, 2016; Milo et al., 2011; Xie et al., 2013; Zhao et al., 2011).

Motifs identify specific interaction patterns between three to five nodes, these patterns might identify important network mechanisms. In turn, a community consists in subsets of nodes that show a particular tendency to be more densely connected with each other, than with the remaining nodes in the network (Christensen et al., 2023). Depending on the community structure global hubs or local hubs might emerge (Fornito et al., 2016; He & Zhang, 2006). Global hubs are nodes that are interconnected with all the network, in turn local hubs are hubs that, although strongly connected, are only connected with a specific subgroup of nodes. This also has important implications for network robustness since the removal of a local or a global hub will have a drastically different impact on the network.

Lastly, micro-level properties focus on the node's characteristics (Vitevitch, 2019). This might be done through several centrality measures, for example, degree, closeness and betweenness (Bloch et al., 2023; Borgatti, 2005). These node measures assess different characteristics of the nodes, for example, closeness provides information on the node proximity to all other nodes and betweenness identifies the node capacity to connect other two nodes (Freeman, 1978). Micro-level properties also allow for the identification of bridge nodes, which are nodes that connect network communities (Jones et al., 2019). Thus, micro-level properties identify the nodes' role in the network (Castro et al., 2019).

To leverage these levels of analysis and integrate the results provided by the initial exploration of symptom networks, the network theory of mental disorders was developed as preliminary theoretical framework for network studies in psychology (Borsboom, 2017; Borsboom et al., 2019).

Network Theory of Mental Disorders

This theory (Borsboom, 2017) focus primarily on phenotypic expression of mental disorders, and it is constituted by five principles that aim to explain the etiopathogenesis of mental disorders: complexity, symptom-component correspondence, direct causal connections, non-trivial topology, and hysteresis.

Network theory postulates that mental disorders can be characterized by the interactions between different components in the psychopathological network – *complexity*. That these components correspond to the proposed symptoms in the current diagnostic manuals – *symptom-component correspondence.* These symptoms, in turn, establish cause-effect relationships that form the network structure – *direct causal connections*. Mental disorders follow this network structure, with the clustering of symptoms that often arise together, establishing the basis for the manifestation of mental disorders – *non-trivial topology*. Finally, network theory proposes that strongly connected symptoms continue to activate each other even after the triggering cause for the symptom has disappeared - *hysteresis*.

Based on these principles, network theory proposes that when an event triggers a symptom, through the network of interactions, other symptoms get activated. After the disappearance of the triggering event, if the connections between the symptoms are strong enough, these symptoms continue to be experienced giving rise to the phenomenological presentation of the mental disorder.

This theoretical formulation positions connectivity between symptoms as the primary property of interest, highlighting its role on the ethiopathogenic and disorder maintenance processes. In this context connectivity as taken the center fold in many psychological network studies being mainly explored at a macro and micro-level, through global connectivity or through centrality measures such as strength and expected

influence (e.g., Beard et al., 2016b; Curtiss & Klemanski, 2016; Groen et al., 2019; Kraft et al., 2019; Schweren et al., 2018a; Wichers & Groot, 2016). Exploring connectivity at two distinct levels of analysis has yielded valuable insights into the potential of network models of mental disorders for informing psychological treatments (Levinson, Vanzhula, & Brosof, 2018; Levinson, Vanzhula, Brosof, et al., 2018; Vanzhula et al., 2019).

Potential of Network Models for Psychological Treatments

At the macro-level of analysis earlier studies with symptom networks suggested that global connectivity might be in fact related to disorder severity (Koenders et al., 2015) and with diagnosis (Boschloo et al., 2016; Schweren et al., 2018). Supporting the network theory proposal (Borsboom, 2017; Borsboom et al., 2019; Borsboom & Cramer, 2013), this suggests that connectivity may be associated with the experience of symptoms. However, pre-, and post-treatment studies have casted doubt on this assumption (Beard et al., 2016; Bos et al., 2018; Snippe et al., 2017). With results displaying increased network connectivity in successful post-treatment networks (Beard et al., 2016; Bos et al., 2018). And with several other studies not being able to identify significant statistical differences between healthy and disordered individuals (Hartung et al., 2019; Montazeri et al., 2019; Silk et al., 2019).

Contrary to the inability to identify differences with network connectivity, significant structural differences were identified in several studies (Curtiss et al., 2019; Groen et al., 2019; Hartung et al., 2019; Montazeri et al., 2019; Silk et al., 2019). This seems to suggest that other structural changes in the network topology might occur independently of the overall network connectivity. Which in turn suggests that other macro-level properties, not contemplated in the network theory, might be useful in the characterization and identification of psychopathological states. However, these

structural differences were never explored or specifically identified in symptom networks.

These structural changes might also be reflected in the meso-level of the network. However, network theory (Borsboom, 2017) lacks an explicit definition regarding the potential roles of meso-level properties besides the theoretical formulation that the phenomenological manifestation of mental disorders is grounded in symptom groupings. These grouping might be viewed as communities, but this is not explicitly articulated in the theory. Moreover, there are numerous algorithms to estimate network communities (Adamcsek et al., 2006; Clauset et al., 2004; Fortunato, 2010; Girvan & Newman, 2002; Zhao et al., 2011), with no clear understanding of which might be more appropriate for symptom networks (Blanken et al., 2018). Nevertheless, identifying the community structure of a psychopathological network might promote insights into the topology and comorbidity structures.

These insights can be used to develop prevention strategies that act on the specific interactions that are behind the emergence of the comorbidity structure. With comorbidity being associated with poorer therapeutic outcomes (Olatunji et al., 2010), the ability to identify the specific paths from which it emerges would allow for the development of more precise interventions (Friston, 2017; Khurana Hershey et al., 2022; Silbersweig & Loscalzo, 2017). In the same sense and following the non-trivial topology principle (Borsboom, 2017), it is possible that specific motifs are more frequent than others and that these motifs, consequently, might have a prominent role in the development and maintenance of mental disorders.

Development and maintenance of mental disorders, following network theory (Borsboom, 2017), is also closely tied to the overall network connectivity, with symptoms remaining activated due to the strong connections with each other (i.e., hysteresis). Due

to this, studies started to explore the micro-level of the network through centrality measures that specifically assessed nodes' connectivity (e.g., strength centrality and expected influence; (Epskamp, Borsboom, et al., 2018; Robinaugh et al., 2016). In turn, these central nodes were proposed as possible treatment targets (Levinson, Vanzhula, & Brosof, 2018) since intervening in them should have a higher impact on the overall network connectivity. However, studies directly testing central nodes as treatment targets displayed inconsistent results (Dablander & Hinne, 2019; Dalgleish et al., 2019; Hallquist et al., 2019; Rodebaugh, Tonge, Piccirillo, et al., 2018; Spiller et al., 2020a) and suggested the use of centrality metrics not focused on network connectivity (Castro et al., 2019; Dablander & Hinne, 2019)

At this level, bridge symptoms were also proposed as important treatment targets since they might prevent the development of comorbidity structures (Cramer, Waldorp, Van Der Maas, et al., 2010). Yet, without a clear definition and method to identify communities at a meso-level, the understanding of comorbidity structures remains rooted in the symptom structure of the diagnostic manuals and not in the network topology. Moreover, comorbidity has be associated with several different factors (Cerdá et al., 2010) and exploring the development of comorbidity structures focusing only on symptom-to-symptom interactions might be insufficient.

In fact, focusing only on symptom networks might be the single most significant problem of network theory of mental disorders (Guloksuz et al., 2017). Mental disorders are complex systems with several components in interaction. The cognitive models of depression (Beck & Bredemeier, 2016; Disner et al., 2011) are constituted by several endophenotypes that impact the phenomenological manifestation of the disorder. Moreover, interventions direct at these endophenotypes, for example, cognitive control training (Calkins et al., 2015), have shown the ability to reduce depression symptoms

(Edwards et al., 2022; Koster et al., 2017). In this context, relying only symptoms interactions to explain depression mechanisms might be a simplistic approach. However, with the tools available for network analysis this statistical framework has potential to surpass both the limitations of network theory (Guloksuz et al., 2017) as well as the limitations in current depression studies (Cuijpers et al., 2021; Lemmens et al., 2016).

Therefore, although overall network connectivity as a macro-level property has been displaying inconsistent results (Hartung et al., 2019; Montazeri et al., 2019; Silk et al., 2019; van Borkulo et al., 2015) and might not be the ubiquitous marker that network theory proposed. Other macro-level properties can be assessed through network analysis that might be important psychopathology markers and help develop the network theory of mental disorders.

The same can be said for meso-level properties, which have been underexplored in symptom networks and only recently have motifs been proposed as an important mechanism in these networks (Letina et al., 2019) besides overall network connectivity and bridge and central symptoms.

On this micro-level of analysis, questions remain due to the inconsistent results that have been found commonly used centrality measures regarding treatment target identification (Dablander & Hinne, 2019; Dalgleish et al., 2019; Hallquist et al., 2019; Rodebaugh, Tonge, Piccirillo, et al., 2018; Spiller et al., 2020). In this level, the excessive focus on connectivity by the network theory has guided the analyses and this might have hindered the potential of network analysis in psychology. This kept the focus on centrality measures that rely on network connectivity and discarded measures based on other properties.

Hence, to fully explore of network analysis for psychological networks, (1) symptom networks must be replaced by networks that encompass the different

endophenotypes and phenotypes that have been proposed for mental disorders and, in the context of this particular study, for depression; (2) exploration of the different levels of analysis for endophenotypes and phenotypes networks to study the possible differential behavior that both these networks might have; (3) and test this behavior on an integrated network model with both the endophenotypes and phenotypes.

Goals, Methodology and Dissertation Structure

Network analysis has the tools to surpass the limitations that have been previously raised in the study of depression (Lemmens et al., 2016) with the lack of models that can integrate the complexity of interactions between the endophenotypes and phenotypes while considering them as independent entities with causal influence in each other. This has been suggested as one of the foremost problems for the development of more effective and precise interventions (Friston, 2017; Silbersweig & Loscalzo, 2017).

In parallel, previous studies applying network analysis as a statistical framework might have been hampered by an overly simplistic network theory of mental disorders (Borsboom, 2017; Guloksuz et al., 2017) that heavily relies on network connectivity to establish its assumptions and does not fully leverage the tools provided by network analysis.

With this in mind, the aim of this thesis was to (1) build a complex integrative model of depression, which has been suggested to be critical to instigate further treatment developments (LeMoult & Gotlib, 2019); and (2) to test the differential impact of specific cognitive endophenotypes in this model through network analysis, which has been proposed from a medical (Barabási et al., 2011; Loscalzo et al., 2017) and psychiatric perspective (Fried et al., 2017; Silbersweig & Loscalzo, 2017) as a promising method to address the complexity inherent to mental disorders, offering potential advancements towards more precise treatments.

To accomplish this however the current limitations of network theory had to be surpassed. Thus, initially this work relied on the exploration of macro, meso and micro level properties. This was a necessary step to understand which properties might provide a better characterization of depression and explore their specificity to the disorder. Chapter I focus specifically on the exploration of macro, and meso-level properties,

exploring the differential role of these properties in the characterization of healthy and disordered individuals in four distinct disorders. Chapter II revolves around micro-level properties and their impact in the network macro structure, assessing the hypothesis of centrality measures as valuable treatment target identifiers. With both these chapters focusing on the phenotypic expression of depression, chapter III provides a complex integrative model of depression, which includes endophenotypes and phenotypes of the proposed cognitive model of depression (LeMoult & Gotlib, 2019). Similar to Chapter II, this chapter focused on the differential impact of specific endophenotypes on the macro properties of the network, in order to identify the roles of these proposed mechanisms in the complex integrative model of depression.

CHAPTER I [1, 2, 3]

Topological Properties of Psychopathological Networks of Healthy and Disordered Individuals across Depressive and Anxiety Disorders

Note:

[1] This chapter has been submitted to the *Journal of Affective Disorders* for publication: Castro, D., Cardoso, J., Araújo, A. S., Rodrigues, A. R., Ferreira, F., Ferreira-Santos, & Ferreira, T. B. (2023). Topological properties of psychopathological networks of healthy and disordered individuals across depressive and anxiety disorders [Manuscript submitted to publication].

[2] Supplementary materials of this paper are available in the Chapter I of the Appendix.

[3] Code to reproduce the analysis the analysis can be found at https://osf.io/naqp3/

Abstract

The identification of psychopathological markers has been the focus of several scientific fields. The results were inconsistent due to lack of a clear nosology. Network analysis, focusing on the interactions between symptoms, provided important insights into the nosology of mental disorders. These interactions originate several topological properties that could constitute markers of psychopathology. One of these properties is network connectivity, which has been explored in recent years. However, the results have been inconsistent, and the topological properties of psychopathological networks remain largely unexplored and unknown. We compared several topological properties (i.e., connectivity, average path length, assortativity, average degree, modularity, global clustering) of psychopathological networks of healthy and disordered participants across depression (N = 2830), generalized anxiety (N = 13463), social anxiety (N = 12814), and obsessive-compulsive disorder (N = 16426). Networks were estimated using Bayesian Gaussian Graphical Models. The Janson-Shannon measure of divergence was used to identify significant differences between the network properties. Network connectivity distinguished healthy and disordered participants' networks in all disorders. However, in depression and generalized anxiety, network connectivity was higher in healthy participants. The presence and number of motifs also distinguished the networks of healthy and disordered participants. Other topological properties (i.e., modularity, clustering, average path length and average degree) seem to be disorder specific. The psychopathological significance of network connectivity must be clarified. Some topological properties of psychopathological networks are promising markers of psychopathology and may contribute to clarifying the nosology of mental disorders.

Keywords: network analysis; connectivity; topological properties;

In recent years, the network analysis of psychopathology has become one of the most promising approaches to the study psychopathology (Borsboom, 2022). The network analysis distinguishes itself from the traditional models of latent common causes by focusing on the interactions between symptoms (Borsboom et al., 2011; Cramer et al., 2010; Fried et al., 2017; Nuijten et al., 2016). In this analysis, networks emerge because of dynamic interactions between individual symptoms, represented as nodes, and the relationships between them, represented as edges.

Network theory of psychopathology (Borsboom, 2017; Borsboom et al., 2019) proposes that it is from interactions between symptoms that the development and maintenance of mental disorders occurs. This has produced numerous insights into the nosology and comorbidity of mental disorders (Castro et al., 2018; Ferreira, Castro, et al., 2022; Ferreira, Gysi, et al., 2022; Garabiles et al., 2019; Jones et al., 2019; Vanzhula et al., 2019). This has been mostly achieved by studying microlevel properties of the psychopathological networks, such as central and bridge symptoms (Castro et al., 2019; Cramer et al., 2010). These microlevel properties help us identify which symptoms might be associated with the development of mental disorders (Blanken et al., 2018; Borsboom & Cramer, 2013; Cramer et al., 2010; Ferreira et al., 2020; Guloksuz et al., 2016), the emergence of comorbidity structures (Castro et al., 2018; Cramer et al., 2010), and which symptoms might be valuable treatment targets (Castro et al., 2019; Elliott et al., 2020; Levinson et al., 2018; Papini et al., 2020; Rodebaugh et al., 2018; Spiller et al., 2020).

Although the microlevel features of the network might provide important information on the processes that occur in the network, the meso- and macro-level properties have also been proposed to be important in the characterization of psychopathological disorders (Letina et al., 2019; Vitevitch, 2019). At the meso-level, it is possible to assess the structural organization of the networks. This has been mostly

done by estimating communities or modules, groups of highly connected nodes (Blanken et al., 2018; Castro et al., 2020; Ferreira, Castro, et al., 2022), to clarify the nosology of mental disorders (Bronchain et al., 2019; McCuish et al., 2019; Olatunji et al., 2018; Silk et al., 2019). However, at this level of analysis, it may also be possible to identify the patterns in the structural organization in psychopathological networks. This can be done through motif analysis, which has recently been introduced into psychopathological networks (Letina et al., 2019). Motifs are interaction patterns that are represented by network subgraphs of three to five nodes with different combinations of positive or negative edges. The increase or decrease in the number or type of motifs present in the network might inform if a network is in a transitional state from healthy to ill, or vice-versa. However, to identify possible states of change in the network structure, a clear characterization of the structural arrangement of the motifs in different network states is a necessary initial condition. For this, we need to identify which motifs characterize each disorder and which motifs might be central processes of the network (Letina et al., 2019).

Besides this meso-level characterization, at the macro-level there are properties that might also be markers of psychopathology. These macro-level properties in psychopathological networks have been studied mainly in terms of the overall connectivity of the network (Bos et al., 2018; Koenders et al., 2015; Pe et al., 2015). Following the network theory of psychopathology (Borsboom, 2017; Borsboom et al., 2019), the overall connectivity of psychopathological networks has been suggested to differentiate between healthy and disordered patients (Pe et al., 2015; Wichers & Groot, 2016) and between varying degrees of severity of mental disorders (Koenders et al., 2015).

However, recent studies have shown that post-treatment networks have a higher connectivity (i.e., sum of the absolute edge weights of the network) than pre-treatment

networks (Beard et al., 2016; Bos et al., 2018) or less connectivity at discharge, but not statistically significant differences compared to admission and placebo and wait-list control group (Snippe et al., 2017). A previous study has also found an increase in connectivity in the network of poor responders in comparison with good responders, while not having statistically significant differences (Schweren et al., 2018). In terms of the ability to discern between different levels of severity, previous studies have also found mixed results. However, initial studies suggested network connectivity as a marker for distinguishing different populations (Pe et al., 2015; Wichers & Groot, 2016). Groen et al. (2019) study could not find any differences in network connectivity between individuals with symptom remission and individuals displaying persistent symptoms. Consistent with this study, Kraft et al. (2019) also did not find differences in network connectivity after a brief intervention; and comparisons between healthy and diagnosed individuals have also not reported significant changes in network connectivity in both dynamic (Curtiss et al., 2019) and cross-sectional networks (Hartung et al., 2019; Montazeri et al., 2019; Silk et al., 2019).

Therefore, network connectivity might not suffice to characterize mental disorders, and different network properties must be explored to differentiate between different mental states. Despite this, several of the studies mentioned above (Curtiss et al., 2019; Groen et al., 2019; Hartung et al., 2019; Kraft et al., 2019; Montazeri et al., 2019; Silk et al., 2019) identified significant differences in the network topology (i.e., the structure of interactions between symptoms). This seems to suggest that these changes in the structure appear to occur independently of changes in the connectivity of the network. This might mean that other network properties are transformed in the transition to or from a psychopathological state. For example, changes in the network topology might reduce the average path length of the network (i.e., the mean of the shortest paths in the network)

and facilitate the activation of the other symptoms in the network. Alternatively, during a psychotherapeutic intervention, a person may stop experiencing a specific symptom (e.g., insomnia) that would make it isolated in the network. This would not necessarily reduce the network's connectivity significantly but could increase the number of components (i.e., portions of the network that are disconnected from the rest of the network) in the network. In fact, Castro et al. (2019) showed that symptoms deactivation in cross-sectional networks leads more rapidly to significant changes in the number of components in the network than in overall connectivity of the network. Thus, although the results of the network connectivity are mixed, changes in the network structure seem to be more prominent.

In this context, the meso- and macrolevel structures of psychopathological networks remain unexplored, and further exploration of network properties at these levels will help to fully understand which of them might be useful markers of a psychopathological state. Understanding which network properties are prone to change, and which identify different psychological states might promote more efficient and personalized treatments, as well as more efficient prevention strategies. In addition, due to the theoretical focus of network theory in the global connectivity, the exploration of other meso- and macro-properties of the network might promote important insights and advances that allow for theoretical growth of network theory.

This study aims to explore this, by comparing the meso- and macro-level properties networks of diagnosed individuals and healthy individuals in four different disorders, namely, Major Depressive Disorder, Generalized Anxiety Disorder, Obsessive-Compulsive Disorder and Social Anxiety Disorder

Method

Sample

To examine the properties of symptom networks of healthy and disordered individuals four datasets were collected from open online repositories. This was a convenience sample where the only requirements were that (1) the datasets had a large sample with healthy and disordered participants, (2) that the dataset contained assessment questionnaires without a skip question structure, and (3) were from different disorders. The first two requirements were used to guarantee the stability and replicability of the estimated networks, which has been shown to be dependent on large samples for specificity and sensitivity (Isvoranu et al., 2021) and to be significantly affected by a skip-structure questionnaire (Borsboom et al., 2017). The third requirement was used to assess whether the network properties differed between disorders. Three datasets were collected from open online repositories, figshare.com and osf.io.

The Major Depression dataset was obtained from Doi and colleagues, (2018) study (https://doi.org/10.1371/journal.pone.0199235.s001). The original study was conducted to assess the validity of the Patient Health Questionnaire – 9 (PHQ-9; Kroenke et al., 2001) for the Japanese population (Doi et al., 2018). This instrument contains nine items to assess and monitor depressive symptoms. The PHQ-9 cut-off point is 10. The scores can range from 0 to 27. This study had 2.830 participants (54.66 % female), between the ages of 19 and 79 years (M = 42.44 years). Of the total of participants, 619 (21.78%) had major depressive disorder.

For Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD), a dataset from a study on gaming habits and psychological well-being was used (https://osf.io/vnbxk/; Sauter et al., 2021). This dataset contains 13464 participants, mostly male (94.3%), between the ages of 18 and 63 (M = 20.93 years). Participants came

from different countries, mostly from the United States (*N* = 4569), Germany (*N* = 1413), United Kingdom (*N* = 1032), and lastly Canada (*N* = 994). To assess GAD, the Generalized Anxiety Disorder 7 (GAD-7; Spitzer et al., 2006), consisting of the seven items of the DSM-5 diagnostic criteria, was used. Each item is rated by the participants on a 5-point Likert scale. The score can range from 0 (meaning no anxiety) to 21 (severe anxiety), and the cut-off score is 10. Social phobia inventory (SPIN; Antony et al., 2006) was used to assess SAD. This inventory consists of 17 items rated on a 5-point Likert scale. The SPIN score can vary between 0 (no social anxiety) and 68 (very severe social anxiety), the cut-off score is 19.

The dataset for obsessive-compulsive disorder was obtained from the Norwegian Workaholism Study (https://doi.org/10.1371/journal.pone.0152978.s001; Andreassen et al., 2016). Obsessive-Compulsive Disorder was assessed with Obsession-Compulsive Inventory-Revised (OCI-R; Foa et al., 2002). This scale evaluates six symptoms of OCD with 18 items. Each item is rated on a 5-point Likert scale from 0 ("Not at all) to 4 ("Extremely"). The cut-off score is 22, with high scores meaning the presence of OCD symptoms. A total of 16,426 participants responded to this instrument. Participants were mainly women (63.8%, *N* = 10487), between the age of 16 and 75 years (*M* = 37.3; *SD* = 11.4). Descriptives for all four studies can be found in Table 1.

Table 1.

Sample characteristics.

Sample	N	Mean *(SD)*	Minimum - Maximum
PHQ - 9	**2830**	**10.42 (7.74)**	**0 - 27**
With MDD	1354	17.20 (5.17)	
Without MDD	1476	4.20 (3.08)	
GAD-7	**13464**	**5.21 (4.71)**	**0 - 21**
With GAD	2352	13.56 (3.16)	
Without GAD	11112	3.45 (2.63)	
SPIN	**12814**	**19.85 (13.48)**	**0 - 68**
With SAD	5927	31.53 (10.39)	
Without SAD	6887	9.79 (5.07)	

OCIR	**16426**	**10.33 (8.5)**	**0 -72**
With OCD	2394	26.44 (7.56)	
Without OCD	14032	7.58 (4.80)	

Data analyses

The first step in the analyzes was to identify which participants in each dataset had clinically significant symptomatology. This was done by identifying which participants were above the cut-off point of the questionnaire. In all the datasets the number of individuals above the cut-off point was lower than the number of individuals below the cut-off point (see Table 1). Since the sample size has a clear effect on the estimation of the networks (Isvoranu et al., 2021), samples were matched by the number of participants by randomly selecting a sample of the same size from the participants below the cut-off point.

The networks of healthy and unhealthy participants were then estimated with Bayesian Gaussian Graphical Models, using *BGGM* package (Williams and Mulder, 2020) for *R* (R Core Team, 2019) and the graphical representation was done with the *qgraph* package (Epskamp et al., 2012) for *R* (R Core Team, 2019). *BGGM* (Williams & Mulder, 2020) allows for an increased sensitivity in the detection of edges in samples over 1000 participants in comparison to other methods used in psychopathological networks (Isvoranu et al., 2021). And since several network properties will depend on the number and strength of the edges detected, sensitivity was taken as a criterion for choosing the network estimation method.

The network properties were estimated with the package *igraph* (Csardi & Nepusz, 2006) for *R* (R Core Team, 2019). The first step in exploring the topology of psychopathological networks was to estimate the network properties, connectivity, average degree, average path length, assortativity, clustering, and modularity. Although most of these metrics have not been formalized theoretically in the context of network

theory, an exploration of the network properties might unveil important insights into the processes of psychopathological networks. Connectivity is the sum of absolute edge weights (van Borkulo et al., 2015). Average degree, the mean number of edges of the network nodes (Barrat et al., 2004). Average path length which is defined as the average number of steps along the shortest paths for all possible pairs of network nodes (Albert & Barabási, 2002). Assortativity is the tendency for nodes to connect to other nodes with similar properties within a network (Noldus & Mieghem, 2014). Modularity the strength of division of network modules (Variano et al., 2004). Clustering measure of the number of closed triplets (i.e., subgraphs with three edges and three nodes) over the total number of triplets (Barrat et al., 2004).

Comparison of the network's properties between healthy and disordered individuals the *BGGM* package for *R* was used (Williams & Mulder, 2020). This package allows for the comparison of network properties through post-predictive check methods, which use the Jensen-Shannon divergence, that symmetrizes the Kullback-Leibler divergence, to assess the distance between distributions (Williams et al., 2020).

The second step to explore the topological structure of each disorder in healthy and disordered participants was the identification of motifs. Motifs are subgraphs of a network from three to five nodes with different combinations of positive or negative edges (Letina et al., 2019). In this study, we searched for 4 types of completely connected subgraphs with 3 nodes. The subgraph types varied according to the types of connections present in them, three positive edges (PPP), two positive edges and one negative edge (PPN), one positive edge and two negative edges (PNN), and three negative edges (NNN). The identification of motifs was done with the *signnet* package (Schoch, 2020) for R (R Core Team, 2019). 200 random networks with the same properties as the estimated

networks, that is, the number of edges, nodes, and the number of negative edges, were generated to assess the validity of the motifs in the networks.

Results

Table 2.

Network properties.

Network	Connec-tivity	Average Degree	Average Path Length	Assortativity	Clustering	Modularity	Communities
With MDD	3.519	1.556	1.750	0.241	0.333	0.222	4
Without MDD	3.884	1.889	1.583	0.027	0.533	0.194	4
With GAD	2.165	1.714	1.429	0.070	0.676	0.080	2
Without GAD	2.423	2	1.333	-0.021	0.719	0.120	2
With SAD	10.856	5.412	1.324	-0.019	0.698	-0.061	6
Without SAD	9.506	4.529	1.434	0.075	0.571	0.053	5
With OCD	11.170	4.167	1.510	0.118	0.536	0.058	6
Without OCD	8.920	2.389	1.908	0.037	0.284	0.220	6

Networks Properties

Networks properties can be seen in Table 2. Only network connectivity distinguished between healthy and disordered states in all disorders (MDD, $p = 0.002$; GAD, $p < .001$; OCD, $p < .001$; SAD, $p < .001$). For SAD and OCD, disordered participant networks showed increased connectivity compared to the healthy participant network ($SAD_{with} = 10.856$, $SAD_{without} = 9.506$; $OCD_{with} = 11.170$, $OCD_{without} = 8.920$). However, in MDD and GAD, healthy participant networks were characterized by a higher density, contrary to healthy states of SAD and OCD ($MDD_{with} = 3.519$, $MDD_{without} = 3.884$; $GAD_{with} = 2.165$, $GAD_{without} = 2.423$).

As with network connectivity, GAD and MDD presented a different behavior than the other two disorders for the average path length. MDD and GAD presented a decreased average path length in healthy participants networks ($MDD_{with} = 1.750$, $MDD_{without} = 1.583$; $GAD_{with} = 1.429$, $GAD_{without} = 1.333$). In turn, the SAD and OCD networks displayed the opposite behavior, with the average path length increasing in healthy

participants networks (SAD_{with} = 1.324, $SAD_{without}$ = 1.434; OCD_{with} = 1.510, $OCD_{without}$ = 1.908). However, average path length only presented significant differences between healthy and disordered in MDD (p = 0.033), SAD (p < .001), OCD (p < .001) and not in GAD (p = 0.236).

The distinct behavior between GAD and MDD, and SAD and OCD continues to be visible in the average degree. While average degree increases in healthy networks of MDD and GAD (MDD_{with} = 1.56, $MDD_{without}$ = 1.889; GAD_{with} = 1.714, $GAD_{without}$ = 2), in SAD and OCD the average degree decreases (SAD_{with} = 5.412, $SAD_{without}$ = 4.529; OCD_{with} = 4.167, $OCD_{without}$ = 2.389). In addition to this, significant differences were only found for GAD (p = 0.025), OCD (p < .001) and SAD (p < .001) but not MDD (p = 0.257).

Network clustering also followed the same pattern as the previous network properties. GAD and MDD displayed an increased clustering in healthy participants' networks compared to disordered participants' networks (MDD_{with} = 0.333, $MDD_{without}$ = 0.533; GAD_{with} = 0.676, $GAD_{without}$ = 0.719). In turn, SAD and OCD showed a decrease in clustering in healthy participants' networks (SAD_{with} = 0.698, $SAD_{without}$ = 0.571; OCD_{with} = 0.536, $OCD_{without}$ = 0.284). However, significant differences were only found between disordered and healthy participants networks of OCD (p < .001) and SAD (p = 0.032) and not between MDD (p = 0.198) and GAD (p = 0.496) networks.

The modularity of the network was higher in the networks of GAD, SAD and OCD (GAD_{with} = 0.080, $GAD_{without}$ = 0.120; SAD_{with} = -0.061, $SAD_{without}$ = 0.053; OCD_{with} = 0.058, $OCD_{without}$ = 0.220). In MDD networks, network modularity was higher in disordered participants' networks than in healthy networks (MDD_{with} = 0.222, $MDD_{without}$ = 0.194). Despite this, significant statistical differences were only found

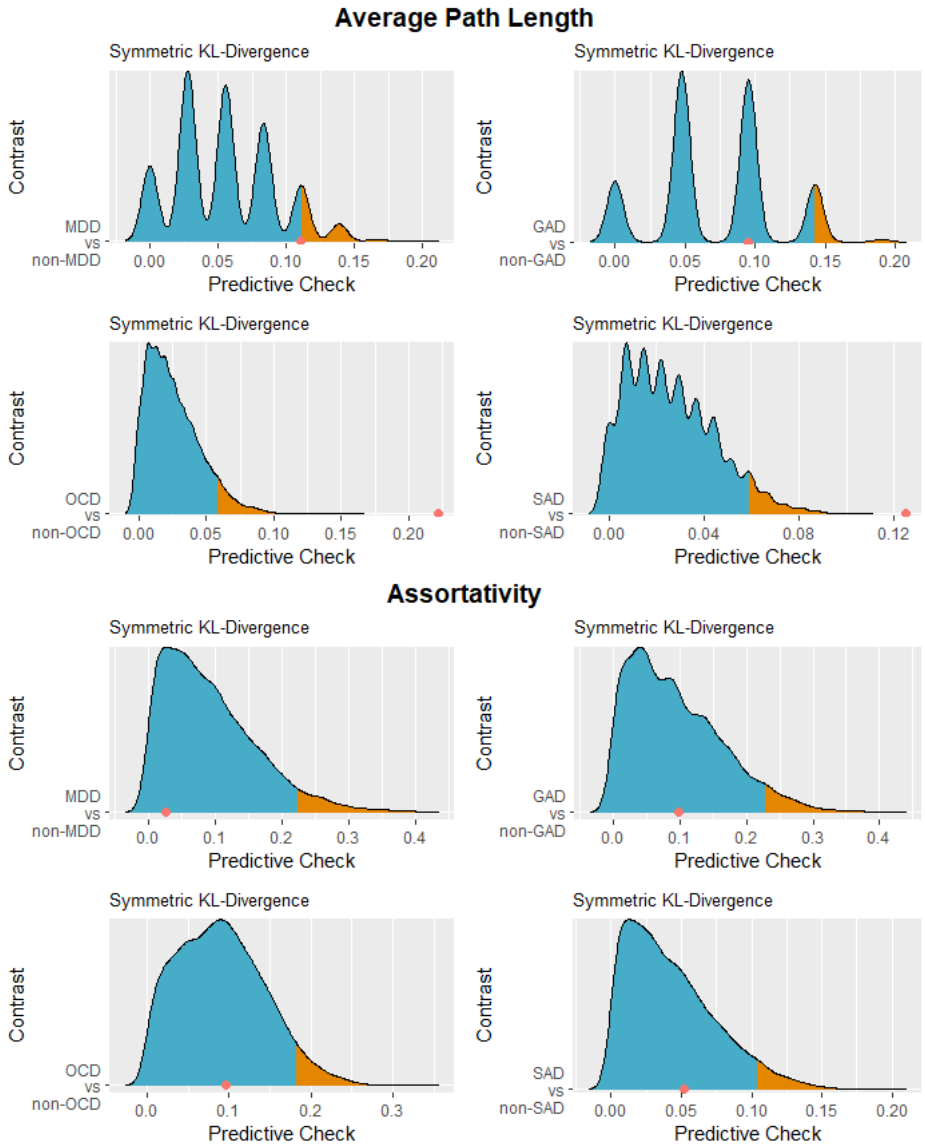
between the networks of healthy and disordered participants in OCD ($p = 0.002$) and not between MDD ($p = 0.749$), GAD ($p = 0.261$), and SAD ($p = 0.755$).

Regarding network assortativity, MDD disordered participants network had an assortativity of 0.241 and the healthy participants network an assortativity value of 0.027 without significant statistical differences ($p = 0.823$). GAD disordered participants network had an assortativity value of 0.070 and GAD healthy participants had a negative assortativity value of -0.021 with no significant statistical differences ($p = 0.407$). No significant statistical differences were found for SAD networks ($p = 0.338$) and with assortativity values for the healthy participants network of 0.075 and for disordered participants of -0.019. No significant statistical differences were found between the OCD networks of healthy and disordered participants ($p = 0.431$) with the healthy participant network having an assortativity value of 0.118 and for disordered participants a value of 0.037.

Figure 1

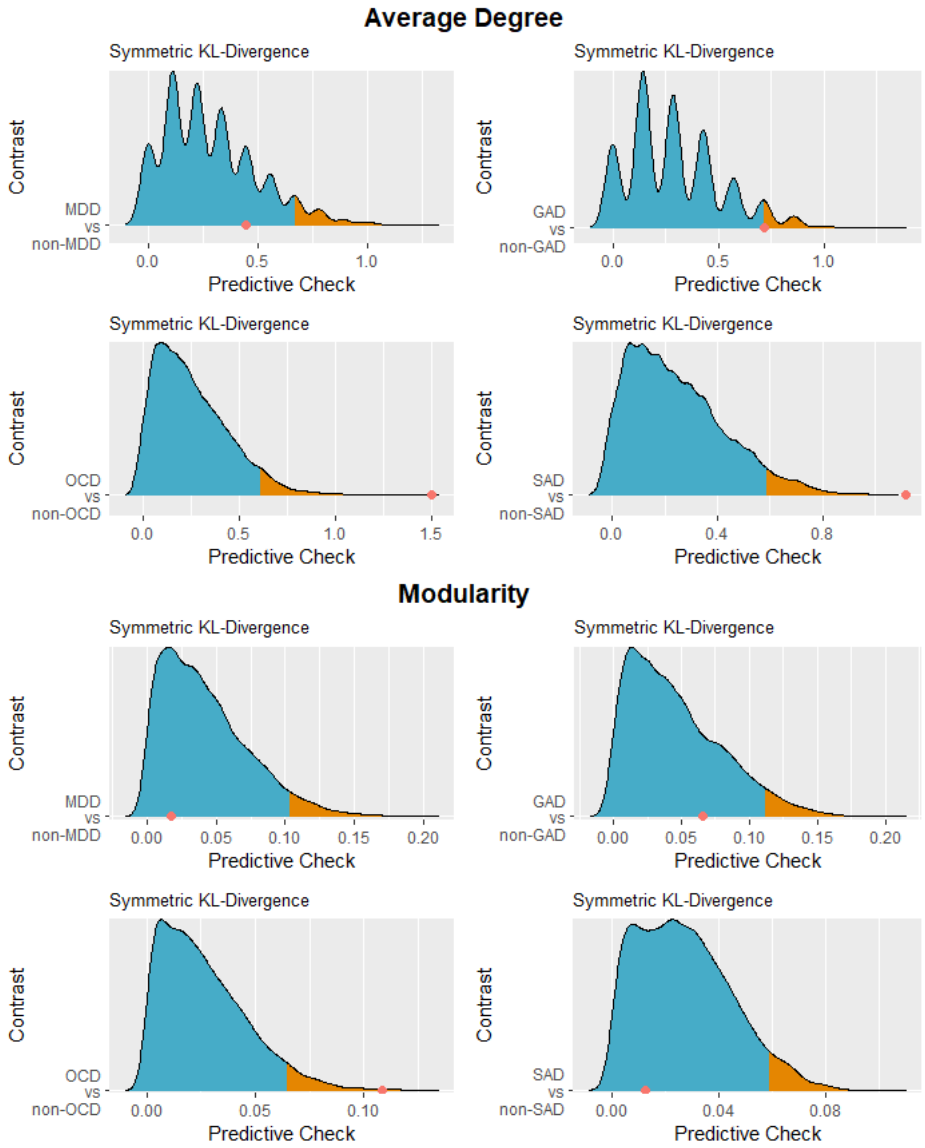
Note. Panel a) shows the symmetric KL-Divergence comparison on network density between disorder state (psychopathological or healthy state) for each disorder; panel b) shows the symmetric KL-Divergence comparison on network clustering between disorder state (psychopathological or healthy state) for each disorder.

Figure 2



Note. Panel a) shows the symmetric KL-Divergence comparison on network average path length between disorder state (psychopathological or healthy state) for each disorder; panel b) shows the symmetric KL-Divergence comparison on network assortativity between disorder state (psychopathological or healthy state) for each disorder.

Figure 3



Note. Panel a) shows the symmetric KL-Divergence comparison on network average degree between disorder state (psychopathological or healthy state) for each disorder; panel b) shows the symmetric KL-Divergence comparison on network modularity between disorder state (psychopathological or healthy state) for each disorder.

Motifs

The results of the motifs analysis can be found in Table 3 and Figures 5, 6, 7, and 8 of the supplementary materials. In GAD and MDD healthy participants' networks displayed a higher number of total motifs compared to the disordered samples, which is contrary to the SAD and OCD networks where the number of motifs increased in the disordered samples' networks.

In MDD, the healthy participants network had only two types of PPP motifs (n = 5) and PPN (n = 3), and the disordered participants network had only PPP type motifs (n = 3). For GAD networks, in the disordered sample two types of motifs were identified PPP (n = 4) and PPN (n = 2), in turn, in the healthy sample only PPP (n = 10) type motifs were identified.

In SAD, both healthy and disordered participants networks had all the motif types explored, with the disordered sample network displaying a higher total number of motifs (n = 216) than the healthy sample (n = 123). In the disordered sample network, the most frequent type of motif was PPN (n = 102), followed by PPP (n = 57), PNN (n = 48) and the least frequent motif type was NNN (n = 9). For the healthy sample network of SAD, the most common motif type was PPP (n = 53), followed by PPN (n = 49), PNN (n = 28), and NNN (n = 3).

For OCD networks, the disordered sample also had a higher number of motifs (n = 100) than the healthy sample (n = 18). The disordered sample network had all types of motifs, with PPN (n = 52) being the most frequent, followed by PNN (n = 28), PPP = 17 and NNN (n = 3). In turn, the healthy sample had only two types of motifs PPP (n = 10) and PPN (n = 8).

Table 3.

Total number of motifs found for each healthy and disordered participants' network.

Network	PPP	PPN	PNN	NNN
With MDD	3	0	0	0
Without MDD	5	3	0	0
With GAD	4	2	0	0
Without GAD	10	0	0	0
With SAD	57	102	48	9
Without SAD	53	49	19	2
With OCD	17	52	28	3
Without OCD	10	8	0	0

Discussion

Network theory presupposes that network connectivity is a synonym of symptom activation and that, consequently, connectivity will be a marker of psychopathology (Borsboom, 2017; Borsboom & Cramer, 2013). However, the results have not been conclusive (Bos et al., 2018; Schweren et al., 2018; van Borkulo et al., 2015) and further exploration of the properties of the network is needed. However, previous studies and theoretical proposals have only focused on the network connectivity, with few studies generating hypothesis about other network properties. In this study, we tried to address this gap by comparing, diagnosed, and healthy individuals across four different disorders on their meso- and macro properties.

The lack of exploration of these properties limits the applied research that can be developed in the field of psychological networks. For example, network connectivity has been central on the applied research developed for the identification of treatment targets (Levinson et al., 2018) and early warning signals (Schweren et al., 2018). Attending to our results this focus on connectivity might not be useful for every mental disorder. In fact, contrary to theoretical expectations (Borsboom, 2017), our results suggest that increased connectivity is not always a characteristic of networks in a psychopathological state. Which limits, for example, the applicability of previous simulation studies on the

identification of treatment targets by modelling the impact on connectivity (Castro et al., 2019; Lunansky et al., 2022).

In our study, healthy state GAD and MDD networks have significantly more connectivity than their psychopathological counterparts and these results are not idiosyncratic. Several studies have reported similar results in depression and anxiety networks (Beard et al., 2016; Bos et al., 2018; Hartung et al., 2019; Kraft et al., 2019; Schweren et al., 2018; Snippe et al., 2017). In turn, for SAD and OCD networks, connectivity had the behavior proposed by network theory, with the psychopathological networks of SAD and OCD having more connectivity than their respective healthy networks. These results suggest that network connectivity might not be a viable psychopathology marker for all mental disorders.

This different behavior of MDD and GAD is also visible in the remaining properties studied. Although, no significant differences were found in the same network macro-properties for both disorders when comparing healthy and psychopathological networks. The global pattern of behavior of these networks was the same, with increases in average degree and clustering and with decreases in average path length and assortativity on healthy state networks. In turn, SAD and OCD have the opposite behavior in these macro-properties. These differences between MDD/GAD and SAD/OCD remain on the meso-properties of the network. MDD/GAD healthy state networks having more motifs than the psychopathological state versions and SAD/OCD had more motifs on their psychopathological state networks.

Thus, our results suggest that macro- and meso-properties for OCD and SAD might be identifying different development or maintenance processes than those in GAD and MDD. More importantly, focusing on a single property like network connectivity

might not be productive, and more research into macro- and meso-properties of psychopathological networks is needed.

In this context, future research should explore and replicate these findings to clarify why network properties differ across these disorders. Clarifying these differences might help the identification of the mechanisms that might be behind these disorders and provide a better understanding of the processes of development and maintenance of psychopathology.

Our results should be interpreted considering some limitations. We used only cross-sectional networks that have been shown to have different properties than longitudinal networks, namely micro-properties such as centrality (Contreras et al., 2019). In addition, we only used a reduced number of disorders, and it is unknown if the macro- and meso- properties pattern found in the studied disorders can be generalized to other disorders. Moreover, we explored a reduced number of macro- and meso- properties of the networks. Network analysis provides several other macro- and meso- properties that might be useful for characterizing mental disorder networks.

In summary, our study contributes to the growing body of literature on network theory and psychopathology by highlighting the nuanced nature of network properties in different disorders. These findings underscore the need for further investigation to elucidate the mechanisms underlying these disorders. Future research should consider longitudinal designs, explore a wider range of disorders, and investigate additional properties of the network to advance our understanding of mental disorders from a network perspective.

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CHAPTER II [1, 2, 3]

Centrality Measures in Psychological Networks: A Simulation Study on Identifying Effective Treatment Targets

Note:

[1] This chapter has been accepted for publication in *PLOS ONE*:

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[2] Supplementary materials of this paper are available in the Chapter II of the Appendix.

[3]Code to reproduce the analysis the analysis can be found at https://osf.io/k2z84/

Abstract

The network theory of psychopathology suggests that symptoms in a disorder form a network and that identifying central symptoms within this network might be important for an effective and personalized treatment. However, recent evidence has been inconclusive.

We analyzed contemporaneous idiographic networks of depression and anxiety symptoms. Two approaches were compared: a cascade-based attack where symptoms were deactivated in decreasing centrality order, and a normal attack where symptoms were deactivated based on original centrality estimates.

Results showed that centrality measures significantly affected the attack's magnitude, particularly the number of components and average path length in both normal and cascade attacks. Degree centrality consistently had the highest impact on the network properties.

This study emphasizes the importance of considering centrality measures when identifying treatment targets in psychological networks. Further research is needed to better understand the causal relationships and predictive capabilities of centrality measures in personalized treatments for mental disorders.

Keywords: network analysis; treatment targets; depression; anxiety; simulation

In recent years, the field of psychology has increasingly acknowledged the necessity of personalized treatments (David et al., 2018; Hofmann & Hayes, 2019; Roche et al., 2014). This recognition has been facilitated by advancements in technology and longitudinal assessment methodologies (Wright & Woods, 2020). Within this context, network analysis emerged as one of the most promising methodological approaches to study this type of data (Bos, Blaauw, et al., 2018; Fisher et al., 2017; van Borkulo et al., 2015). By modeling mental disorders as a network of symptoms, where symptoms are viewed as nodes and connections between them as edges (Borsboom & Cramer, 2013). From this methodological approach, the network theory of psychopathology emerged (Borsboom, 2017; Borsboom et al., 2019; Borsboom & Cramer, 2013; Nuijten et al., 2016). The network theory of psychopathology (Borsboom, 2017; Borsboom et al., 2019) proposes that when a symptom is activated (such as by an external event) a signal diffuses through the network, activating other symptoms. The activation of other symptoms increases the network connectivity and the system transitions into a disease state. Thus, a symptom with more connections might activate several other symptoms and might have an essential role in sustaining the disease. Due to this, these symptoms have been suggested to be preferential treatment targets (Borsboom & Cramer, 2013; Hofmann et al., 2016).

In network analysis the identification of these symptoms can be performed through the estimation of centrality measures, such as degree, strength, betweenness, and closeness, which uncover each symptoms' connectivity. With these measures, and with the proposal from the network theory of psychopathology, several studies suggested possible treatment targets based on network centrality measures (McElroy et al., 2018; Olatunji et al., 2018; Rhemtulla et al., 2016; Stochl et al., 2019). However, recent evidence showed that closeness and betweenness centrality are not adequate in

psychopathological networks, given their bias in the covariance and sampling variability (Epskamp, Borsboom, et al., 2018; Hallquist et al., 2019). Dablander and Hinne (2019) shown that the most common centrality measures used in psychology are not related to causality, except for eigenvector centrality. This is partially validated by the inconsistent results shown by studies examining the central symptoms as psychotherapeutic targets (Bos et al., 2018; Papini et al., 2020; Rodebaugh, Tonge, Piccirillo, et al., 2018; Spiller et al., 2020).

Studies found central symptoms to predict changes in the remaining symptoms (Elliott et al., 2020; Robinaugh et al., 2016) and enable the evolution to a psychopathological condition (Boschloo et al., 2016). However, Bos and colleagues (2018) have not found evidence to support the hypothesis that symptom centrality is associated with changes in symptoms over time across cross-sectional networks. Furthermore, three other studies used the same procedure in three different samples finding only moderate support for this hypothesis. Rodebaugh and colleagues (2018) explored if a cross-sectional network of social anxiety symptoms predicted changes in another sample of individuals who undertook treatment for the same disorder. The authors concluded that symptom centrality was not generalized across measures and frequency of symptom endorsement also predicted change while being generalized across measures. Spiller and colleagues (Spiller et al., 2020) and Papini and colleagues (2020) have also concluded that symptom endorsement was a better predictor of change than the centrality measures, with only expected influence predicting how changes in symptoms were associated with changes in the remainder of the symptoms. In fact, deactivating symptoms according to their centrality does not seem to significantly reduce network density more than the random deactivation of symptoms (Castro et al., 2019).

Despite this, and in line with the studies that reported changes in the network structure when comparing psychological networks at different stages (Curtiss et al., 2019; Groen et al., 2019; Hartung et al., 2019; Kraft et al., 2019; Montazeri et al., 2019; Silk et al., 2019), when symptoms are deactivated according to their degree centrality there are significant changes in the number of components of the network (Castro et al., 2019). However, most of these studies were performed using cross-sectional networks (Beard et al., 2016; Bos et al., 2018; Papini et al., 2020; Rodebaugh, Tonge, Piccirill, et al., 2018; Schweren et al., 2018; Spiller et al., 2020) which might have hampered their findings, due to individuals' idiosyncrasy that is lost in the cross-sectional analysis (Fisher, 2015).

As a potential framework to unveil the individual-level differences one can leverage idiographic networks (Bringmann et al., 2013), which allow for a detailed understanding of the associations between symptoms, their directionality, and how different processes (e.g., thoughts, feelings, and behaviors) fluctuate over time (Wichers & Groot, 2016). It is based on this dynamicity that we can understand the diversity of clinical and symptomatologic trajectories. This idiographic dynamic view, coupled with the hypothesis of central symptoms being more efficient treatment targets, might promote the development of better personalized treatments. In fact, Levinson, and colleagues (2023) reported initial evidence that identifying treatment targets through strength centrality in idiographic networks might improve treatments efficacy. However, Levinson and colleagues (2023) only identified treatment targets at a single point (i.e., third session), which disregards the changes in the network that might occur after that point. It is expected that after an intervention directed to a symptom, changes in the network structure occur (Borsboom & Cramer, 2013). If these changes occur, a new central symptom may emerge, which should become the primary treatment target (Castro et al.,

2019). Failing to account for this possibility may result in an intervention that does not target the most central symptom, potentially reducing the efficacy of the treatment.

Considering this, the hypothesis that central symptoms might be valuable therapeutic targets remains open. Here we address this hypothesis by assessing the impact of symptom deactivation on idiographic networks according to different centrality measures. We do it, by comparing the impact of symptom deactivation using two different types of symptom deactivation procedures, one procedure based only on a single point estimate of centrality measures and a second procedure in which the centrality measures are re-estimated every time a symptom is deactivated. As usual in network science, the impact of symptom deactivation according to the centrality estimates is evaluated in comparison to the random deactivation of symptoms.

Method

Data

This study involved an analysis of existing data rather than new data collection. Datasets analyzed in the current study are publicly available (available at https://osf.io/mgdp6). Data was accessed in 9 of January of 2019 the authors did not had access to information that could identify individual participants. The ethics committee approval, the accordance of all the methods with relevant guidelines and regulations, and the informed consent were obtained in a previous published study by different authors (Fisher et al., 2017). The authors of this manuscript had no control over these data collection procedures. All the code used in this study is available at https://osf.io/k2z84/.

We analyze contemporaneous idiographic networks of depression and anxiety symptoms from 40 participants (Fisher et al., 2017), which, in the original study, aimed to explore the idiographic structure of mood and anxiety symptomatology via

contemporaneous and temporal networks. The participants had to have a diagnosis of major depressive disorder (MDD) or generalized anxiety disorder (GAD) and an age of 18 to 65 years, participants with a history of psychosis or mania were excluded. Most of the participants were female (65%), and 25 participants met the criteria for current GAD and 15 for current MDD (all the demographic data made available by the original study is presented in Table S1 in the S1 Appendix), network basic features are presented in Table S2. Participants rated their symptoms for 30 days, four times per day through an Experience Sample Survey (ESS), which we used here to estimate temporal and contemporaneous networks of MDD and GAD symptoms for each participant. The ESS consisted of DSM-5 symptoms for MDD and GAD, where each participant rated their experience of each symptom in the preceding hours on a 0-100 scale and provided a mean (*M*) of 130.43 observations with a standard deviation (SD) of 19.27.

Here we focus on the contemporaneous networks. Contemporaneous networks can identify connections that would not be visible in temporal networks. This happens because temporal networks model the relationships that are predicted from one window of measurement to the next (Epskamp, van Borkulo, et al., 2018), which are, usually, in an interval of a few hours (Bos et al., 2015; Fried et al., 2022; Rath et al., 2019). However, it is possible for causal relationships between variables to occur within timeframes that differ from those used to assess them but that can be identified through contemporaneous networks (Epskamp, van Borkulo, et al., 2018). Thus, within-person contemporaneous networks might provide better identification of treatment targets. Therefore, here we focus on within-person contemporaneous networks to identify psychotherapeutic targets using centrality measures.

Data analyses

For each participant, in the original study (Fisher et al., 2017), a contemporaneous correlation matrix was extracted and then a sparse partial correlation network was estimated using the Least Absolute Shrinkage and Selection Operator (LASSO) regularization method (Epskamp, Borsboom, et al., 2018). On the original study (Fisher et al., 2017), model fit was assessed with RMSEA, Browns chi-square goodness-of-fit test, and the CFI. The authors considered non-significant chi-square tests, RMSEA values less than .060 and CFI values equal or greater than .95 to reflect an excellent fit. All participants exhibited an excellent fit on both chi-square and CFI. On RMSEA only one participant had a value of 0.062, with all the other participants exhibiting values below 0.060.

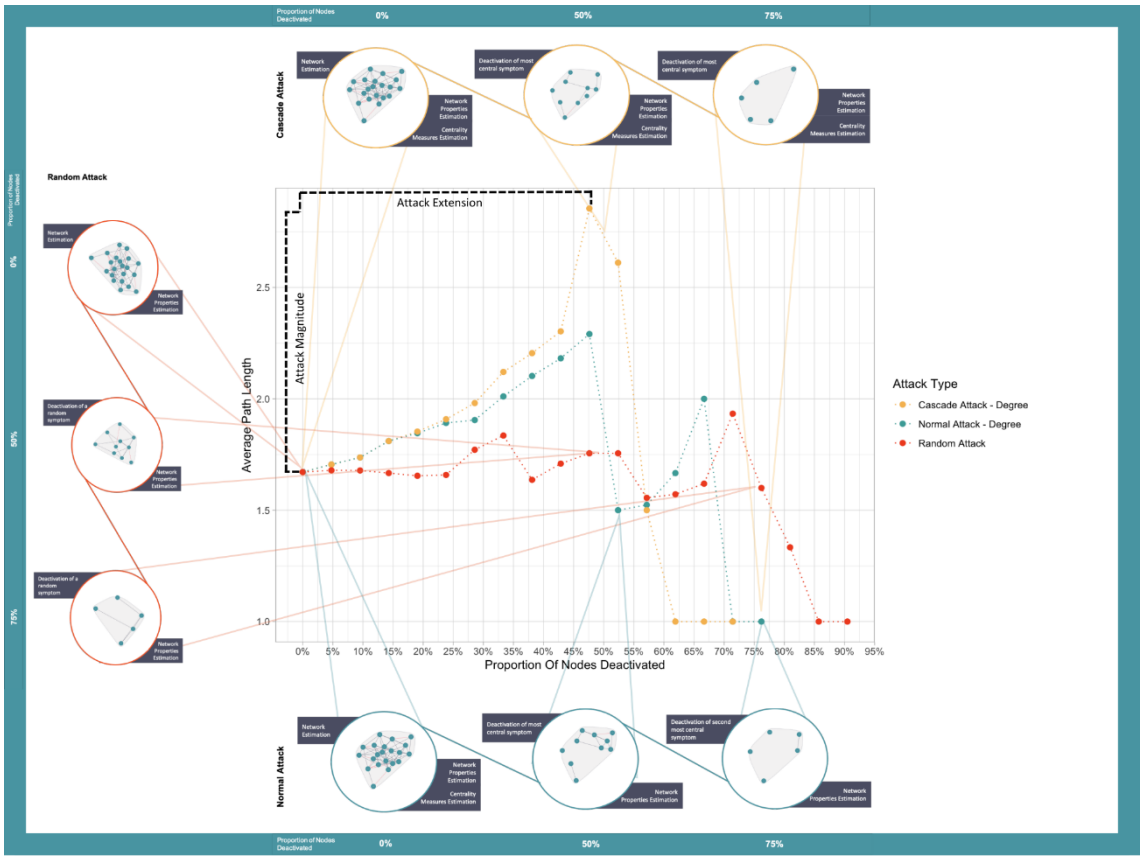
To identify the central nodes and their effect on individual networks, we perform a two-step analysis: i) the identification of central symptoms and ii) the exploration of the differential impact of symptoms' deactivation in the network. We investigate symptom deactivation as an indirect measure of symptom improvement, operating under the assumption that a symptom's complete recovery would result in its removal from the network of symptoms. This is done to simulate the effect of detecting a central symptom and then acting on it and improving it until the symptom is not felt / reported by participants.

The network exploration of symptom deactivation is performed as a cascade-based attack and a normal attack. In a cascade-based attack, symptoms are deactivated in their decreasing order according to their centrality, which is iteratively calculated at every symptom removal. In normal attack (Castro et al., 2019), symptoms were deactivated according to their original centrality. We compare this with random attack symptom deactivation procedure, where symptoms are randomly deactivated. In each type of attack

a symptom is identified as a treatment target and deactivated from the network. For the cascade-based attack, symptom networks and treatment target selection are constantly being estimated and selected after each symptom deactivation. In the normal attack the treatment targets order is determined based on the initial symptom network of the participant and the attack follows that order without estimating the network again. Fig 1 illustrates an example of each attack and their differential impact on the average path length.

Figure 1

Example representation of the 3 types of attacks and the 2 outcome measures 1.



Note. An example representation of the 3 types of attacks (random attack and degree-based normal and cascade attack) and the 2 outcome measures (attack magnitude and attack extension). Attack methods are exemplified by the colored circles, yellow circles represent the cascade attack, orange circles the random attack, and green circles the

normal attack. Colored dots represent the average path length of the network after the deactivation of the symptom identified by the attack. The X-axis represents the proportion of nodes deactivated and the Y-axis represents the average path length after each node deactivation.

In the cascade-based attack and in the normal attack procedures' we identified the central symptoms through five different centrality measures: strength centrality, degree centrality, one-step and two-step expected influence centrality, and eigenvector centrality. Strength centrality, one-step and two-step expected influence were chosen due to their extensive use in psychopathological networks (Birkeland & Heir, 2017; Gauld et al., 2023; Richetin et al., 2017). In addition, degree and eigenvector were selected due to being suggested as alternatives for better identification of treatment targets (Castro et al., 2019; Dablander & Hinne, 2019). After each symptom deactivation, a set of network properties was measured (i.e., network density, number of components, and average path length). The network density is the ratio between the number of edges in the network and all the potential edges (Wasserman & Faust, 1994), while the number of components in the network refers to the number of symptoms or groups of symptoms that are disconnected from the rest of the network and might be able to help us with the identification of groups of active symptoms. Finally, the average path length concerns the mean of the shortest paths in the networks and might identify if network symptoms activation is more likely due to the shortest distance between network symptoms.

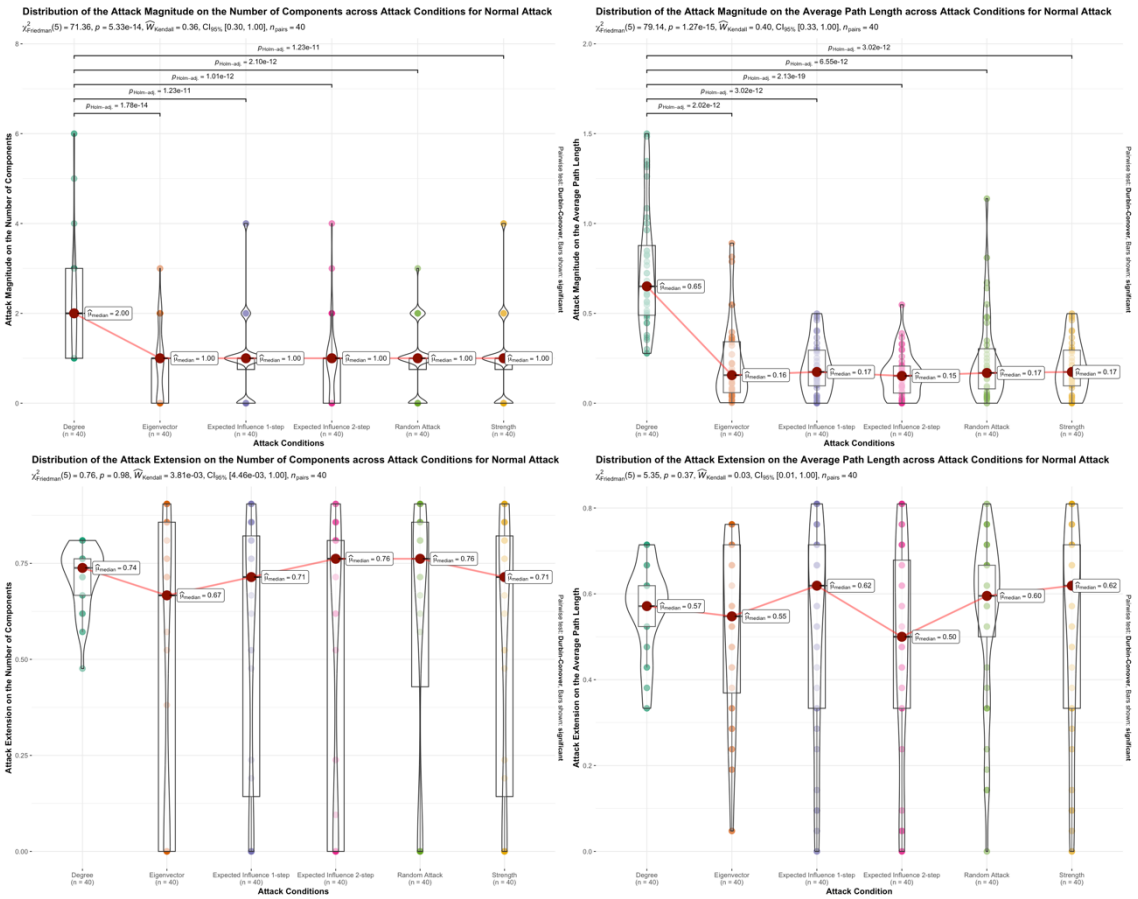
For each centrality measure, we assessed the differential impact of symptom deactivation by computing the magnitude and extent of the attack in the network, where the impact magnitude consists of the difference between the maximum values of average path length and components and their initial values. We next measured the attack extent by computing the proportion of nodes that needed to be deactivated to achieve the

maximum value of average path length and number of components. To assess the impact of symptom deactivation on the network density we computed the density of the network at 50% of the symptoms deactivated. All these analyses were performed in the package *psychNetsAttack* (Castro, 2021) for *R* (R Core Team, 2019). We did this to each of the 40 networks (Fig. S3 – S83 in theS1 Appendix) and then aggregated the results from each of the 40 networks to compare the results of each centrality measure.

To compare each centrality measure attack magnitude and extent on the number of components, average path length, and network density for both normal and cascade attack we used a Friedmann's Test, we followed by a Kendall's coefficient of concordance to estimate the effect and Durbin-Conover test for post-hoc test. We performed this analysis in the *R* (R Core Team, 2019) package *ggstatsplot* (Patil, 2021). These results are presented in Figs 2 – 4.

Figure 2

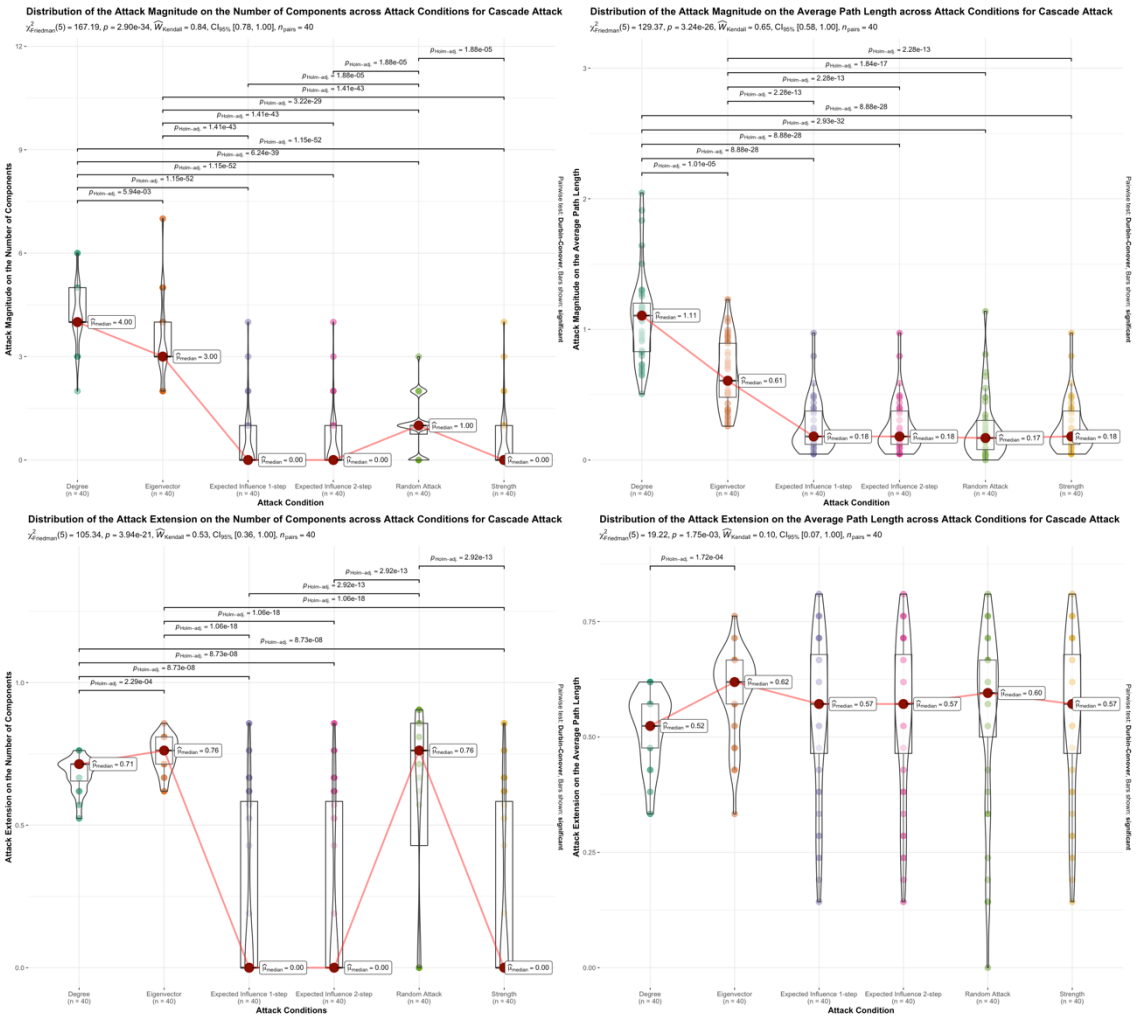
Graphical representation of normal attack magnitude and extension results across the 5 attack conditions.



Note. Graphical representation of normal attack magnitude and extension results across the 5 attack conditions, degree, eigenvector, expected influence 1-step, expected influence 2-step. In each panel result of the Friedman rank-sum test for differences between attack, and conditions are presented on top. The significant differences found between attack conditions, in the Durbin-Conover post-hoc test, are represented by lines between attack conditions and with the Holm corrected p-value above. Only significant differences are represented. Boxplots represent the interquartile range, the median and the outliers for attack magnitude or extension range for each attack condition. Violin plots display the probability density of the data.

Figure 3

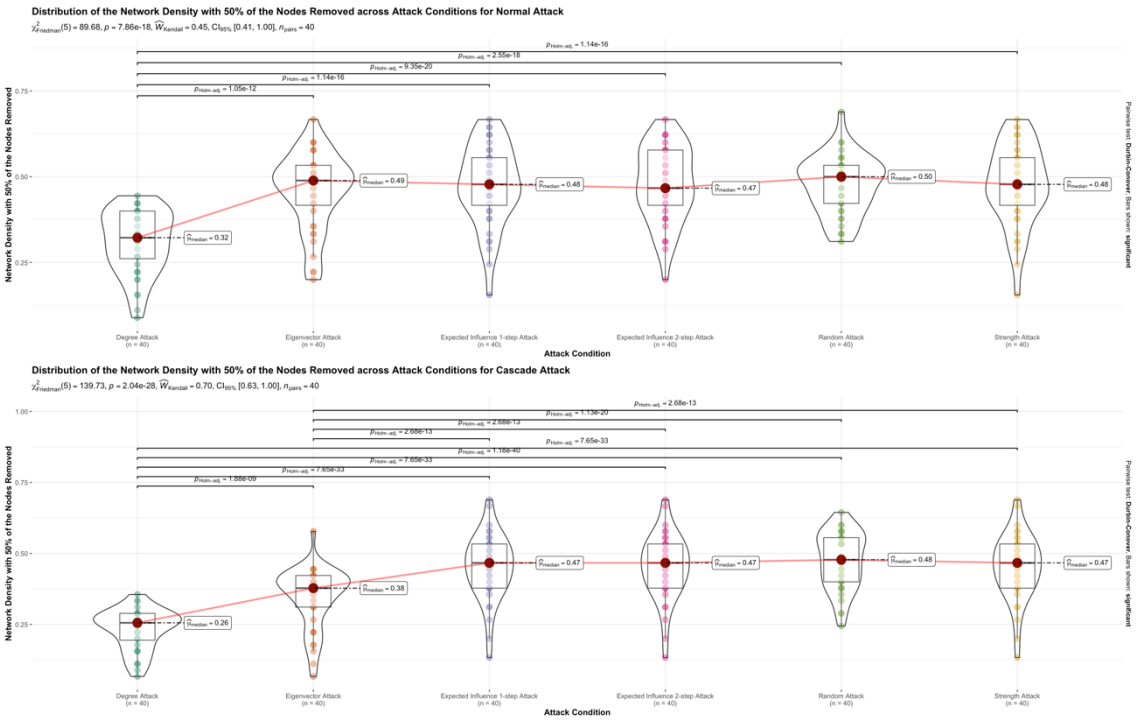
Graphical representation of cascade attack magnitude and extension results across the 5 attack conditions.



Note. Graphical representation of normal attack magnitude and extension results across the 5 attack conditions, degree, eigenvector, expected influence 1-step, expected influence 2-step. In each panel result of the Friedman rank-sum test for differences between attack, and conditions are presented. The significant differences found between attack conditions, in the Durbin-Conover post-hoc test, are represented by lines between attack conditions and with the Holm corrected p-value above. Only significant differences are represented. Boxplots represent the interquartile range, the median and the outliers for attack magnitude or extension range for each attack condition. Violin plots display the probability density of the data.

Figure 4

Graphical representation of the results for network density with 50% of the nodes removed.



Note. Graphical representation of the results for network density with 50% of the nodes removed in normal and cascade attack across the 5 attack conditions, degree, eigenvector, expected influence 1-step, expected influence 2-step. In each panel result of the Friedman rank-sum test for differences between attack, and conditions are presented. The significant differences found between attack conditions, in the Durbin-Conover post-hoc test, are represented by lines between attack conditions and with the Holm corrected p-value above. Only significant differences are represented. Boxplots represent the interquartile range, the median and the outliers for attack magnitude or extension range for each attack condition. Violin plots display the probability density of the data.

Results

Figs 2 through 4 visually depict the influence of the centrality measures on attack extent or magnitude concerning both the number of components and the average path length in the 40 studied networks. Additionally, these figures present the statistical

outcomes of the Friedman's Test and highlight significant findings obtained through the Durbin-Conover post-hoc test.

For a normal attack, the extent and magnitude of the attack on the number of components and the average path length of each centrality measure are presented in Table 1. Normal attack distributions for attack extent and magnitude of these properties can be seen in Fig 2, as well as the significant results from the post-hoc comparison tests. We observed a statistically significant effect of centrality measures on the magnitude of the normal attack on the number of components ($X^2_F(5) = 71.02$, $p < .001$, $W_k = 0.40$, 95% CI [0.36, 0.61]) and on the average path length ($X^2_F(5) = 79.14$, $p < .001$, $W_k = 0.43$, 95% CI [0.34, 0.74]), post hoc comparisons suggest that degree centrality had a significant higher attack magnitude on the number of components and on the average path length than all the other centrality measures and the random attack. The extent of the normal attack on the number of components ($X^2_F(5) = 0.47$, $p = 0.993$, $W_k = 0.23$, 95% CI [0.20, 0.71]) and on the average path ($X^2_F(5) = 6.26$, $p = 0.281$, $W_k = 0.33$, 95% CI [0.32, 0.63]) did not show statistically significant effects.

Table 1.
Descriptive statistics for normal attack.

Network characteristic / attack condition	Attack Magnitude			Attack Extent		
	Mean (SD*)	Median (MAD**)	Minimum - maximum	Mean (SD)	Median (MAD)	Minimum - maximum
Components						
Degree	2.30 (1.26)	2.00 (1.48)	1 - 6	0.72 (0.08)	0.74 (0.04)	0.48 - 0.81
Strength	1.02 (0.92)	1.00 (0.00)	0 - 4	0.55 (0.36)	0.71 (0.21)	0 - 0.90
Expected Influence 1-step	1.02 (0.92)	1.00 (0.00)	0 - 4	0.55 (0.36)	0.71 (0.21)	0 - 0.90
Expected Influence 2-step	0.95 (0.85)	1.00 (0.00)	0 - 4	0.54 (0.37)	0.76 (0.14)	0 - 0.90
Eigenvector	0.88 (0.82)	1.00 (1.48)	0 - 3	0.49 (0.40)	0.67 (0.35)	0 - 0.90
Random	0.95 (0.85)	1.00 (0.00)	0 - 3	0.51 (0.36)	0.76 (0.14)	0 - 0.90

Average Path Length						
Degree	0.74 (0.34)	0.65 (0.28)	0.28 - 1.50	0.56 (0.10)	0.57 (0.07)	0.33 - 0.71
Strength	0.20 (0.15)	0.17 (0.18)	0 - 0.50	0.52 (0.25)	0.62 (0.21)	0 - 0.81
Expected Influence 1-step	0.20 (0.15)	0.17 (0.18)	0 - 0.50	0.52 (0.25)	0.62 (0.21)	0 - 0.81
Expected Influence 2-step	0.16 (0.13)	0.15 (0.12)	0 - 0.55	0.48 (0.26)	0.50 (0.25)	0 - 0.81
Eigenvector	0.23 (0.23)	0.16 (0.17)	0 - 0.89	0.52 (0.21)	0.55 (0.25)	0.05 - 0.76
Random	0.28 (0.16)	0.18 (0.18)	0.01 - 0.68	0.59 (0.15)	0.62 (0.14)	0.19 - 0.81

	50% of nodes deactivated		
	Mean (SD)	Median (MAD)	Minimum - Maximum
Density			
Degree	0.31 (0.09)	0.32 (0.12)	0.09 – 0.44
Strength	0.47 (0.12)	0.48 (0.12)	0.16 – 0.67
Expected Influence 1-step	0.47 (0.12)	0.48 (0.12)	0.16 – 0.67
Expected Influence 2-step	0.48 (0.11)	0.47 (0.13)	0.20 – 0.67
Eigenvector	0.46 (0.11)	0.49 (0.08)	0.20 – 0.67
Random	0.47 (0.09)	0.50 (0.08)	0.31 -0.69

Descriptive statistics for normal attack magnitude and extent on the number of components and average path length and network density with 50% of the nodes deactivated.
* Standard deviation
** Median Absolute Deviation

Regarding the cascade attack, the extent and magnitude of the different centrality measures are presented in Table 2, and Fig 3 shows the distributions for the different centrality measures. Magnitude of the attack showed statistically significant effect of centrality measures on the median attack magnitude on the number of components, X^2_F (5) = 165.57, $p < .001$, $W_k = 0.35$, 95% CI [0.33, 0.59], and on the average path X^2_F (5) = 129.37, $p < .001$, $W_k = 0.40$, 95% CI [0.32, 0.76]. Post hoc comparisons suggest that degree centrality and eigenvector centrality yielded a significantly higher attack magnitude on the number of components than the random attack and the remaining centrality measures. The random attack also had a statistically higher attack magnitude

on the number of components than strength centrality and expected influence one-step and two-step. On the average path length, post hoc comparisons on the cascade attack magnitude were also significantly higher for degree centrality and eigenvector centrality. The remaining centrality measures did not present significant differences between them.

Table 2.
Descriptive statistics for cascade attack.

Network characteristic /attack condition	Attack Magnitude -Mean (SD*)	Median (MAD**)	Minimum maximum	Attack Extent -Mean (SD)	Median (MAD)	Minimum - maximum
Components						
Degree	4.20 (0.88)	4.00 (0.74)	2.00 – 6.00	0.68 (0.06)	0.71 (0.07)	0.52 – 0.76
Strength	0.55 (0.90)	0.00 (0.00)	0.00 – 4.00	0.23 (0.32)	0.00 (0.00)	0.00 – 0.86
Expected Influence 1-step	0.55 (0.90)	0.00 (0.00)	0.00 – 4.00	0.23 (0.32)	0.00 (0.00)	0.00 – 0.86
Expected Influence 2-step	0.55 (0.90)	0.00 (0.00)	0.00 – 4.00	0.23 (0.32)	0.00 (0.00)	0.00 – 0.86
Eigenvector	3.50 (1.24)	3.00 (1.48)	2.00 – 7.00	0.75 (0.06)	0.76 (0.07)	0.62 – 0.86
Random	0.98 (0.73)	1.00 (0.00)	0.00 – 3.00	0.59 (0.36)	0.76 (0.14)	0 – 0.90
Average Path Length						
Degree	1.09 (0.35)	1.11 (0.28)	0.51 – 2.05	0.52 (0.08)	0.52 (0.07)	0.33 – 0.62
Strength	0.26 (0.21)	0.18 (0.13)	0.05 – 0.97	0.55 (0.17)	0.57 (0.18)	0.14 – 0.81
Expected Influence 1-step	0.26 (0.21)	0.18 (0.13)	0.05 – 0.97	0.55 (0.17)	0.57 (0.18)	0.14 – 0.81
Expected Influence 2-step	0.26 (0.21)	0.18 (0.13)	0.05 – 0.97	0.55 (0.17)	0.57 (0.18)	0.14 – 0.81
Eigenvector	0.66 (0.26)	0.61 (0.32)	0.26 – 1.23	0.60 (0.09)	0.62 (0.07)	0.33 – 0.76
Random	0.25 (0.24)	0.18 (0.18)	0.00 – 1.14	0.55 (0.19)	0.62 (0.14)	0.00 – 0.81
	50% of nodes deactivated					
	Mean (SD)		Median (MAD)		Minimum - Maximum	
Density						
Degree	0.23 (0.07)		0.26 (0.05)		0.07 – 0.36	
Strength	0.45 (0.11)		0.47 (0.10)		0.13 – 0.69	
Expected Influence 1-step	0.45 (0.11)		0.47 (0.10)		0.13 – 0.69	
Expected Influence 2-step	0.45 (0.11)		0.47 (0.10)		0.13 – 0.69	
Eigenvector	0.35 (0.11)		0.38 (0.07)		0.07 – 0.58	
Random	0.47 (0.10)		0.48 (0.12)		0.24 – 0.64	

Descriptive statistics for cascade attack magnitude and extent on the number of components and average path length and network density with 50% of the nodes deactivated.
* Standard deviation
** Median Absolute Deviation

Similarly, cascade attack extent on the number of components returned a statistically significant effect X^2_F (5) = 101.05, p < .001, W_k = 0.22, 95% CI [0.21, 0.56] with the faster centrality measures to achieve maximum value on the number of components being expected influence one-step and two-step and strength centrality. However, as aforementioned, the attack extension is the proportion of symptoms that need to be deactivated to achieve the maximum value. Thus, the lower the score in the attack extension the better. However, expected influence one-step and two-step and strength centrality, as can be seen in the attack magnitude results, did not promote any change in the network (M_{dn} = 0). Accordingly, the maximum value equals the initial value of the network and, consequently, the median number of symptoms that need to be deactivated to achieve the maximum number of components is 0. The two centrality measures that promoted a change in the number of components (attack magnitude), degree and eigenvector centrality, did not show any significant differences with the random attack on the attack extent. On the average path length, the cascade attack extent presented a statistically significant difference, X^2_F (5) = 19.89, p = 0.001, W_k = 0.50, 95% CI [0.45, 0.89] with post hoc comparisons suggesting a better performance of degree centrality over the other centrality measures and random attack.

Concerning network density with 50% of the symptoms deactivated for normal and cascade attacks, distributions can be found in Fig 4. Normal attack showed significant effects between centrality measures, X^2_F (5) = 89.68, p < .001, W_k = 0.70, 95% CI [0.66, 0.94]. Post hoc comparisons suggest that degree centrality has a significantly higher impact in reducing the network density in comparison to all other centrality measures and the random attack. For the cascade attack significant effects were also found, X^2_F (5) = 139.08, p < .001, W_k = 0.69, 95% CI [0.67, 0.88]. As observed in the post hoc comparisons, the eigenvector centrality cascade attack promoted a higher decrease in

network density than all other centrality measures, except degree centrality, and the random attack. Degree centrality promoted the most significant reduction of the network density, outperforming all other measures, including eigenvector centrality, and random attack.

Attending to these results, a post hoc analysis was made to compare the magnitude and extent of the effect of degree centrality under normal and cascade attacks on the network characteristics. Results suggest that the degree centrality cascade attack outperformed the normal attack in all the network properties examined, yielding a higher magnitude, a lower extension, and density. Results from this analysis are presented in Figs S1 and S2 in the S1 Appendix.

Discussion

Our findings indicate that the most significant alterations in the network properties primarily manifest through degree-based attacks. Notably a degree-based normal attack also exerts a more substantial influence in the network properties than any other centrality measure studied, a result consistent with prior study (Castro et al., 2019). Furthermore, in the context of cascade attacks, eigenvector centrality emerges as the central measure with the greatest impact on the network, surpassing all other centrality measures except for degree. This observation aligns with earlier research by Dablander and Hinne (2019), which suggested that eigenvector centrality serves as a superior proxy for causality compared to the commonly employed centrality measures in psychological networks. These findings carry significant implications for the field of psychopathology within the framework of network theory.

Network theory of psychopathology has suggested that central symptoms might be valuable therapeutic targets, due to their proposed ability to fasten the deactivation of

connections between symptoms (Bekhuis et al., 2016; Borsboom & Cramer, 2013; Bryant et al., 2017; Knefel et al., 2016; McElroy et al., 2018; Olatunji et al., 2018; Rhemtulla et al., 2016; Robinaugh et al., 2016; Stochl et al., 2019). This is one of the core propellers of the network theory of psychopathology, that lead to its growth in recent years (Contreras et al., 2019; Malgaroli et al., 2021). However, evidence for this hypothesis is still scarce with studies focusing on cross-sectional networks and grounding the identification of possible therapeutic targets on the initial estimations of centrality measures(Castro et al., 2019; Papini et al., 2020; Rodebaugh, Tonge, Piccirillo, et al., 2018; Spiller et al., 2020). Due to these inconclusive results, it has been recognized that there are changes in symptoms centrality that occur during treatment (Park et al., 2021) and that idiographic networks might be more appropriate to identify treatment targets (Bringmann et al., 2013). This might have important implications for treatment personalization.

In this context, we explored the impact of deactivating symptoms in contemporaneous idiographic networks through two distinct procedures. The first is based on a single time point estimate of network centrality (normal attack), and a second procedure, where, after each symptom deactivation, centrality measures are estimated again (cascade attack). The impact of symptom deactivation was assessed through a set of network properties since it has been suggested changes in the network density might be able to differentiate between different clinical presentations(Pe et al., 2015; Wichers & Groot, 2016). However, due to the conflicting results in previous studies regarding the association between symptoms' remission and networks connectivity (Beard et al., 2016; Bos et al., 2018a) and the identified changes in the network topology (Curtiss et al., 2019; Groen et al., 2019; Hartung et al., 2019; Kraft et al., 2019; Montazeri et al., 2019; Silk et

al., 2019) we have explored the impact of symptom deactivation in two more network properties, average path length and the number of components.

Globally, our results suggest that changes in psychopathological network structure are best achieved through degree centrality. In comparison with the most common centrality metrics in psychopathological networks (i.e., strength centrality and expected influence one-step and two-step), the deactivation of symptoms by the absolute number of connections (i.e., degree centrality) seems to have a higher impact on the network structure. A previous study using cross-sectional networks (Castro et al., 2019) also found that degree centrality was the only centrality measure that was able to produce significant changes in the network structure. However, this study (Castro et al., 2019) only found significant changes in the number of components of the networks. In turn, the present study suggests that for contemporaneous within-person networks all the three network properties examined are transformed through a degree-based attack. These results suggest that different properties might be of interest according to the nature of the network (nomothetic or idiographic). In fact, previous research has also pointed to this need of further exploration and clarification of the properties of interest in psychological network (Christensen & Golino, 2020) and the impact of these networks' structural properties in the selection of centrality measures (Bockholt & Zweig, 2020).

With the field focusing on the strength centrality and expected influence measures to identify important symptoms in the network, it's of relevance that neither of these measures was able to promote significant changes in the network structure. Interestingly, the random deactivation of symptoms revealed a significantly higher impact magnitude in the number of components than a cascade attack through expected influence one and two-step and strength centrality. Thus, if changes in a person's symptomatology are identifiable by changes in the network structure, the traditional psychopathological

centrality metrics do not seem able to induce significant changes. Consequently, this might explain the inconclusive results in previous studies that explored if these centrality measures were related to changes in symptomatology(Papini et al., 2020a; Rodebaugh, Tonge, Piccirillo, et al., 2018; Spiller et al., 2020).

It has been suggested that all centrality measures make implicit assumptions about the network processes of node-to-node transmission and the type of trajectories followed (Bockholt & Zweig, 2020; Borgatti, 2006). The case may be that common centrality metrics in psychopathological networks are not accessing the specific processes that occur in these networks or are accessing some other processes that are not related to network transformation. For example, they might be identifying emergent phenomena in the network that need to be addressed (e.g., a very active symptom) but not phenomena related to disorder maintenance (e.g., symptoms that sustain the disorder). However, in psychological networks, the processes within the networks that generate and maintain mental disorders are still unknown. Interestingly, with a cascade attack, eigenvector centrality produced significant changes in the network structure. This might be due to its suggested proximity to the causality structure of the network (Dablander & Hinne, 2019) and might mean that this measure is tapping into a specific process in psychological networks. Understanding these processes will advance the identification of treatment targets by enabling an enhanced selection of centrality metrics.

Besides exploring which network centrality measure promoted changes in the network structure, we have also tested two types of attacks, normal and cascade. Although degree centrality had a better performance than any other measure in both attacks. In the cascade attack, the magnitude and the extension were significantly higher than in a normal attack. This suggests that it might be of importance to estimate symptoms' centrality each time before an intervention is deployed to act on the symptom with the highest degree at

any given time point. The dynamic fluctuations of central symptoms during a psychotherapeutic process have been highlighted by previous studies (Park et al., 2021) and our results suggest that assessing and intervening in which symptom is central at any given time-point might produce faster recoveries. Consequently, the estimation at a single time-point of centrality measures to establish treatment targets for intervention might not be the most effective procedure to promote changes in the network structure.

This has important implications for treatment personalization. Our results suggest that to promote more effective treatments the assessment of the central symptoms must be done each time before the intervention is done. Meaning that, in the context of idiographic networks, symptomatology needs to continuously be assessed through, for example, ecological momentary assessments (Robinaugh et al., 2020; Shiffman et al., 2008) for the duration of treatment to determine, at each session, in which symptom the treatment should focus. This has not been the current practice on open trial studies using centrality metrics for treatment target identification and intervention guidance (Howe et al., 2020; Levinson et al., 2023). This, in addition to the positive results that these studies have shown, raises an important question about the specificity of the psychotherapeutic strategies. Do psychotherapeutic strategies and psychopharmacological treatments have the specificity needed to act on a specific central symptom at each time? And is this a negative constraint of the treatments or is it a positive consequence? The answers to these questions are still unknown but the first results seem promising (Blanken et al., 2019; Lancee et al., 2022). Although targeting psychological symptoms and behaviors is inherently distinct from targeting genes or computer networks, recent studies (Bekhuis et al., 2018; Blanken et al., 2019; Fishbein et al., 2023; Lancee et al., 2022; Norton et al., 2022; Scott et al., 2022) have started to reveal contrasting effects not only among different treatment modalities (Bekhuis et al., 2018; Fishbein et al., 2023; Norton et al., 2022; Scott

et al., 2022), but also throughout the course of treatment (Blanken et al., 2019; Lancee et al., 2022). These early results suggest that achieving a remarkable level of precision in psychological treatments may be attainable. This in addition with the selection of treatment targets through network centrality measures has the potential to position psychology on the forefront of precision medicine (Friston, 2017; Khurana Hershey et al., 2022; Silbersweig & Loscalzo, 2017) with more effective, precise, and personalized treatment strategies.

Besides this, some limitations of our study should be pointed out. First, both of our procedures remove the deactivated symptoms from the network. This might be a strong assumption for some of the symptoms. For example, anxiety might always fluctuate at lower levels, without ever being completely absent of the network. In turn, insomnia or obsessions and compulsions might in fact be completely absent of the network if a person does not have a psychopathology. In our study we treated all symptoms equally, assuming that all symptoms would be absent from the network after treatment. However, this is in fact a strong assumption and future studies should explore this question. Moreover, our study only targets nodes and some interventions might not act on the nodes its selves but rearrange the connections between them. With this in mind, we think future studies with frameworks like the one proposed by Blanken and colleagues (2019) might provide important insights about the specificity of psychological interventions.

Secondly, we used only centrality measures, leaving another important concept of psychopathological networks, bridge symptoms, outside of our study. Bridge symptoms have been proposed as symptoms that connect two different disorders and that acting in these symptoms might promote a faster disintegration of a comorbidity network (Cramer et al., 2010; Jones et al., 2019). Our network is a comorbidity network comprising

symptoms of depression and anxiety and identifying and deactivating bridge symptoms might had led to faster deactivation of the network. Furthermore, there are several unexplored centrality measures that can be explored in the context of psychopathological networks, such as the recently developed hybrid centrality measure (Christensen et al., 2018; Pozzi et al., 2013). Hybrid centrality measures group together several rankings of other centrality measures (Pozzi et al., 2013) and can potentially yield valuable insights for the refinement of treatment target selection.

In addition, since we have used within-person contemporaneous networks our centrality measures lack the directionality that could be obtained with the use of temporal networks. Nevertheless, due to the strong model assumptions about the temporal effects (Epskamp, van Borkulo, et al., 2018), meaning that all relevant temporal symptom dynamics can be captured in the ESM or EMA time scale, we opted for contemporaneous networks. However, with passive data (Byanjankar et al., 2021; Cornet & Holden, 2018; Fukazawa et al., 2019; Lekkas et al., 2022; Sheikh et al., 2021), future studies can surpass the temporal dynamics problem that emerge from ESM and EMA methods since passive data can be collect continuously.

Another important limitation in our work is that we assume, as has been proposed in previous studies (Pe et al., 2015; Wichers & Groot, 2016), that network properties identify psychological states, although this hypothesis is currently lacking consistent evidence (Beard et al., 2016; Bos, Fried, et al., 2018a). In previous studies that focused on the idiographic network, a relationship between network density and psychopathological states was found (Pe et al., 2015; Wichers & Groot, 2016) and our results show that there are clear changes in the network density after the deactivation of 50% of the symptoms. However, we also use two network properties rarely studied in psychopathological networks and without a clear theoretical formulation, although we

think it's important to explore these new properties, we also acknowledge that there's a need to theoretically frame these properties.

Finally, a sensitivity analysis based on demographic variables such as sex or age could provide further insights into the selection of treatment targets, by understanding if different centrality measures are better suited for different groups of the population.

Conclusion

Our study provides the first simulation study in idiographic networks to examine symptom deactivation through several centrality measures. The emergence of degree centrality as a measure more suitable to transform the network might be of relevance for further studies trying to identify treatment targets through network analysis. Further exploration of network properties is needed, but, if changes in the network structure are aligned with psychopathological and healthy states, deactivating symptoms through a cascade attack based on degree centrality might promote faster and more effective treatments.

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CHAPTER III [1, 2, 3]

The Differential Impact of Processing Speed and Cognitive Flexibility on Cognitive Emotion Regulation Strategies and Depression

Note:

[1] This chapter has been submitted to *Cognition and Emotion* for publication:

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[2] Supplementary materials of this paper are available in the Chapter III of the Appendix.

[3]Code to reproduce the analysis the analysis can be found at https://osf.io/c729f/

Abstract

Existing cognitive models for depression oversimplify the complex interactions between cognitive emotion regulation strategies (CERS) and cognitive processes. Not considering this complexity might explain the inconsistent results in the efficacy of cognitive training interventions. We aimed to construct and explore the micro-level properties of a network model that can integrate this complexity of the interactions and explore through computational simulations the differential impact of improvements/deterioration in cognitive flexibility and processing speed in the network.

We used the Leipzig Study for Mind-Body-Emotion Interactions dataset (N = 227). The Trail Making Test assessed processing speed and cognitive flexibility, while depression and CERS were measured using the Hamilton Depression Rating Scale and the Cognitive Emotional Regulation Questionnaire. The network was estimated using the Mixed Graphical Model. Expected influence, bridge expected influence and predictability were explored as micro-level properties. Simulation procedures were done by estimating the expected network activity and comparing it with the baseline network activity.

Processing speed emerges as a mediator with a bridging role, while cognitive flexibility seems to have a more substantial impact in overall connectivity. Rumination, exhibit high centrality, suggesting a pivotal role in the network. Impact of these roles for treatment development is discussed.

Keywords: network analysis, cognitive flexibility, processing speed, depression, emotion regulation

Major Depressive Disorder is one of world's most prevalent disorders, affecting estimably 5% of the adult population (World Health Organization, 2023). Although several treatments are proposed for addressing depression (American Psychological Association, 2019), the recurrence and relapse rates (Richards, 2011), point to the lack of comprehension about the development and maintenance mechanisms of the disorder (Lemmens et al., 2016). Current cognitive models of depression posit that the interplay between emotion regulation strategies and cognitive impairments might be integral to these maintenance mechanisms (Beck & Bredemeier, 2016; Disner et al., 2011; LeMoult & Gotlib, 2019). However, these models remain theoretical and scarcely detailed and are unable to accommodate the complexity of interactions identified in recent studies (Everaert et al., 2017; Sanchez et al., 2017). This limitation impedes our ability to identify the mechanisms involved in the development and maintenance of mental disorders.

One of those proposed mechanisms are the emotion regulation strategies which have been proposed by Beck's (Beck, 1976) cognitive therapy and Nolen-Hoeksema's (Aldao et al., 2010) response styles theory. These strategies refer to the thoughts and actions that individuals employ to manage their emotions in response to a stimulus, can be conscious or unconscious, and may be used to alter the intensity, duration, or overall experience of the emotional response (Campbell-Sills & Barlow, 2007; Williams et al., 2009). Several empirical studies have demonstrated an association between specific cognitive emotion regulation strategies and depression (D'Avanzato et al., 2013; Schwert et al., 2017). However, most of these studies isolate a specific strategy (Bernstein et al.,

2017; Schwert et al., 2017; Wallace-Hadrill & Kamboj, 2016), contradicting recent research that shows that individuals use multiple strategies simultaneously (Thuillard & Dan-Glauser, 2020) and that these strategies interact with each other (De Neve et al., 2023).

In addition to the demonstrated relationship between emotion regulation strategies and depression (Rutherford et al., 2023; Vanderlind et al., 2021; Visted et al., 2018), these strategies have also been associated with a variety of cognitive impairments (Conner et al., 2023; Demeyer et al., 2012; Vilgis et al., 2015). However, most of this research was done by studying the cognitive processes also in isolation without considering their interactions. Recent research has challenged this approach by highlighting the interconnected nature of these cognitive processes (Bernstein et al., 2017; Hoorelbeke et al., 2016; Menu et al., 2022) and their differential influence on depression (Schwert et al., 2017; Zainal & Newman, 2023). The existence of all these interactions between the constituted components of depression suggest that current models are an oversimplified view of depression. Thus, statistical approaches that can model these complex interactions and construct these more complex models are needed.

Network analysis has been considered from both a medical (Silbersweig & Loscalzo, 2017) and psychological perspective (Borsboom & Cramer, 2013; A. Cramer & Borsboom, 2015; Fried & Cramer, 2017; Kossakowski & Cramer, 2017) as one of the most promising methods to address this complexity. From a psychological perspective, network theory of psychopathology proposes that mental disorders are interacting systems of its constituents (Borsboom, 2017; Borsboom et al., 2019), with each of these constituents being represented by a node in the network and the interactions between them as edges. Network theory suggests that it's from these complex interactions that mental disorders develop and are maintained (Borsboom, 2017; Borsboom et al., 2019). In fact,

the increased connectivity of the network's has been associated with psychopathological processes (van Borkulo et al., 2015) and the distinctive interactions established between the network constituents might identify possible disorder development paths (Isvoranu et al., 2016, 2020) or comorbidity structures (Cramer et al., 2010). This has helped the clarification of the nosology and comorbidity structures of several mental disorders (Beard et al., 2016; Castro et al., 2018; Ross et al., 2018; Smith et al., 2019; Sobański et al., 2023; Van den Bergh et al., 2020). However, network analysis studies have primarily concentrated on understanding the interactions between individual symptoms (Price et al., 2019) or between emotion regulation strategies (De Neve et al., 2023) or cognitive processes (Bernstein et al., 2017) isolated.

Whitin the context of depression networks, studies have explored the interplay between emotion regulation strategies and depression symptoms (Conner et al., 2023), and between cognitive processes and depression symptoms (Zainal & Newman, 2023). Networks encompassing emotion regulation strategies and depressive symptoms have shown an interplay between the emotion regulation strategies and a differential impact on the depressive symptoms (Everaert et al., 2017; Everaert & Joormann, 2019). With "Putting into Perspective", for example, presenting a connection with other emotion regulation strategies but not with depressive symptoms (Zhang et al., 2022). In turn cognitive processes and depression symptoms networks have also shown interactions between the cognitive processes but interactions with lower strength between these processes and depressive symptoms (Bai et al., 2023; Zainal & Newman, 2023). In fact, previous research has shown that emotion regulation strategies might mediate the relationship between cognitive processes and depressive symptoms (Demeyer et al., 2012; Mori & Tanno, 2015). Thus, the low strength in the connections between cognitive processes and depressive symptoms might be due to the lack on integration on the

emotion regulation strategies on these network models. The integration of these components in a network model might provide a more detailed and comprehensive cognitive model of depression (LeMoult & Gotlib, 2019) that can further inform psychological interventions through the identification of treatment targets (Epskamp et al., 2018; Fried et al., 2016; Henry et al., 2020).

Network theory suggests that this identification can be done through the analysis of micro-level network properties (Castro et al., 2019). These micro-level properties consist mainly in different centrality measures, which inform about a node importance in the network. Most widely used centrality measures in psychology are strength centrality (Opsahl et al., 2010) and expected influence (Robinaugh et al., 2016) that provide information about the connectivity of the node in the network. Since an increase in overall connectivity has been shown to relate to psychopathological states (van Borkulo et al., 2015), an intervention in a central node (i.e., a node with high connectivity) might reduce the overall network connectivity and consequently the psychopathology severity. Besides central symptoms, network theory also suggests that bridge symptoms might also be important treatment targets (Castro et al., 2019; Guo et al., 2023; Jones et al., 2019; Van den Bergh et al., 2020; Wang et al., 2022). Bridge symptoms are symptoms that connect different groups of symptoms in the network (Jones et al., 2019) and have been suggested to be responsible for the emergence of comorbidity structures (Cramer et al., 2010). Thus, targeting these symptoms might prevent the deterioration of the mental condition. This would constitute a major step towards a precision psychotherapy (Fraguas et al., 2017; Hebbrecht et al., 2020; Levinson et al., 2018; Robinaugh et al., 2020).

However, identification of treatment targets through centrality measures has been showing inconsistent results (Dablander & Hinne, 2019; Dalgleish et al., 2019; Hallquist et al., 2019; Rodebaugh et al., 2018; Spiller et al., 2020). Central symptoms seem to not

be able to predict treatment outcome (Robinaugh et al., 2016) and symptom endorsement seems to be a better predictor of change (Papini et al., 2020; Spiller et al., 2020). Besides this, changes in the network overall connectivity or in the network topology seem to be prominent in different psychopathological states (Groen et al., 2019; Hartung et al., 2019; Montazeri et al., 2019; Silk et al., 2019; Wichers & Groot, 2016) and pre- and post-treatment (Curtiss et al., 2020; Kraft et al., 2019). Thus, identifying which network nodes generate substantial change in the network might be a promising method for identifying possible treatment targets.

Lunansky and colleagues (2021) proposed a framework to assess the differential impact in overall network connectivity that a specific node promotes. This framework through computational simulations can be used to infer the change that a specific node causes in the overall connectivity of the network and might give us new insights on possible disorder mechanisms and, consequently, identifying treatment targets. Since cognitive impairments have been proposed as possible treatment targets by means of cognitive control training interventions (Greenwood & Parasuraman, 2016; Jopling et al., 2020; Sala et al., 2019), evaluating the differential impact of these impairments might provide important insights about which cognitive impairments generate most significant changes in the network structure. This is important since, in depression, these interventions continue to demonstrate inconsistent results on the reduction of symptomatology (Edwards et al., 2022; Koster et al., 2017; von Bastian & Oberauer, 2014), with studies observing cognitive change but without a reduction in depressive symptoms (Koster et al., 2017).

Processing speed and cognitive flexibility are two of these processes that have been shown to improve with cognitive control training (Shahar & Meiran, 2015) and that have been related to depression (Figueroa et al., 2019; Goodall et al., 2018; Lerche et al.,

2018). However, the improvement in these processes does not seem to translate to symptom improvement and, when symptom improvement occurs, cognitive change does not (Koster et al., 2017). This suggests that change in these processes does not relate directly with depression symptoms. In fact, processing speed have shown to have an association with rumination (Schwert et al., 2017), cognitive flexibility has also shown a relationship with suppression (Ghosh & Halder, 2020). Thus, these two processes seem to suggest a differential impact on the mental disorder system, suggesting that interventions like cognitive training might be improved and tailored to the individual if we can assess the specific impact of each of these processes.

In this context, network analysis by allowing the modelling of the complex dynamic interactions (Epskamp et al., 2018) and the simulation of the differential impact of specific nodes (Lunansky et al., 2021) might allow us to promote better understanding of the mental disorder mechanisms and, consequently, better treatment targets that would allow us to develop better interventions. With this in mind, we aimed to explore the differential impact of processing speed and cognitive flexibility on a network composed by emotion regulation strategies and depression. To this end we (1) construct a network of interactions between these cognitive processes, emotion regulation strategies and depression and (2) explore its micro-level properties and (3) simulate the differential impact of an improvement and deterioration of performance in these cognitive processes on the network.

Methods

Sample

To simulate the impact of processing speed and cognitive flexibility on the cognitive emotion regulation strategies and depression, we used the dataset from the

Leipzig Study for Mind-Body-Emotion interactions (LEMON; Babayan et al., 2019). This dataset provides information on physiological, psychological and neuroimaging of a sample of 227 participants in two age groups, a young group, and an older group. The younger group comprised of 153 participants aged between 20 and 35 years (N = 153, 45 females, median age = 24 years, mean age = 25.1 years, standard deviation (SD) = 3.1). Conversely, the elderly age group encompassed 74 individuals aged 59 to 77 years (N = 74, 37 females, median age = 67 years, mean age = 67.6 years, SD = 4.7).

For the present study, we used data from the Trail Making Test (TMT; Reitan & Wolfson, 1993) for processing speed and cognitive flexibility. TMT consists in two subtests. Subtest A (TMT-A) consists in connecting circles containing numbers from 1 to 25, that are randomly distributed in a piece of paper, in the correct order. Subset B (TMT-B) also consists in connecting randomly distributed circles but in this case, circles contain numbers and letters that must be connected in alternating and increasing order. In this study we used the completion time of TMT-A to assess processing speed and TMT-B completion time to assess cognitive flexibility.

As a depression assessment we used the total score of Hamilton Depression Rating Scale (HDRS; Hamilton, 1960). HDRS consists in 21-items, but the total score is calculated only based on the first 17. Scores over 17 suggests the presence of depression. And for the cognitive emotional regulation, we used the Cognitive Emotional Regulation Questionnaire (CERQ; Garnefski et al., 2001). CERQ evaluates cognitive emotion regulation strategies with nine subscales, acceptance, positive refocusing, refocusing on planning, positive reappraisal, putting into perspective, self-blame, rumination, catastrophizing, and blaming others.

Network estimation and visualization

Network estimation was done with Mixed Graphical Models in the *mgm* package (Haslbeck & Waldorp, 2020) for *R* software (R Core Team, 2019). This model employs a nodewise regression approach to assess the relationships between nodes. It calculates an intercept and a beta-coefficient for each variable. The intercept signifies the node's threshold, while the beta-coefficients indicate the strength of connection with the neighboring nodes. To prevent excessive false-positive connections, the model applies regularization, pushing many edges with low values toward zero resulting in a sparser model with fewer connections of minimal significance (Haslbeck & Waldorp, 2020).

For this network we evaluated the node importance in the network with expected influence and predictability. Expected influence is determined by summing the weights of a node's edges shared with the other nodes in the network (Robinaugh et al., 2016) and was estimated with the *bootnet* package (Epskamp et al., 2018). Bridge centrality was assessed with bridge expected influence with the package *networktools* (Jones, 2023) for *R* (R Core Team, 2019). Predictability, in turn, was estimated with the *mgm* package (Haslbeck & Waldorp, 2020) for *R* (R Core Team, 2019). Predictability assesses how much of the variance of a node is explained by the neighboring nodes well node A is predicted by all its neighboring nodes (Haslbeck & Fried, 2017).

Then, to understand which nodes are predicted by a particular neighboring node, we have estimated a relative importance network. The relative importance network was estimated with the *relaimpo* package (Grömping, 2006). In a relative importance network, every edge signifies the weight of how much node X contributes to predicting node Y, considering all other variables in the analysis. To put it differently, the relative importance weight quantifies the proportion of variance in the outcome variable that can be attributed to each predictor, while also accounting for potential multicollinearity, and assigning a

relative importance metric (*lmg*) between 0 and 1 to each edge (Grömping, 2006). Centrality indices were also computed for this network namely, in-strength and out-strength. In-strength is the sum of the directed edge weights originating from all other nodes to a given node. Out-strength is the sum of the directed edge weights originating from a given node to all other nodes.

For both networks we performed a stability estimation, examining the edge accuracy and the centrality stability with the *bootnet* package (Epskamp et al., 2018). All the graphical representations of the networks were done in the *qgraph* package (Epskamp et al., 2012). This package was also used to determine the shortest path from both cognitive processes to depression. The shortest path represents the minimum number of steps needed to go from one node to the other (Brandes, 2008) and it was computed with the Dijkstra's algorithm (Dijkstra, 1959).

Expected Network Activity

To explore the differential impact of cognitive flexibility and processing speed on the network of cognitive emotion regulation strategies and depression, we used the same approach proposed by Lunansky and colleagues (2021). Lunansky and colleagues (2021) explored the symptom activity level change due to the presence or absence of risk and protective factors. Here, we apply the same principles to the emotion regulation and depression network. However, our focus diverged from risk and protective factors to the role of cognitive processes in influencing the emotion regulation and depression network.

Following the approach introduced by Lunansky and colleagues (2021), we used the Mixed Graphical Model (MGM) estimated previously to compute the baseline network activity. Baseline network activity (BNA) was computed by summing the mean values of all individual nodes in the network. Subsequently, we conditioned the baseline

model to the highest and lowest values for both cognitive processes integrated in the network. With the conditioned model, expected network activity can be computed, which represents the sum of the individual node means as a function of the cognitive processes. It is important to note that any change in the activity of a network node occurs only when exists a direct or indirect connection between the node and the cognitive process.

In this study we explored 4 scenarios by conditioning the cognitive processes to their highest and lowest sample values. Given that cognitive processes were evaluated using the completion time for TMT-A and TMT-B tasks, it's important to note that a lower completion time indicates a quicker response, and consequently, a lower value corresponds to a higher capacity in the specific cognitive process being assessed. In the first scenario, we conditioned processing speed to the highest sample value and the cognitive flexibility to the lowest sample value. The second scenario both cognitive processes were conditioned to their respective highest sample value. The third scenario, processing speed was conditioned to the lowest sample value and cognitive flexibility to highest sample value. In the last scenario both cognitive processes were conditioned to their lowest sample value. Expected Network Activity analyses were conducted in the *ENA* package (Castro, 2023) for *R* (R Core Team, 2019). The script used for conducting the analysis is available at https://osf.io/c729f/.

Results

In the first estimated network, the MGM model, there were a total of 80 with 26 negative edges (Figure 1B). The network showed an adequate stability with a CS-coefficient of 0.361 for node strength. Centrality estimation in this network (Figure 1A) showed that rumination and catastrophizing were the nodes with the highest expected influence. While depression and self-blame were the nodes with the lowest values of

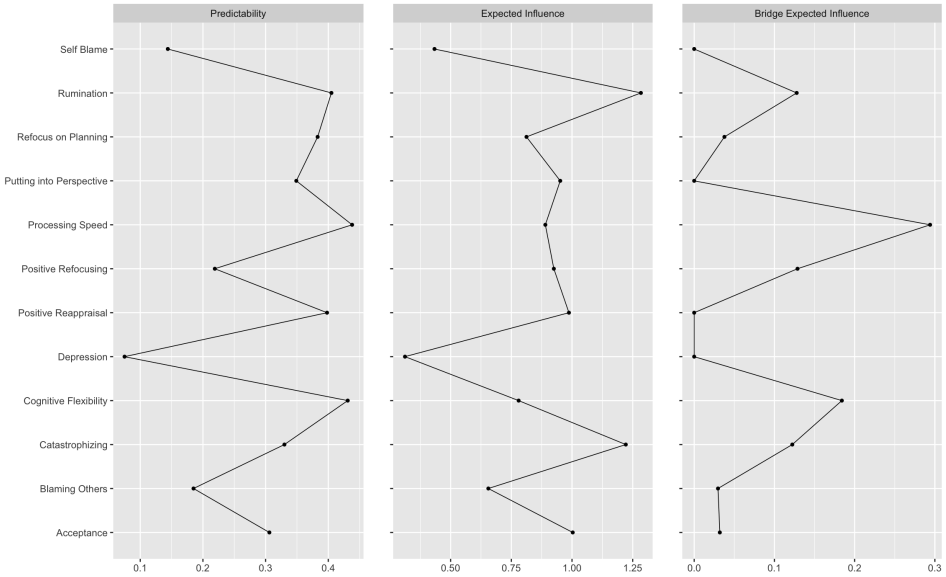
expected influence. In turn, for predictability the nodes with the highest values of predictability were processing speed, cognitive flexibility, rumination, and positive reappraisal. With the lowest values of predictability, we have again depression and self-blame.

For the relative importance network there were a total of 132 edges all positive (Figure 2B). The network also showed an adequate stability with a CS-coefficient of 0.593 for in- and out-strength. The strongest edges were between processing speed and cognitive flexibility (*lmg* = 0.395), and between positive reappraisal and positive refocus (*lmg* = 0.169). The weakest edges were found between depression and cognitive flexibility (*lmg* = 0.001) and between processing speed and putting into perspective (*lmg* = 0.001). Centrality analysis of this network (Figure 2A) showed that there were no differences between In-Strength and Out-Strength, with the nodes with the highest centrality being the same as the nodes with the highest predictability**.**

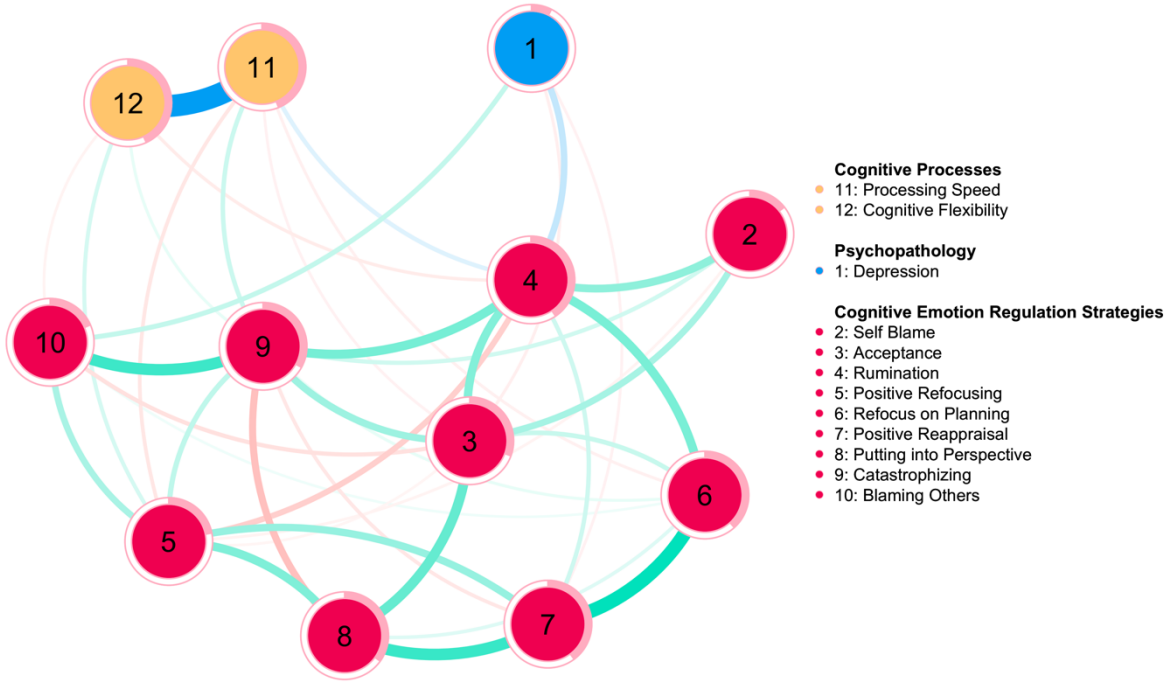
Figure 1

Centrality estimation and graphical representation of the MGM network.

A)



B)

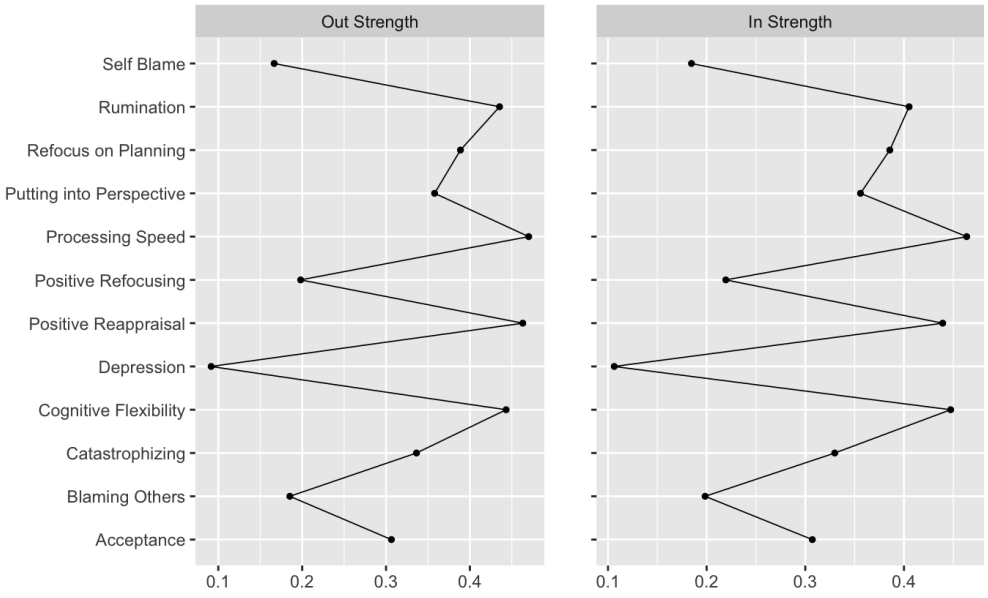


Note. Panel A) shows the Predictability, Expected Influence and Bridge Expected Influence of each node of the network. Panel B) shows the graphical representation of the MGM network. Nodes in red identify the Cognitive Emotion Regulation Strategies, in yellow are identify the cognitive processes and the node in blue identifies depression score. Positive edges are represented in green, and negative edges are represented in red. Edges represented in blue show the shortest path between the two cognitive processes and depression. The pie charts around the nodes shows the predictability value of the node.

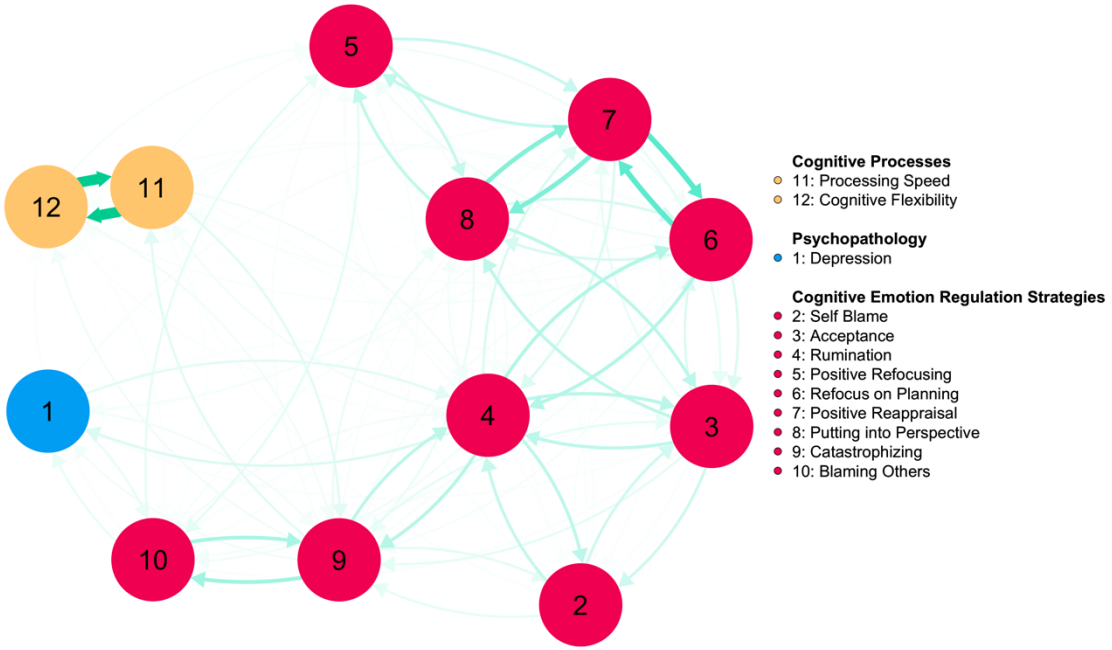
Figure 2

Centrality estimation and graphical representation of the Relative Importance network.

A)



B)



Note. Panel A) shows the Out-Strength and In-Strength of each node of the network. Panel B) shows the graphical representation of the relative importance network. Nodes in red identify the Cognitive Emotion Regulation Strategies, in yellow are identify the cognitive processes and the node in blue identifies depression score. Edges are represented in green and negative edges are represented in red. Edges represented in blue show the shortest path between the two cognitive processes and depression.

Expected Network Activity

To simulate the impact of cognitive flexibility and processing speed on the emotion regulation strategies and depression, we utilized the framework proposed by Lunansky and colleagues (2021) to test the network resilience. Table 1 presents the results of this analysis. The estimation of the baseline network connectivity yields a result of 50.63, that was then compared to the four simulated scenarios. In the first simulation, with low processing speed and a high cognitive flexibility, there was a reduction of 0.06 in the network connectivity with an estimated ENA of 50.57. In the second simulation, with low processing speed and cognitive flexibility, there was an increase of 1.17 in the network connectivity. The third simulation, with a high processing speed and a low cognitive flexibility, also showed an increase in network connectivity with an estimated ENA of 1.13. In the last simulation, with both high processing speed and cognitive flexibility, there was also a reduction in the network connectivity, with an estimated ENA of 50.16 corresponding to a decrease of 0.47 in symptom activity.

Table 1

Simulation Characteristics and Network Activity Metrics.

	Processing Speed	Cognitive Flexibility	Expected Network Activity	Baseline Network Activity
Simulation 1	Low	High	50.57	50.63
Simulation 2	Low	Low	51.8	
Simulation 3	High	Low	51.4	
Simulation 4	High	High	50.16	

Discussion

Previous research suggests that theoretical models of depression (Beck & Bredemeier, 2016; Disner et al., 2011; LeMoult & Gotlib, 2019) are an oversimplification of the complex dynamic interactions that are established by the proposed disorder constituents (Everaert et al., 2017; Everaert & Joormann, 2019; Menu et al., 2022; Sanchez et al., 2017). Then a complex integrative model is the first step to improve our understanding of mental disorders and help develop better interventions. Network analysis can provide a framework to model these complex interactions (Borsboom & Cramer, 2013), determine the importance of a specific component through the assessment of micro-level properties (Castro et al., 2019), and simulate the differential impact of an improvement or a deterioration of a specific component of the network (Lunansky et al., 2021). Our study aimed to apply this framework to estimate a network model of depression, explore its micro-level properties and simulate the differential impact of processing speed and cognitive flexibility.

First, our results suggest that cognitive flexibility and processing speed impact on the depression is mediated by cognitive emotion regulation strategies without a direct connection between either of these processes and depression. This is contrary to theoretical expectations of the cognitive models of depression (Beck & Bredemeier, 2016; LeMoult & Gotlib, 2019) that propose direct interactions between cognitive processes and depression. The inexistence of this direct connection suggests that interventions aiming to reduce symptoms by acting on cognitive processes might not have a direct impact on depression. Which, consequently, might explain the inconclusive results found for cognitive training-based interventions (Edwards et al., 2022; Koster et al., 2017; von Bastian & Oberauer, 2014).

Second, our findings suggest that these processes have different roles in the network. In the case of processing speed seems to have a mediator role due to its high values of bridge expected influence. This means that processing speed has several connections with the remaining components of the network, and consequently mediating the relationships between the various components of the network. This bridging role as been suggested, in symptom networks, to be responsible for the emergence of comorbidity structures (Cramer et al., 2010). Since our network only consists of proposed components of depression (LeMoult & Gotlib, 2019), this bridging role might be associated with the development of the disorder. Thus, cognitive training strategies that improve processing speed might be important prevention strategies. In fact, it has been previously shown that processing speed training improves everyday functioning in older adults (Edwards et al., 2018). This bridging role with cognitive emotion regulation strategies might be the reason for this improvement.

Interestingly, despite its bridging role, our findings indicate that processing speed has comparatively lesser influence on the overall network connectivity when contrasted with cognitive flexibility. Specifically, a higher level of cognitive flexibility, when coupled with a lower processing speed, diminishes network connectivity. Conversely, a higher processing speed paired with lower cognitive flexibility increases network connectivity compared to the baseline. This might mean that cognitive flexibility promotes more change in the network connectivity than processing speed. With network connectivity being associated with a reduced experience of symptomatology, these results suggest that interventions that improve cognitive flexibility might help reduce depression symptomatology. Which is in convergence with previous studies that showed poorer cognitive flexibility was associated with depression (Conner et al., 2023; Gohier et al., 2009).

In this context, cognitive flexibility seems to drive alterations in the overall network connectivity, while processing speed seems to act as a mediator of the interactions among the different components of depression. Acknowledging these roles might be of value when selecting possible treatment targets, since in different stages of the disorder might be more related with one of these roles. For example, for depression disorder prevention might be more useful to target processing speed due to its bridging characteristics (Castro et al., 2019). While for symptom reduction might be more effective to improve cognitive flexibility due to the decrease in connectivity it produces.

In addition to these differentiate roles in the network, our findings also show that both these cognitive processes are highly predictable, meaning that an important part of the variance of these nodes is explained by the remaining nodes connected to them. Which could suggest, since the connections these processes establish in the network are with the cognitive emotion regulation strategies, that these strategies had an important impact on the performance of these cognitive processes. However, on the relative importance network, most of the predictability attributed to both processes derives from the high capacity that each cognitive process has of predicting each other and less with the connections with the remaining network nodes. Thus, although they have important role in the network, these cognitive processes do not seem to be central to network.

In fact, our results suggest that cognitive emotion regulation strategies have a more prominent role in the network as shown by the expected influence, in-, and out-strength scores. Mainly rumination, catastrophizing and positive reappraisal which were the most central nodes in the network. These strategies have been consistently found to be more central in individuals with depression (Demeyer et al., 2012; Zhang et al., 2022). Rumination was also the cognitive emotion regulation strategy which mediated the shortest path between the cognitive processes and depression, which has also been shown

in previous studies (Everaert et al., 2017)**.** This suggests that preventing rumination might prevent the development of depression.

Attending to the relative importance network results, preventing rumination might be done by increasing or decreasing the usage of the emotion regulation strategies directedly connected to it. Rumination it's one of the nodes with the highest predictability in the network and most of this predictability derives from the cognitive emotion regulation strategies connected to it. Thus, changes in the cognitive emotion regulation strategies connected to it will change the amount of rumination realized.

Interestingly, although rumination was the most central node in the network, configured the shortest path between the cognitive processes and depression, and is widely proposed has a depression related strategy (Aldao et al., 2010), had a low predictive capacity of depression in our results. This might mean that, despite these important roles that rumination has in the network, other processes not included in our study might have a more prominent impact on depression. For example, cognitive biases have also been proposed as a cognitive mechanism of depression and showed interactions with emotion regulation strategies and depression (Everaert et al., 2017). In fact, the depression node had the lowest scores in all the micro-level measures used in our study, suggesting that the nodes in the network explain only a small part of the variance in depression symptomatology. These results suggest the need to study depression networks with an even more detailed and fine-grained perspective, including more of the theoretical proposed components (Beck & Bredemeier, 2016; LeMoult & Gotlib, 2019) and studying depression symptoms individually (Fried, 2015; Fried & Nesse, 2015).

In this context our study should be seen in the light of some limitations. As aforementioned, we did not include all the theoretically proposed components for cognitive models of depression, and this might have result in the low predictability of the

depression node. Another limitation is related to the fact that in our network depression was assessed as a single node. This might also have influenced the low predictability found in the depression node. Since network theory of psychopathology suggest that mental disorders emerge as the result of the interactions between symptoms (Borsboom, 2017; Borsboom et al., 2019; Borsboom & Cramer, 2013) and these were not considered. This might have also influenced the network roles identified. For example, we found that processing speed did not have a direct connection with depression, but if symptoms were considered this might not be the case. Shi and colleagues (2023), through network analysis, showed that processing speed had a specific connection with two depressive symptoms, lack of energy and psychomotor symptoms. Finally, our study used cross-sectional data which have been showing inconsistent results in treatment targets identification (Dablander & Hinne, 2019; Dalgleish et al., 2019; Rodebaugh et al., 2018). We also considered network connectivity as a marker for psychopathology as has been proposed by network theory (Borsboom, 2017; Borsboom et al., 2019; Cramer & Borsboom, 2015), however, inconsistent results have been found (Bos et al., 2018; Koenders et al., 2015; Pe et al., 2015). Moreover, the connectivity proposal by network theory is related with symptom networks (Borsboom, 2017; Borsboom et al., 2019; Cramer & Borsboom, 2015) and there is currently no proposed framework for psychological networks not consisting of symptoms.

Therefore, future studies should consider (1) integrating more of the proposed theoretical components to understand if these components can predict the variance in depression, (2) include depression symptoms to get a more detailed perspective on the possible roles of each network component and (3) utilize a clinical sample. In addition to this, further theoretical studies of the network theory of psychopathology (Borsboom, 2017; Borsboom et al., 2019; Cramer & Borsboom, 2015) are needed to understand

exactly how micro-level (e.g. centrality measures) and macro-level (e.g. overall network connectivity) properties relate to psychopathological processes of development or maintenance of a disorder.

In conclusion, this study utilized network analysis to explore the intricate interactions among two cognitive processes, cognitive emotion regulation strategies, and depression within a comprehensive framework. Notably, processing speed emerges as a mediator with a bridging role, influencing the relationships among various components of the network, while cognitive flexibility plays a more direct and influential role in altering overall network connectivity. The centrality of cognitive emotion regulation strategies, particularly rumination, suggests their pivotal role in shaping the network and potential avenues for intervention. The insights gained from this study contribute to a nuanced understanding of the complex mechanisms underlying depression, offering valuable implications for personalized interventions and the refinement of treatment targets identification.

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Final Considerations

This thesis aimed to address common problems in depression research by employing a network approach to the study of a complex integrative model of depression. Complex integrative models have been deemed crucial to surpass the current existent limitations in the study of depression (LeMoult & Gotlib, 2019). These limitations center around the lack of studies that accommodate the complexity of interactions between phenotypes and endophenotypes of depression (Miller & Rockstroh, 2013). Not taking into account these interactions (Everaert & Joormann, 2019; Hsu et al., 2022), disorder specificity cannot be addressed and, without specificity, the identification of endophenotypes as mechanisms of depression is undermined (Goldstein & Klein, 2014; Hasler et al., 2004; Miller & Rockstroh, 2013). Consequently, this leads to increased difficulties in the development of more effective and precise treatments (Simon & Perlis, 2010).

Network analysis has been viewed as a statistical framework that can model these complex interactions established between endophenotypes and phenotypes of mental disorders (Everaert & Joormann, 2019). Despite this, the network analysis approach to mental disorders might have been hampered by the network theory of mental disorders. This theory constitutes a tentative theoretical framework to explain mental disorders etiopathogenesis. However, results from previous studies (Montazeri et al., 2019; Schweren et al., 2018; Spiller et al., 2020) suggest that the excessive focus of its theoretical formulation on network connectivity its overly simplistic and does not translate the etiopathogenic processes of mental disorders.

Thus, the exploration of network analysis tools is needed to continue the development of network theory. In turn, development of network theory will provide a consolidated framework to surpass the current limitations in depression research

(Cuijpers et al., 2021) and provide new venues for more effective and precise treatments (Friston, 2017; Robinaugh et al., 2020; Silbersweig & Loscalzo, 2017).

In this context, this work contributes to the study of depression by constructing a comprehensive integrative model and investigating the impact of specific cognitive endophenotypes through network analysis. To this end, this work focused initially on the exploration of network properties that are not theoretically formulated by the network theory of mental disorders. This exploration was prompted by the inconsistent results found in previous network studies of depression (Bos et al., 2018; Schweren et al., 2018). Across the three studies included in this thesis, several contributes were made to the characterization of network models of depression by exploring different macro, meso and micro network properties.

At the macro-level, the two initial studies demonstrate that network connectivity, in its current theoretical formulation (Borsboom, 2017; Borsboom et al., 2019; Borsboom & Cramer, 2013), does not suffice to characterize different psychological states. As presented in Chapter I, the comparison between healthy and disordered individuals shows that, contrary to the network theory proposal, depressed individuals display a network with less overall connectivity than healthy ones and a result that has also been found in previous studies (Bos, Fried, et al., 2018a; Hartung et al., 2019; Montazeri et al., 2019). These results might have important implications for network theory and for applied research on the identification of treatment targets.

In fact, in Chapter II results show that selecting treatment targets for depression with micro-level properties that are based on local connectivity does not promote significant changes in the network structure. Combining these results with previous studies that compare pre and post treatment depression networks and show significant structural changes in the network but not connectivity changes (Curtiss et al., 2019; Groen

et al., 2019; Hartung et al., 2019; Kraft et al., 2019; Montazeri et al., 2019; Silk et al., 2019) further suggests that network connectivity might not be an appropriate measure to characterize depression networks. Moreover, this might not only be true to MDD but also to generalized anxiety disorder (GAD).

Returning to Chapter I, results show that MDD and GAD were found to be similar in their macro-properties' behavior but distinct from obsessive-compulsive disorder (OCD) and social anxiety disorder (SAD). With both OCD and SAD overall network connectivity following the pattern proposed by network theory (Borsboom, 2017) with disordered individuals of both conditions showing a higher overall connectivity and with the same pattern of behavior in the remaining macro-properties. These differences suggest that the etiopathogenic and maintenance processes of these disorders differ.

It has been suggested that these mechanisms might be better identified through meso-level properties (Letina et al., 2019). In fact, the meso-level analysis realized in Chapter II shows that both disordered OCD and SAD individuals have an increased number of motifs while disordered MDD and GAD individuals have a decrease. Thus, the differential behavior of network properties seems to traverse both macro and meso-properties, with micro-properties being able to change the phenotypic network structure of depression.

With changes in the network structure aligned with the transition from psychopathological to healthy states, Chapter II shows that not all methods for selecting treatment targets are equal. Choosing treatment targets through strength or degree centrality, for example, imposes very different structural changes. This is important, since, for example, a recent study selected treatment targets for intervening on eating disorder through strength centrality (Levinson, et al., 2018). If eating disorders are demonstrated to be similar in their macro and meso properties patterns to OCD and SAD,

then strength centrality might be an effective treatment target. However, if, in turn, eating disorders present the same behavior of MDD or GAD, then using strength centrality which will reduce the network connectivity will have the exact opposite effect since psychopathological process is associated with decreased connectivity. Then, the lack of a clear characterization of mental disorders macro-properties, might have led to an excessive belief in the network theory of mental disorders and might explain the inconsistent results found in the studies exploring centrality measures for treatment target selection (Dablander & Hinne, 2019; Dalgleish et al., 2019; Rodebaugh, Tonge, Piccirillo, et al., 2018). Additionally, identifying treatment targets only through the phenotypic expression of the disorder might be problematic when several interventions have demonstrated efficacy by acting on proposed endophenotypes of mental disorders (Calkins et al., 2015; Koster et al., 2017).

Thus, although Chapters I and II focused on the phenotypic structure of depression and promoted important insights and developments for the network theory, for these advances to be clearly translated into depression research, the construction of a complex integrative model and its subsequent analysis was needed. This constitutes the third Chapter of this thesis.

Following the assumption from the cognitive model of depression (LeMoult & Gotlib, 2019), in Chapter III a network comprising of two cognitive processes, emotion regulation strategies and depression was constructed. This integrative model shows that the impact of cognitive processes in depression are mediated by cognitive emotion regulation strategies and that these processes do not directly impact depression. Although, theoretical models propose these direct interaction (Beck & Bredemeier, 2016; LeMoult & Gotlib, 2019) and with cognitive training interventions that are aimed at specifically at these processes to reduce depression (Calkins et al., 2015), results suggest that changes

in these processes will not immediately translate into changes in depression. Consequently, these results highlight the pivotal role of cognitive emotion regulation strategies in depression, featuring the main role of rumination as the connecting path between cognitive processes and depression.

Besides the role of rumination, this fine-grained view provided by the network analysis, enabled the identification of distinct roles for both cognitive processes. Processing speed had a bridging role, demonstrated by its capacity to connect cognitive processes with cognitive emotion regulation strategies, while cognitive flexibility role was associated with alterations in the overall network connectivity. Paradoxically, although it is processing speed that is connected to the remainder of the network, it was cognitive flexibility that drives more changes on the overall connectivity. Interestingly, although in the phenotypic expression of depression psychopathological processes being associated with less connectivity, a deteriorated cognitive flexibility was associated with increases in the overall network connectivity. Since this deteriorated capacity has been associated with psychopathology (Conner et al., 2023; Gohier et al., 2009), these results suggest that a higher connectivity is synonymous of psychopathology. Therefore, these findings also underscore the significance of the nature of the nodes as a crucial factor in interpreting network properties.

In this context, this study offers additional validation for the network approach to studying depression by (1) informing network theory about the distinct behaviors of network properties in this disorder; (2) identifying the differential roles played by the proposed cognitive endophenotypes within the network.

Altogether this work has profound implications to the study of depression from a network perspective, identifying which properties are related to psychopathological processes and, consequently which measures might be better to inform treatment target

selection. From a cognitive depression perspective, this work also produced important insights by modeling the complex interactions between the proposed constituents of depression (LeMoult & Gotlib, 2019) and by identifying differential roles for each of these components.

In spite of these insights, it's important to note that the integrative model studied lacked a number of the proposed endophenotypes by the cognitive model of depression like other cognitive processes and cognitive biases (Everaert et al., 2012). And that these missing endophenotypes might also have important roles in the network and that the identified roles for the endophenotypes of depression might change with their addition. For example, various cognitive biases have been shown to mediate the relationship between cognitive processes and emotion regulation strategies (Everaert, et al., 2017). Thus, future research should construct depression network models that add more of the proposed endophenotypes to the model. However, with the actual sample requirements for network models estimation (Isvoranu & Epskamp, 2023) this will require a concerted effort from the field.

These changes of roles that might occur with the construction of a more complete cognitive network model of depression would possibly have an impact on treatment target selection due to the change in the interaction structure. But, more importantly, it is still not clear that psychological treatments or interventions might be able to act at such a specific level. In this work, for example, in the phenotypic expression were identified symptoms that could potentiate a faster recovery from depression and on the endophenotypic expression the differential impact of processing speed and cognitive flexibility was tested. However, evidence for the capacity to produce these precise interventions is scarce (Blanken et al., 2019; Fishbein et al., 2023; Lancee et al., 2022; Norton et al., 2022). Even in cognitive control interventions that aim at specific cognitive

processes there is inconsistent evidence for this precision (Pahor et al., 2022; Sala et al., 2019).

In conclusion, this work advances our understanding of depression by exploring the complex interactions within the cognitive model of depression and offering insights into the roles played by different cognitive processes. By addressing these complexities through network analysis, this thesis contributes with knowledge that can guide future research and potentially inform more effective and precise treatments for individuals experiencing depression.

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APPENDIX

Supplementary Materials for Chapter I [1, 2, 3]

Topological Properties of Psychopathological Networks of Healthy and Disordered Individuals across Depressive and Anxiety Disorder

Note:

[1] This chapter has been submitted to the *Journal of Affective Disorders* for publication: Castro, D., Cardoso, J., Araújo, A. S., Rodrigues, A. R., Ferreira, F., Ferreira-Santos, & Ferreira, T. B. (2023). Topological properties of psychopathological networks of healthy and disordered individuals across depressive and anxiety disorders [Manuscript submitted to publication].

[2] Supplementary materials of this paper are available in the Chapter I of the Appendix.

[3] Code to reproduce the analysis the analysis can be found at https://osf.io/naqp3/

Index

1- Graphical Representation and Centrality Estimates for MDD networks

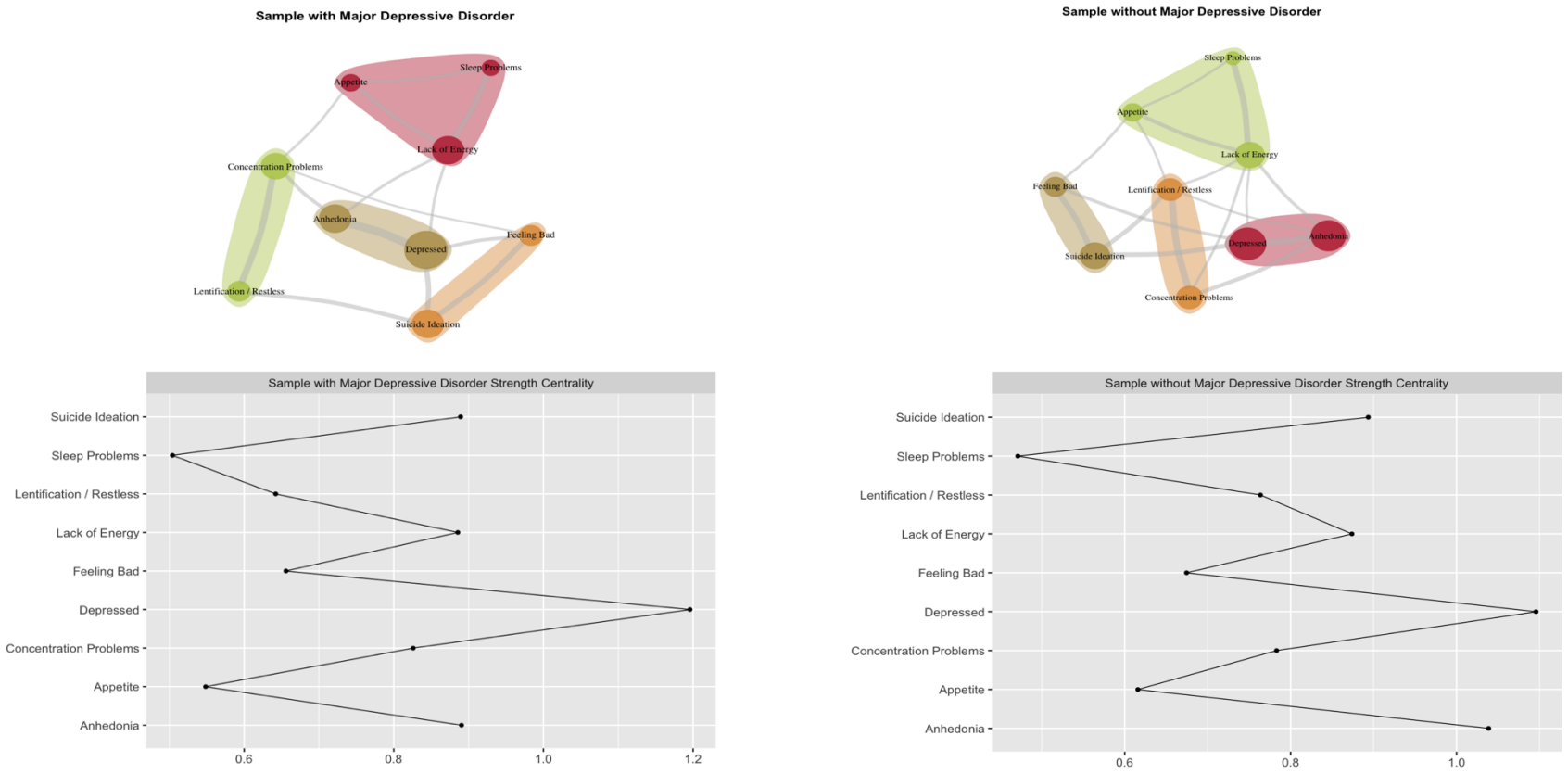


Figure 1.
Panel a) shows the graphical representation of the networks of Major Depressive Disorder (MDD), on the left is the graphical representation of the sample with MDD and on the right is the graphical representation of the sample without MDD. Nodes represent each symptom of the disorder and the edges the interactions between symptoms. The shadows behind the symptoms represent communities of symptoms, each color represents a distinct community. Panel b) shows the strength centrality of each symptom in the network.

2- Graphical Representation and Centrality Estimates for GAD networks

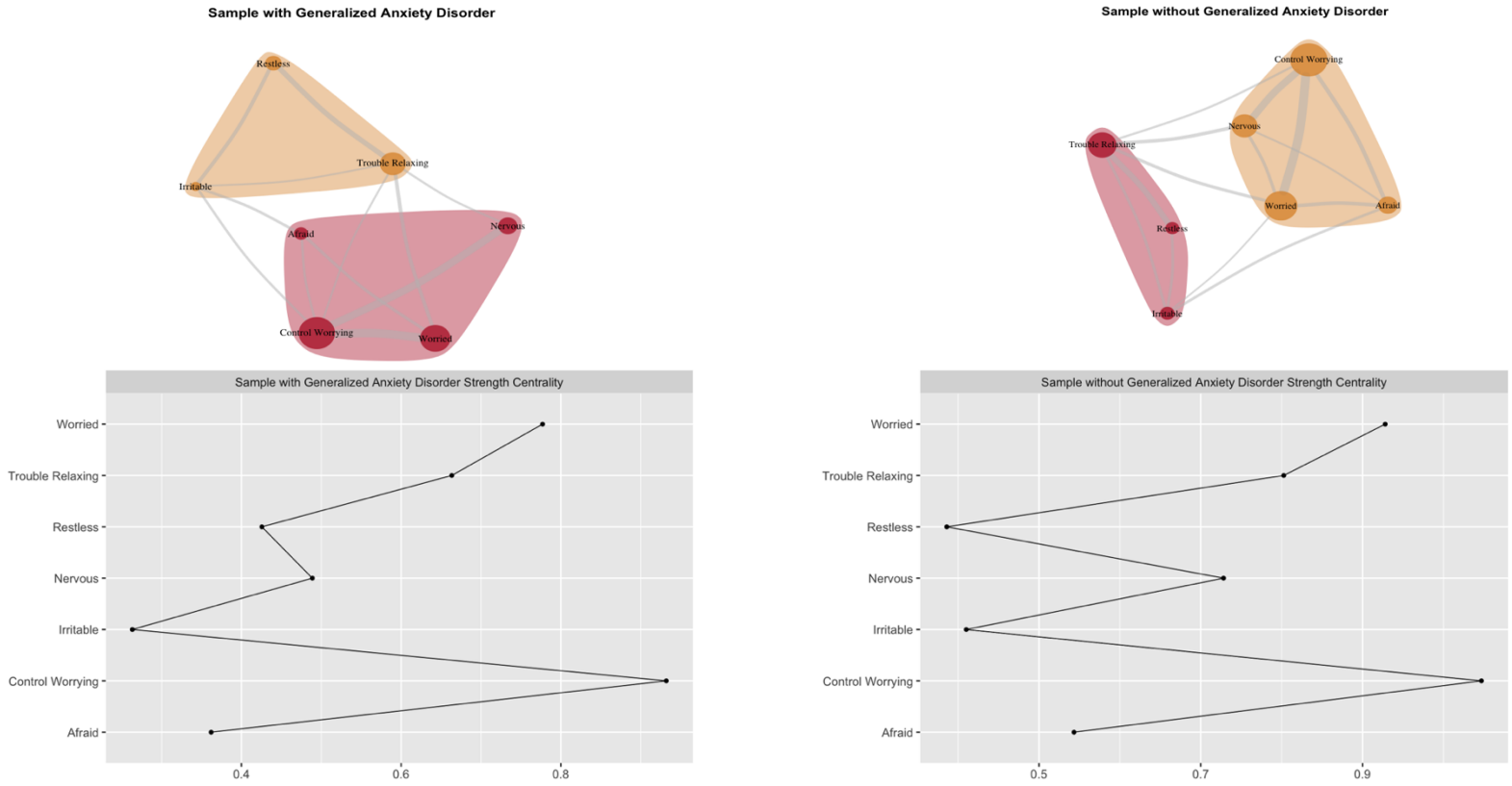


Figure 2
Panel a) shows the graphical representation of the networks of Generalized Anxiety Disorder (GAD), on the left is the graphical representation of the sample with GAD and on the right is the graphical representation of the sample without GAD. Nodes represent each symptom of the disorder and the edges the interactions between symptoms. The shadows behind the symptoms represent communities of symptoms, each color represents a distinct community.
Panel b) shows the strength centrality of each symptom in the network.

3- Graphical Representation and Centrality Estimates for OCD networks

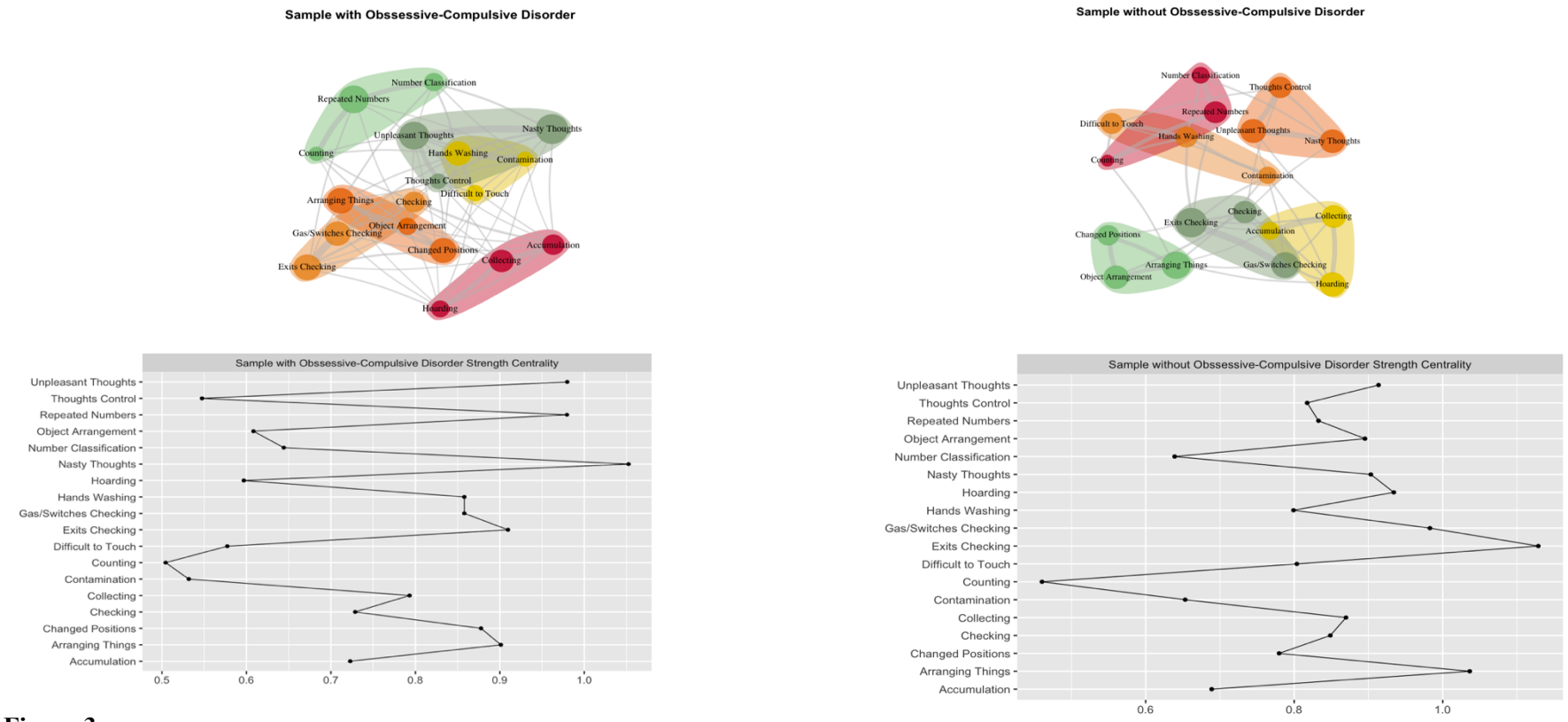


Figure 3

Panel a) shows the graphical representation of the networks of Obssessive-Compulsive Disorder (OCD), on the left is the graphical representation of the sample with OCD and on the right is the graphical representation of the sample without OCD. Nodes represent each symptom of the disorder and the edges the interactions between symptoms. The shadows behind the symptoms represent communities of symptoms, each color represents a distinct community.
Panel b) shows the strength centrality of each symptom in the network.

4- Graphical Representation and Centrality Estimates for SAD networks

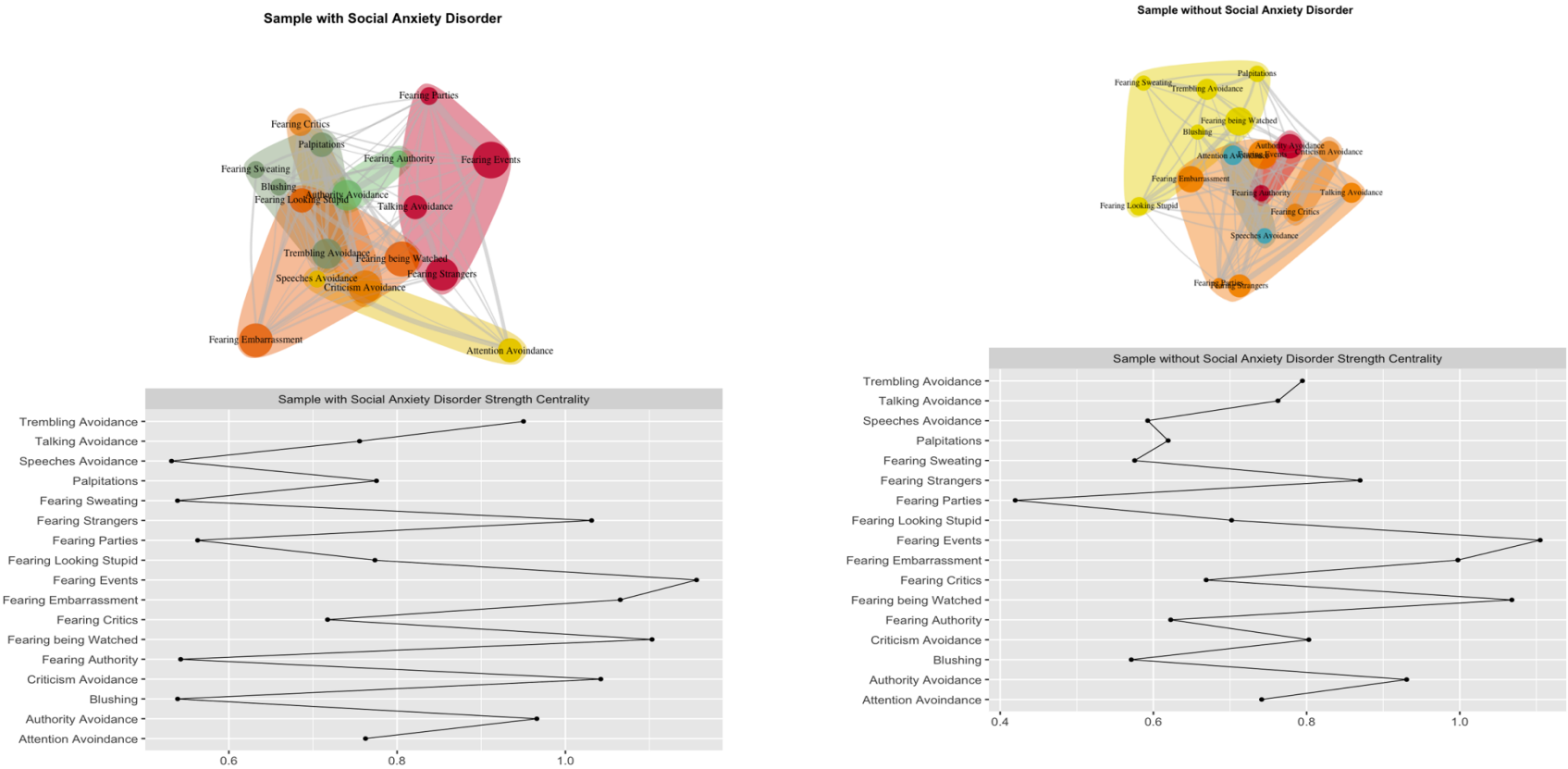


Figure 4

Panel a) shows the graphical representation of the networks of Social Anxiety Disorder (SAD), on the left is the graphical representation of the sample with SAD and on the right is the graphical representation of the sample without SAD. Nodes represent each symptom of the disorder and the edges the interactions between symptoms. The shadows behind the symptoms represent communities of symptoms, each color represents a distinct community.
Panel b) shows the strength centrality of each symptom in the network.

5- Motifs with 3 Positive Edges

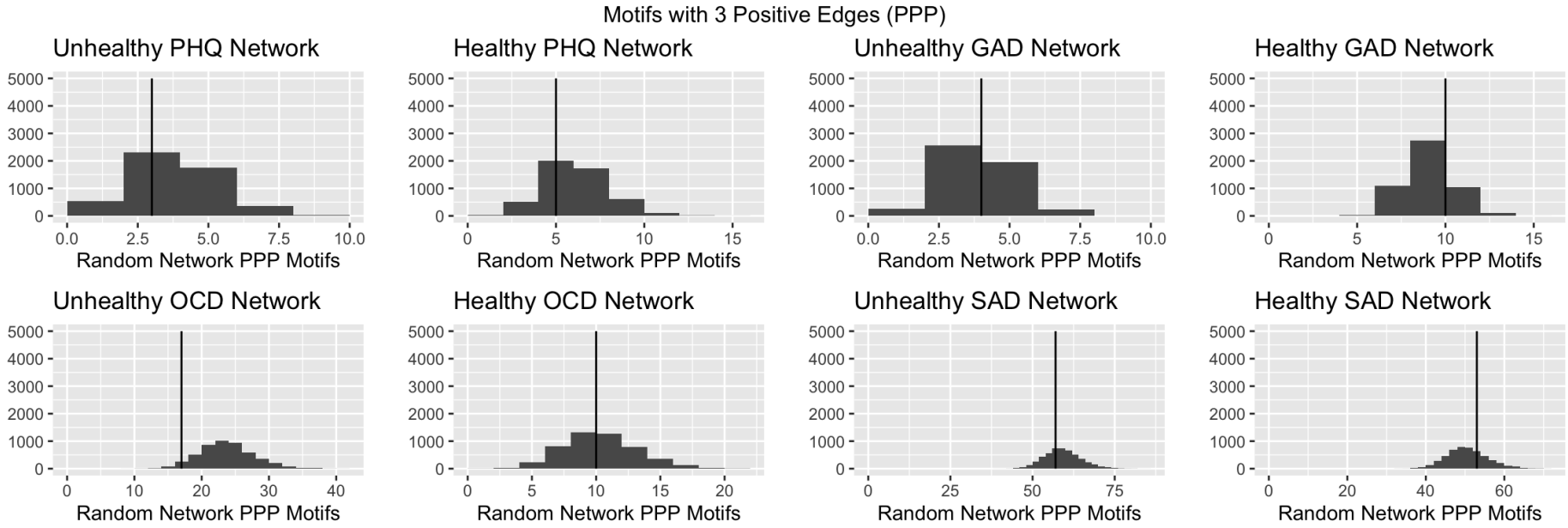


Figure 5
Histogram of the network motifs with 3 positive edges (PPP) in 5000 simulated networks obtained by randomizing the edges of each disorder network. Vertical line identifies the observed value of the PPP type motif for each disorder network.

6- Motifs with 2 Positive Edges and 1 Negative Edge

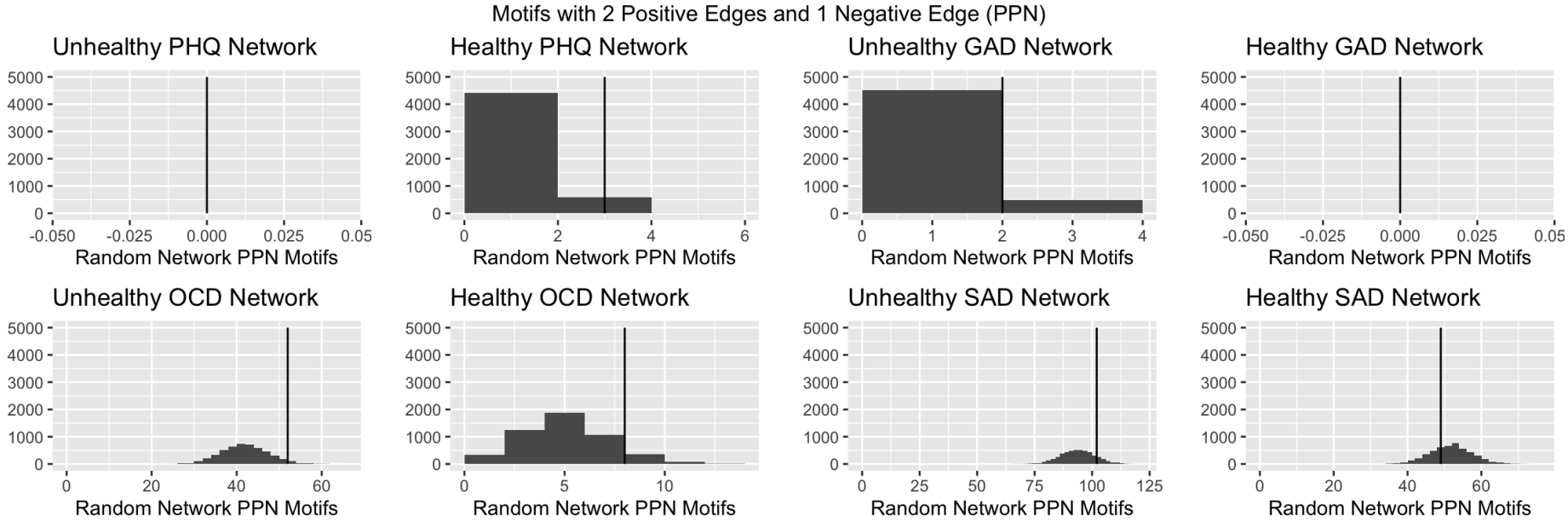


Figure 6
Histogram of the network motifs with 2 positive edges and 1 negative edge (PPN) in 5000 simulated networks obtained by randomizing the edges of each disorder network. Vertical line identifies the observed value of the PPN type motif for each disorder network.

7- Motifs with 1 Positive Edges and 2 Negative Edge

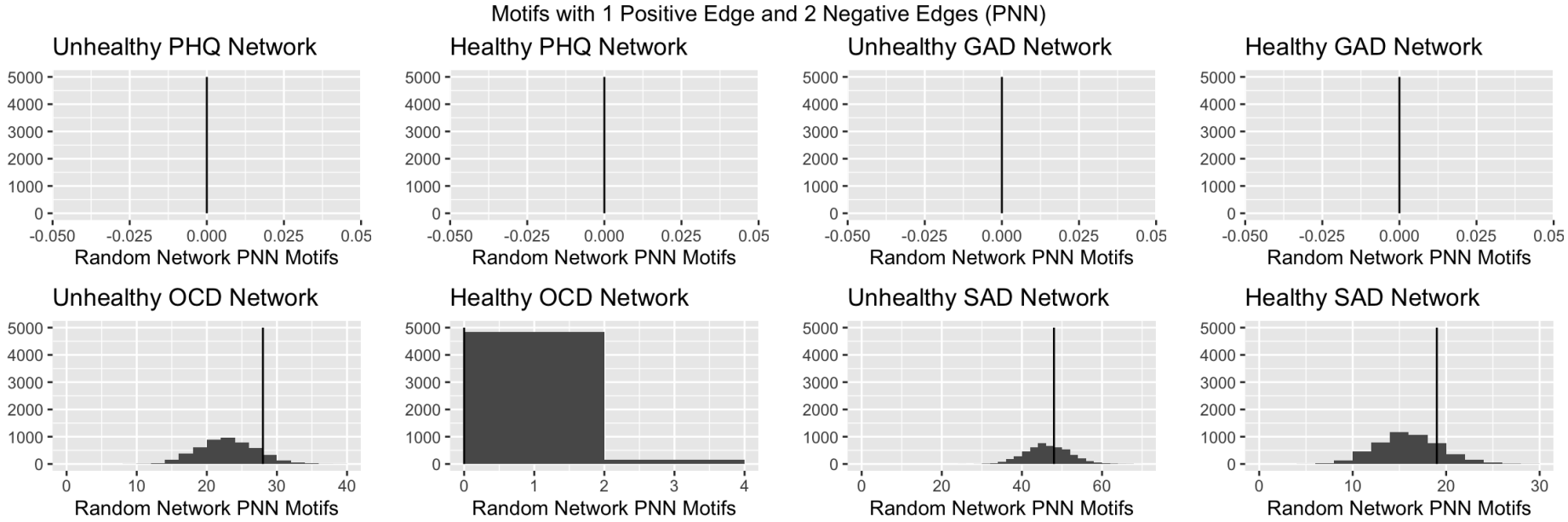


Figure 7
Histogram of the network motifs with 1 positive edges and 2 negative edge (PNN) in 5000 simulated networks obtained by randomizing the edges of each disorder network. Vertical line identifies the observed value of the PNN type motif for each disorder network.

8- Motifs with 3 Negative Edges

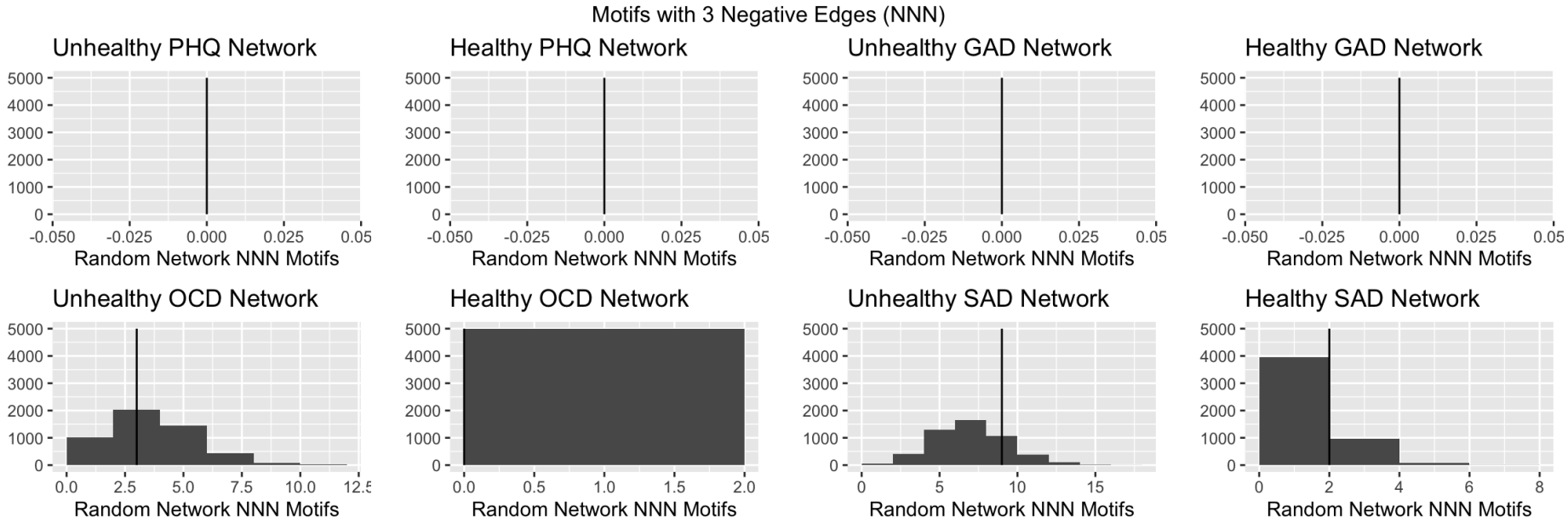


Figure 8
Histogram of the network motifs with 3 negative edges (NNN) in 5000 simulated networks obtained by randomizing the edges of each disorder network. Vertical line identifies the observed value of the NNN type motif for each disorder network.

9- Network Stability

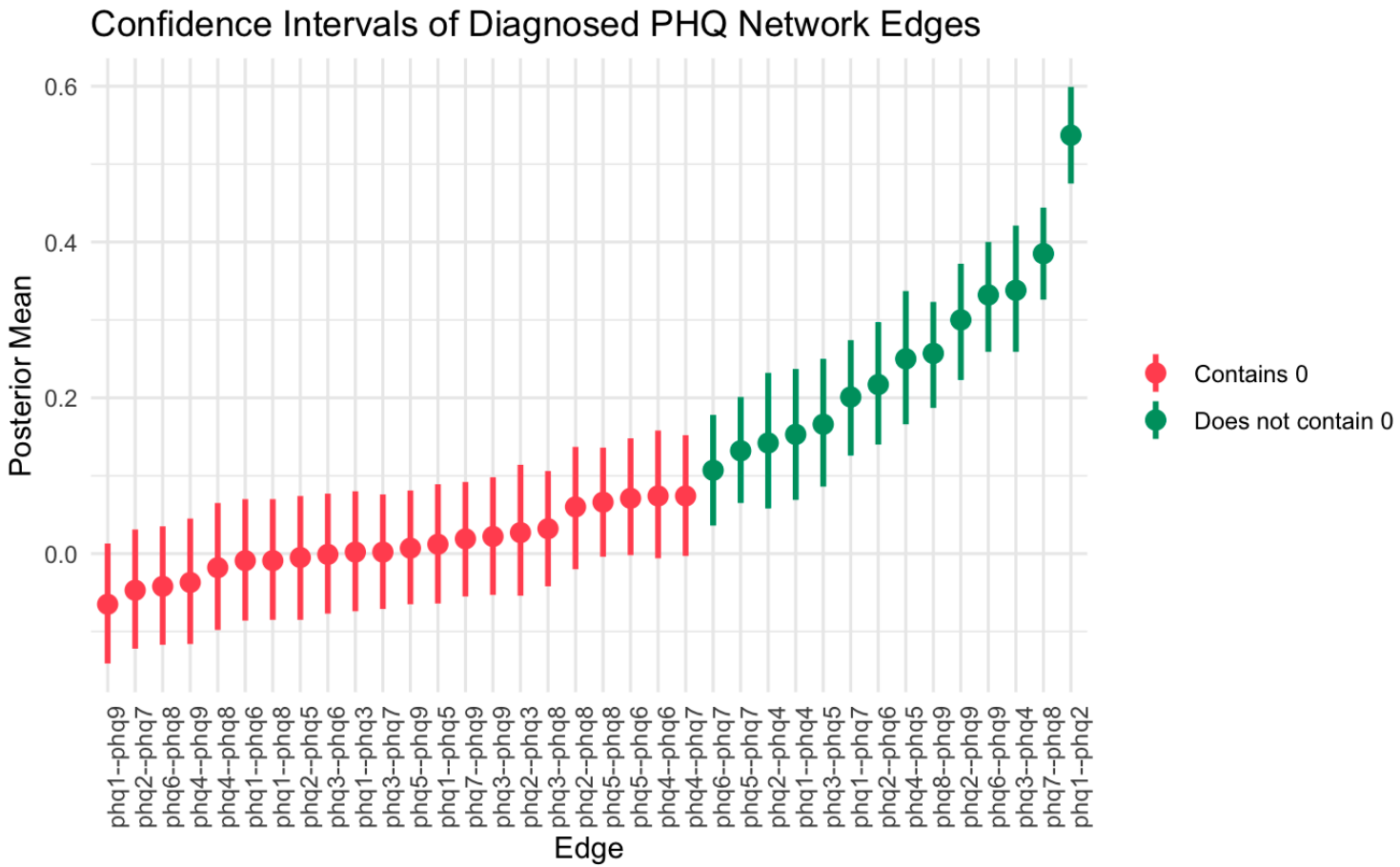


Figure 9. Graphical representation of diagnosed PHQ network edges posterior mean and confidence intervals of each edge.

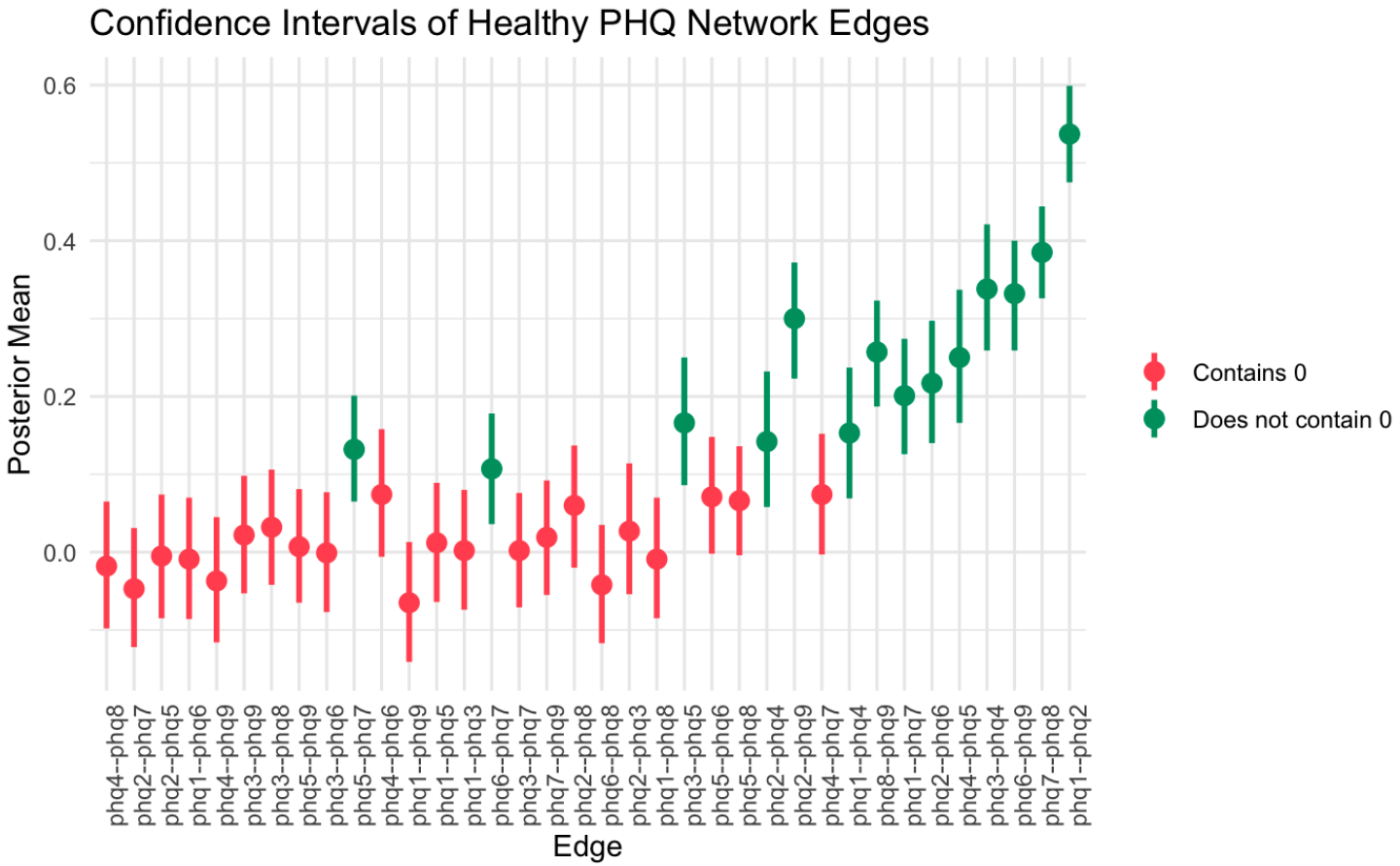


Figure 10. Graphical representation of healthy PHQ network edges posterior mean and confidence intervals of each edge. Green bars and dots identify confidence intervals of edges that do not have 0 in them. Red bars and dots identify confidence intervals of edges that have 0 in them.

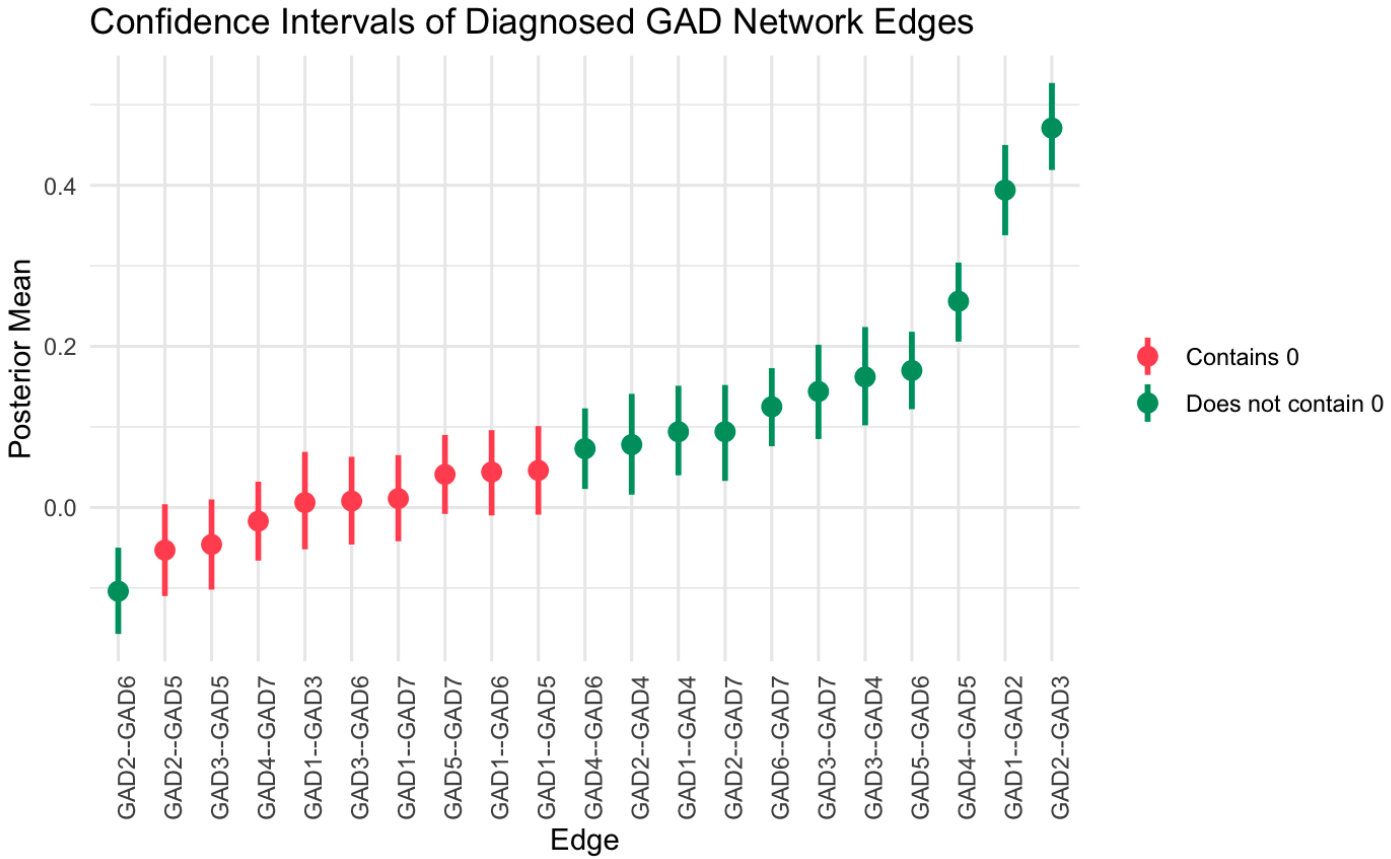


Figure 11. Graphical representation of diagnosed GAD network edges posterior mean and confidence intervals of each edge. Green bars and dots identify confidence intervals of edges that do not have 0 in them. Red bars and dots identify confidence intervals of edges that have 0 in them.

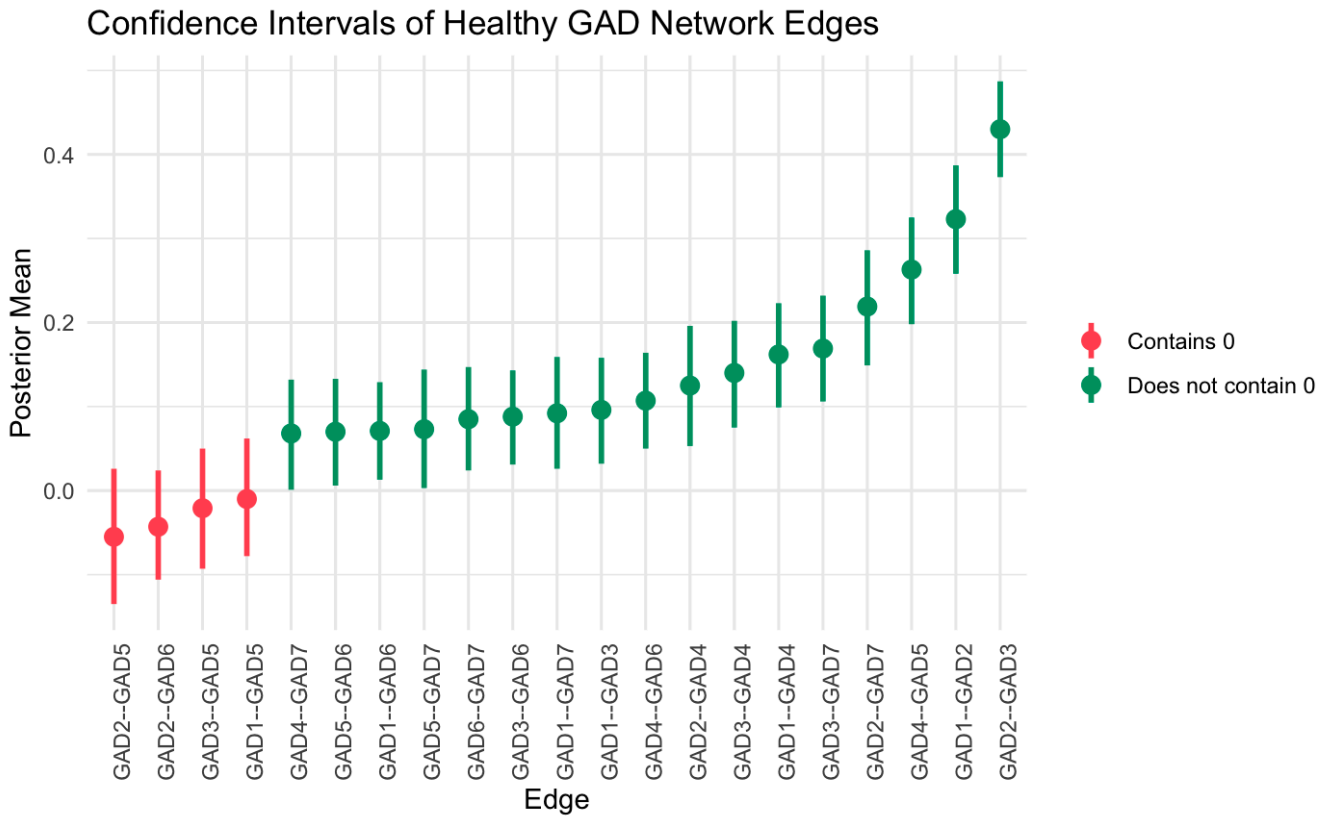


Figure 12. Graphical representation of healthy GAD network edges posterior mean and confidence intervals of each edge. Green bars and dots identify confidence intervals of edges that do not have 0 in them. Red bars and dots identify confidence intervals of edges that have 0 in them.

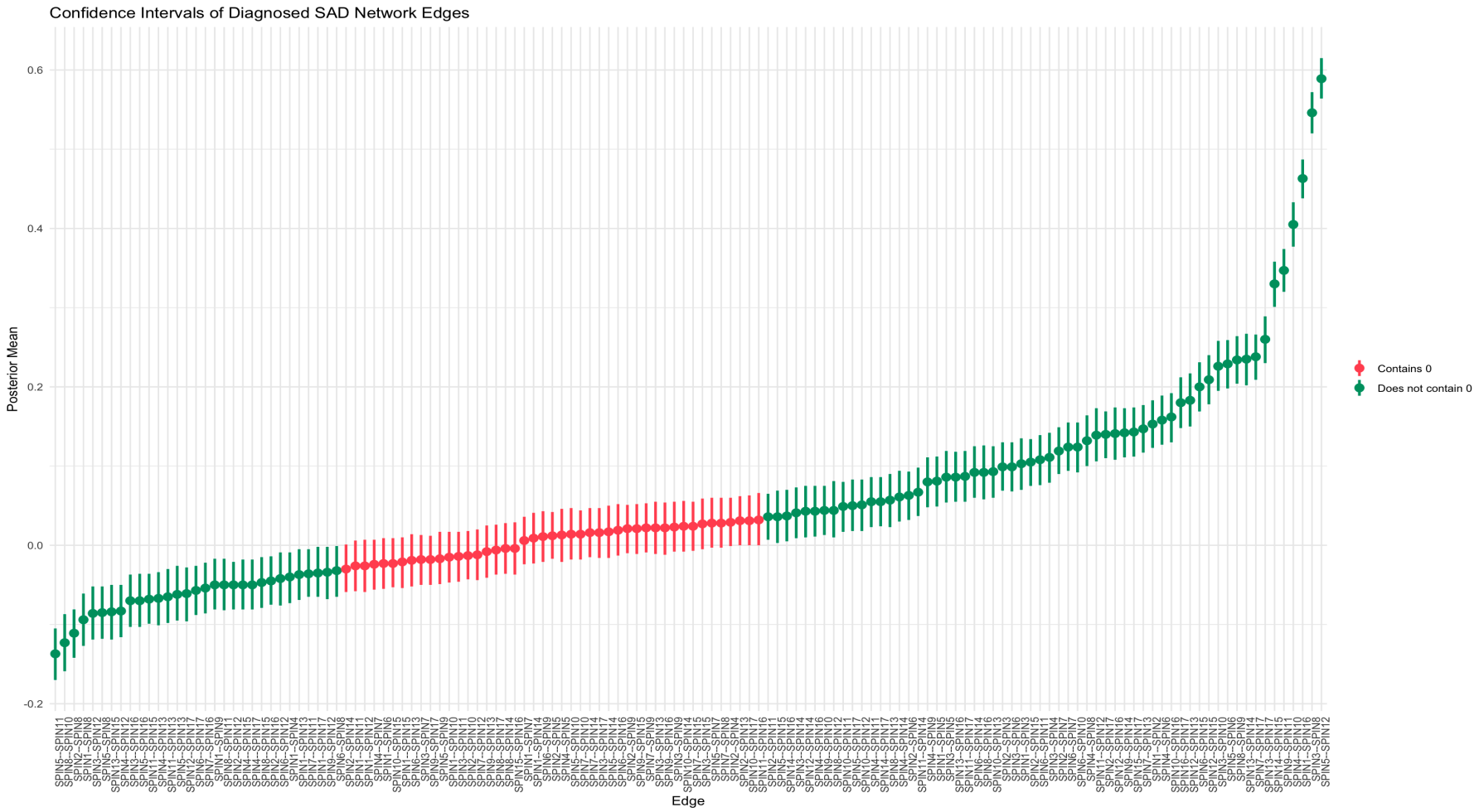


Figure 13. Graphical representation of diagnosed SAD network edges posterior mean and confidence intervals of each edge. Green bars and dots identify confidence intervals of edges that do not have 0 in them. Red bars and dots identify confidence intervals of edges that have 0 in them.

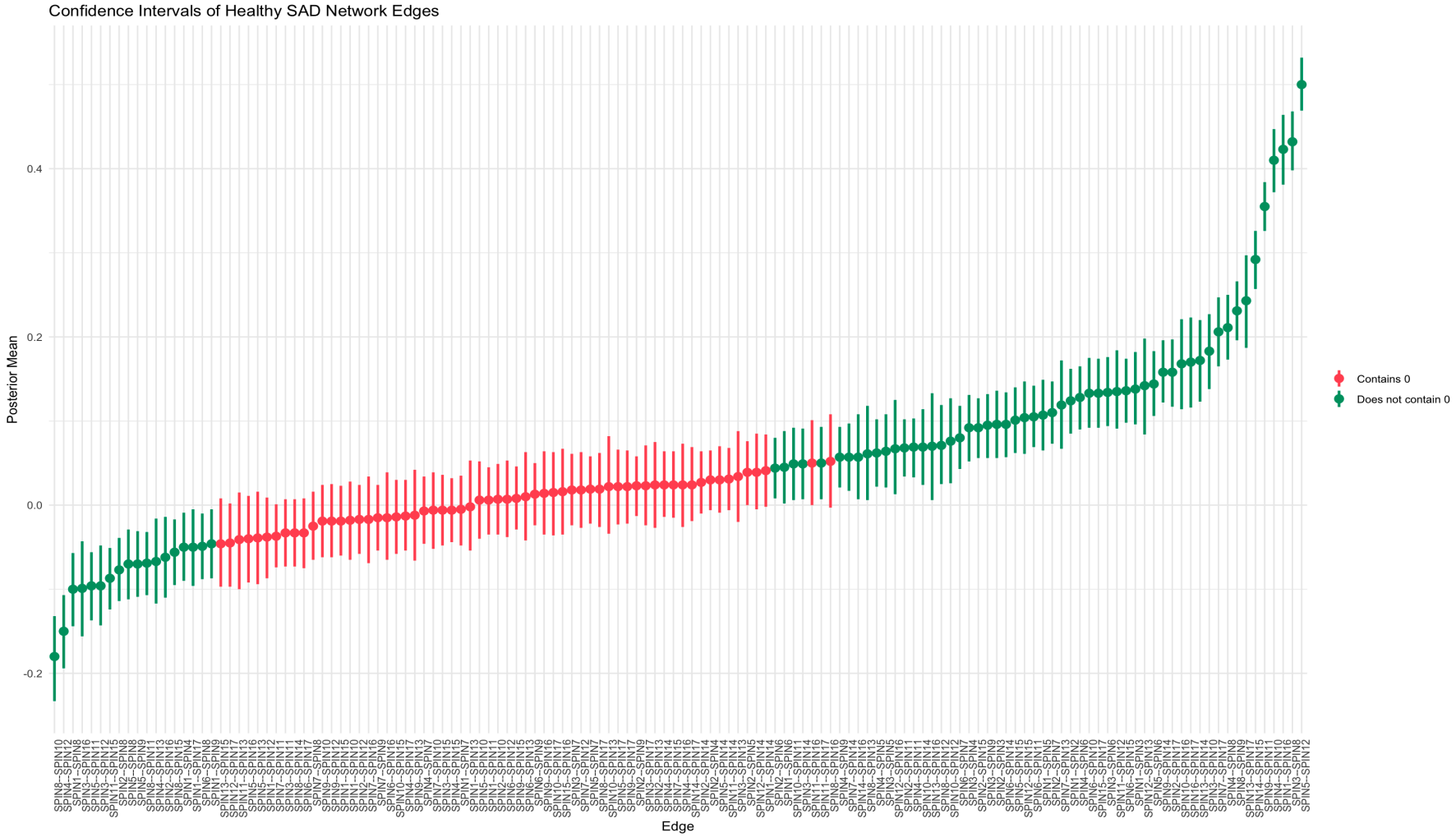


Figure 14. Graphical representation of healthy SAD network edges posterior mean and confidence intervals of each edge. Green bars and dots identify confidence intervals of edges that do not have 0 in them. Red bars and dots identify confidence intervals of edges that have 0 in them.

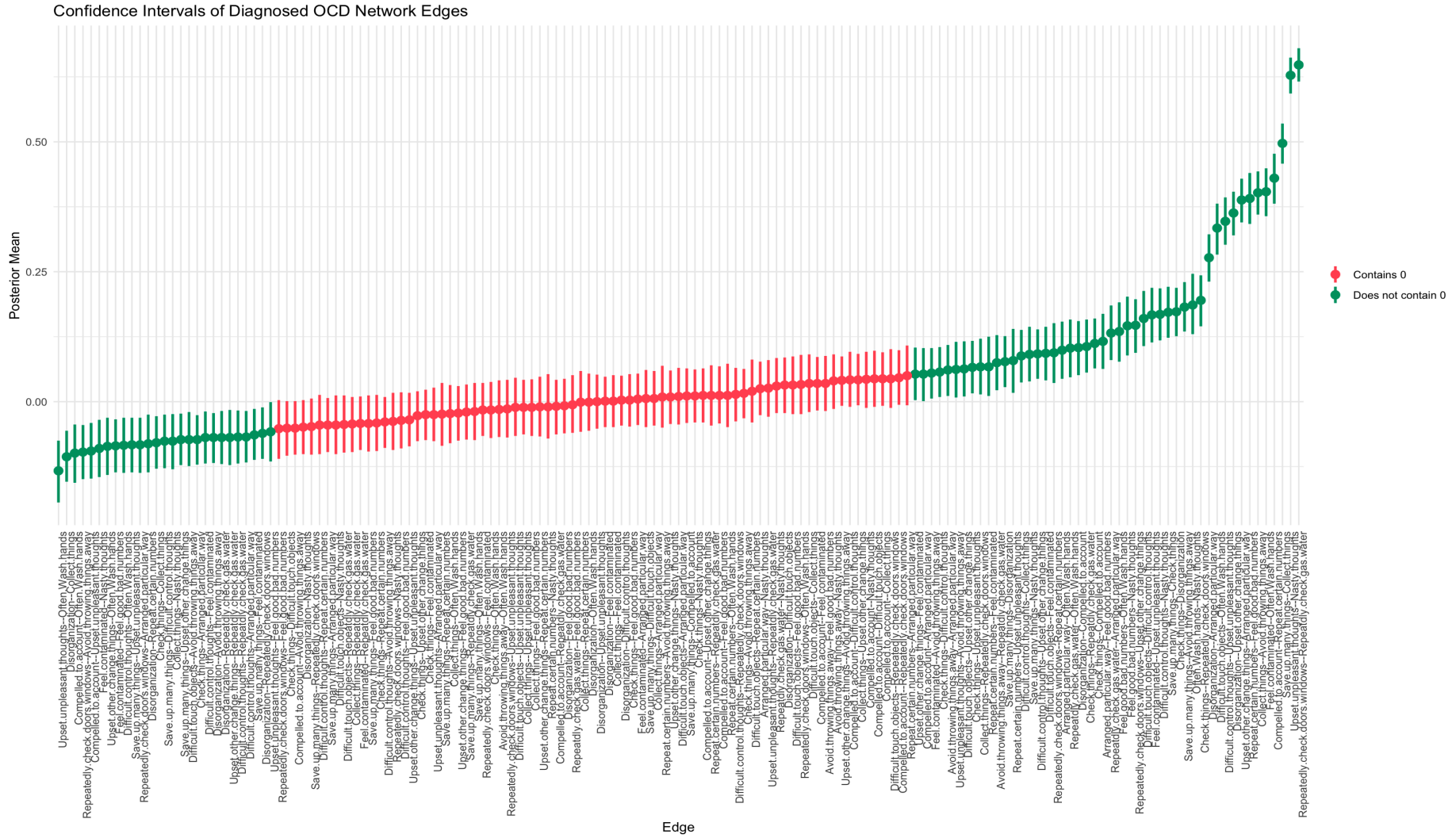


Figure 15. Graphical representation of diagnosed OCD network edges posterior mean and confidence intervals of each edge. Green bars and dots identify confidence intervals of edges that do not have 0 in them. Red bars and dots identify confidence intervals of edges that have 0 in them.

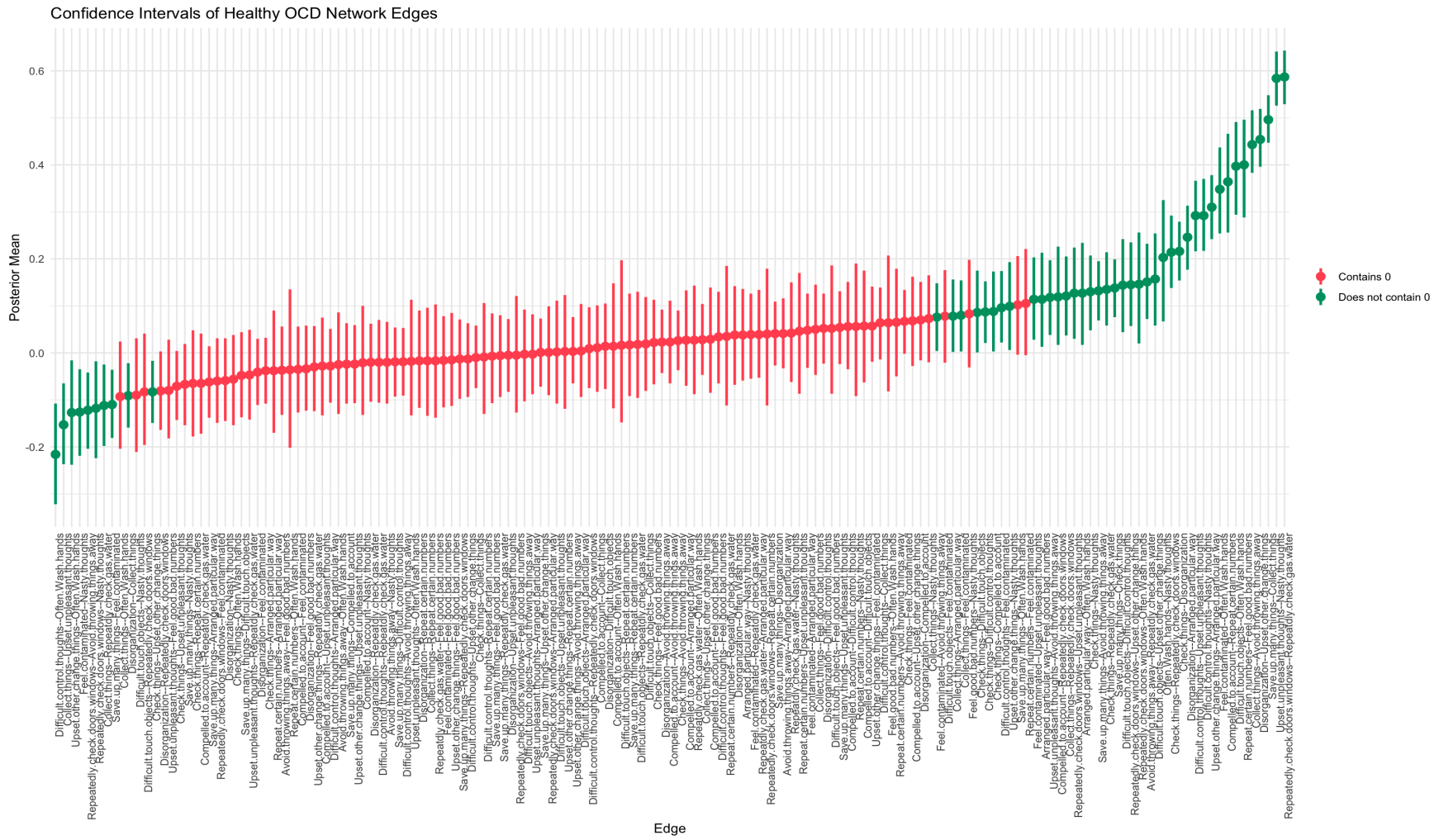


Figure 16. Graphical representation of healthy OCD network edges posterior mean and confidence intervals of each edge. Green bars and dots identify confidence intervals of edges that do not have 0 in them. Red bars and dots identify confidence intervals of edges that have 0 in them.

Supplementary Materials for Chapter II [1, 2, 3]

Centrality Measures in Psychological Networks: A Simulation Study on Identifying Effective Treatment Targets

Note:

[1] This chapter has been accepted for publication in *PLOS ONE*:

Castro, D., Gysi, D., Ferreira, F., Ferreira-Santos, F., & Ferreira, T. B. (2024). Centrality measures in psychological networks: A simulation study on identifying effective treatment targets. *PLOS ONE.*

[2] Supplementary materials of this paper are available in the Chapter II of the Appendix.

[3]Code to reproduce the analysis the analysis can be found at https://osf.io/k2z84/

Index

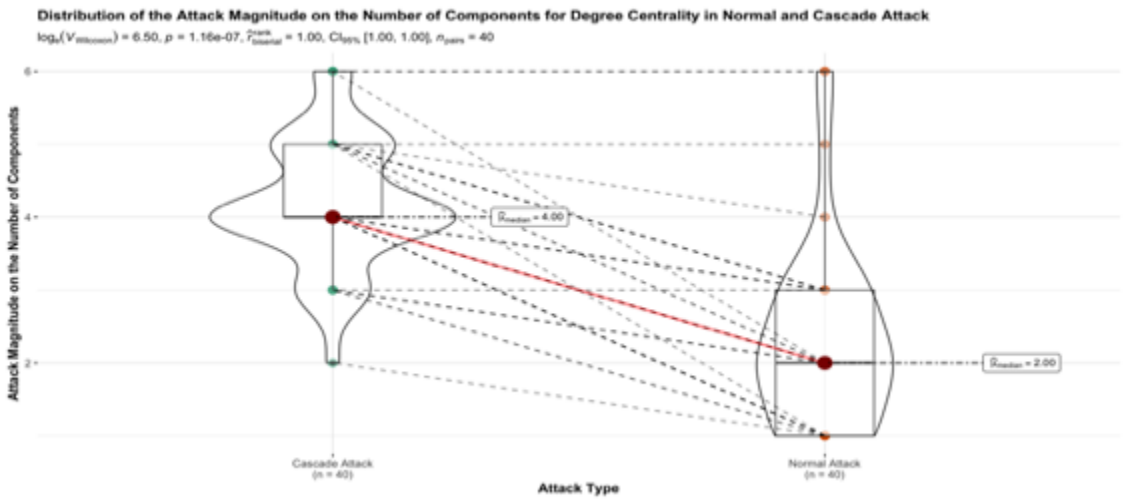
Table S1. Participants Characteristics

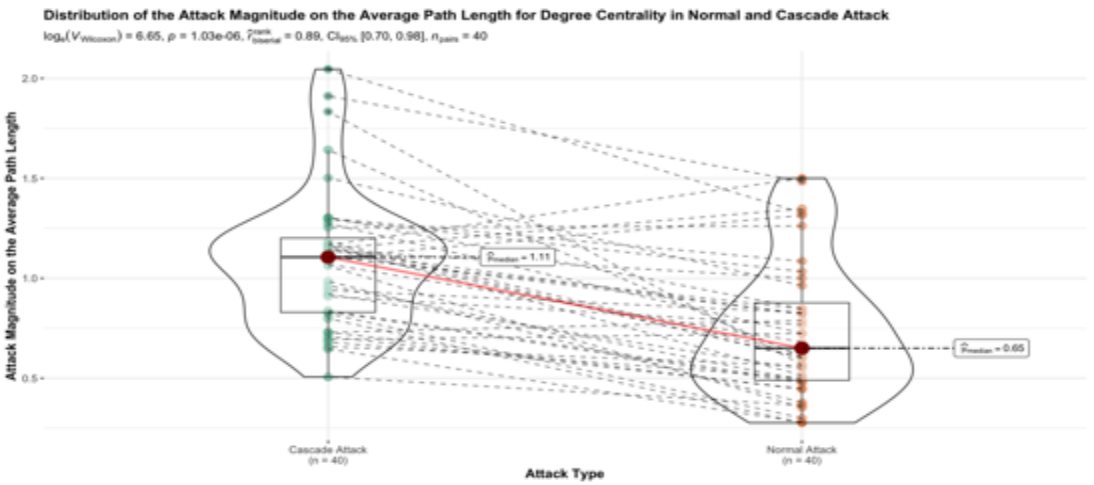
Network	Sex	Age	Ethnicity	Primary Diagnosis	Comorbidities	HAM-D	HAM-A
1	Female	18 - 24	Latino	MDD	YES	23	27
2	Male	25 - 30	White	MDD	YES	16	15
3	Female	25 - 30	Latino	GAD	NO	16	33
4	Male	18 - 24	White	MDD	YES	13	13
5	Female	25 - 30	Black	MDD	YES	11	17
6	Female	18 - 24	Asian American	MDD	YES	19	15
7	Female	18 - 24	Other	MDD	YES	17	9
8	Male	25 - 30	Asian American	GAD	YES	22	22
9	Female	31 - 40	Latino	GAD	YES	9	13
10	Male	18 - 24	White	GAD	YES	14	19
11	Male	18 – 24	Latino	GAD	NO	10	12
12	Female	25 – 30	Asian American	MDD	YES	10	10
13	Male	51 – 60	Other	MDD	YES	15	16
14	Female	51 – 60	White	GAD	NO	8	7
15	Male	25 – 30	White	GAD	YES	15	14
16	Female	18 - 24	White	GAD	YES	8	14
17	Female	18 – 24	Latino	GAD	YES	12	23
18	Female	25 – 30	White	GAD	YES	21	41
19	Male	51 – 60	Asian American	GAD	YES	14	17
20	Female	31 – 40	White	MDD	NO	11	14
21	Female	31 – 40	Asian American	GAD	YES	15	13
22	Female	51 – 60	White	MDD	NO	12	10
23	Female	18 – 24	White	MDD	NO	18	23
24	Male	25 – 30	White	GAD	YES	7	14
25	Female	18 – 24	Asian American	GAD	YES	18	15
26	Female	41 – 50	Black	GAD	YES	4	15
27	Female	31 – 40	White	GAD	YES	18	19
28	Male	51 – 60	White	MDD	YES	12	18
29	Male	25 – 30	Latino	GAD	YES	9	13
30	Male	41 – 50	Asian American	MDD	NO	16	15
31	Female	51 – 60	White	MDD	YES	14	12
32	Female	41 – 50	Other	GAD	YES	21	30
33	Male	41 – 50	White	GAD	YES	13	11
34	Female	51 – 60	Asian American	MDD	YES	16	16
35	Male	25 – 30	White	MDD	NO	13	15
36	Female	31 – 40	White	GAD	YES	10	11
37	Female	18 – 24	Asian American	GAD	YES	18	20
38	Female	51 – 60	White	GAD	NO	12	16
39	Female	31 - 40	Black	GAD	NO	17	23
40	Female	25 - 30	White	GAD	YES	17	14

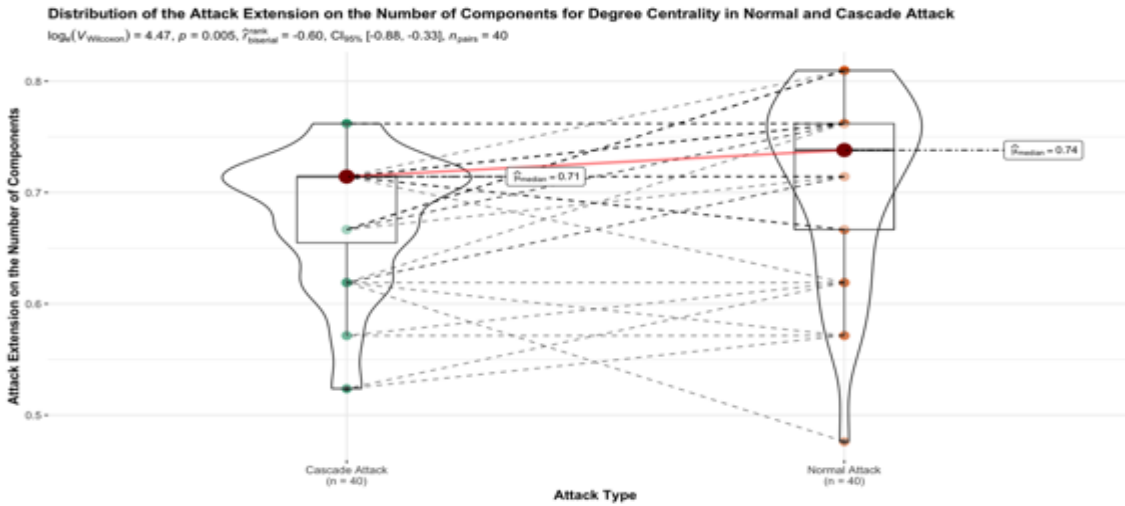
Table S2. Network Basic Features

Network Characteristics	Networks (n=40)		
	Mean (SD)	**Median (MAD)**	**Minimum-maximum**
Nodes	21	21 (0.00)	
Edges	96.08 (15.42)	101.00 (10.38)	61 - 124
Density	0.46 (0.07)	0.48 (0.05)	0.29 - 0.59
Components	1	1 (0.00)	
Average Path Length	1.56 (0.11)	1.52 (0.05)	1.41 - 1.91

Comparison between Degree Cascade Attack and Degree Normal Attack







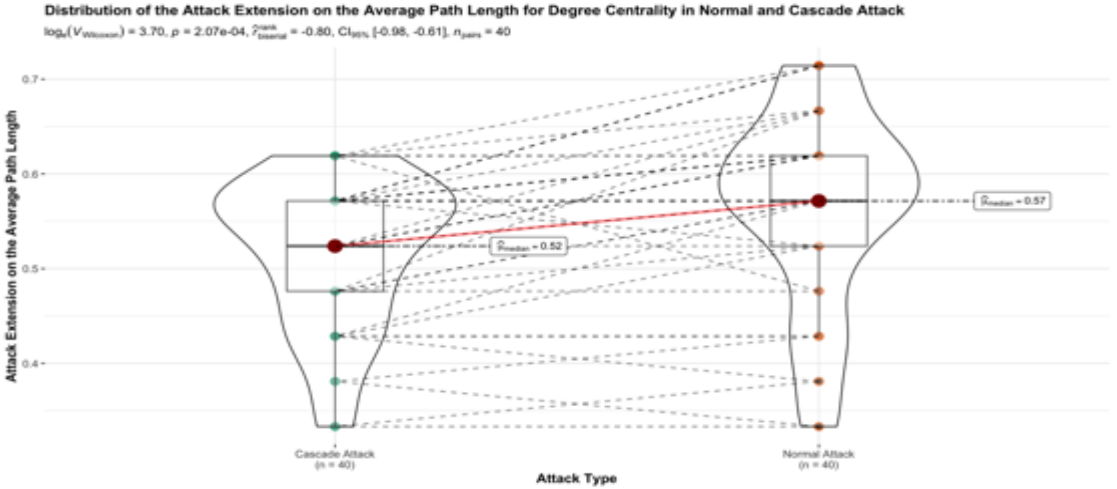


Figure S1. Graphical representation of the comparison between a degree-based normal attack and a degree-based cascade attack for the number of components and the average path length. In each panel, the result of the Wilcoxon signed-rank test for differences between the two attack conditions is presented. Boxplots represent the network density results range for each attack condition.

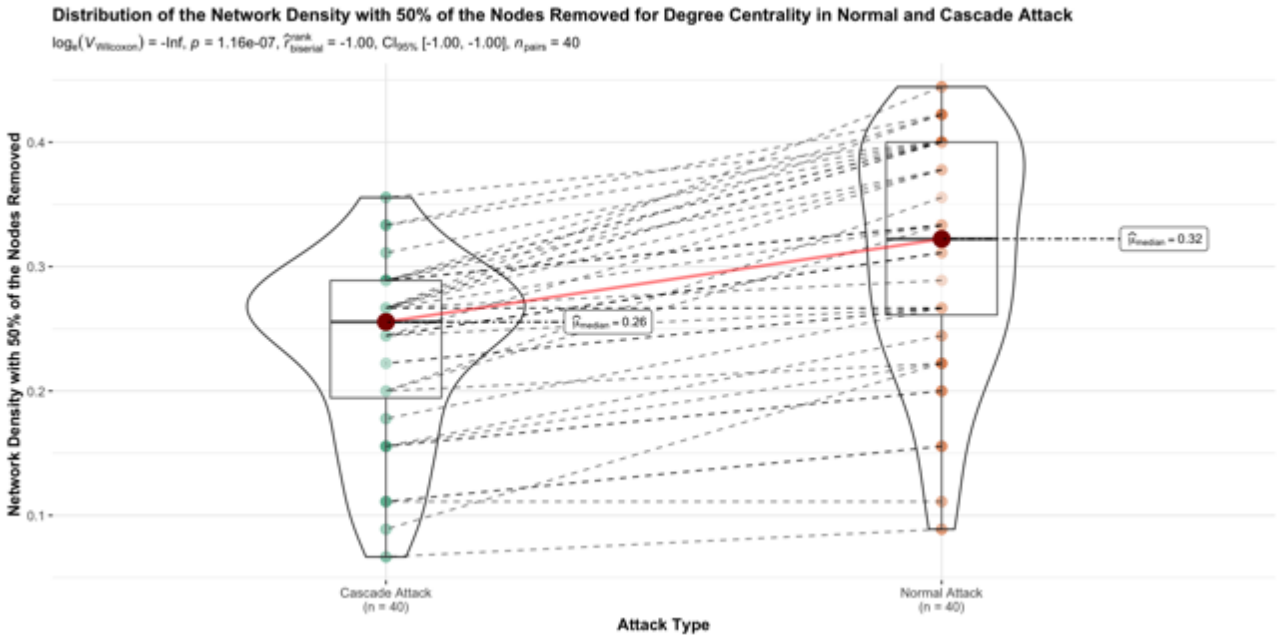
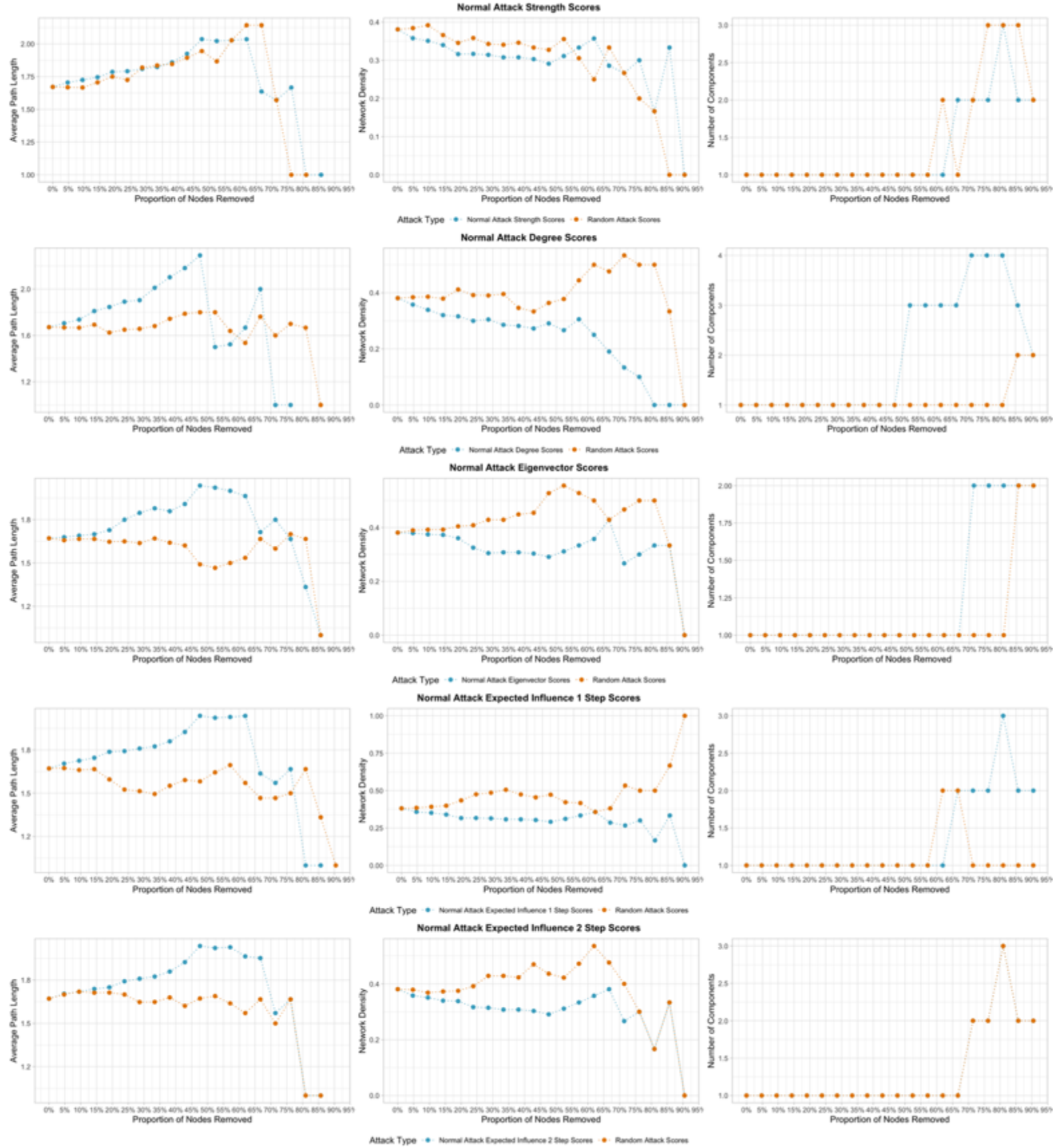


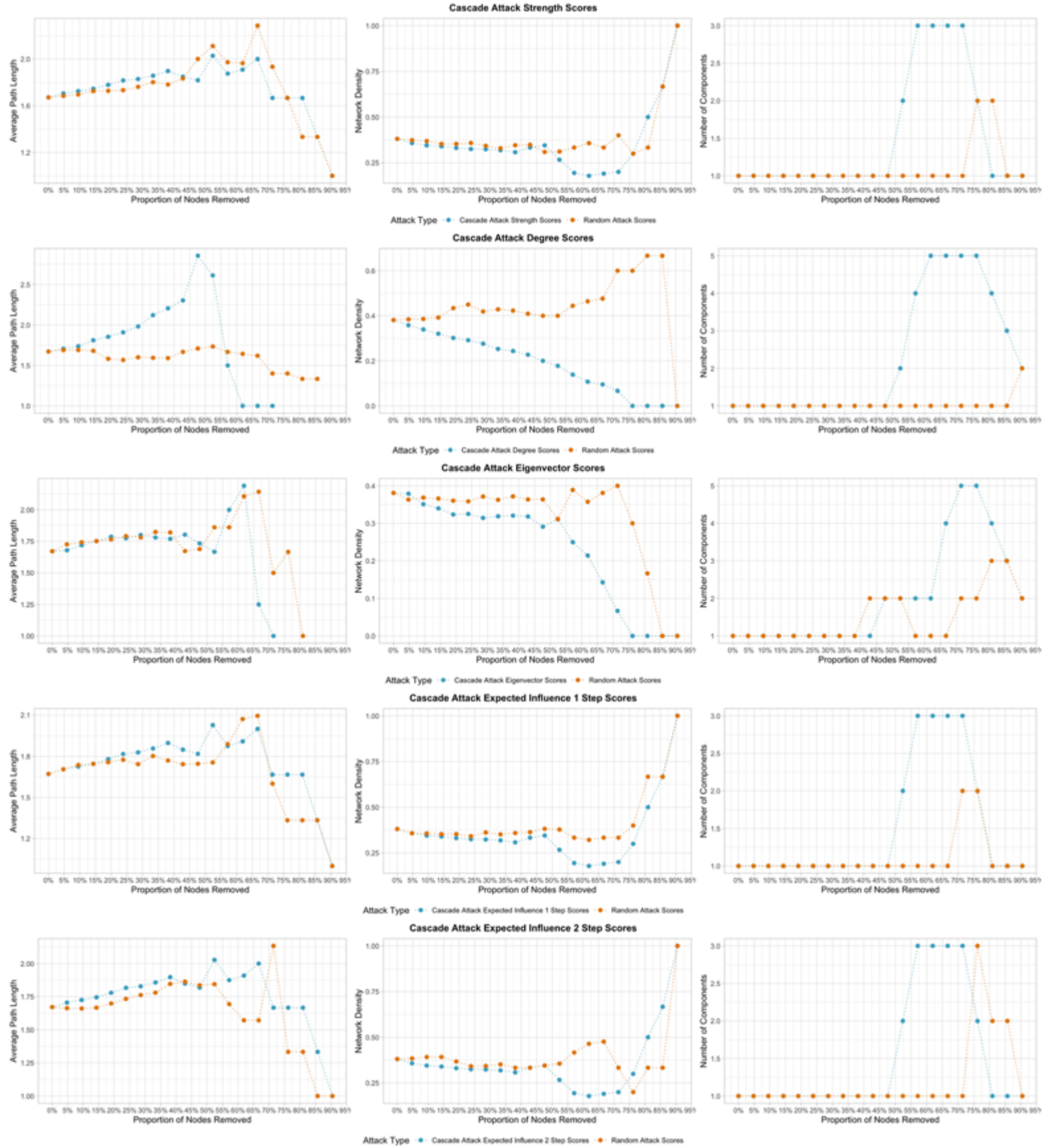
Figure S2. Graphical representation of the comparison between a degree-based normal attack and a degree-based cascade attack for network density with 50% of the nodes removed. In each panel, the result of the Wilcoxon signed-rank test for differences between the two attack conditions is presented. Boxplots represent the network density results range for each attack condition

Plots Displaying Attack Results for Each Individual Network

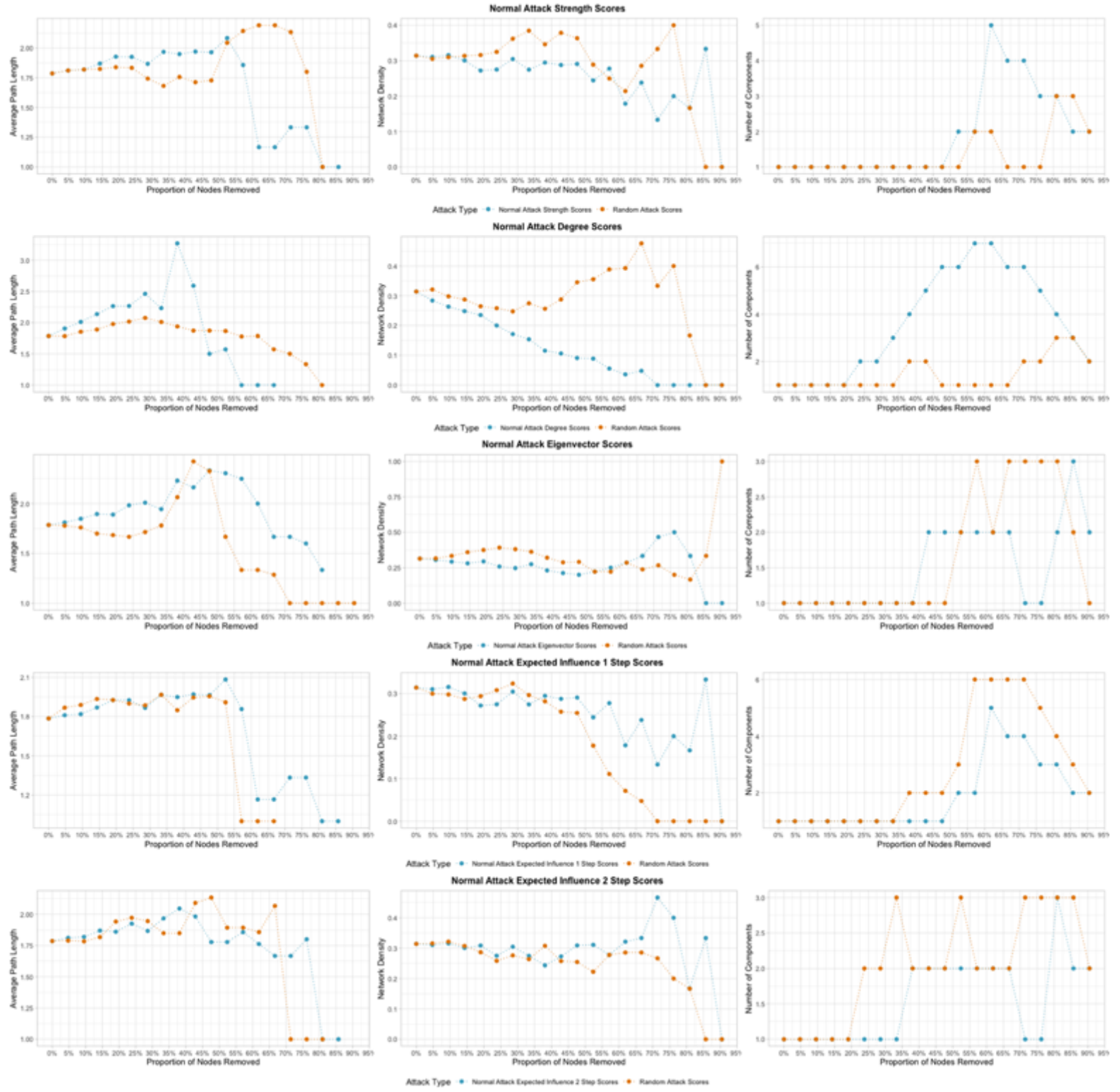
Plots displaying normal attack results for network 1



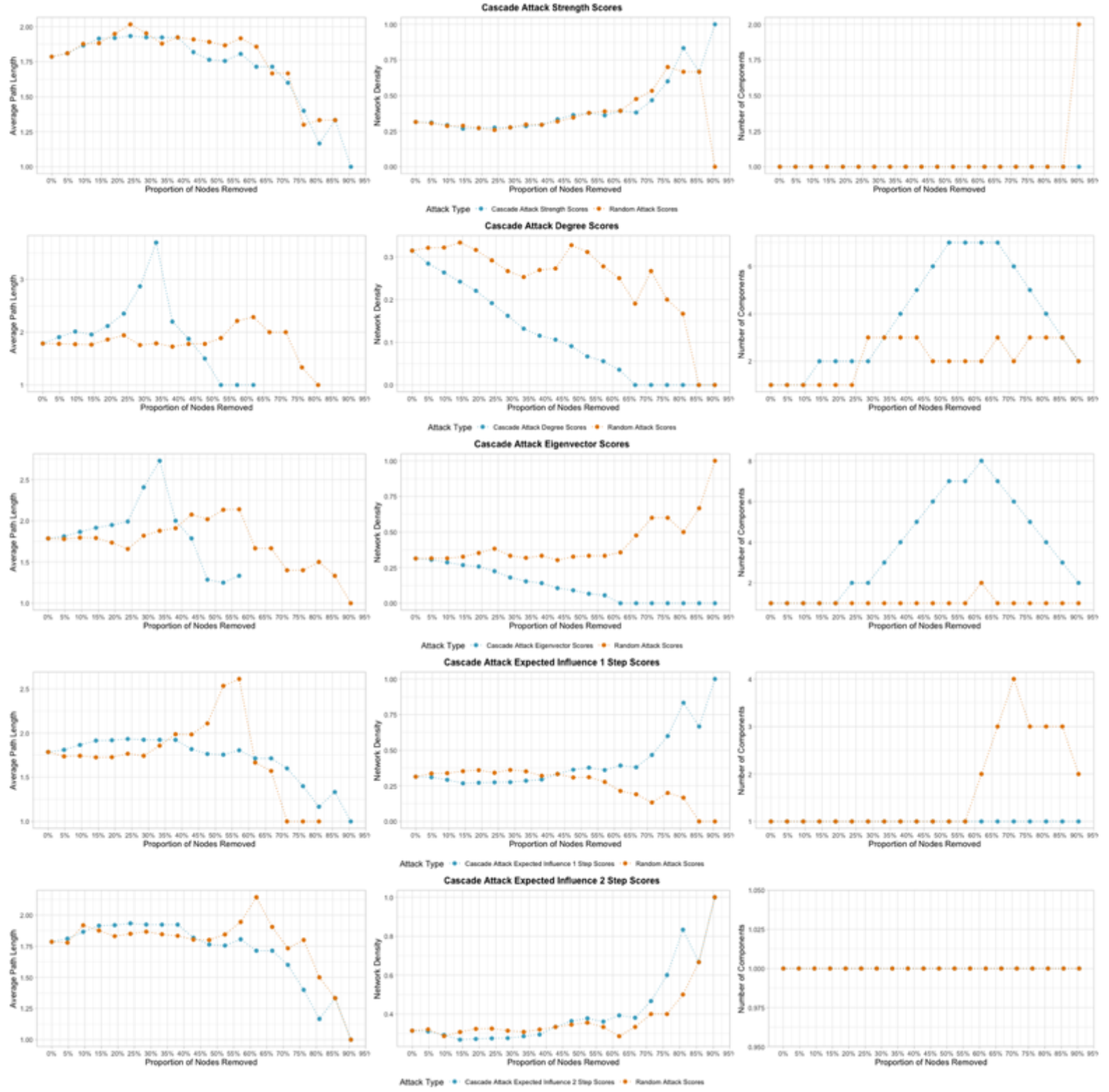
Plots displaying cascade attack results for network 1



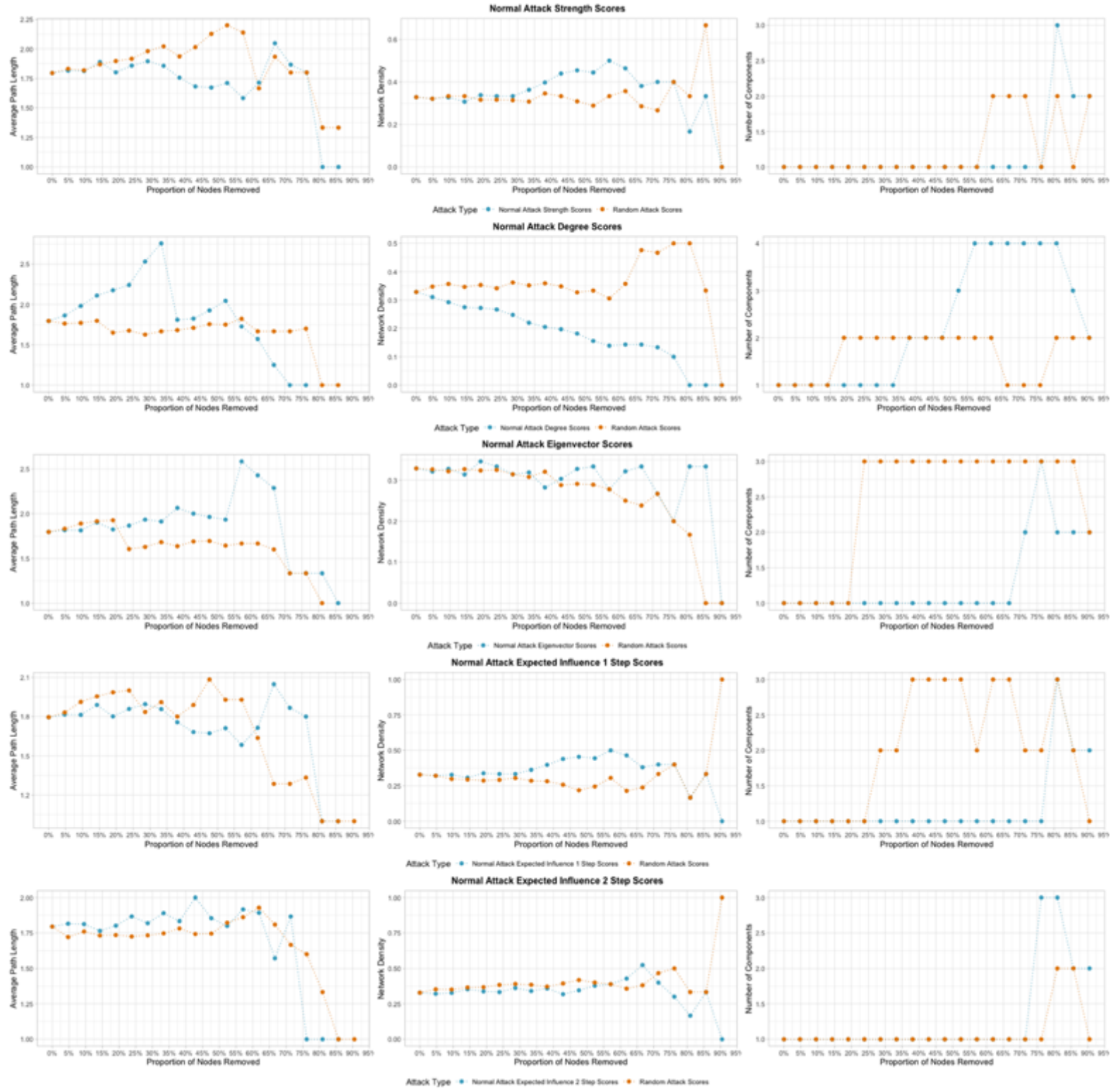
Plots displaying normal attack results for network 2



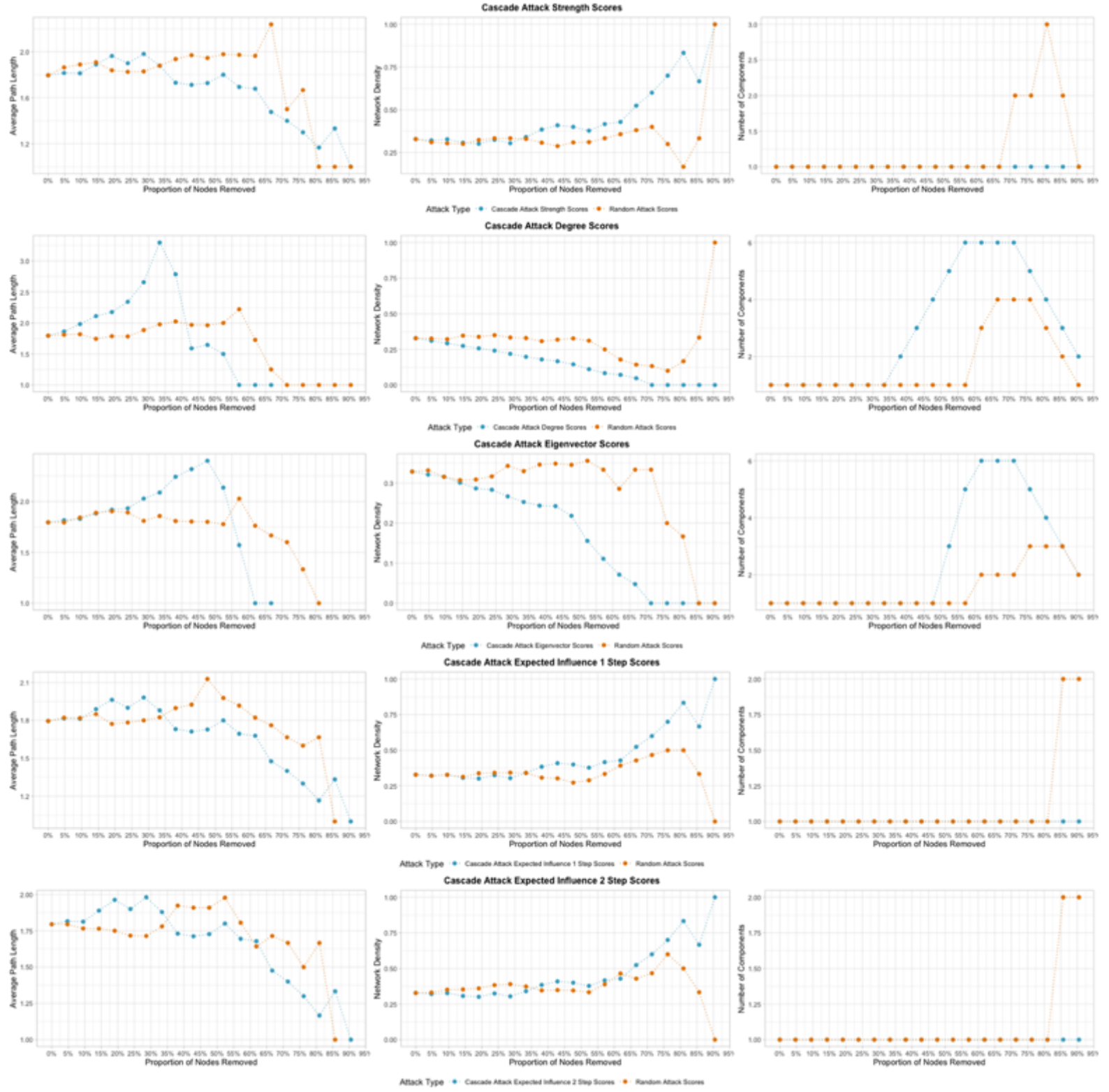
Plots displaying cascade attack results for network 2



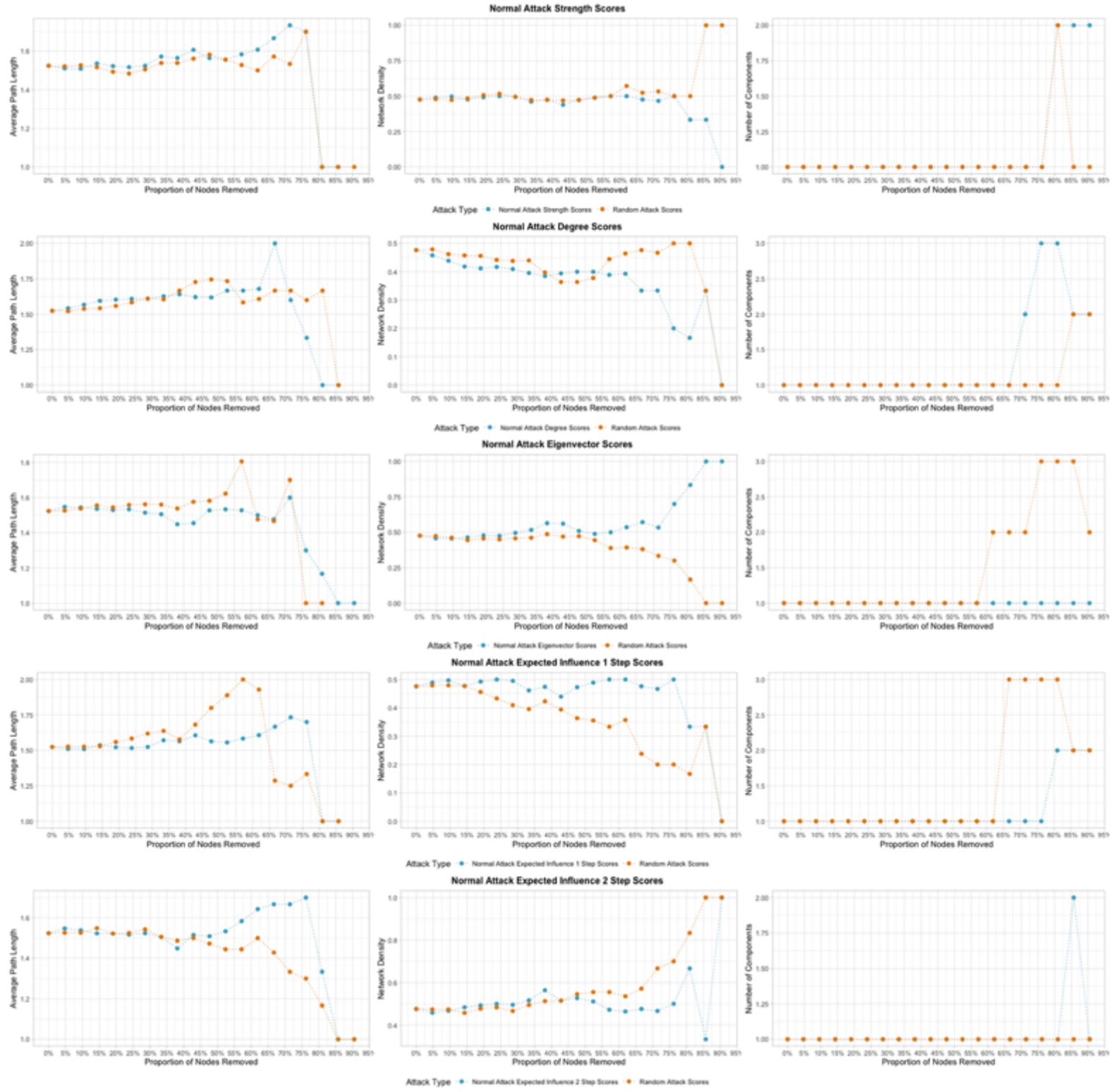
Plots displaying normal attack results for network 3



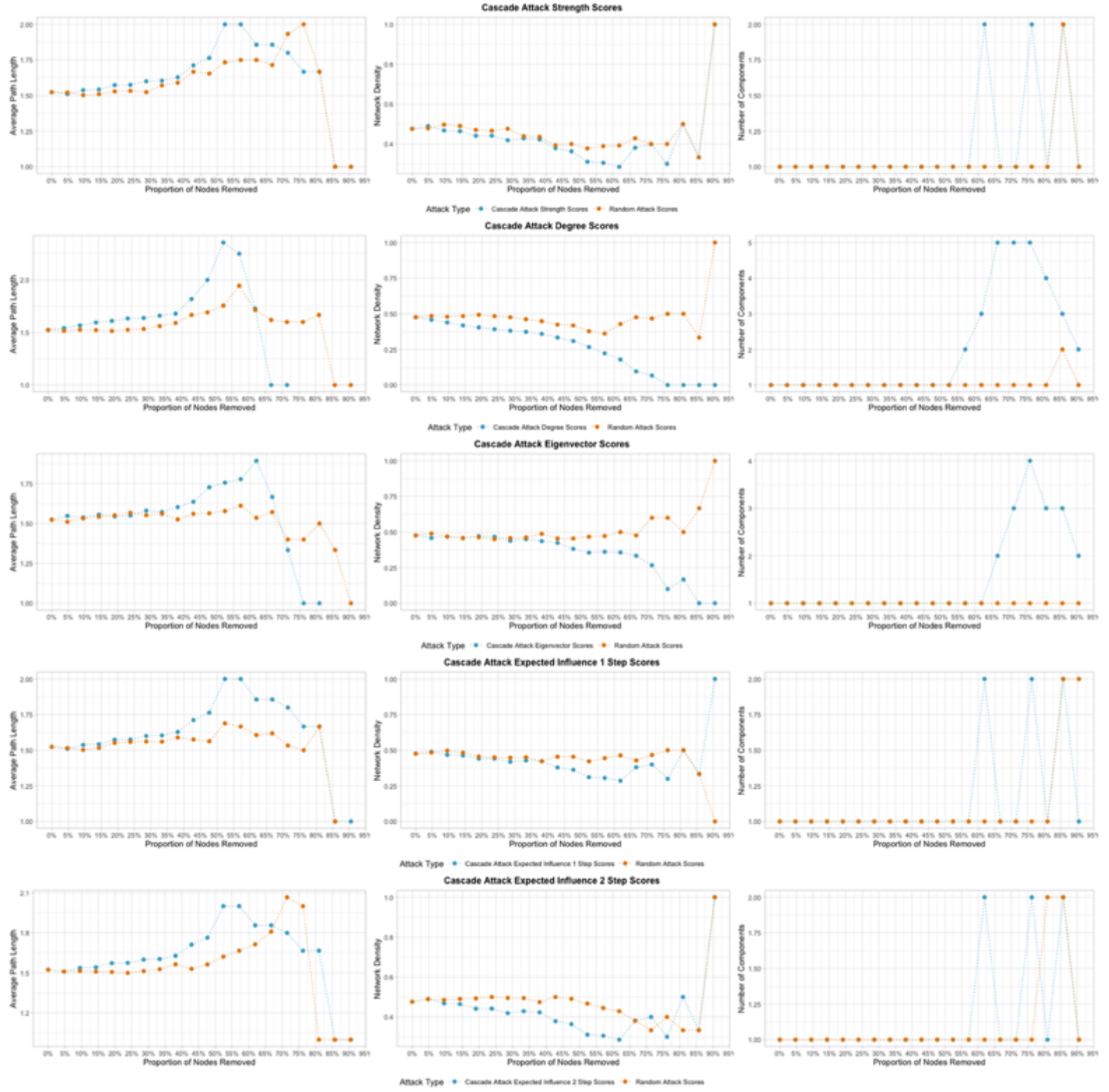
Plots displaying cascade attack results for network 3



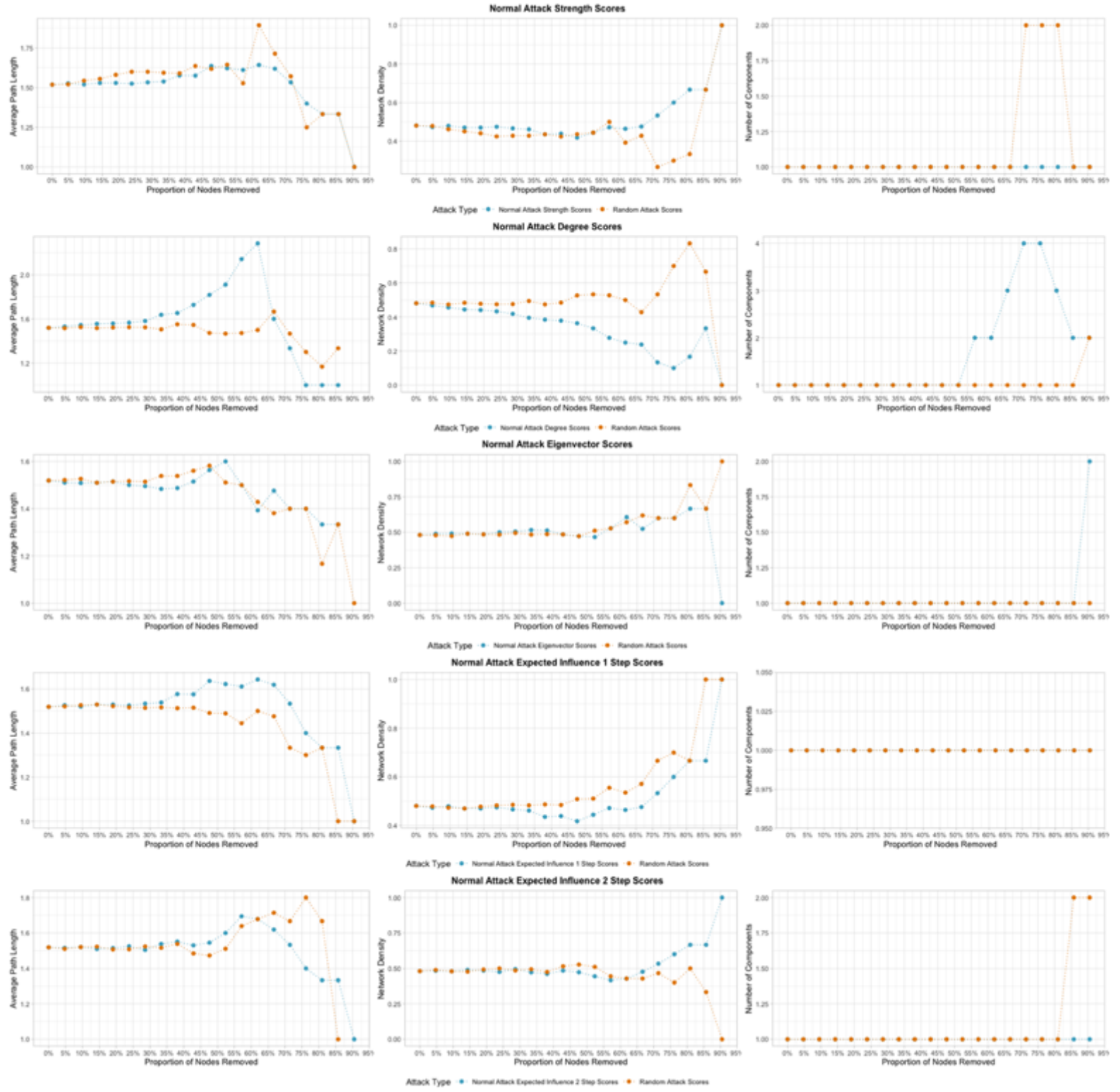
Plots displaying normal attack results for network 4



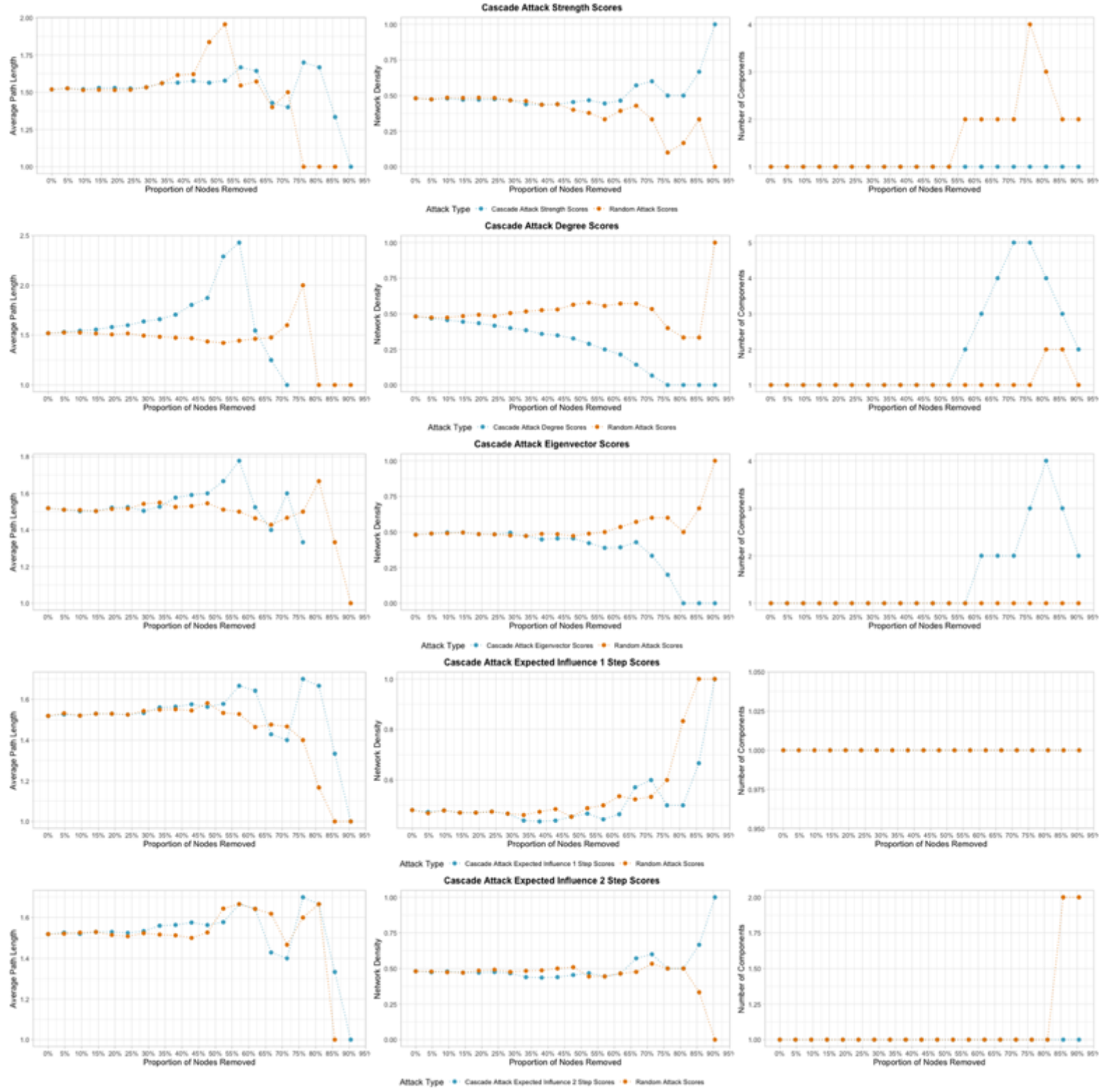
Plots displaying cascade attack results for network 4



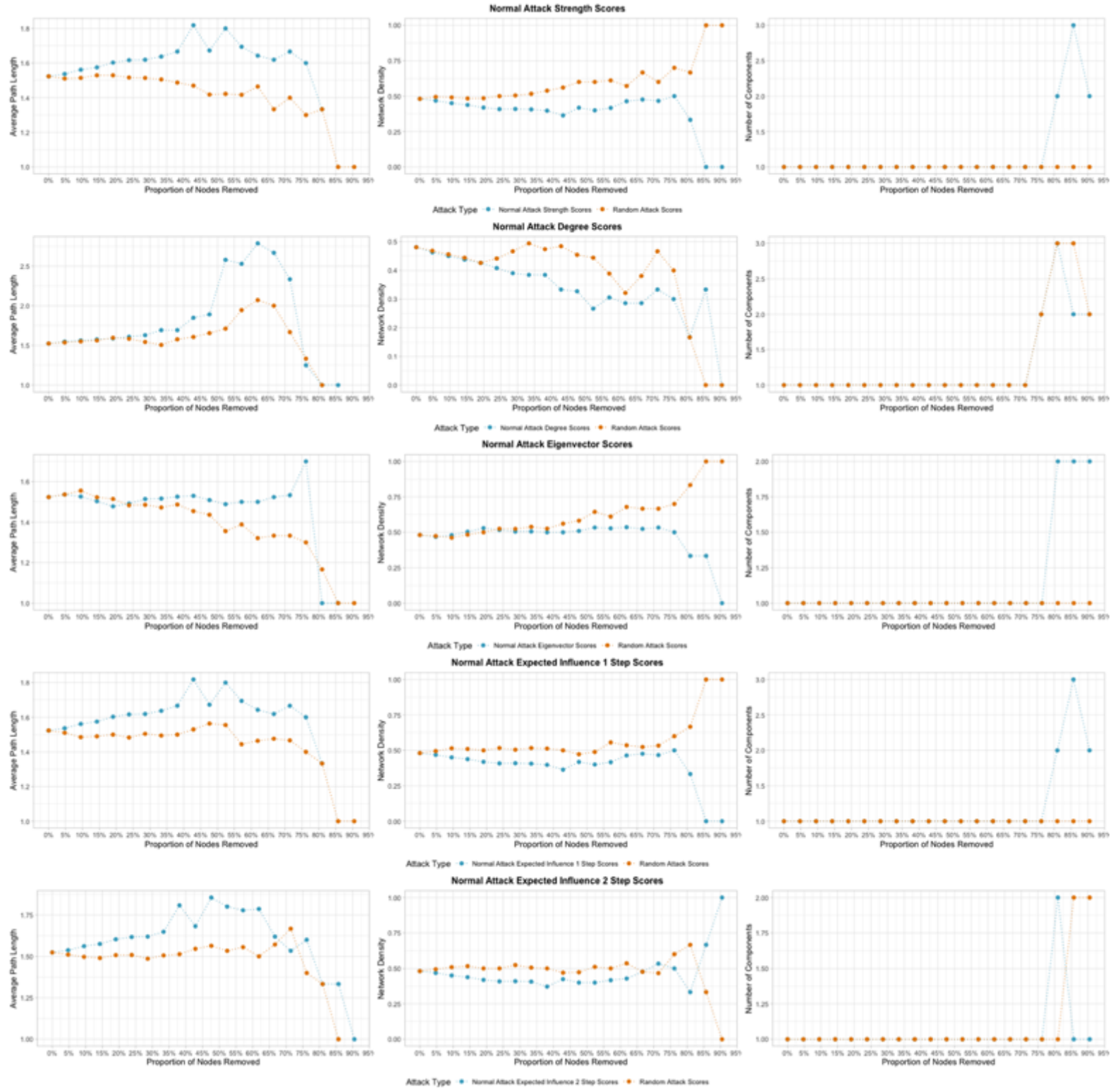
Plots displaying normal attack results for network 5



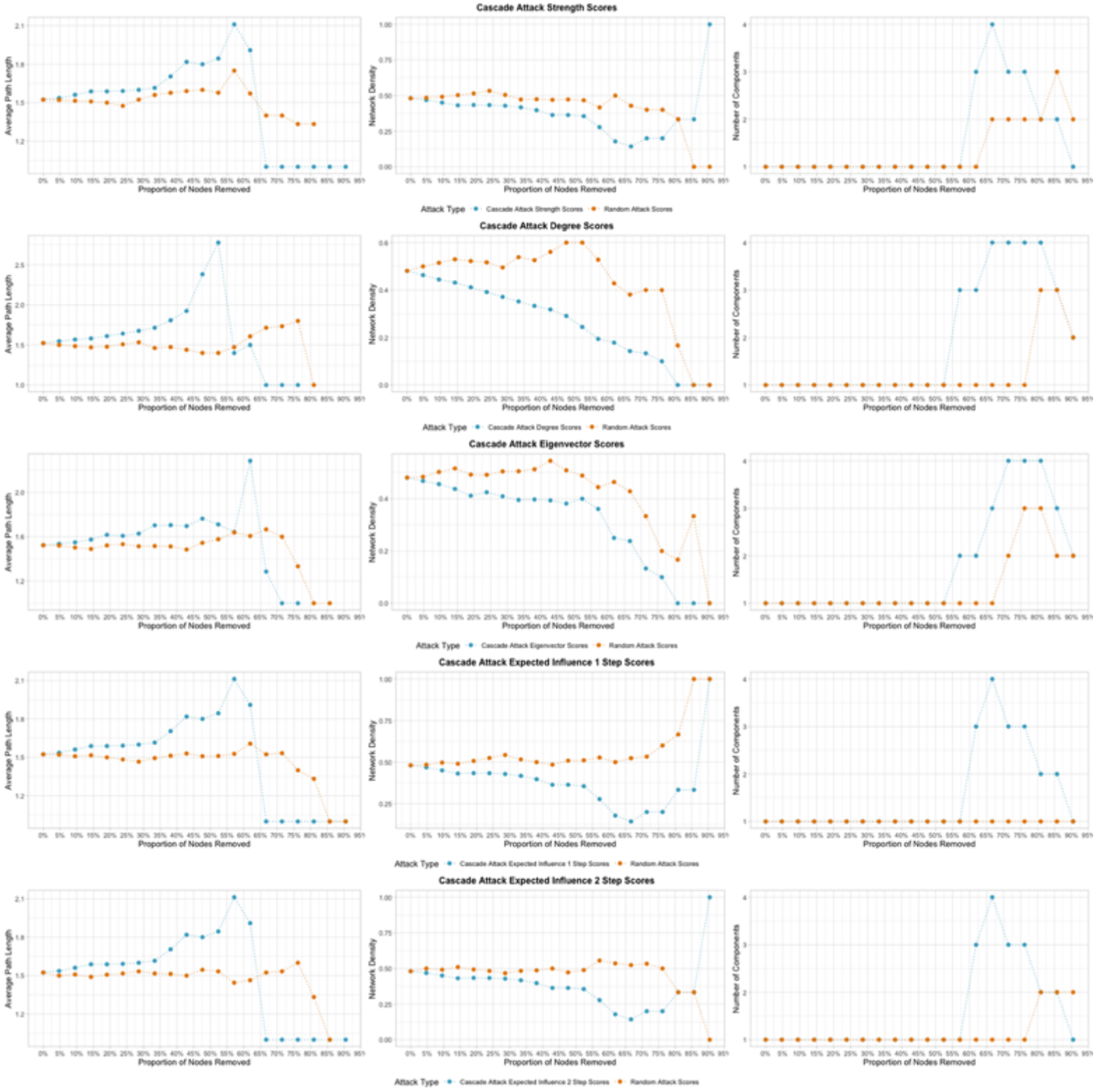
Plots displaying cascade attack results for network 5



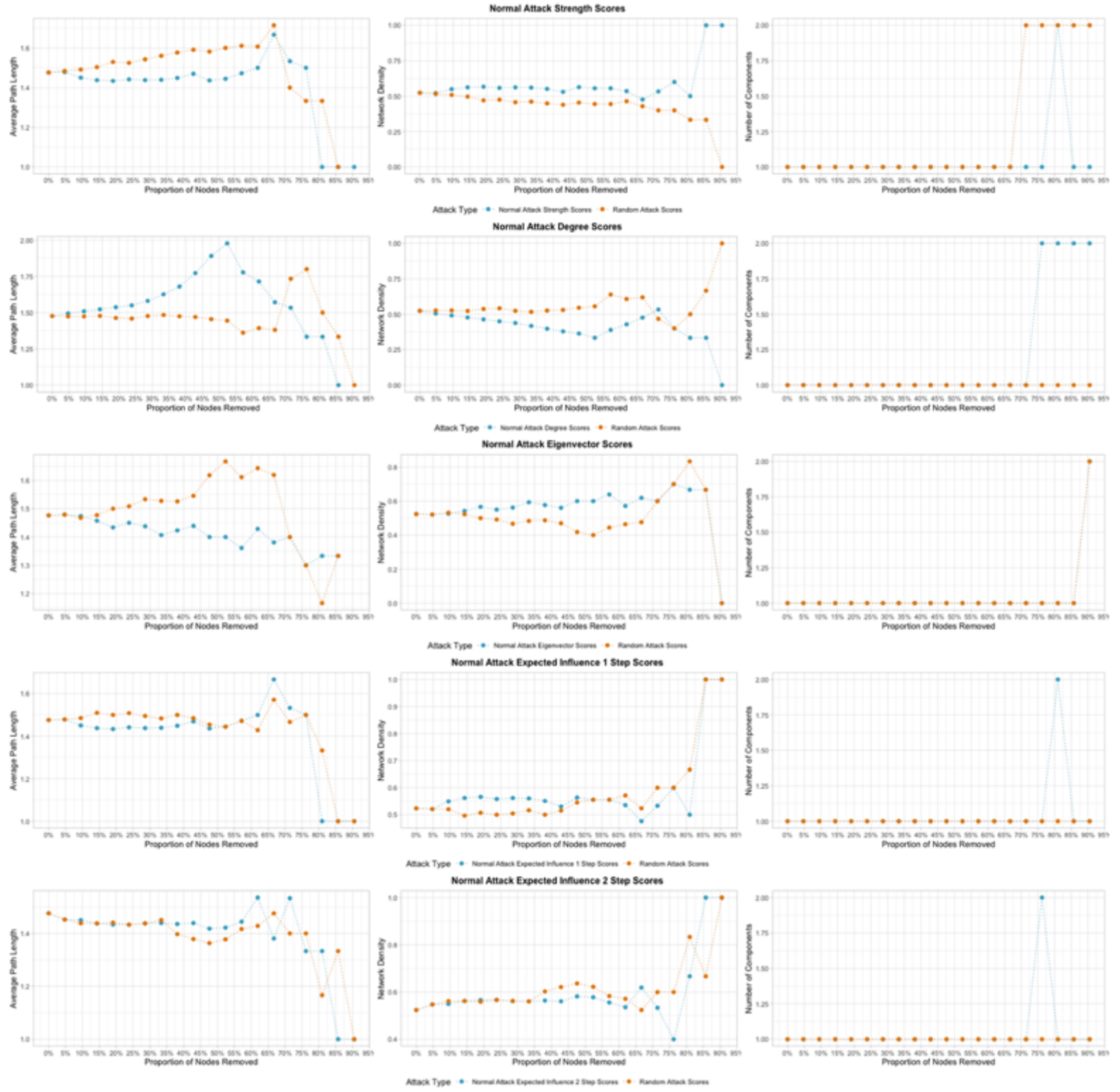
Plots displaying normal attack results for network 6



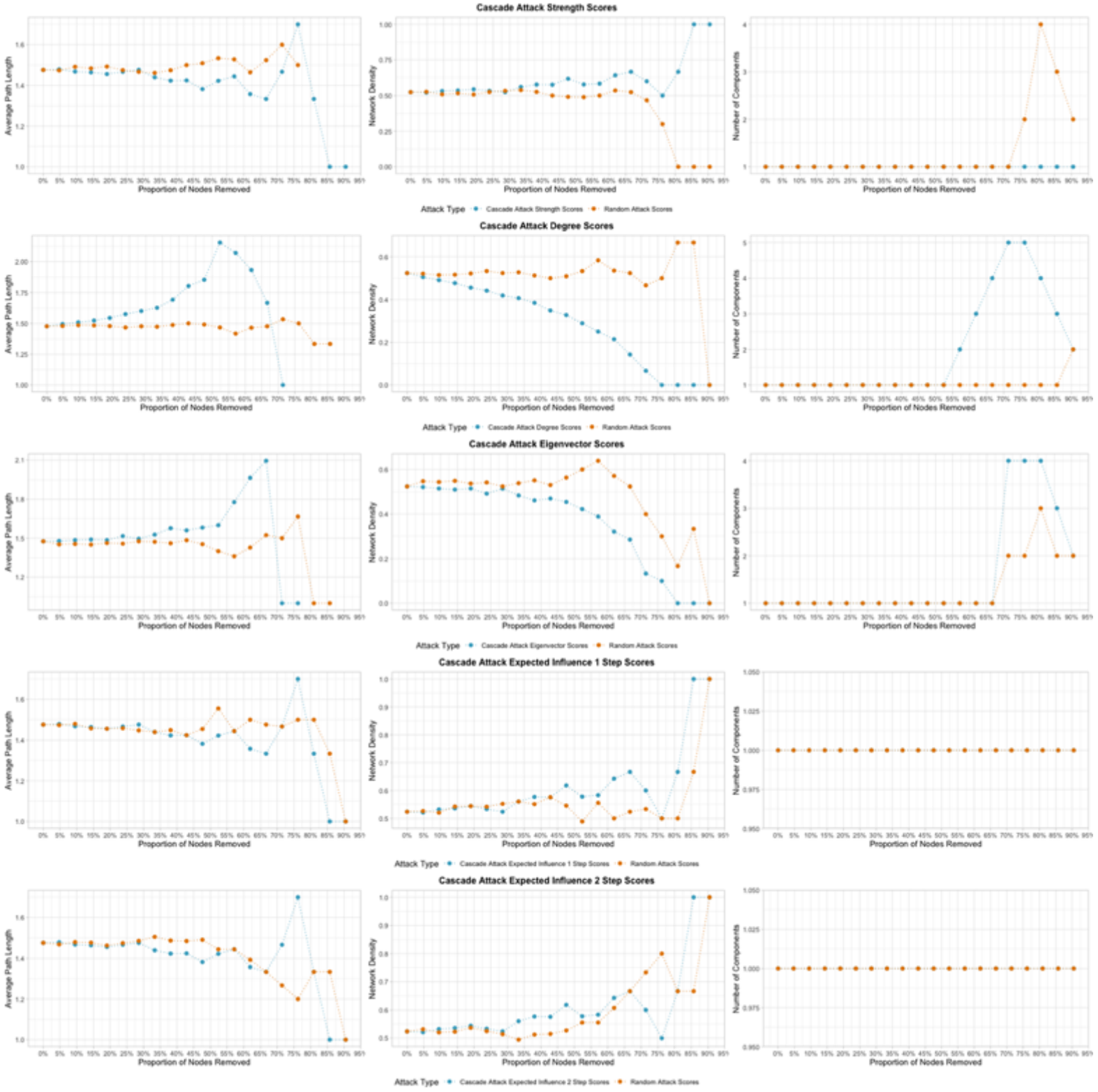
Plots displaying cascade attack results for network 6



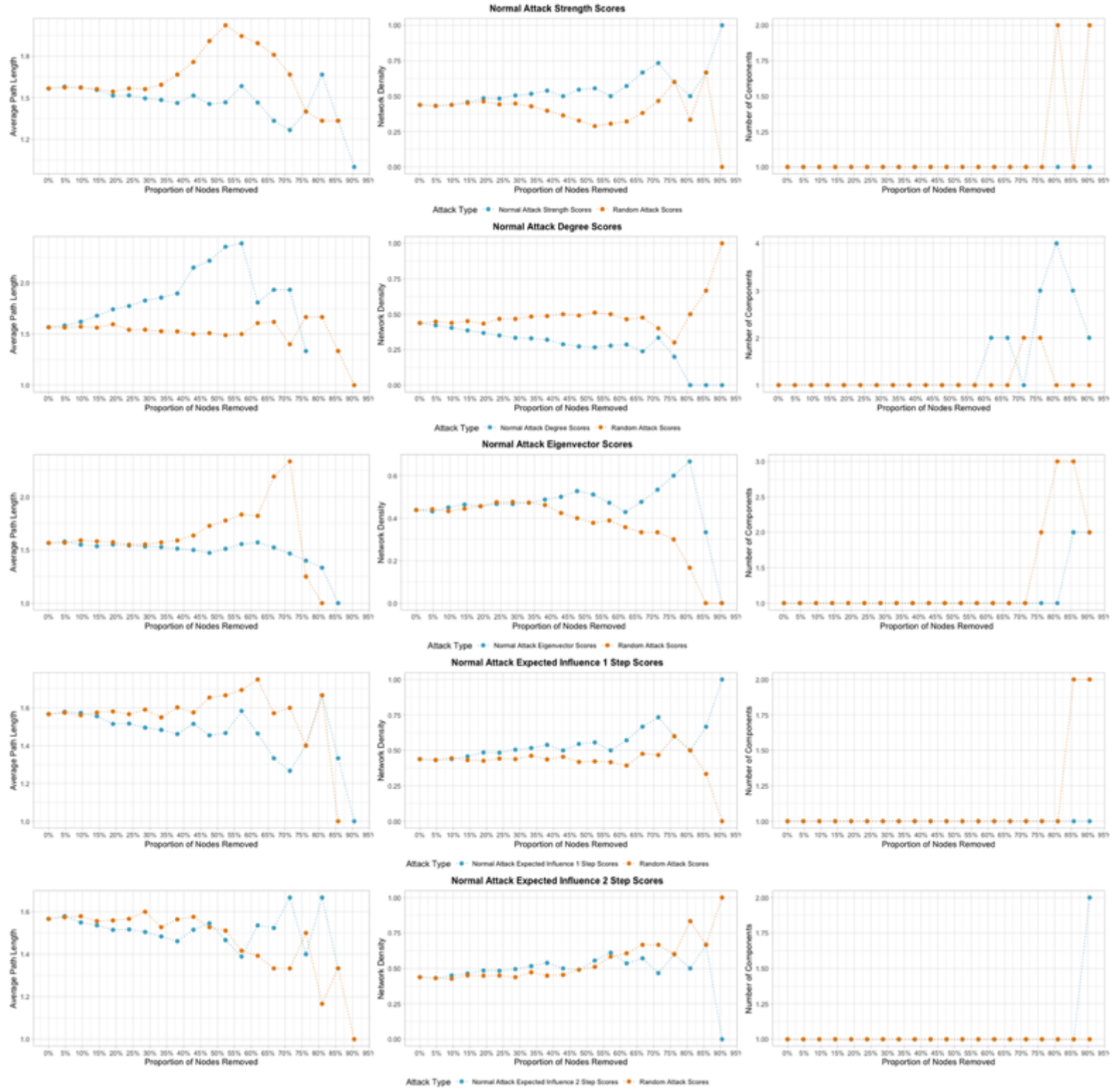
Plots displaying normal attack results for network 7



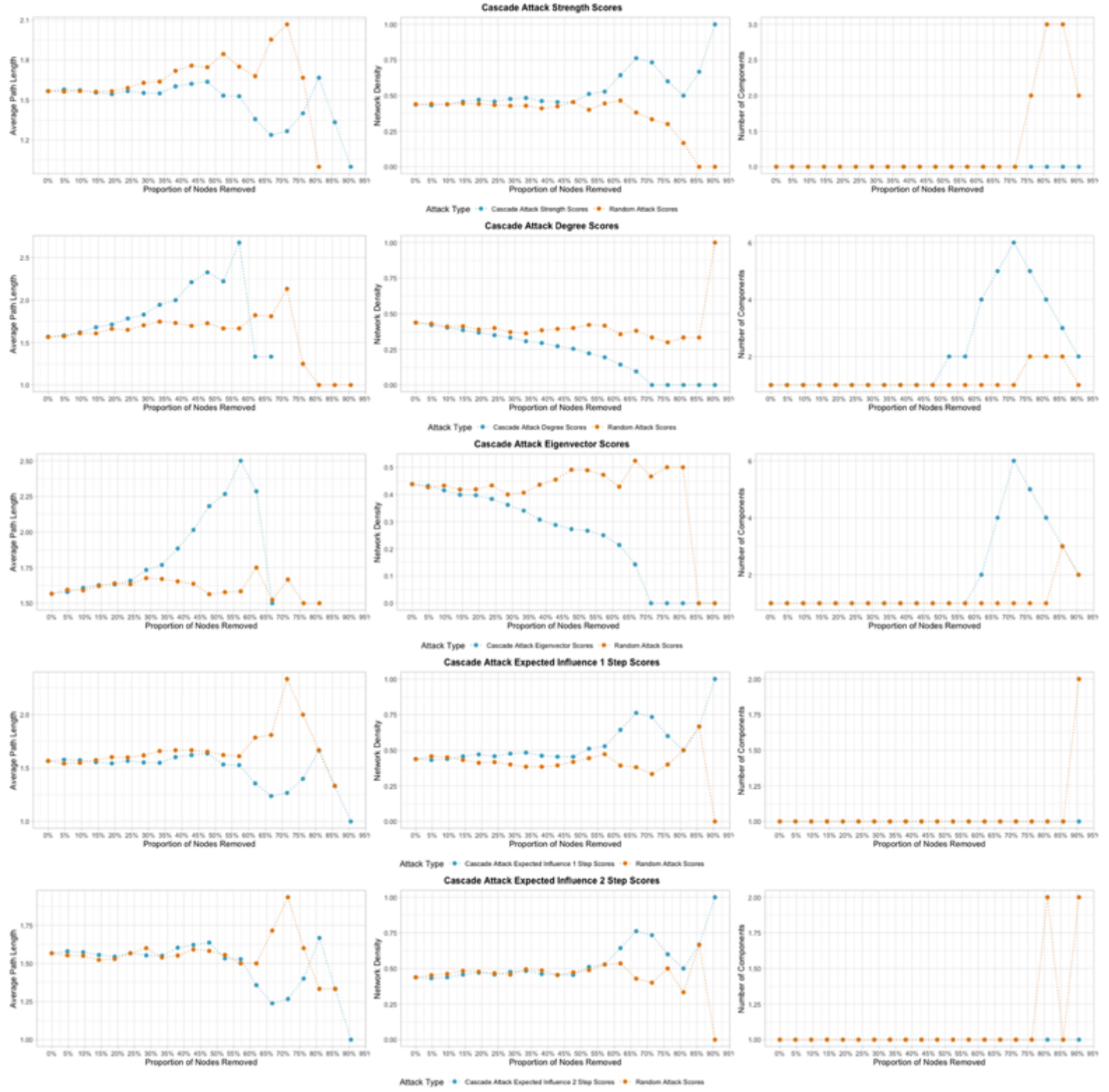
Plots displaying cascade attack results for network 7



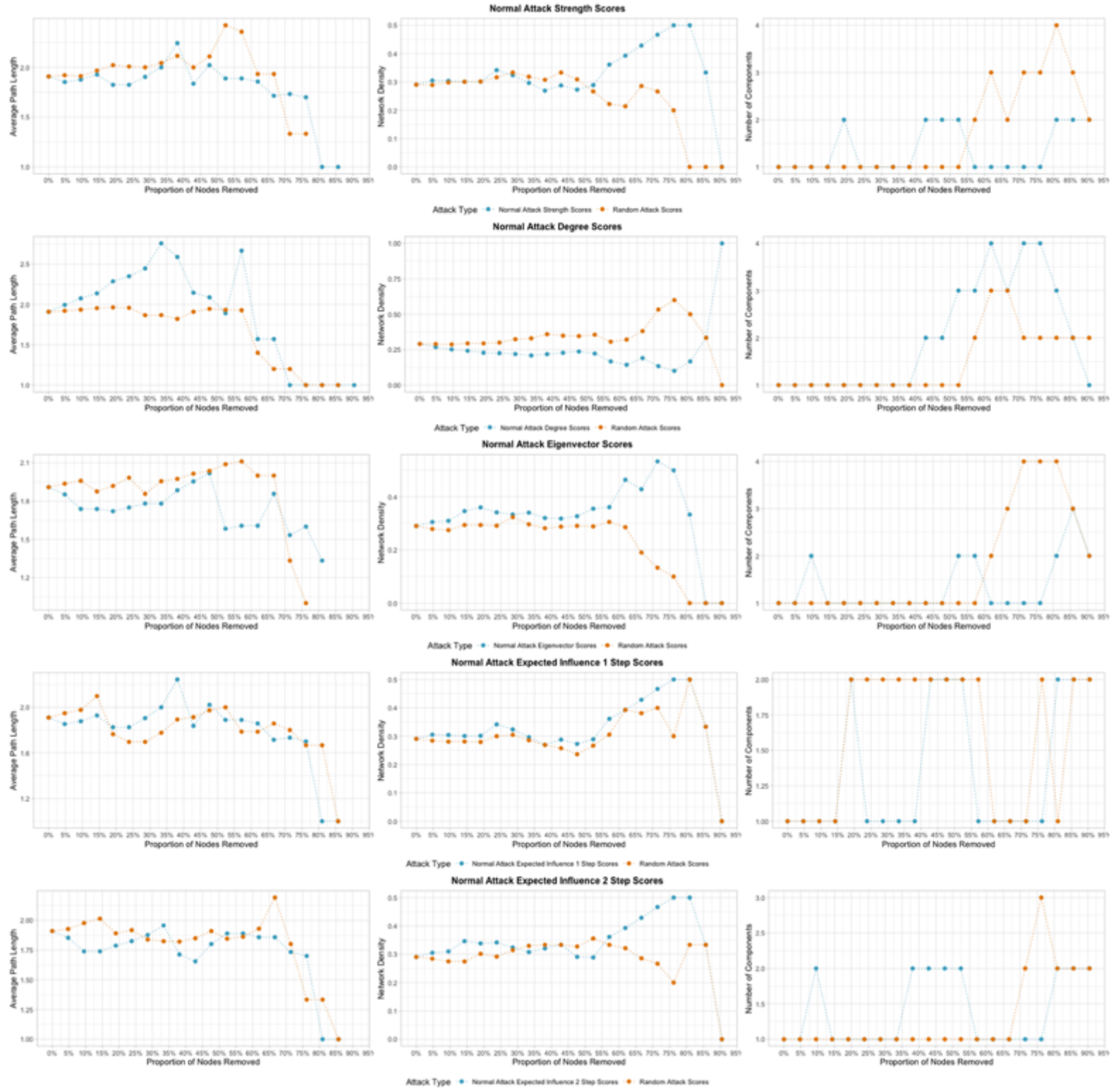
Plots displaying normal attack results for network 8



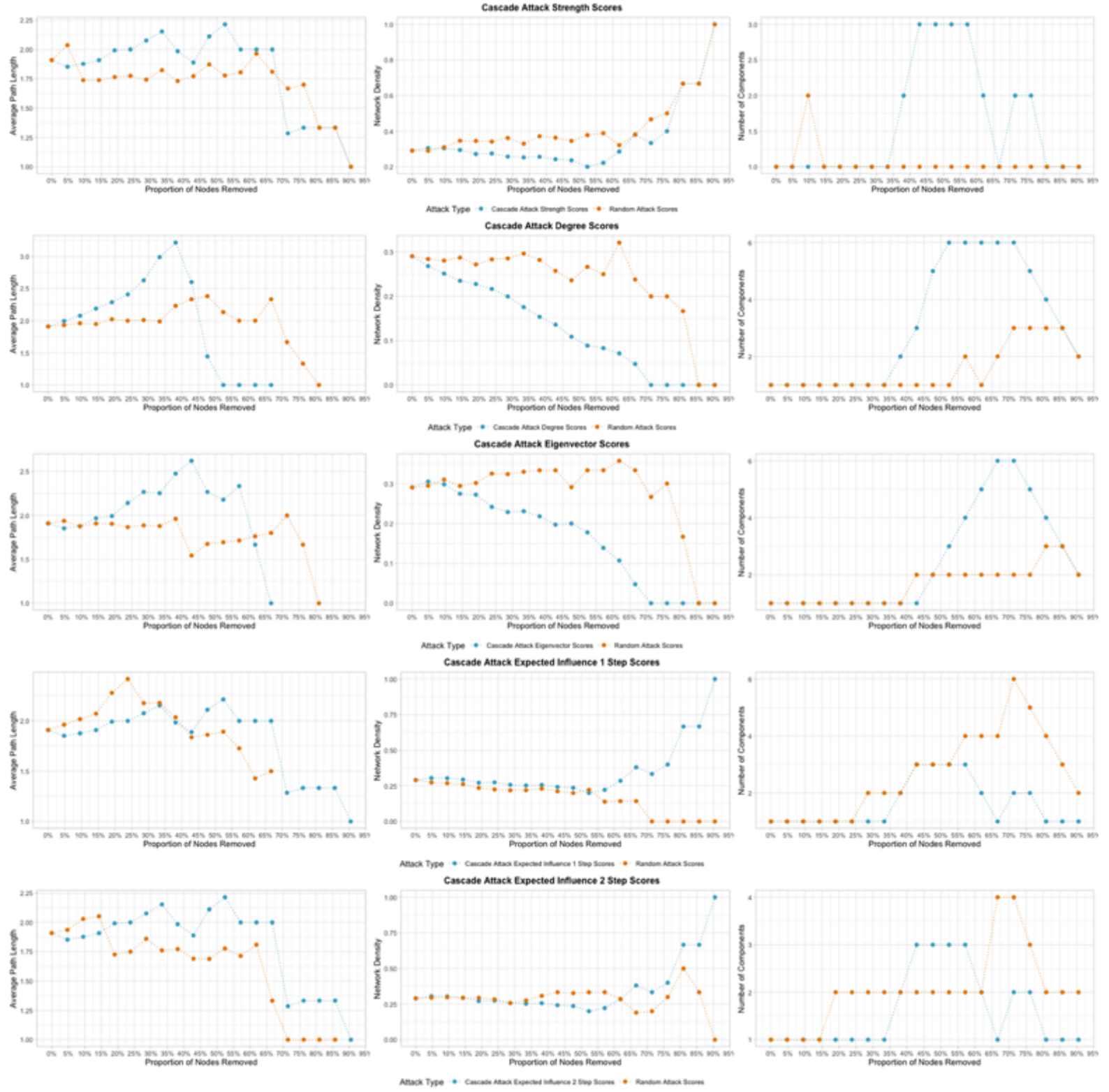
Plots displaying cascade attack results for network 8



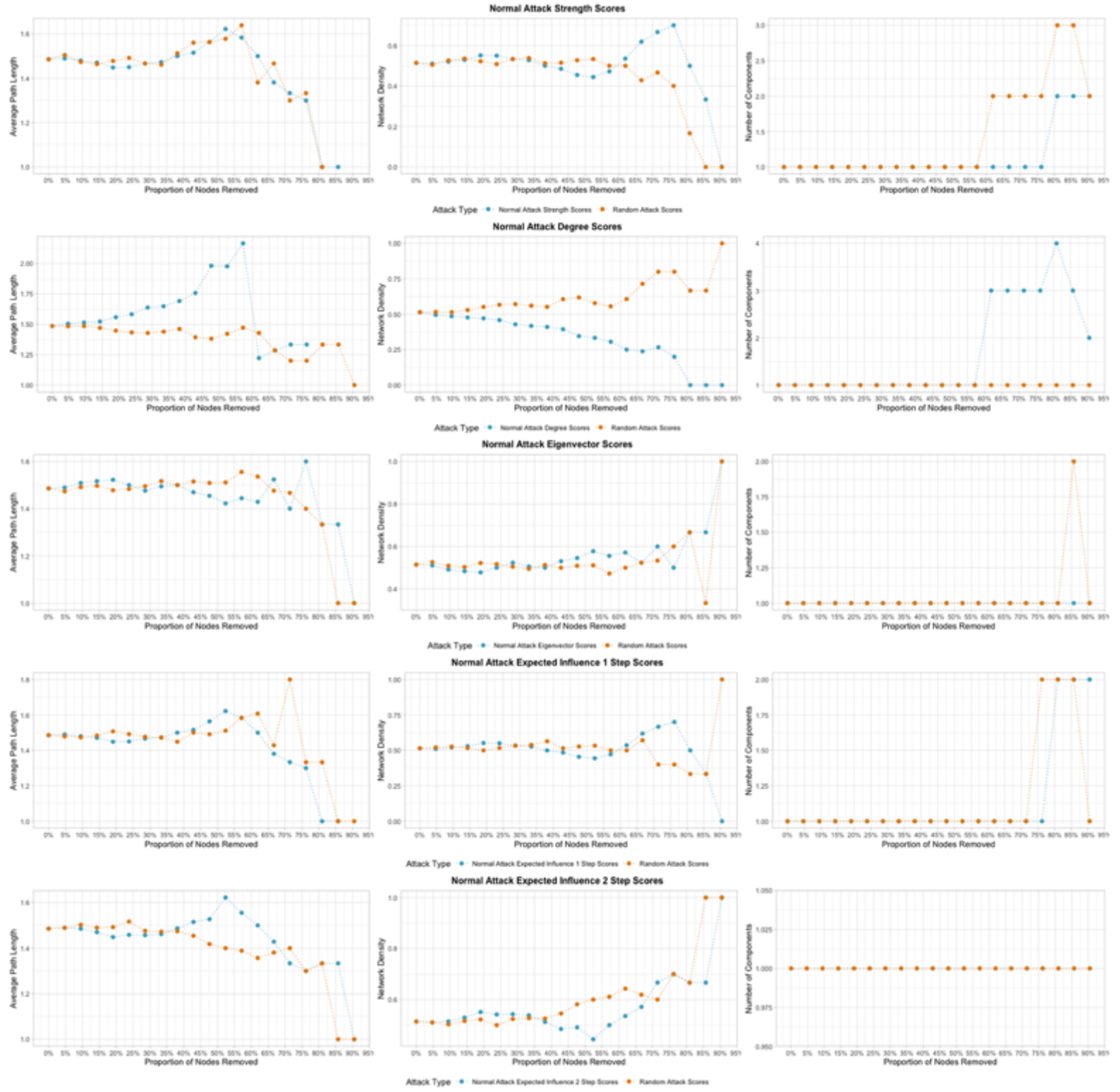
Plots displaying normal attack results for network 9



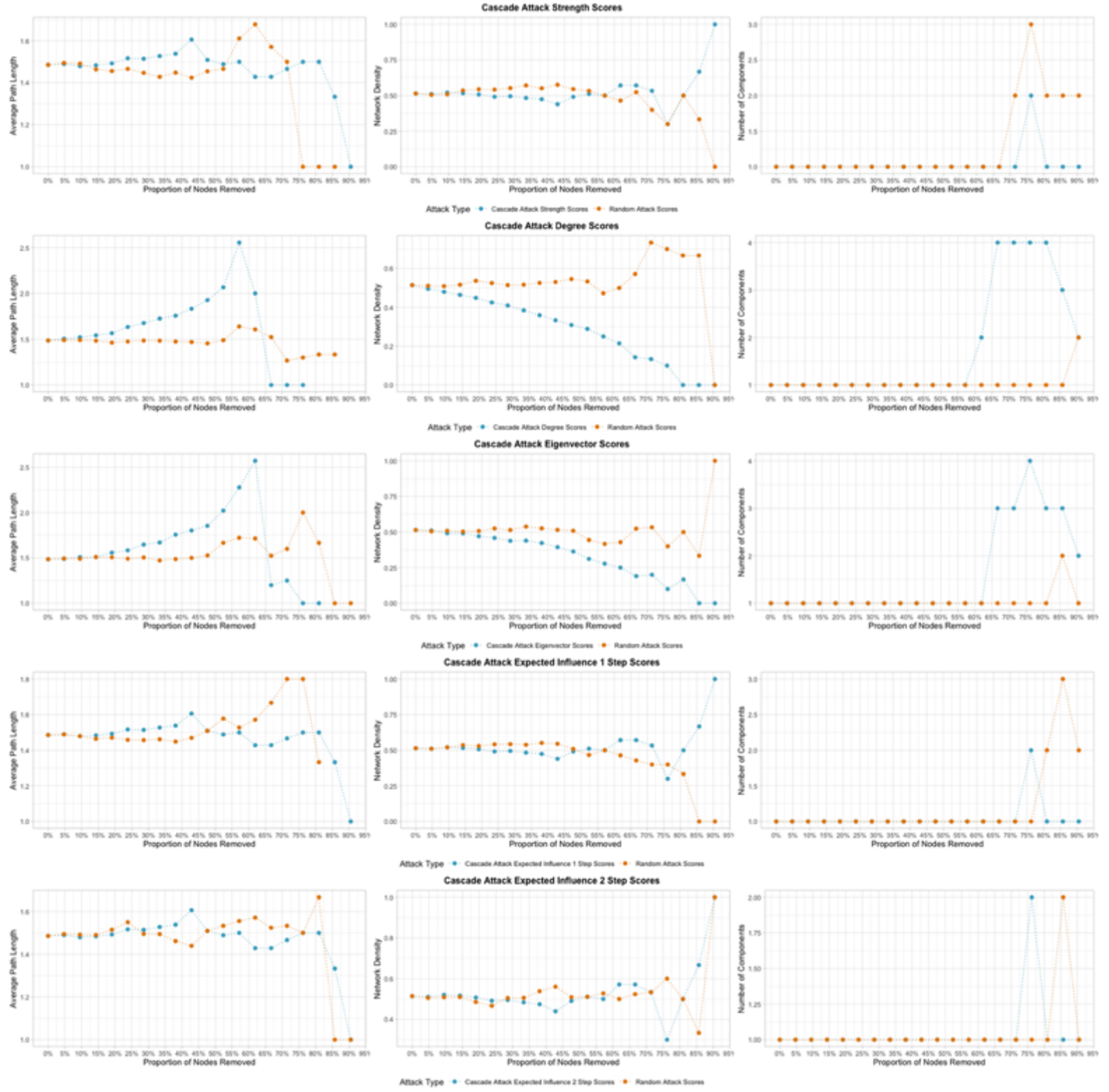
Plots displaying cascade attack results for network 9



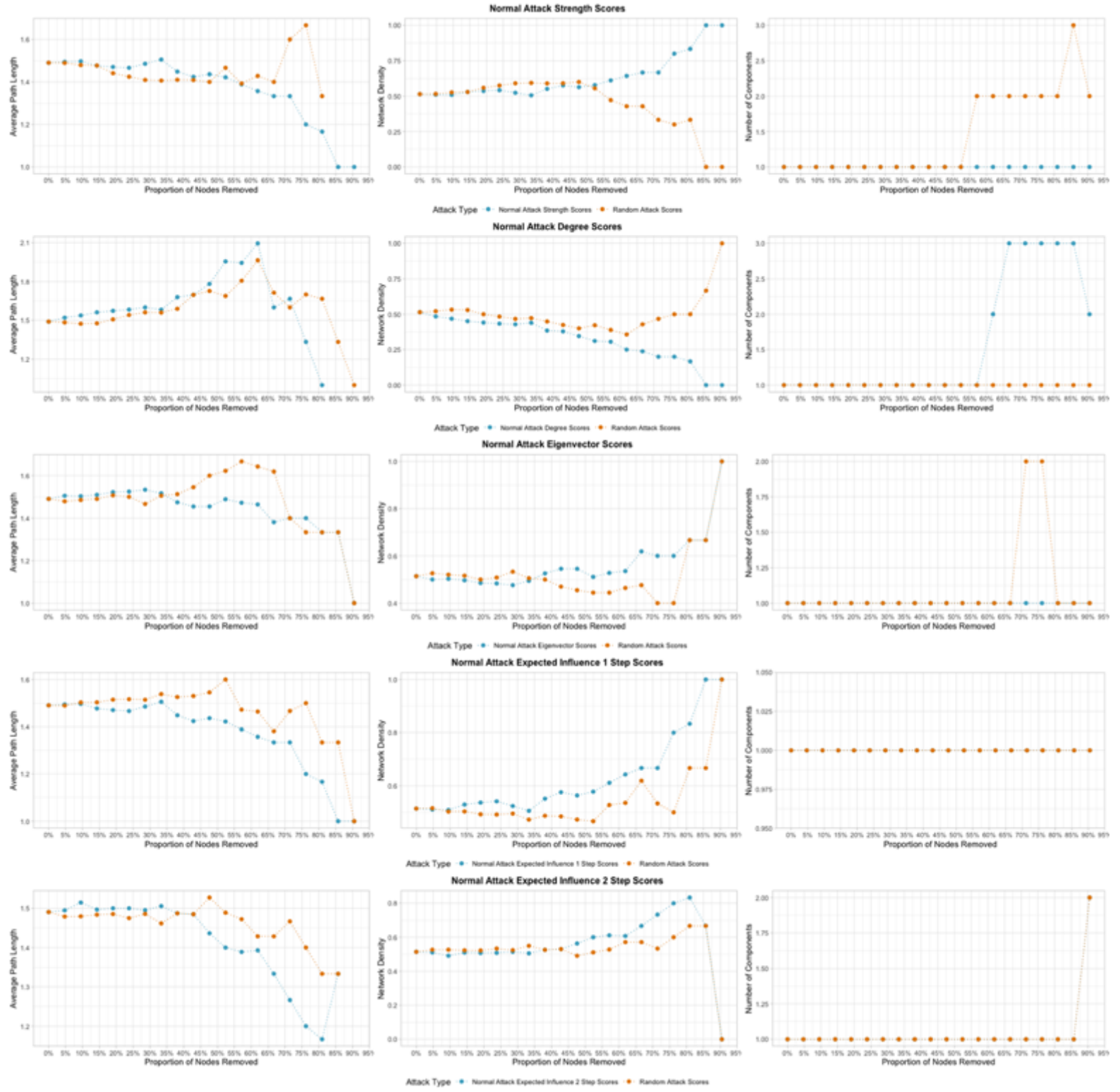
Plots displaying normal attack results for network 10



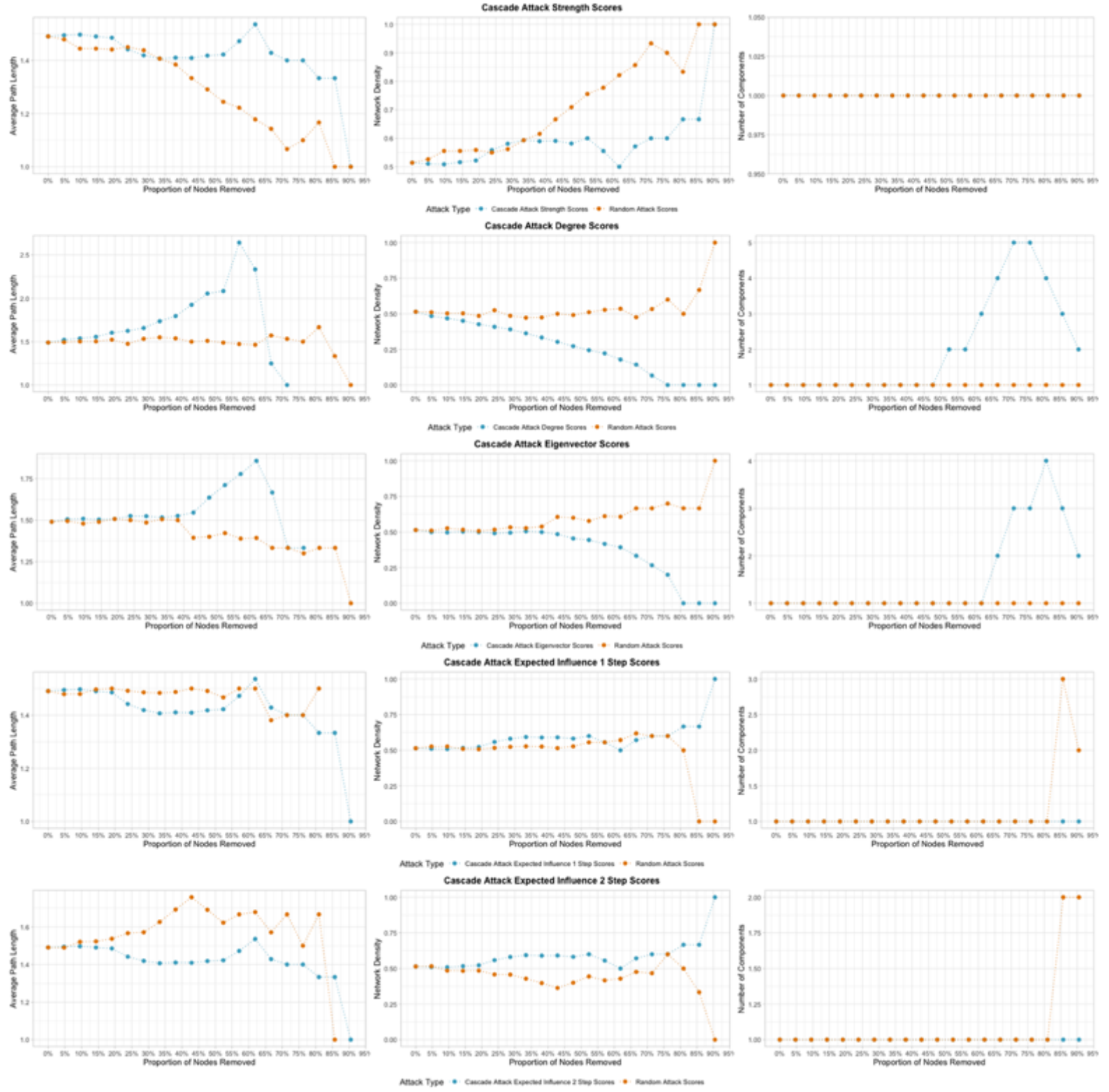
Plots displaying cascade attack results for network 10



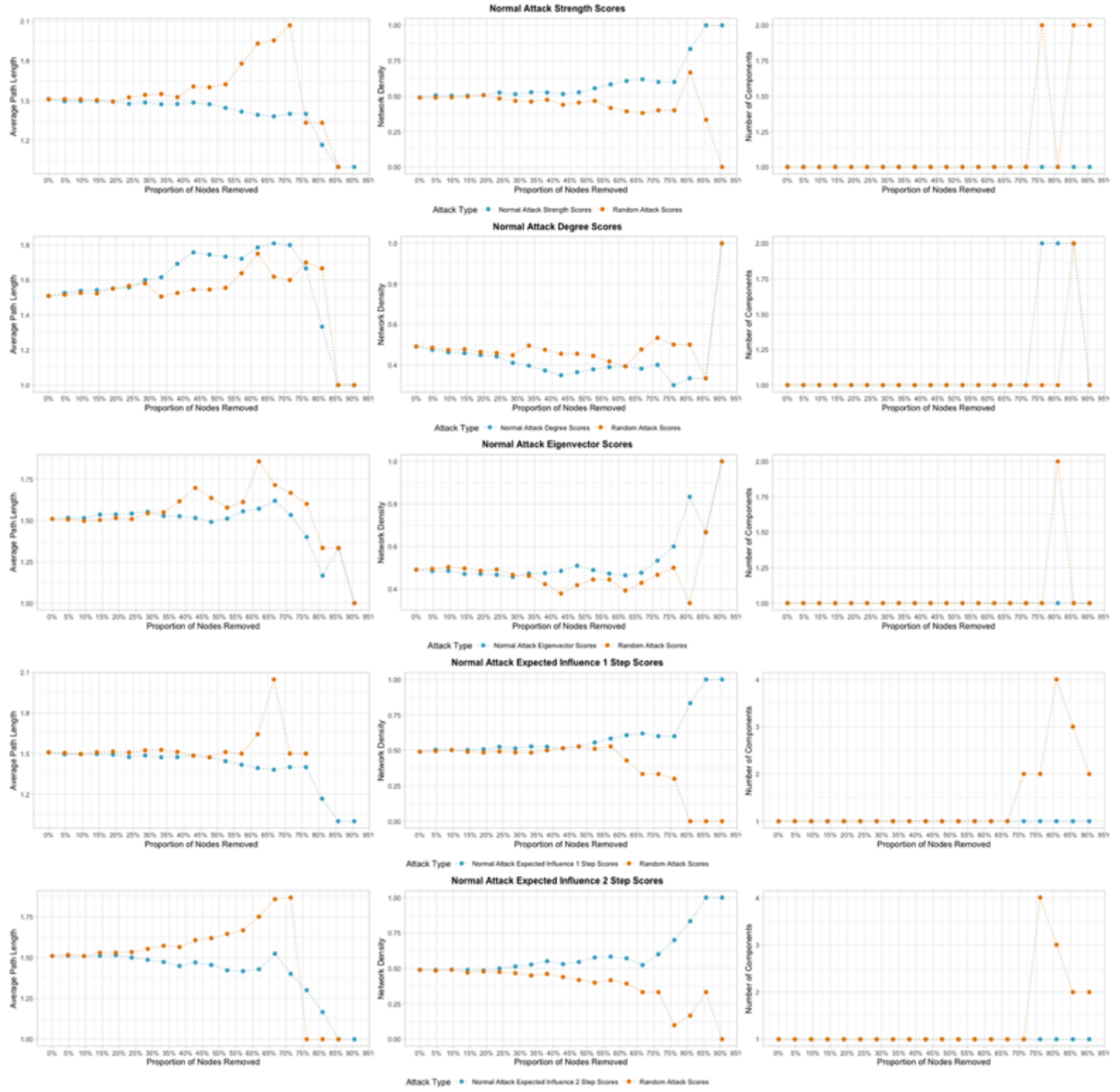
Plots displaying normal attack results for network 11



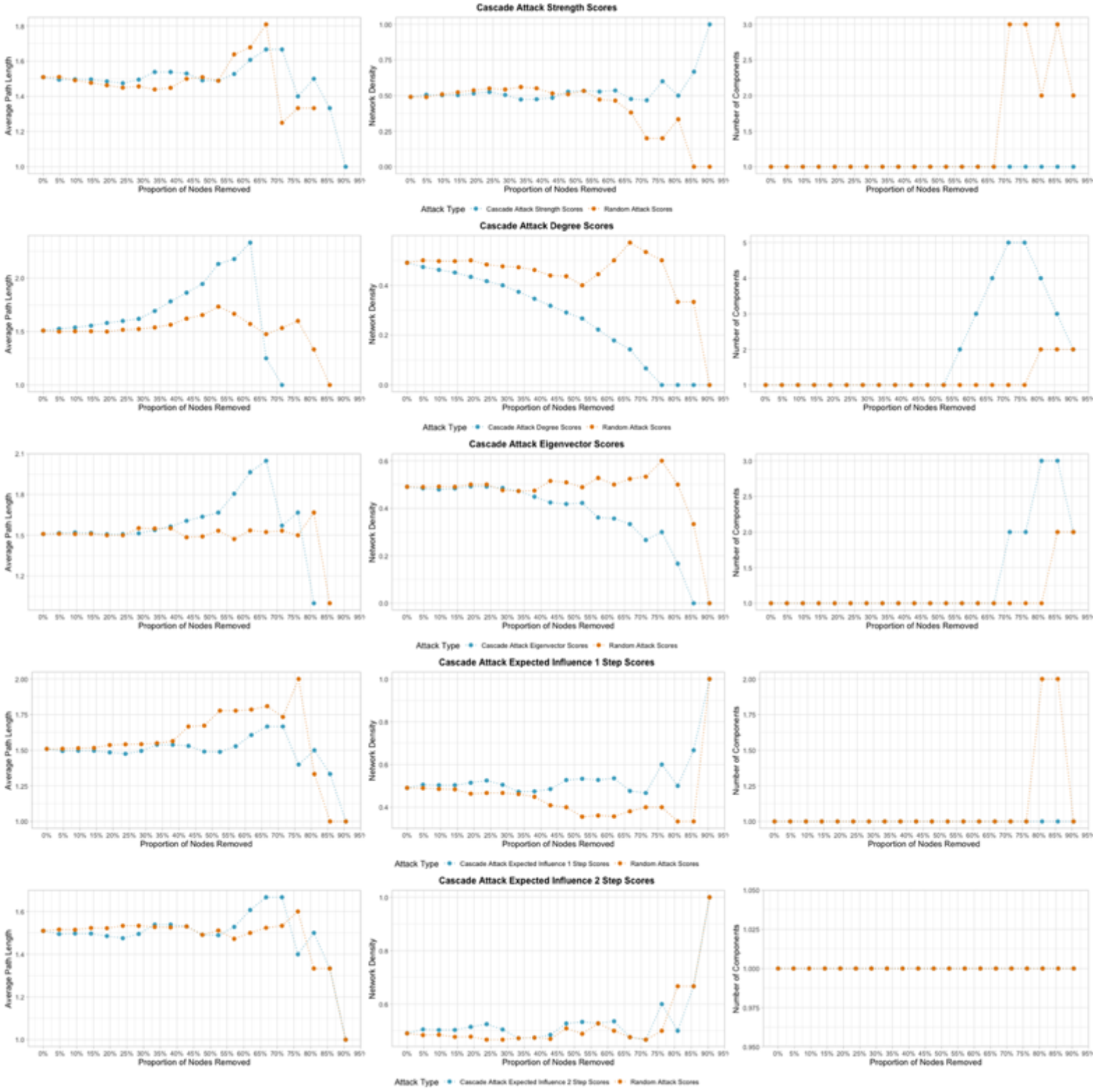
Plots displaying cascade attack results for network 11



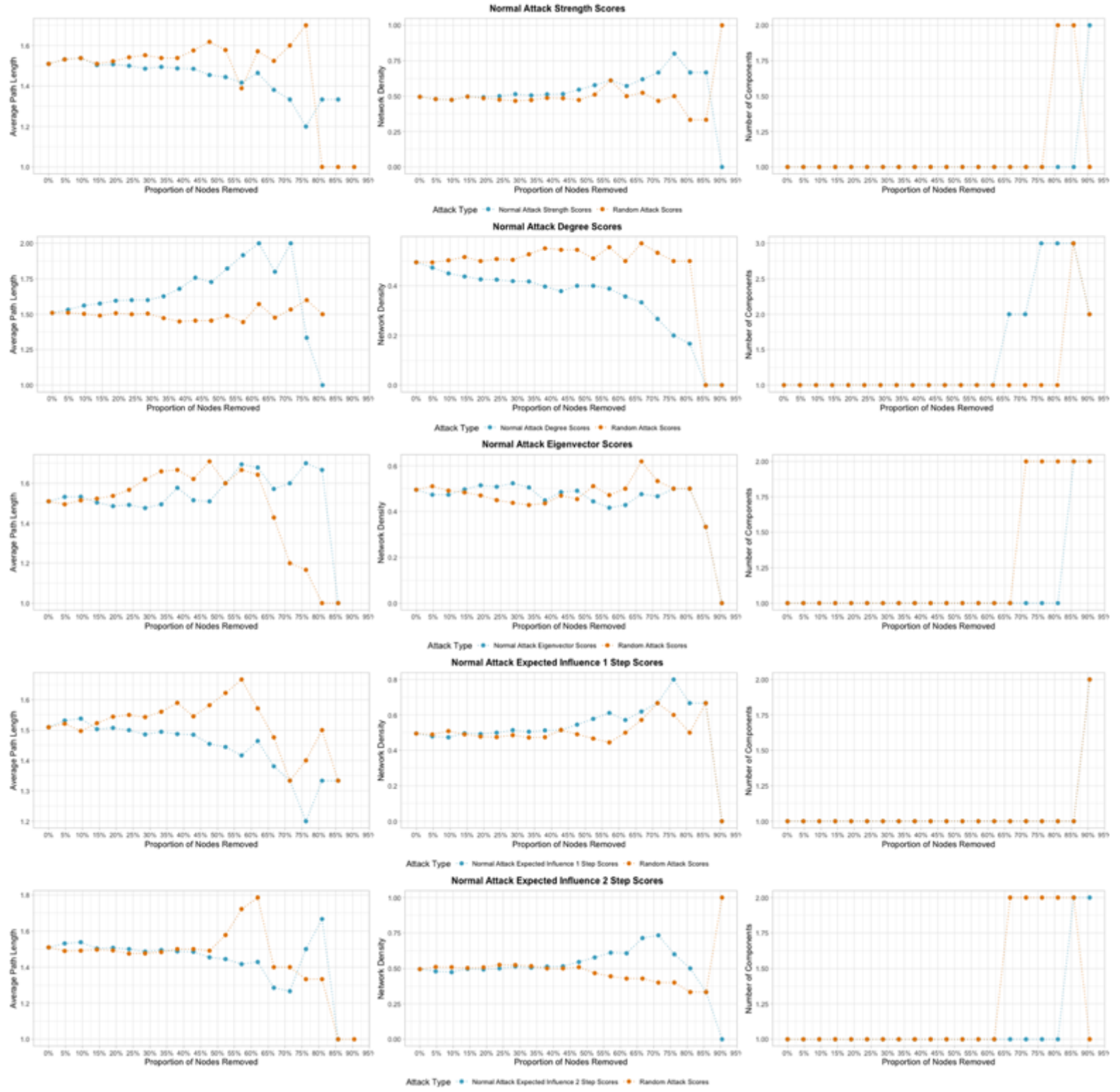
Plots displaying normal attack results for network 12



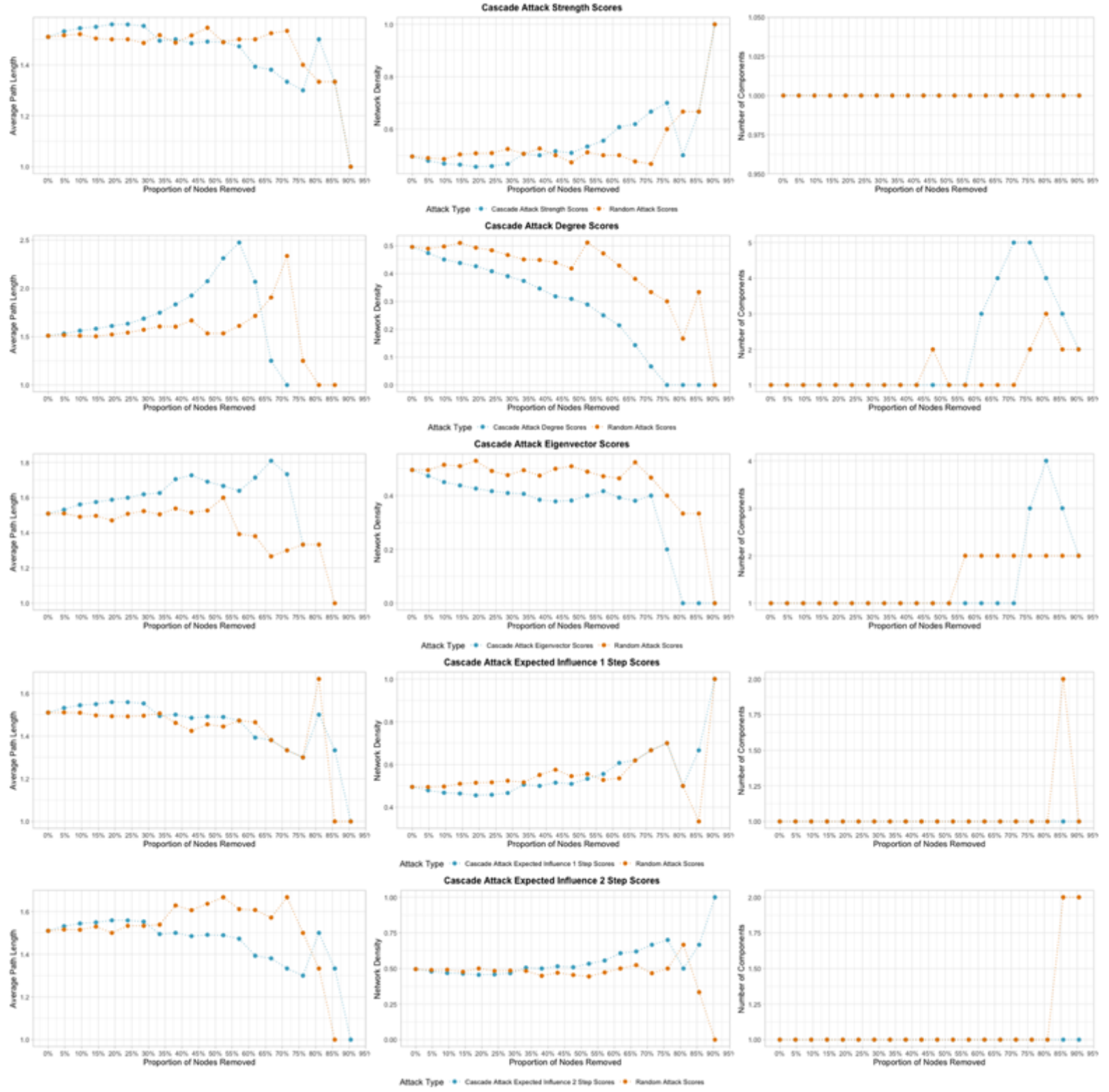
Plots displaying cascade attack results for network 12



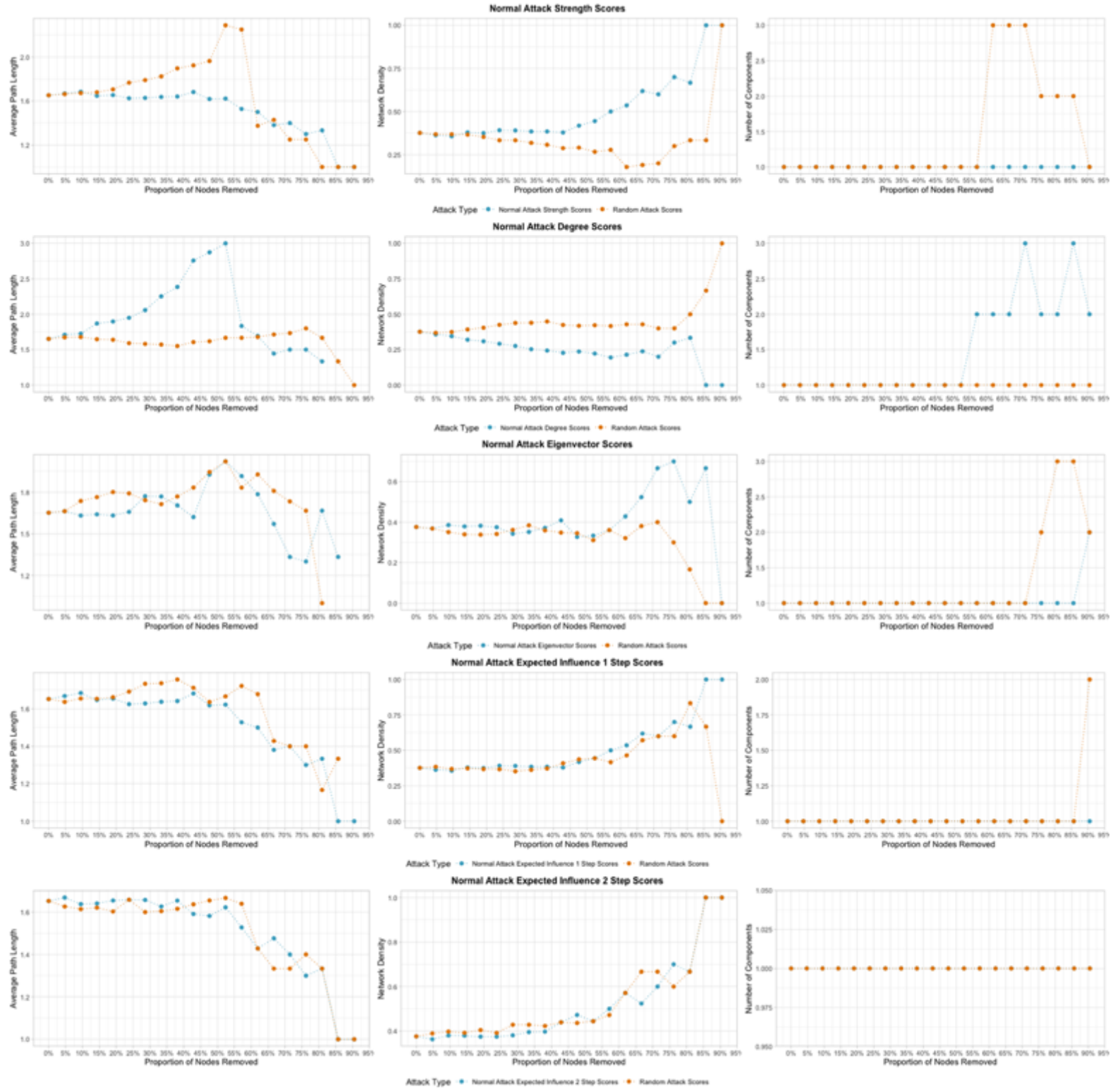
Plots displaying normal attack results for network 13



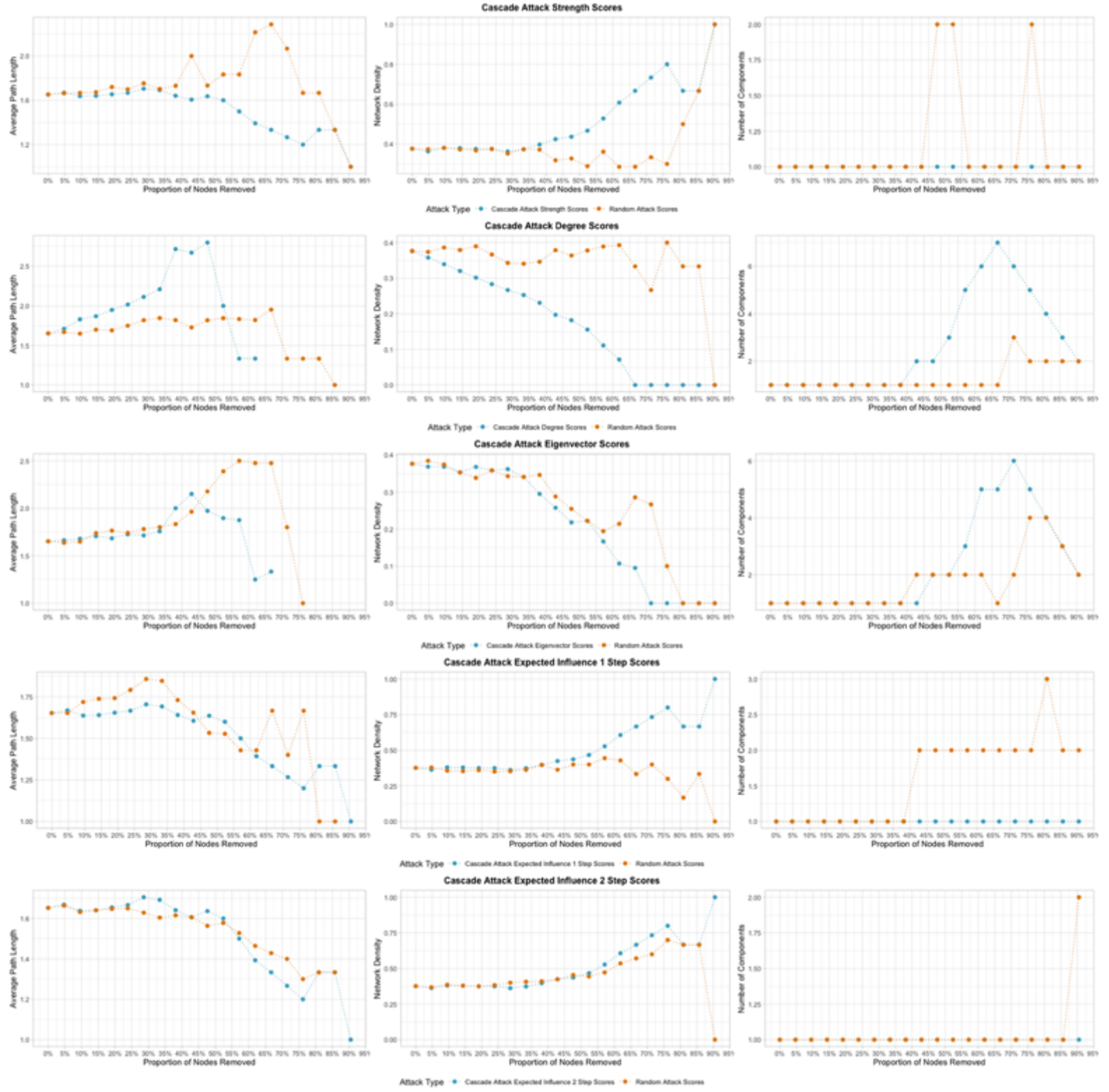
Plots displaying cascade attack results for network 13



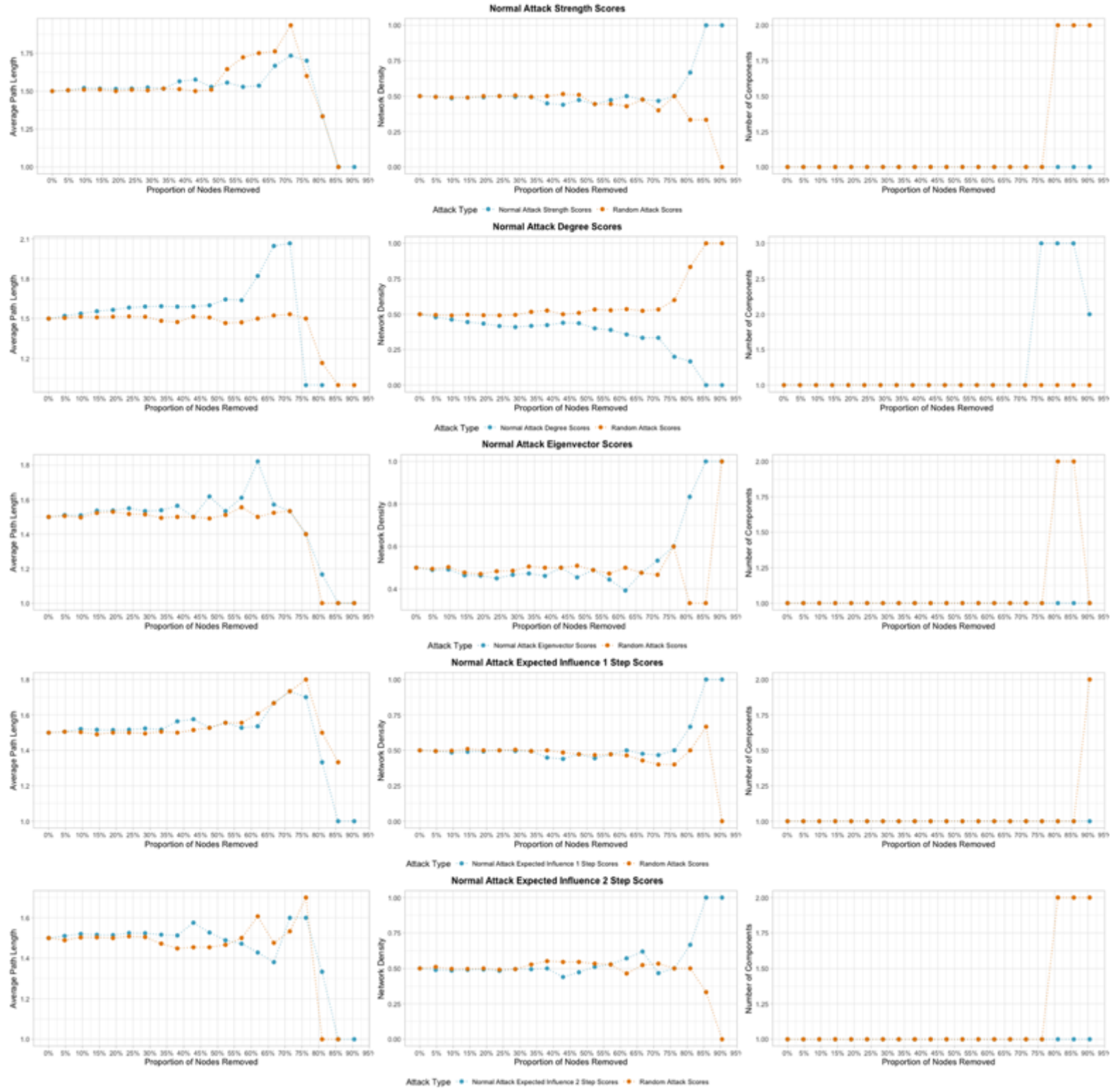
Plots displaying normal attack results for network 14



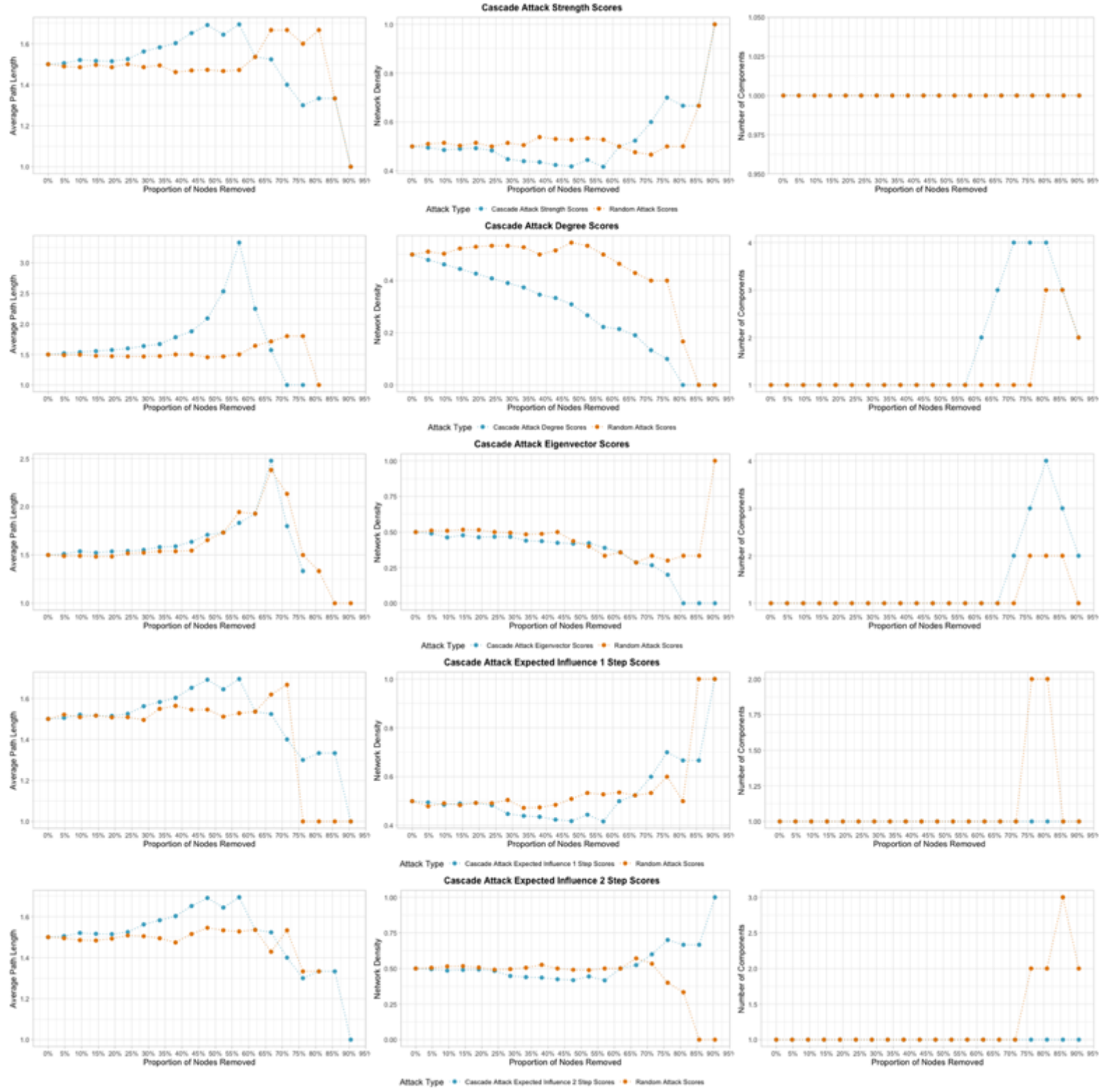
Plots displaying cascade attack results for network 14



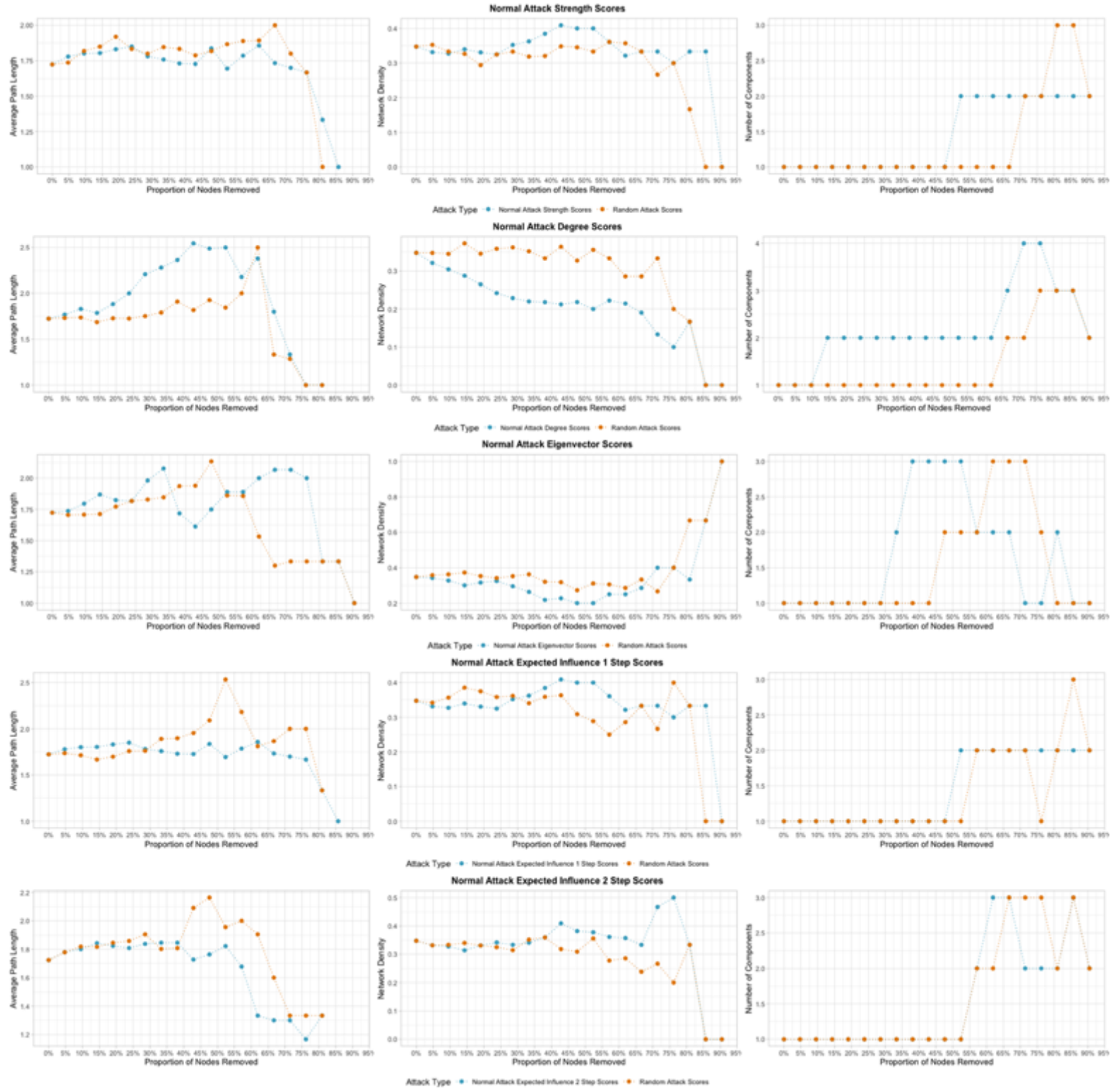
Plots displaying normal attack results for network 15



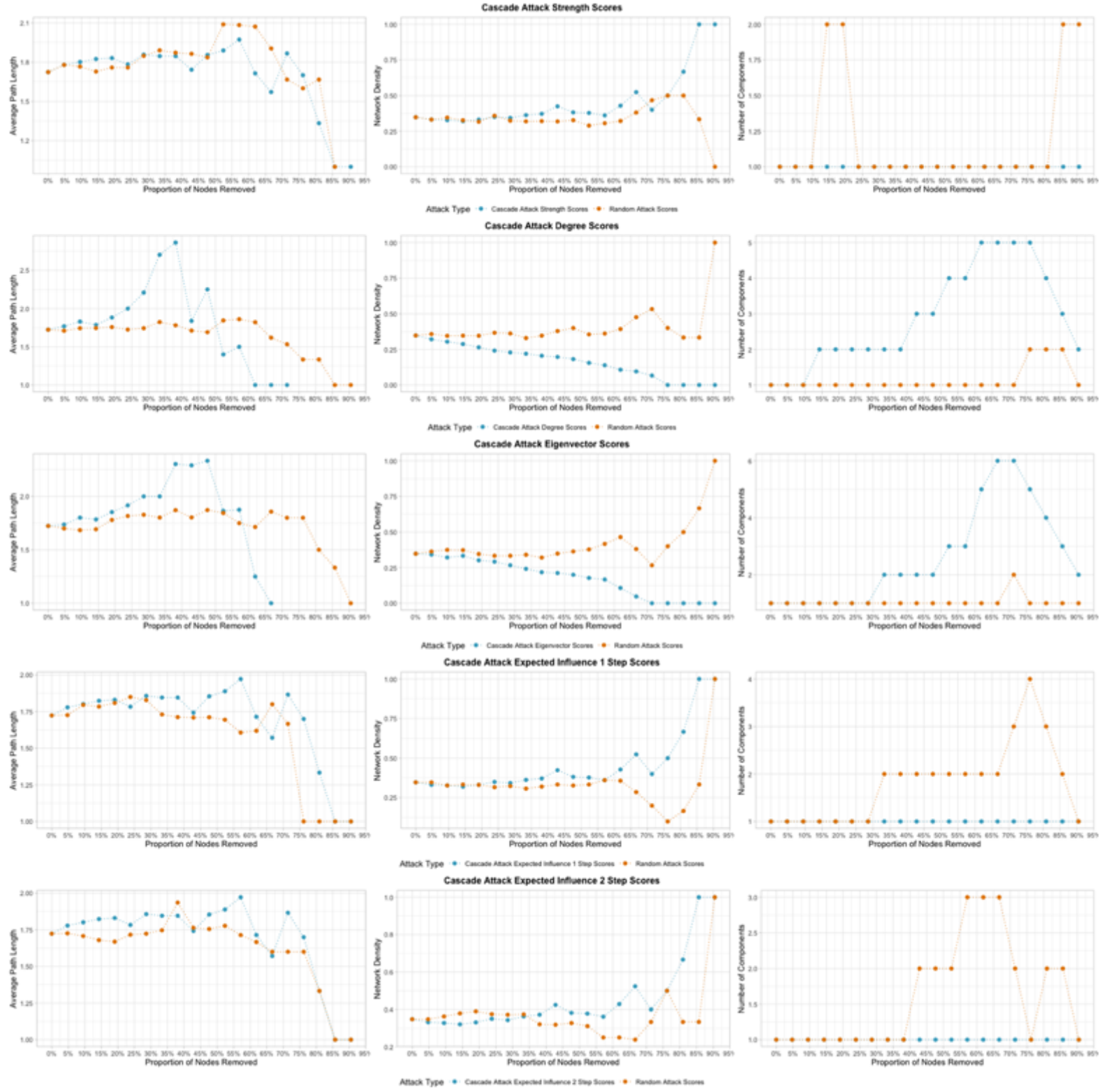
Plots displaying cascade attack results for network 15



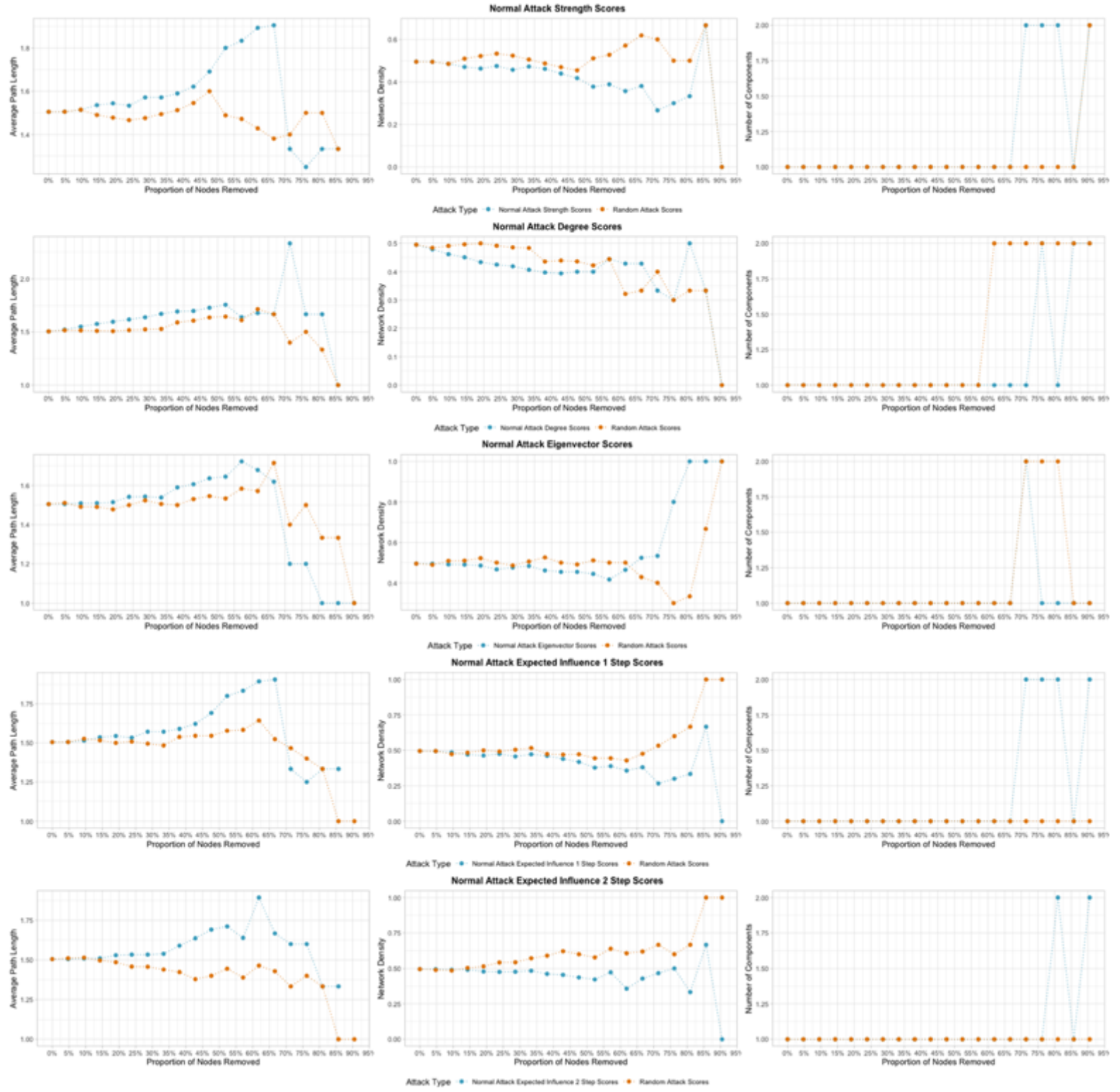
Plots displaying normal attack results for network 16



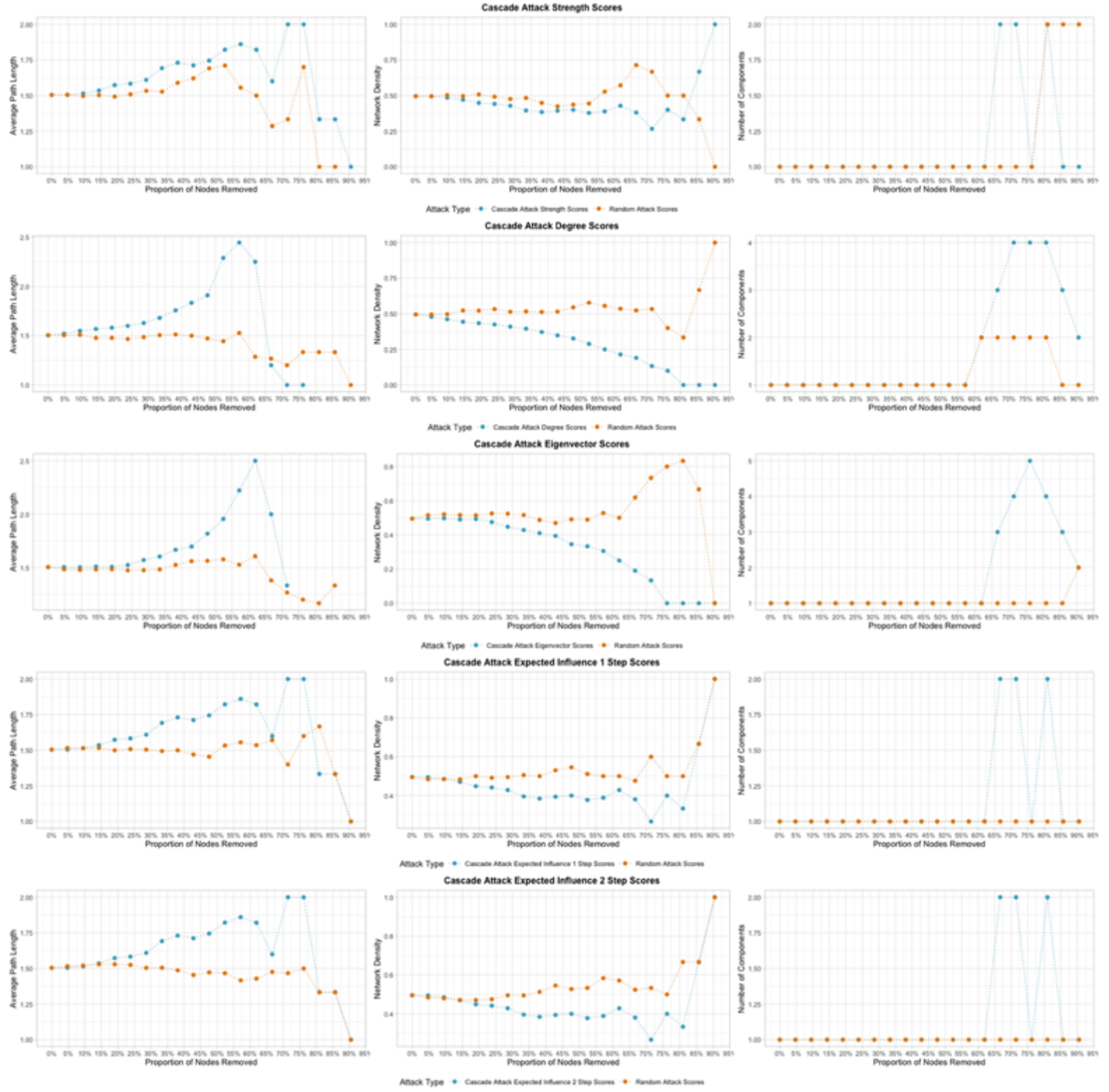
Plots displaying cascade attack results for network 16



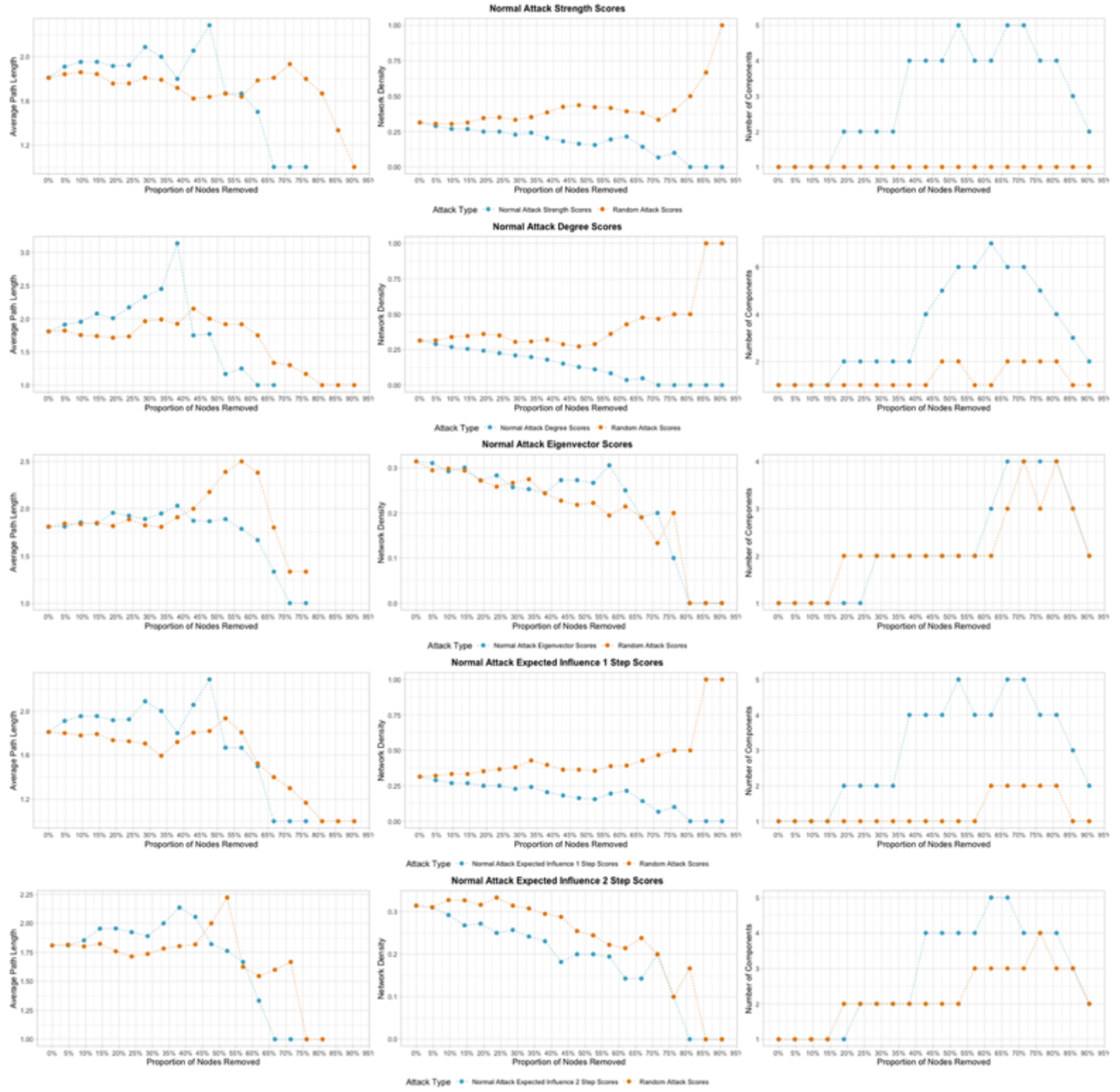
Plots displaying normal attack results for network 17



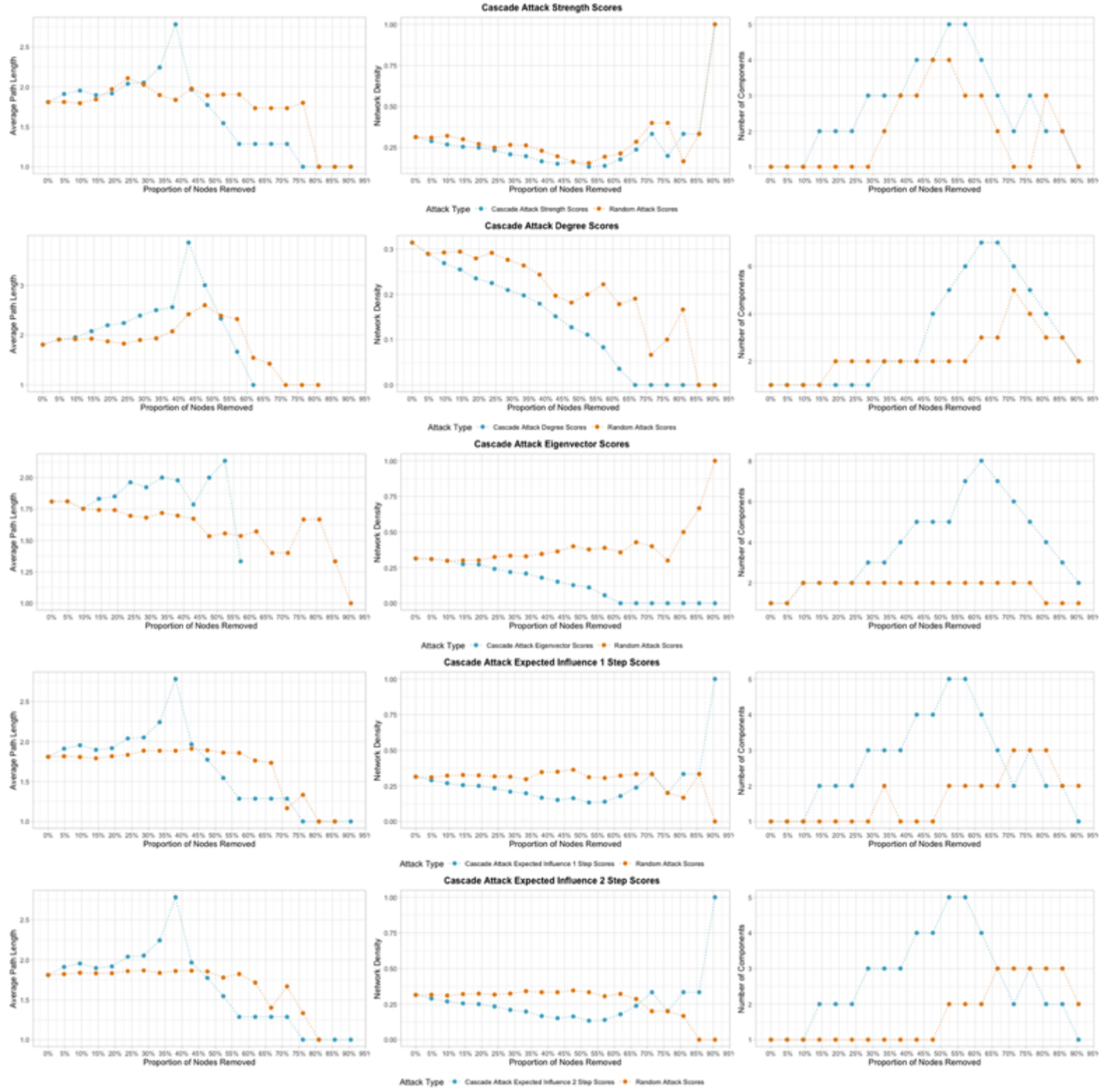
Plots displaying cascade attack results for network 17



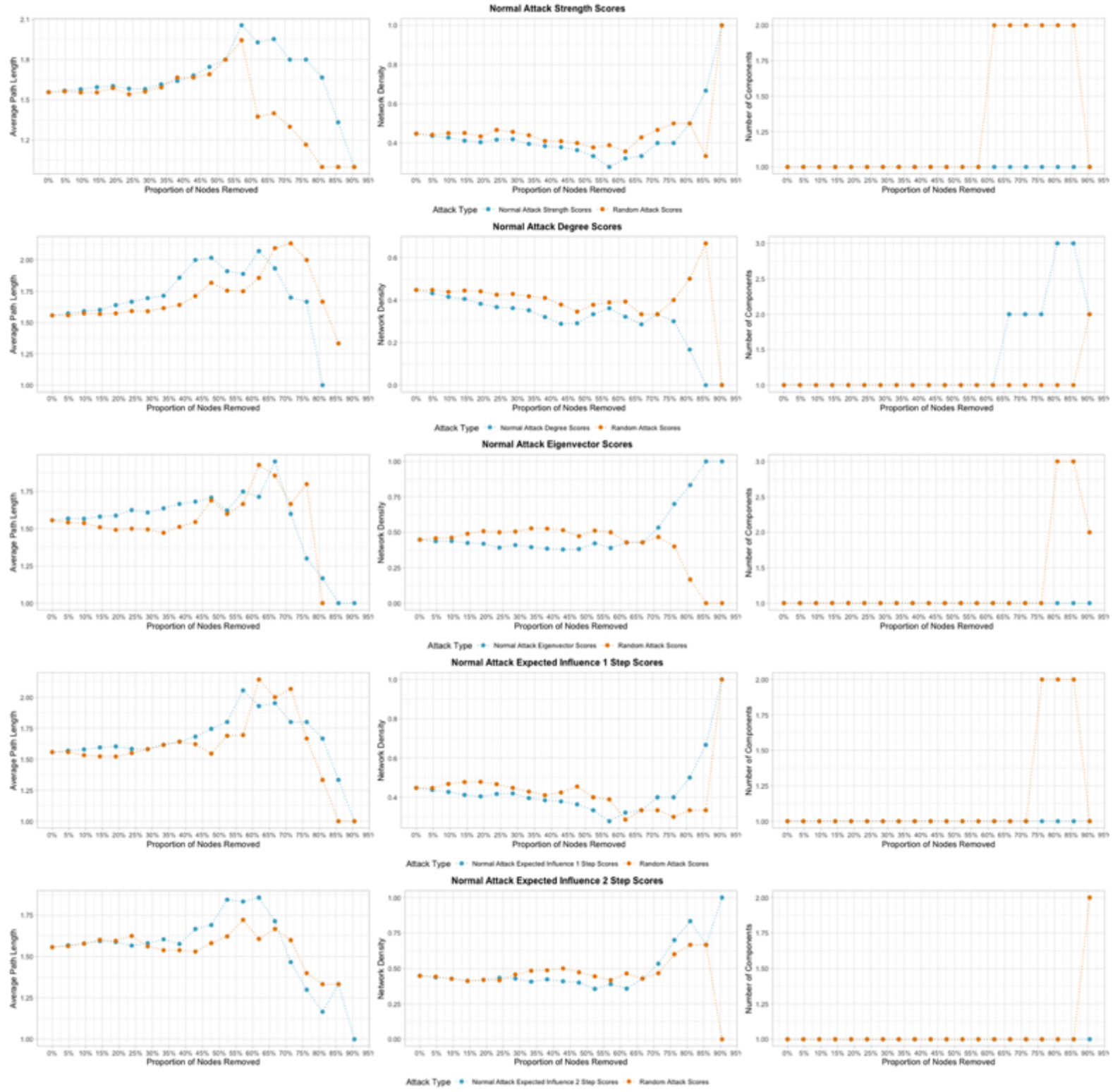
Plots displaying normal attack results for network 18



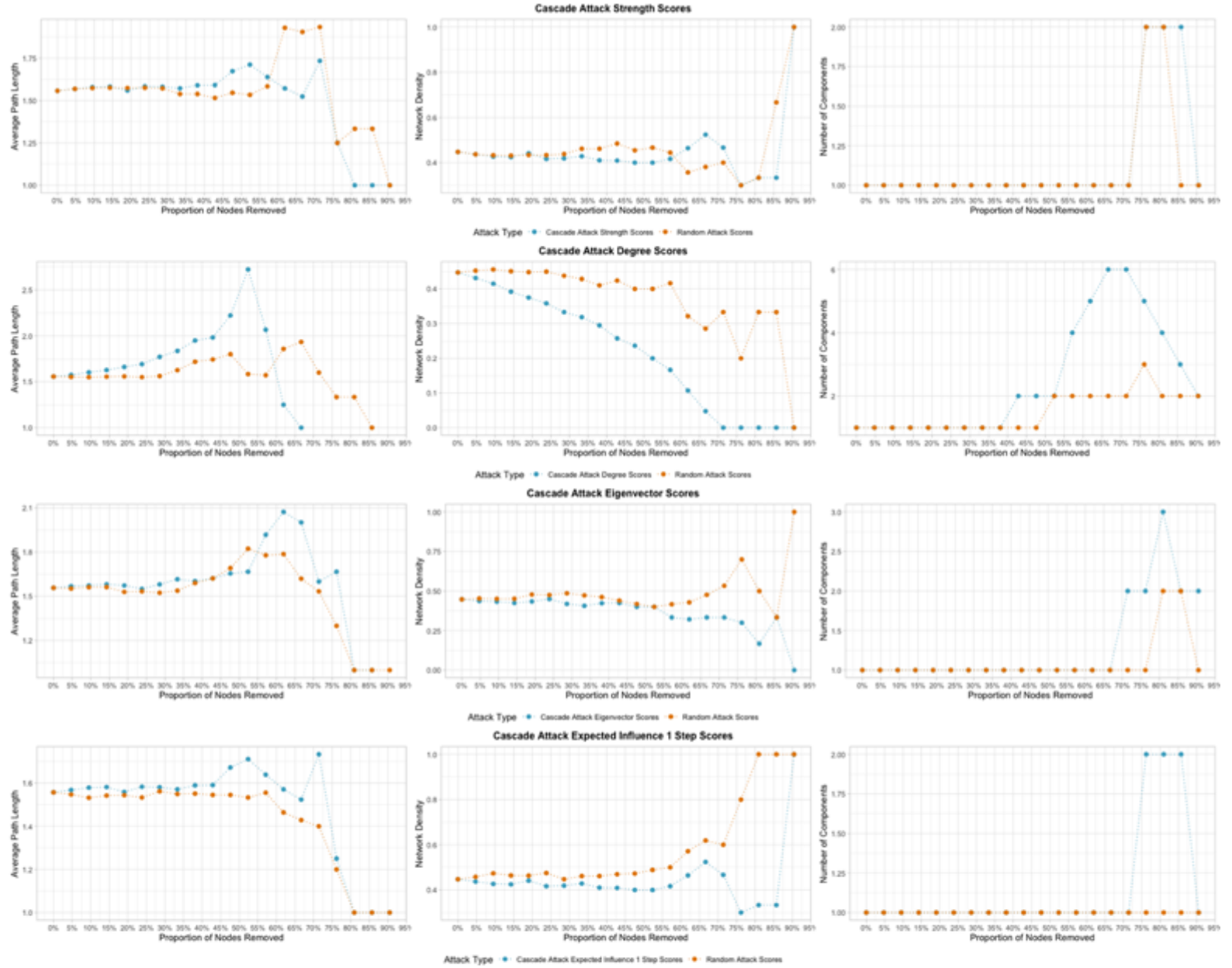
Plots displaying cascade attack results for network 18



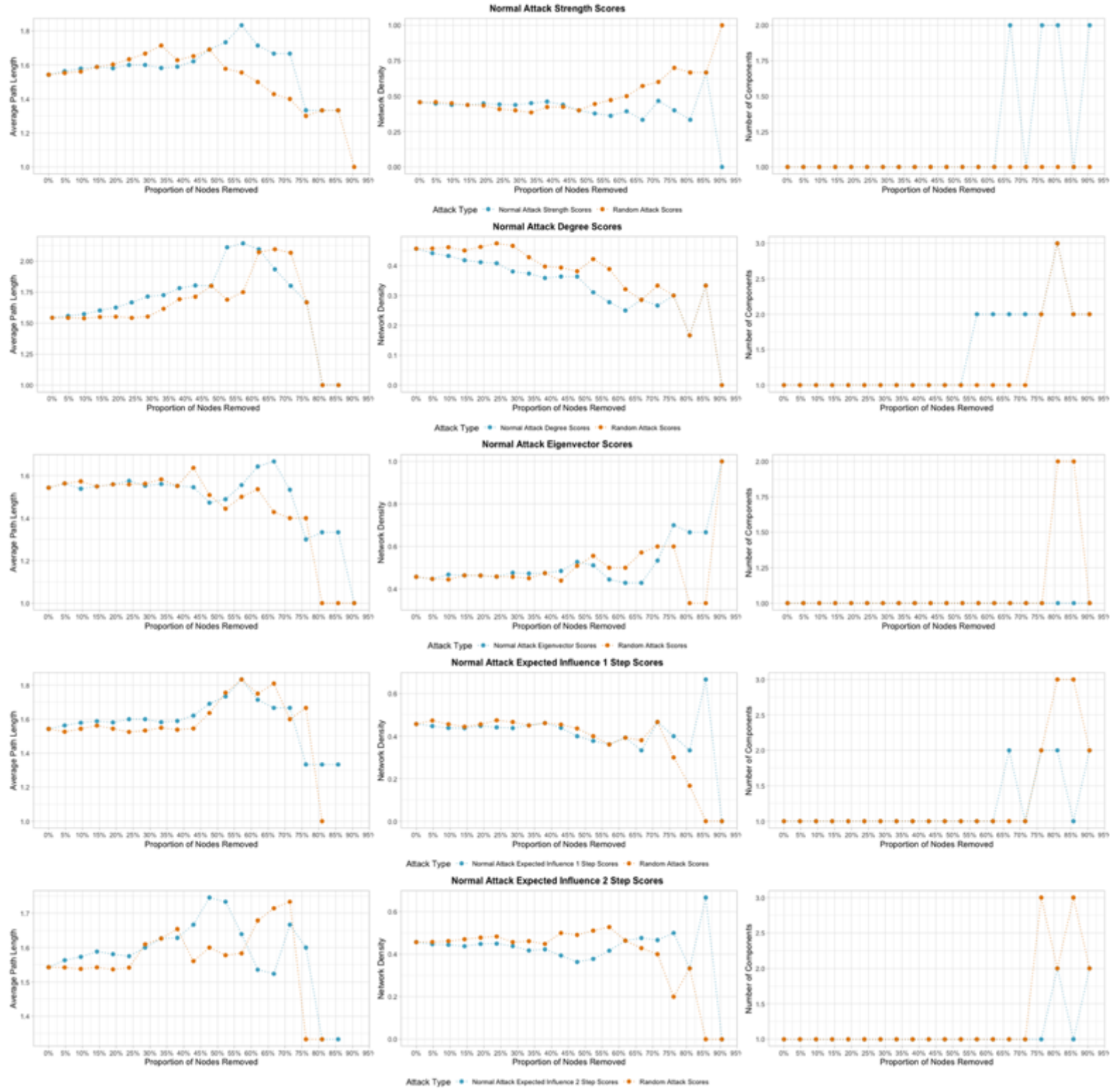
Plots displaying normal attack results for network 19



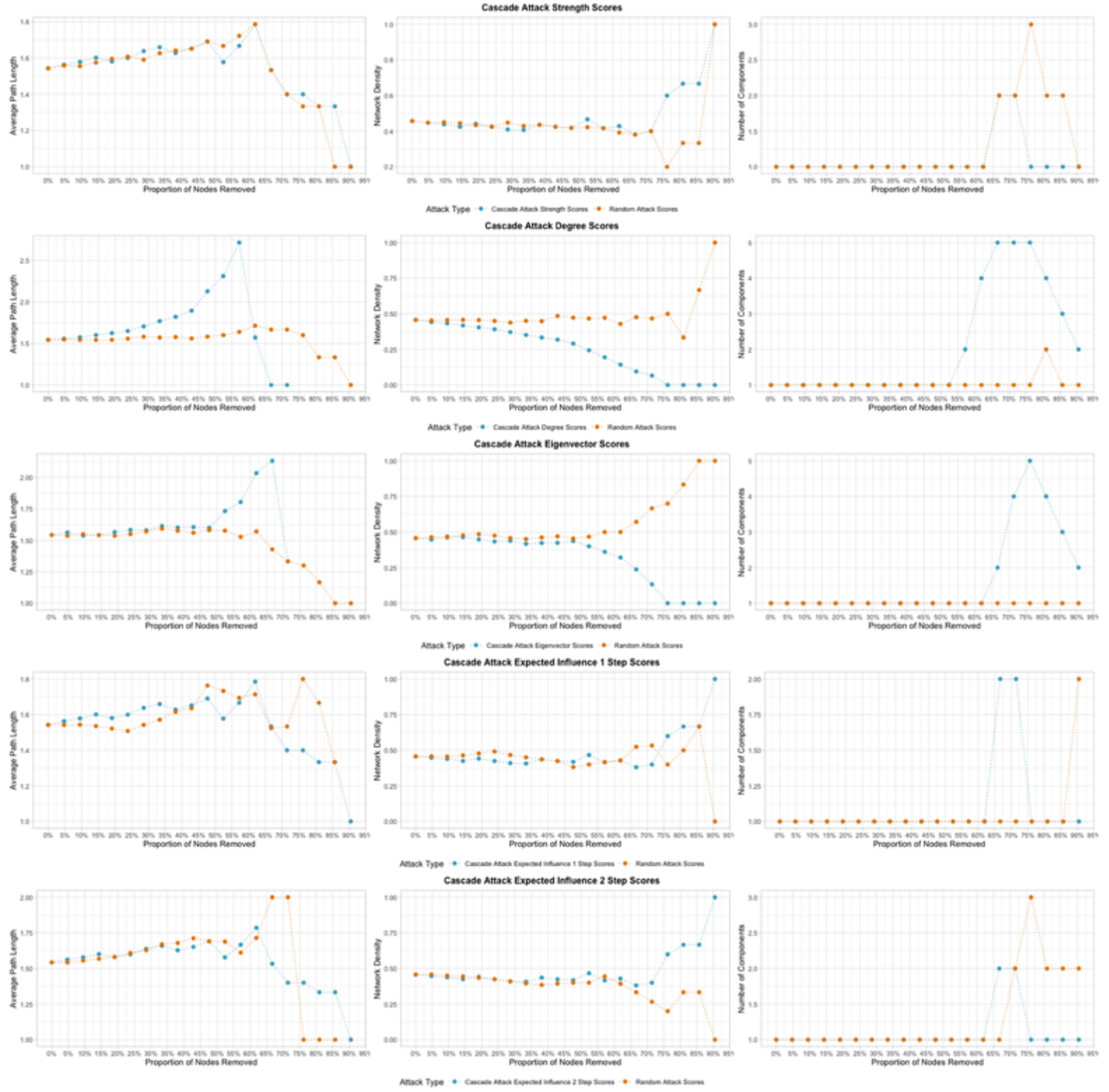
Plots displaying cascade attack results for network 19



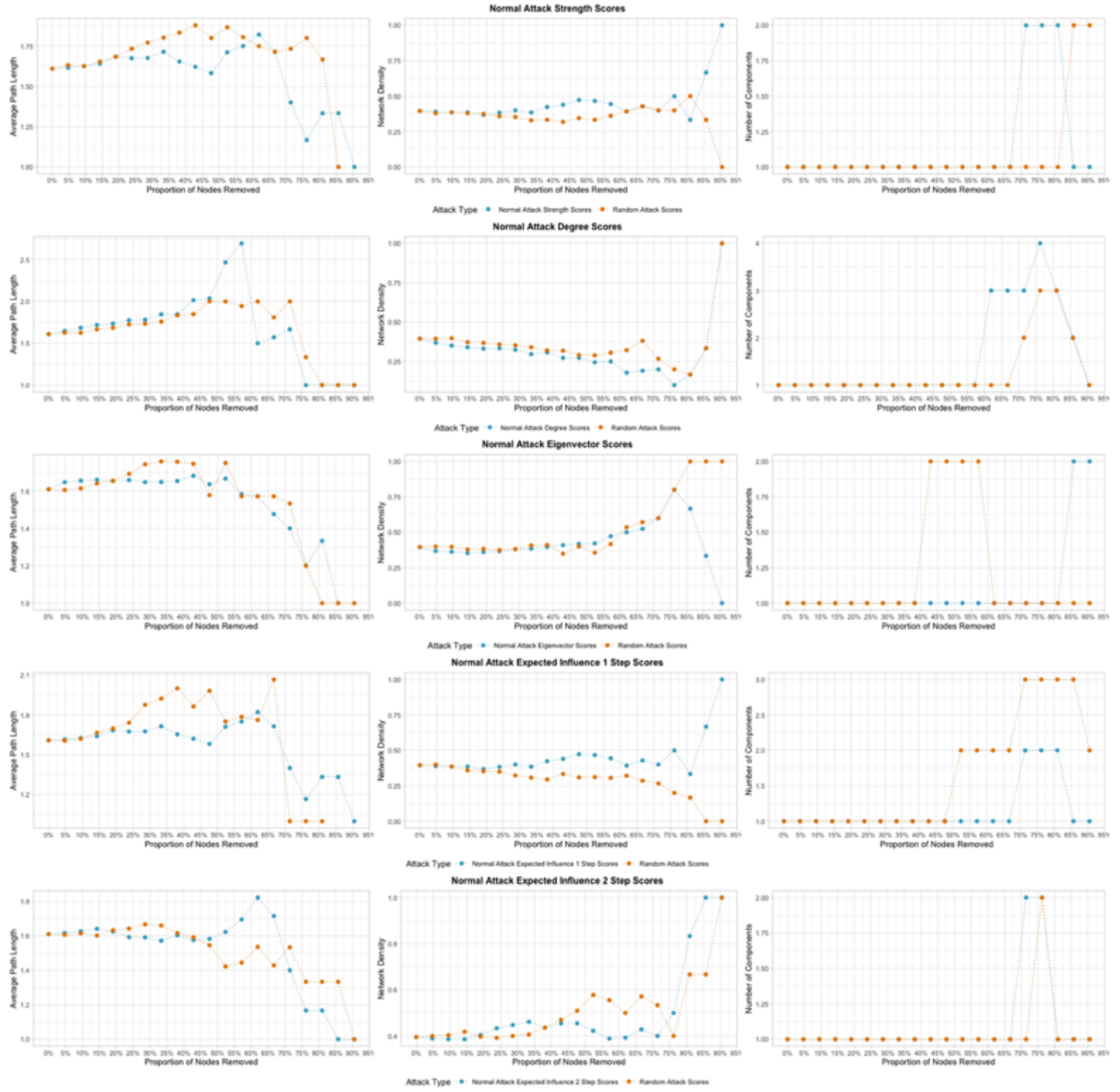
Plots displaying normal attack results for network 20



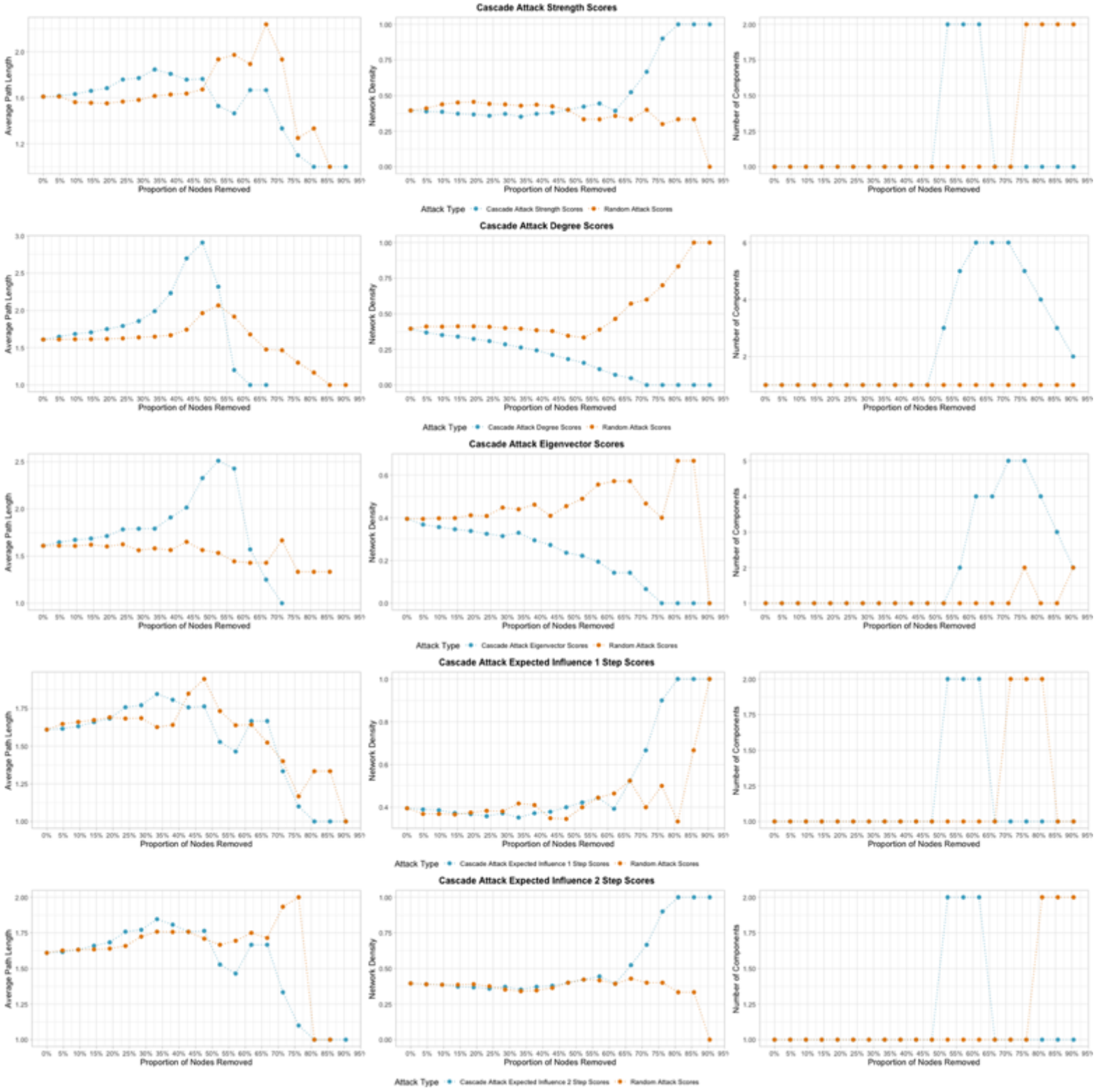
Plots displaying cascade attack results for network 20



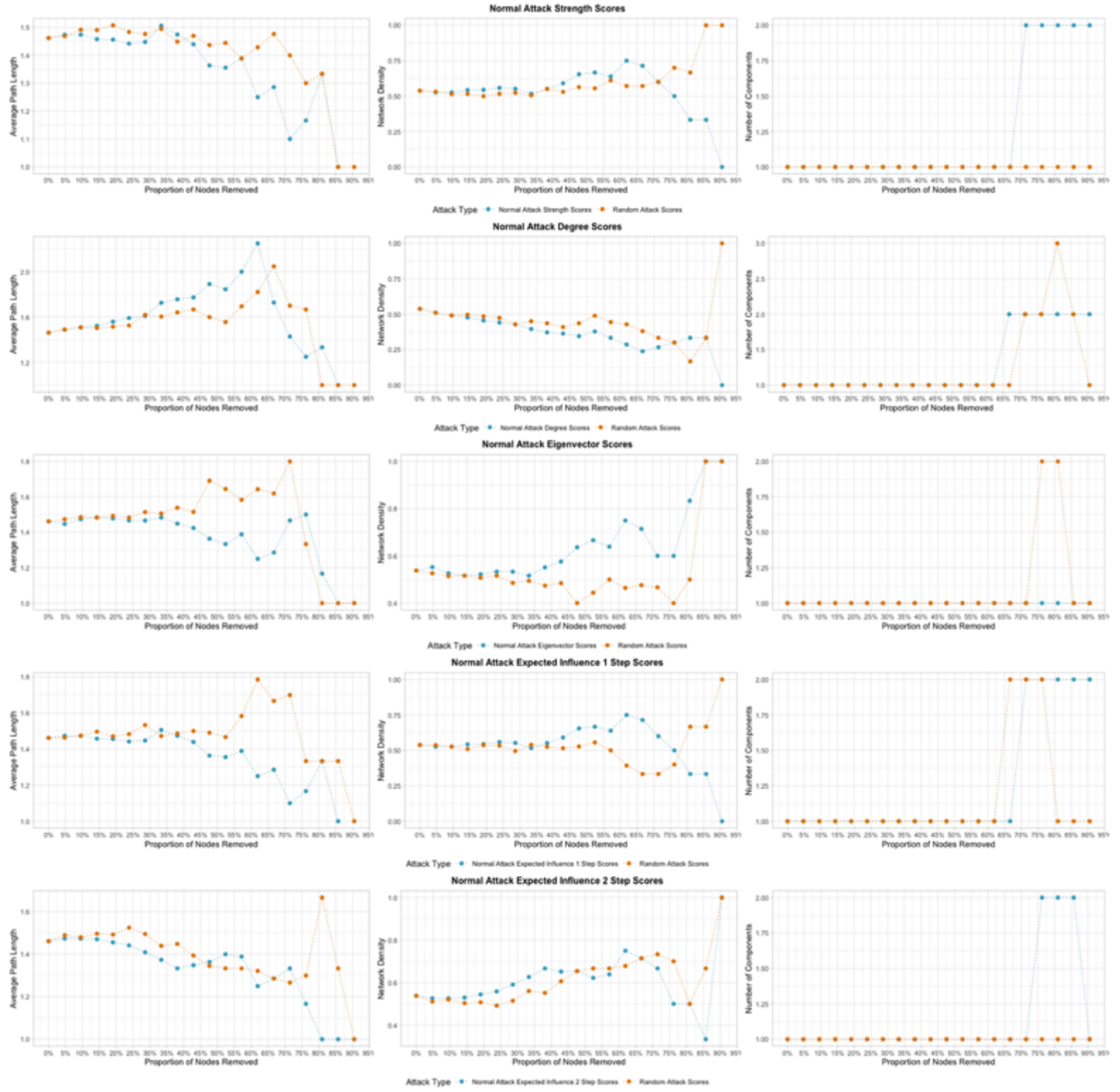
Plots displaying normal attack results for network 21



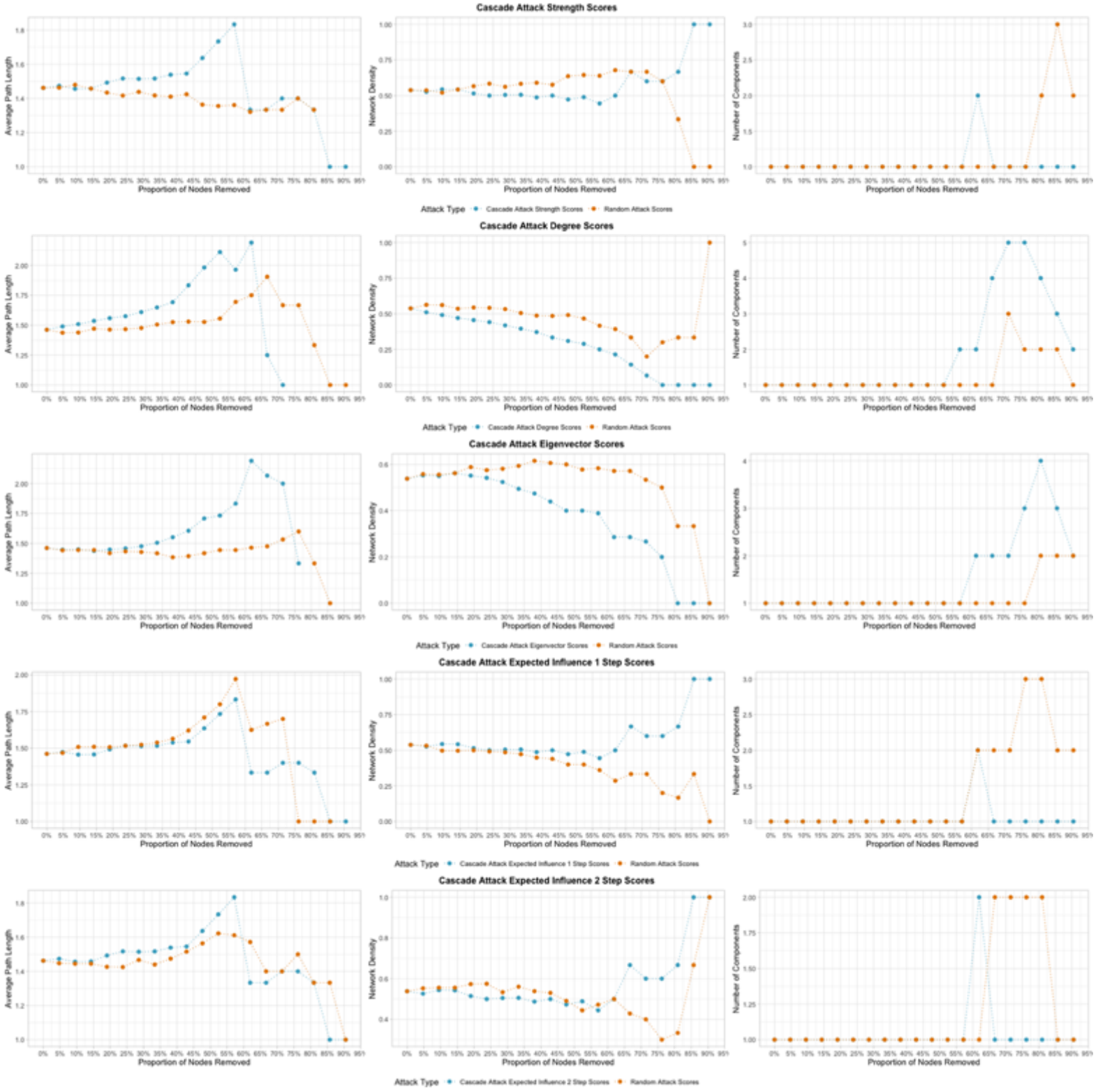
Plots displaying cascade attack results for network 21



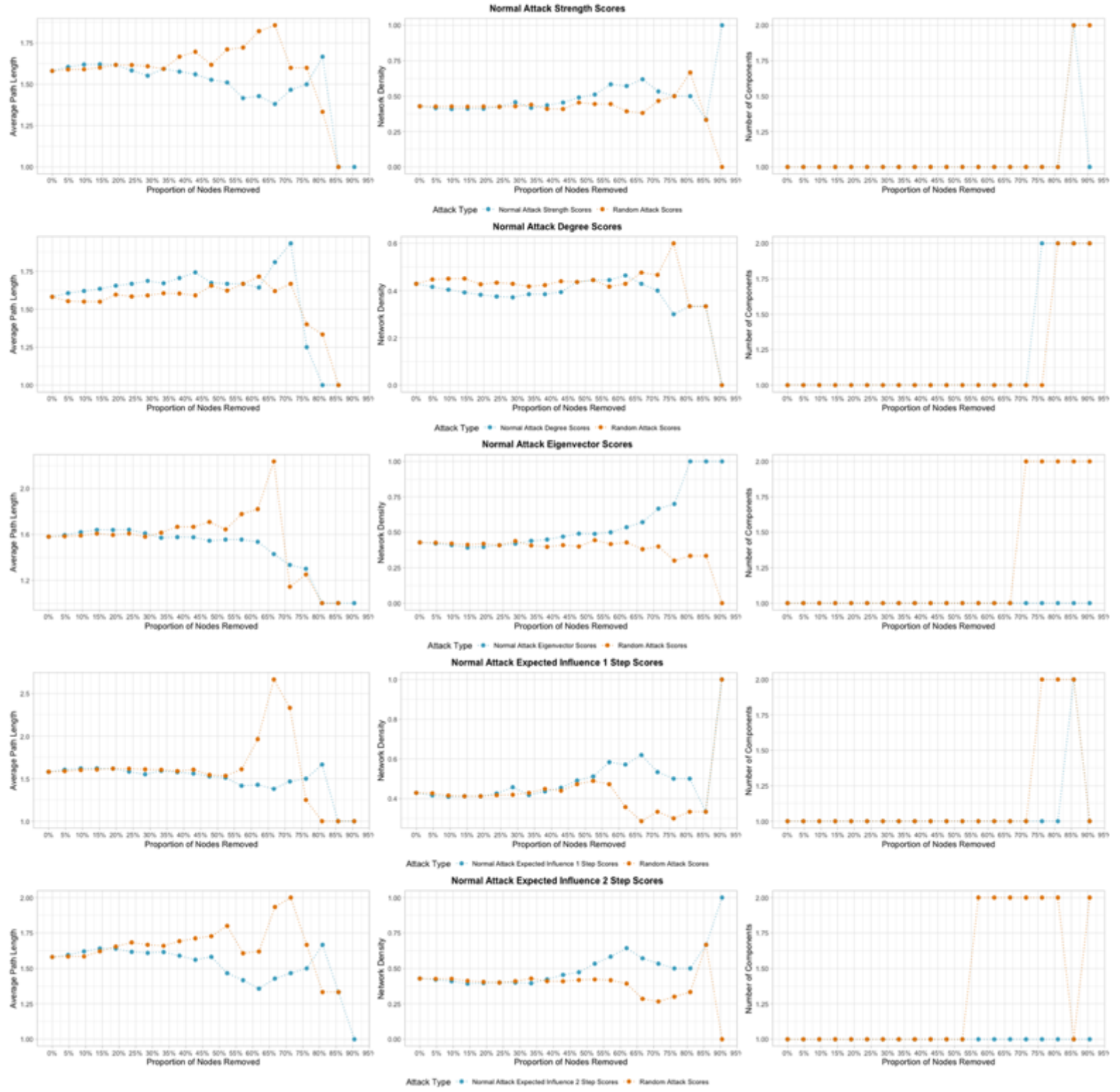
Plots displaying normal attack results for network 22



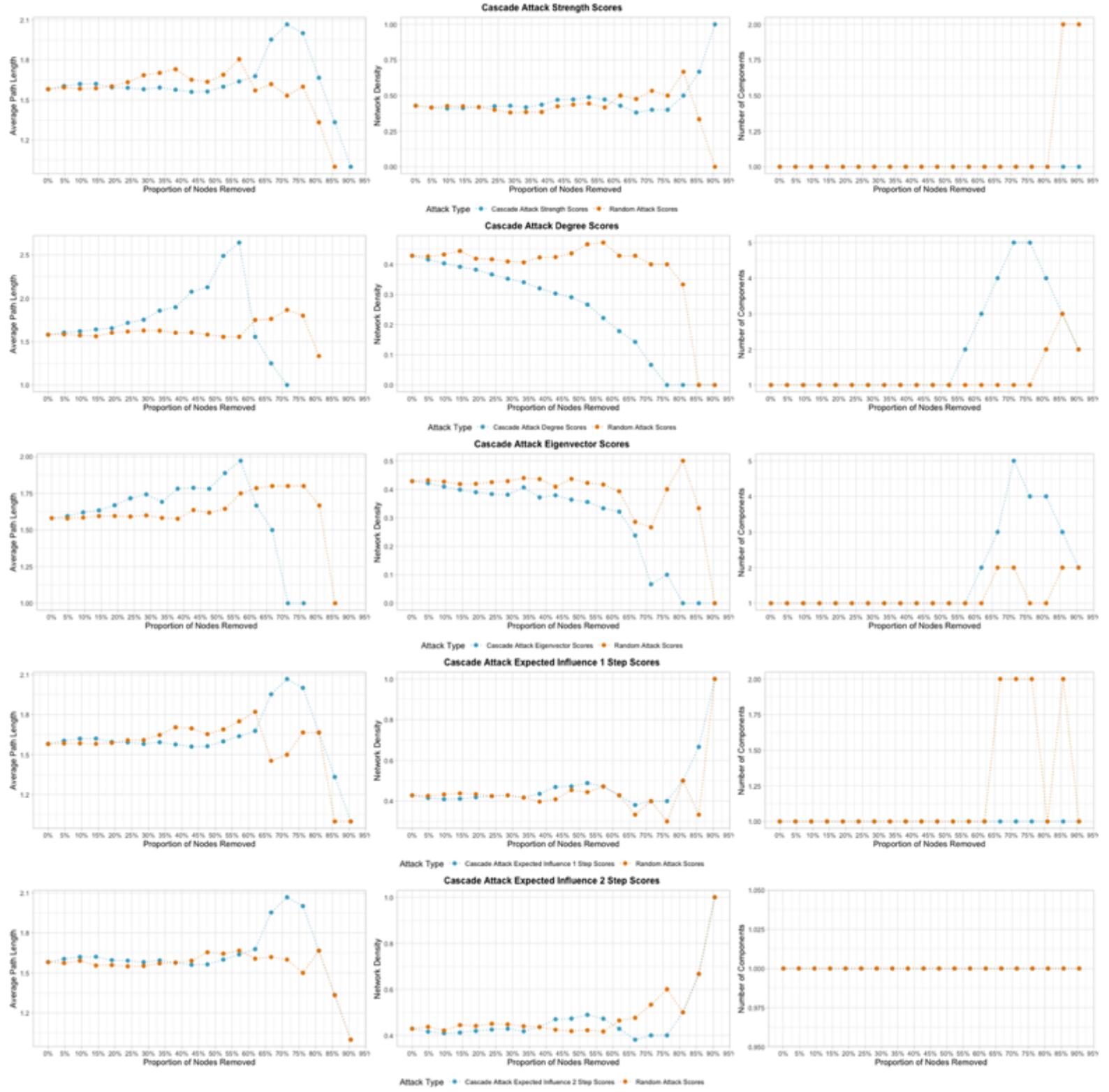
Plots displaying cascade attack results for network 22



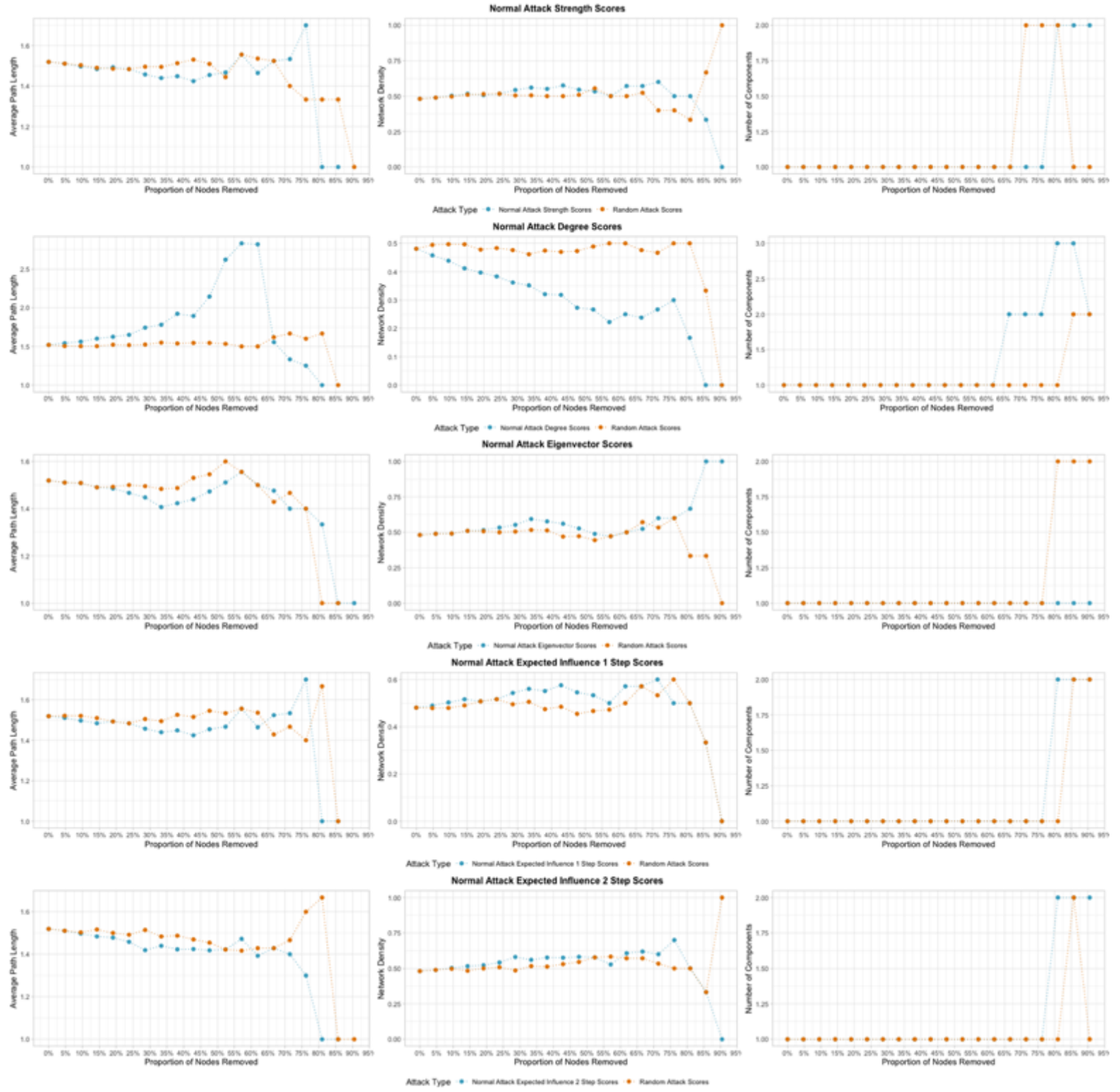
Plots displaying normal attack results for network 23



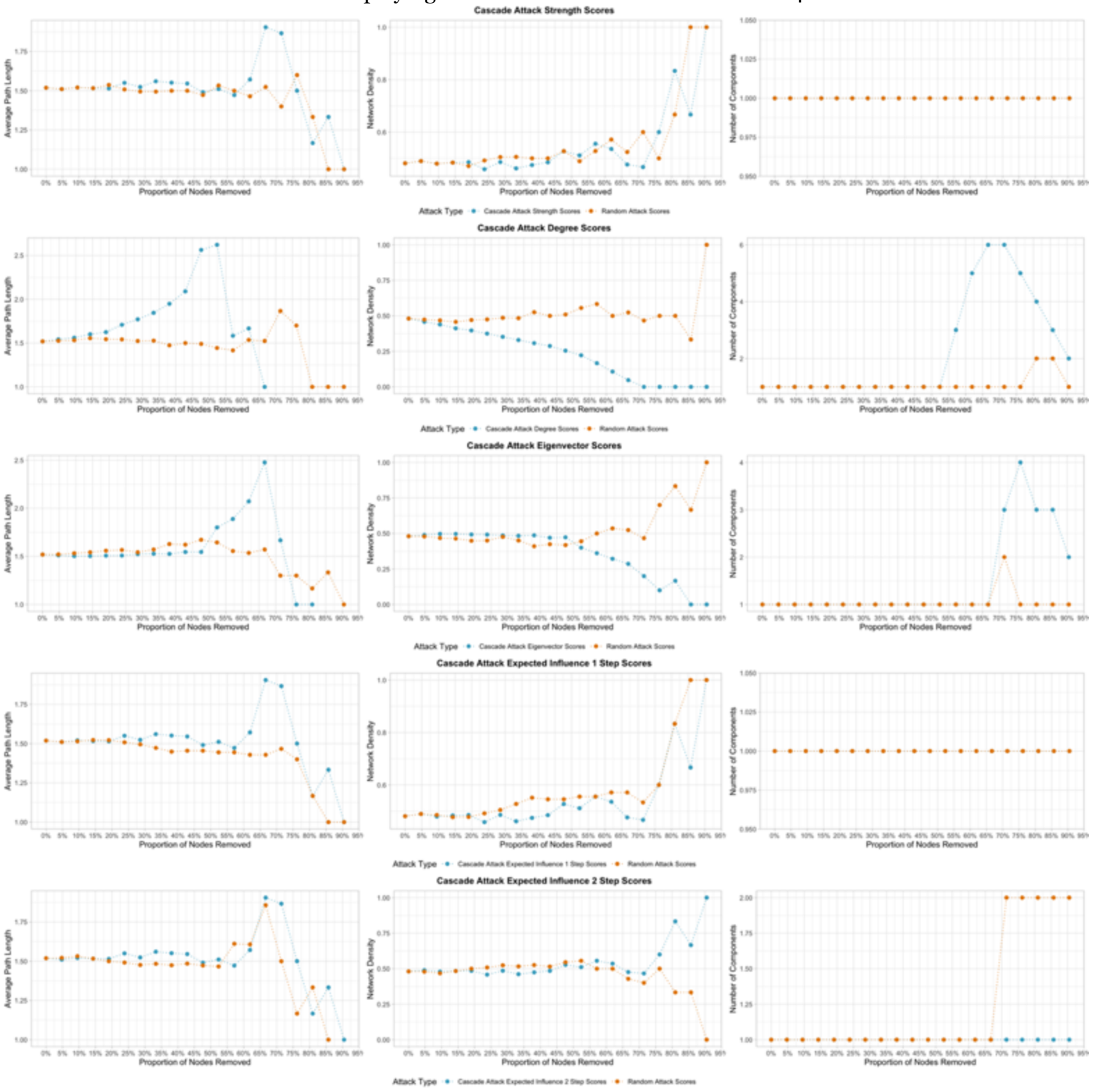
Plots displaying cascade attack results for network 23



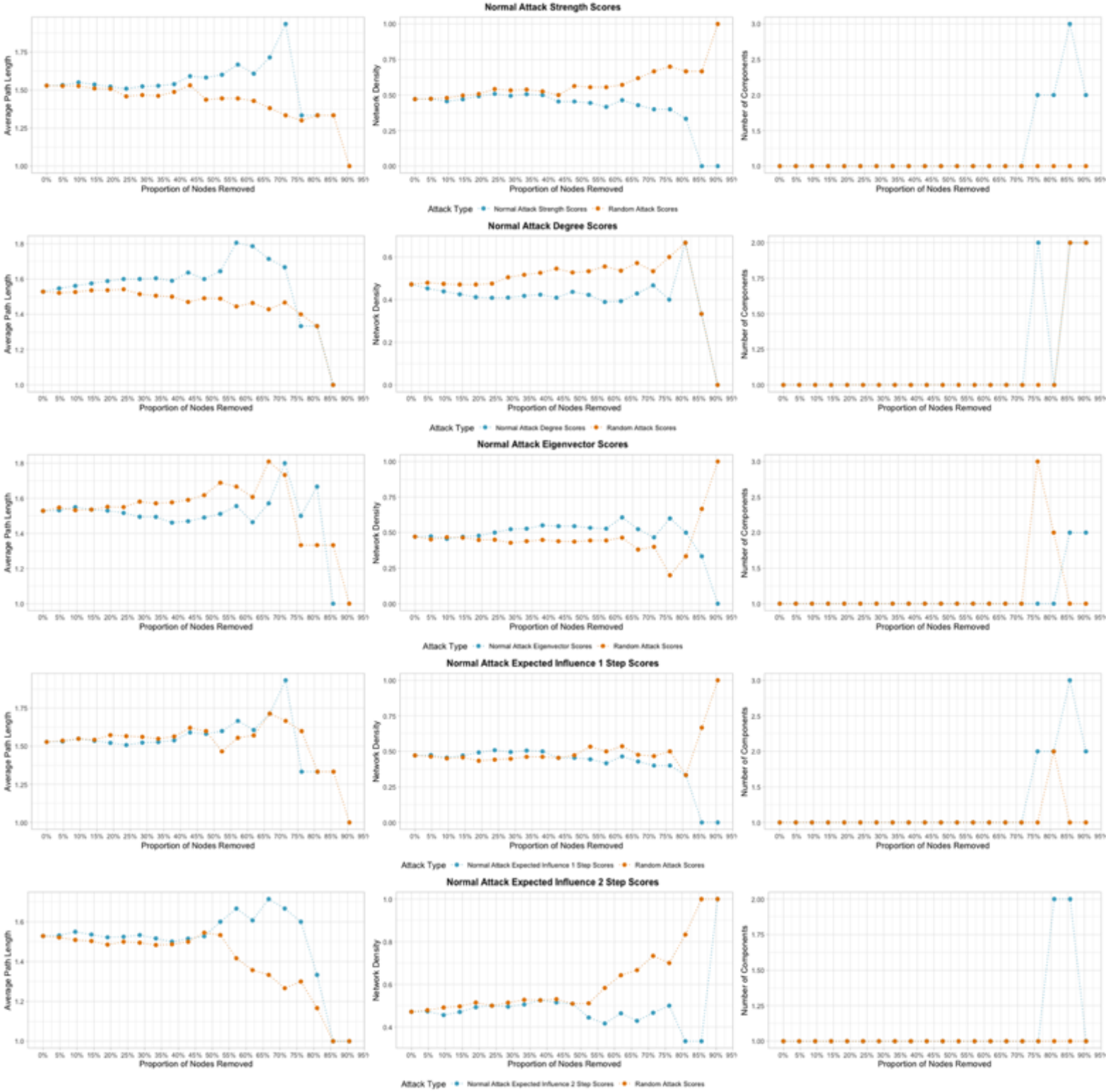
Plots displaying normal attack results for network 24



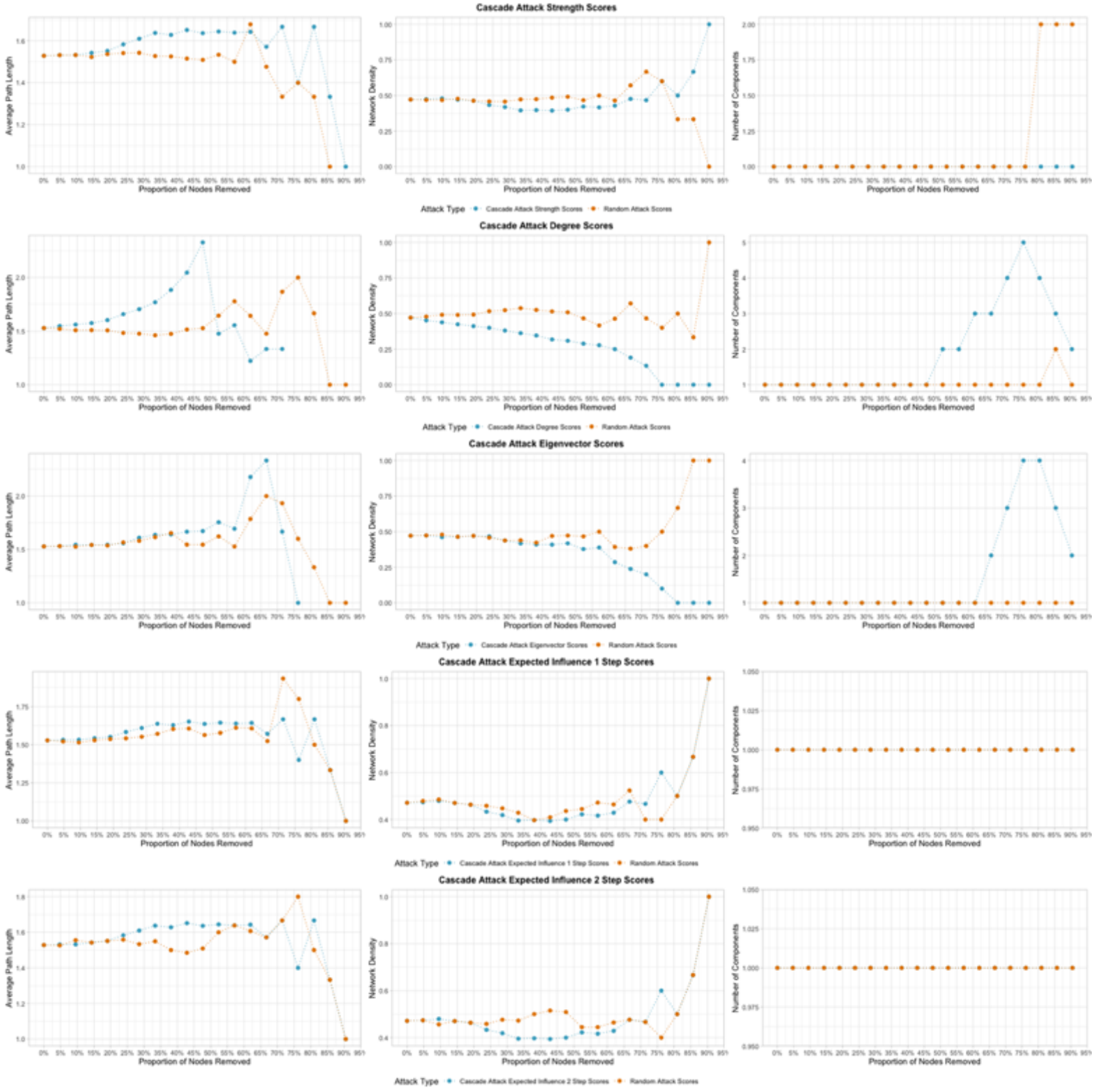
Plots displaying cascade attack results for network 24



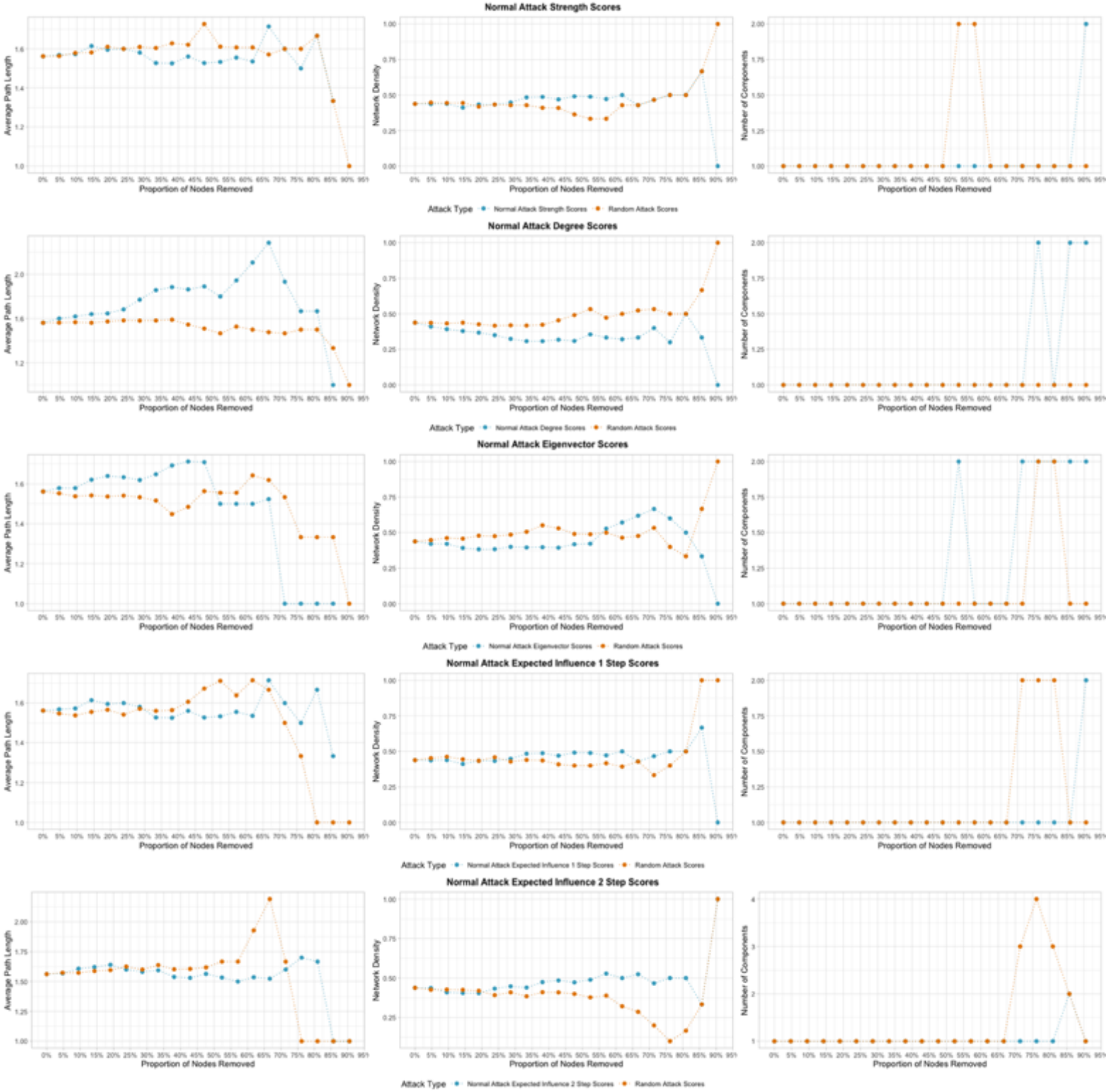
Plots displaying normal attack results for network 25



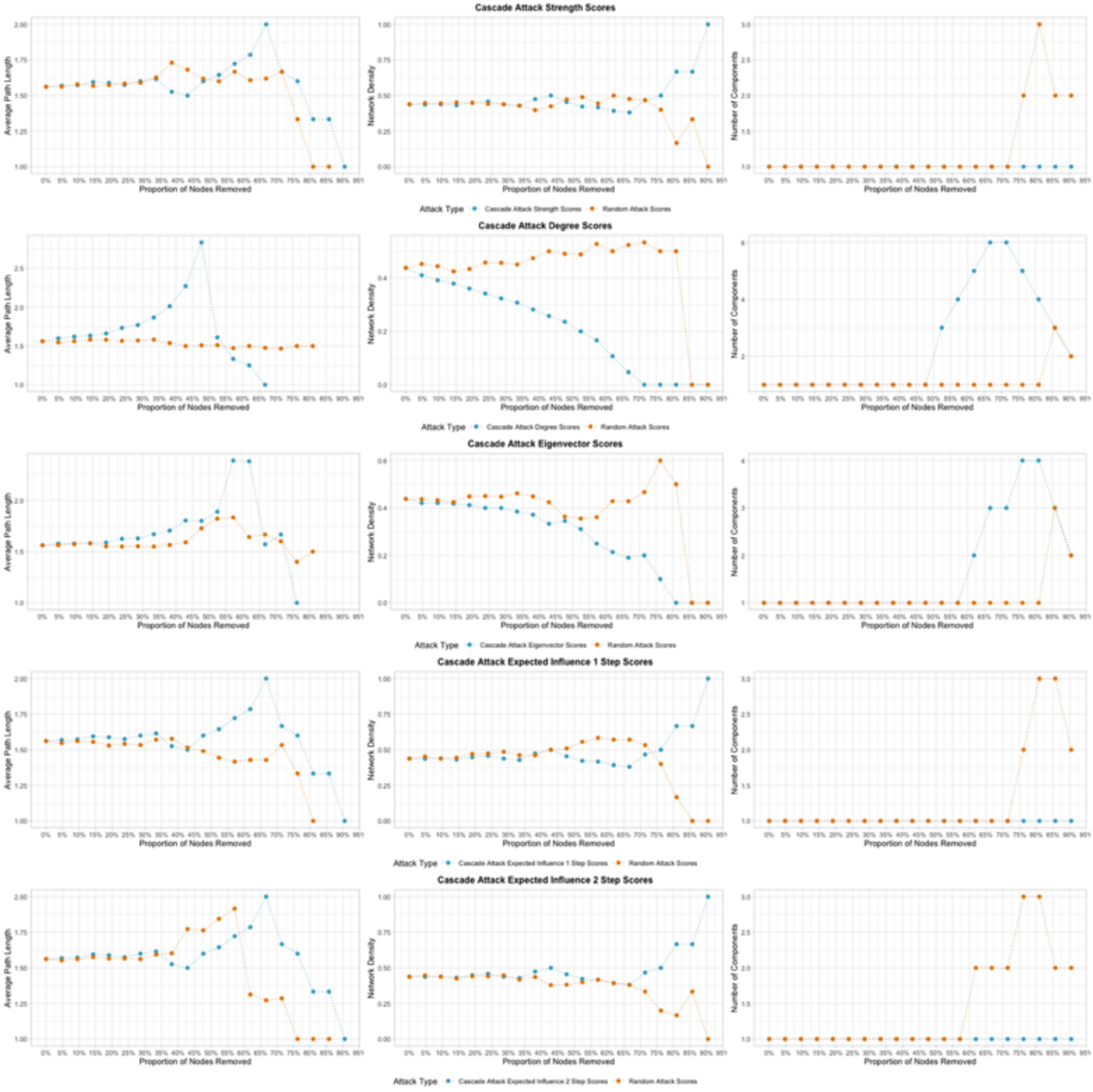
Plots displaying cascade attack results for network 25



Plots displaying normal attack results for network 26

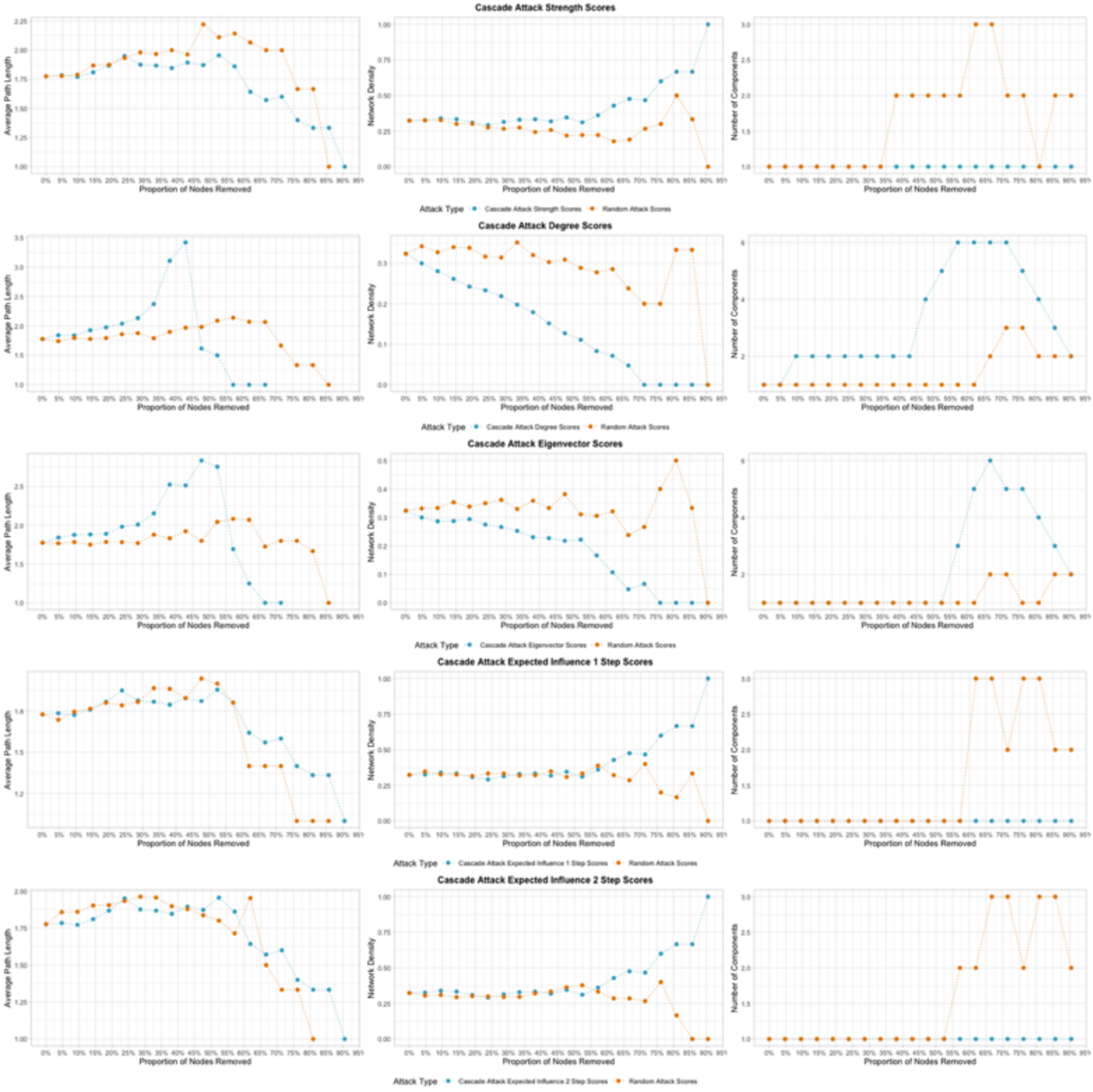


Plots displaying cascade attack results for network 26

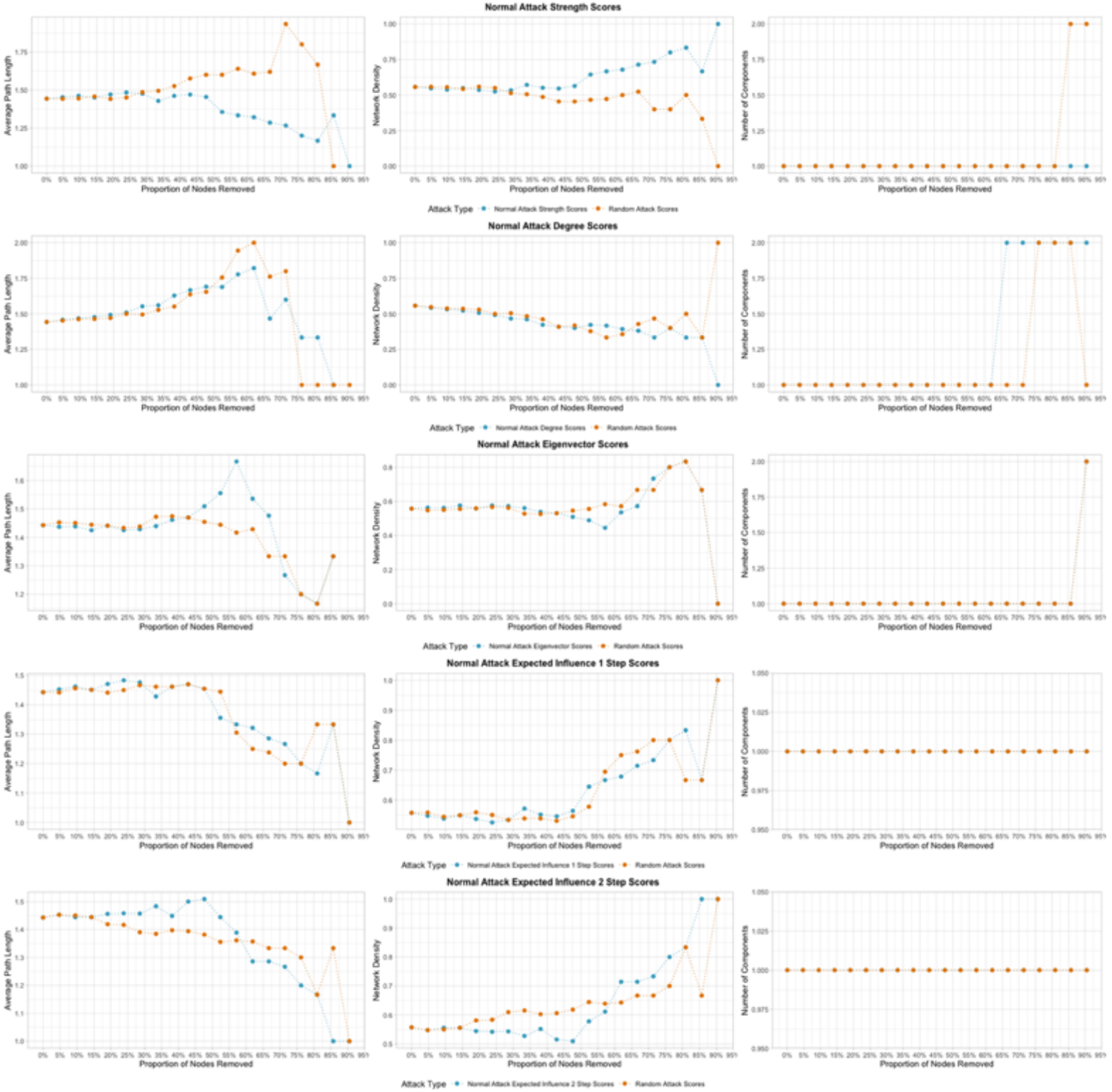


Plots displaying normal attack results for network 27

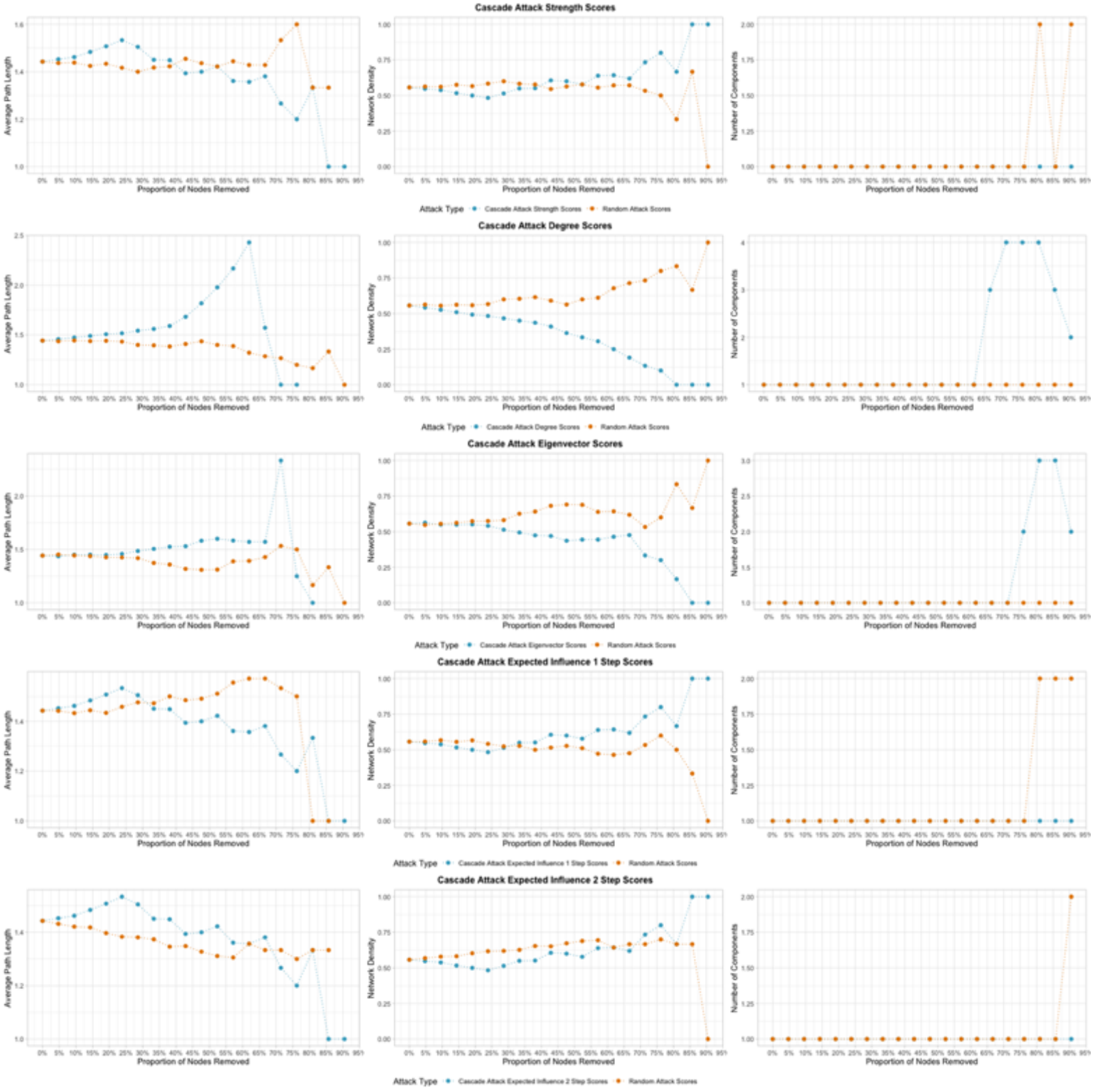
Plots displaying cascade attack results for network 27



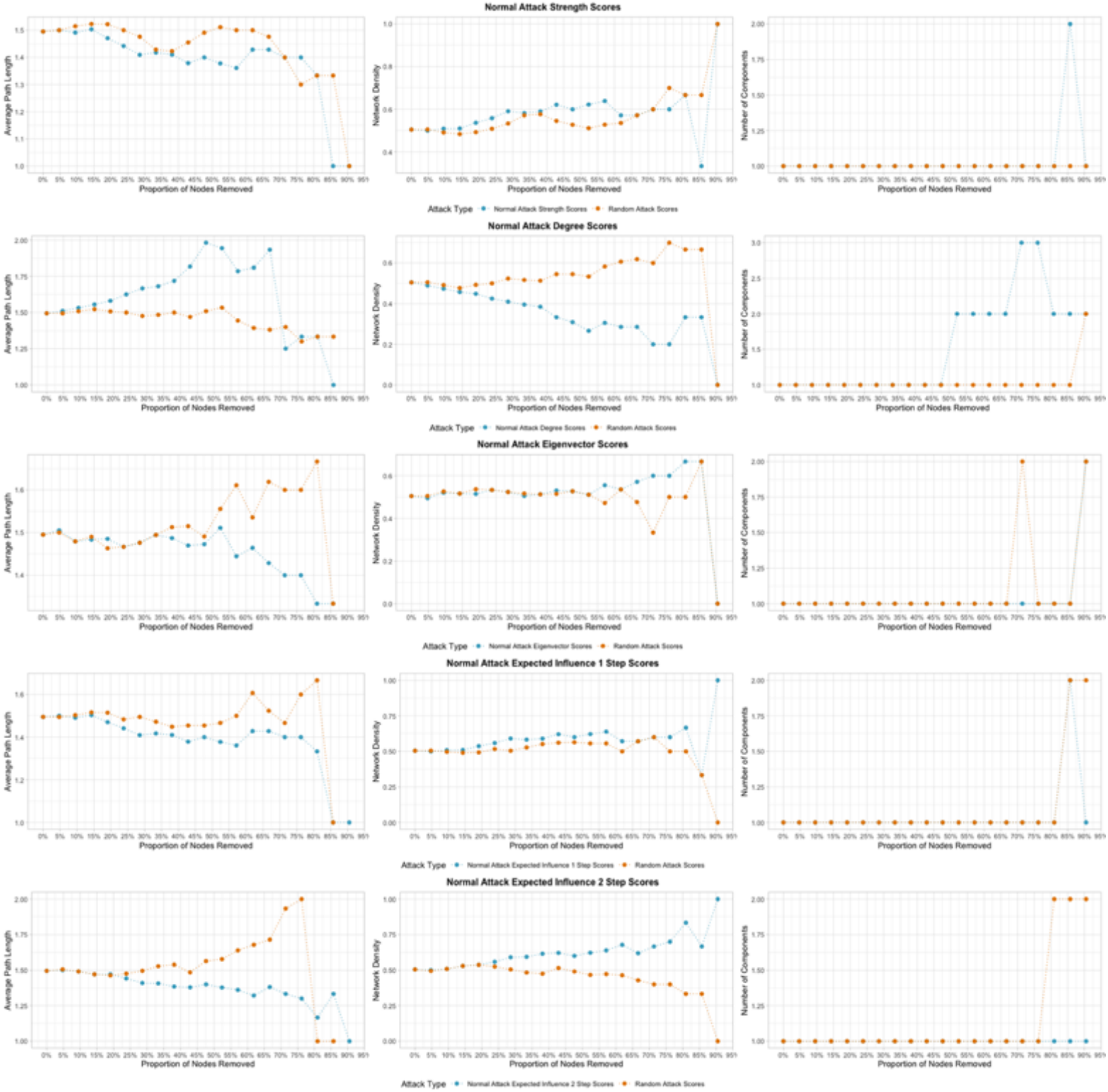
Plots displaying normal attack results for network 28



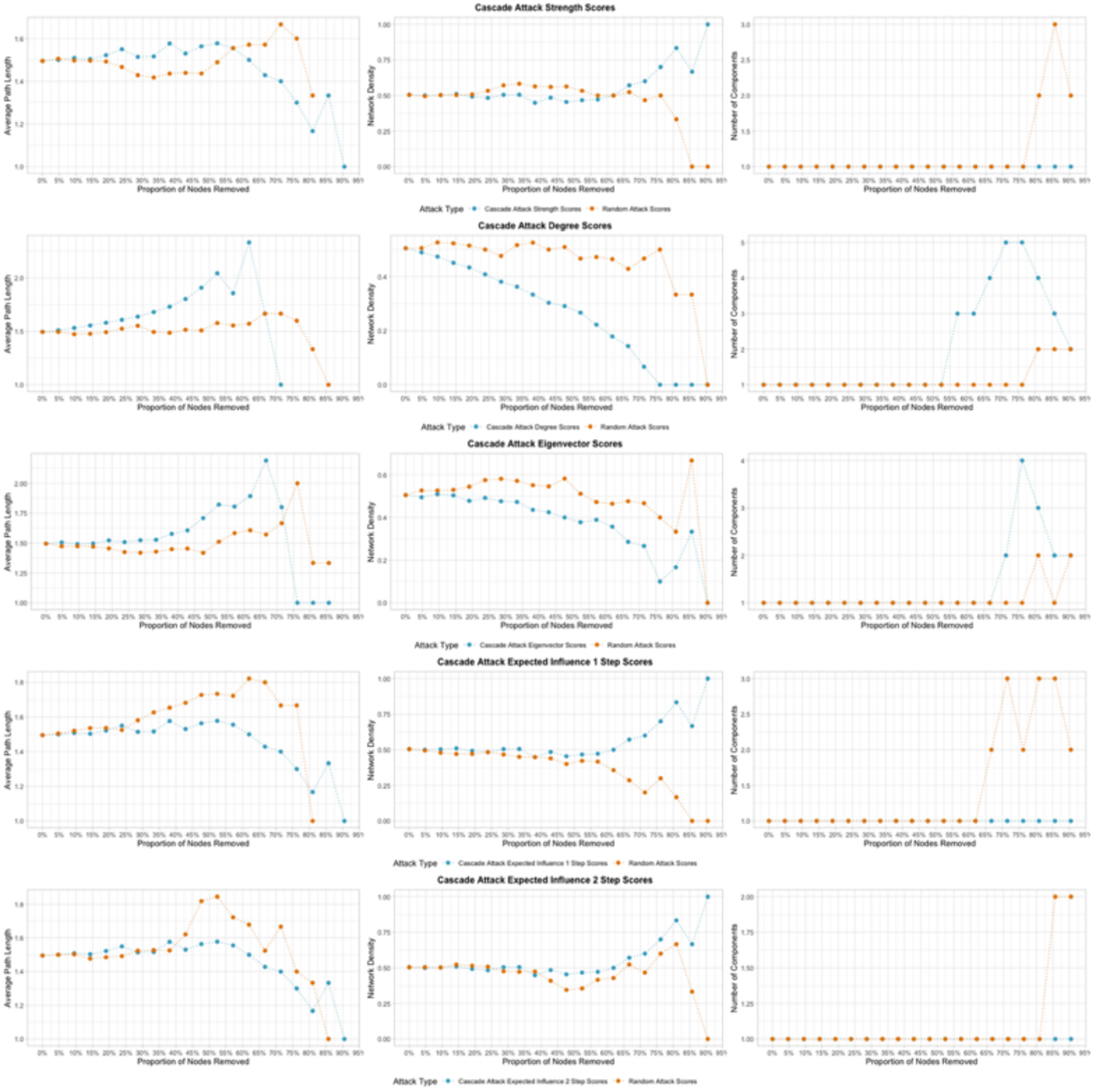
Plots displaying cascade attack results for network 28



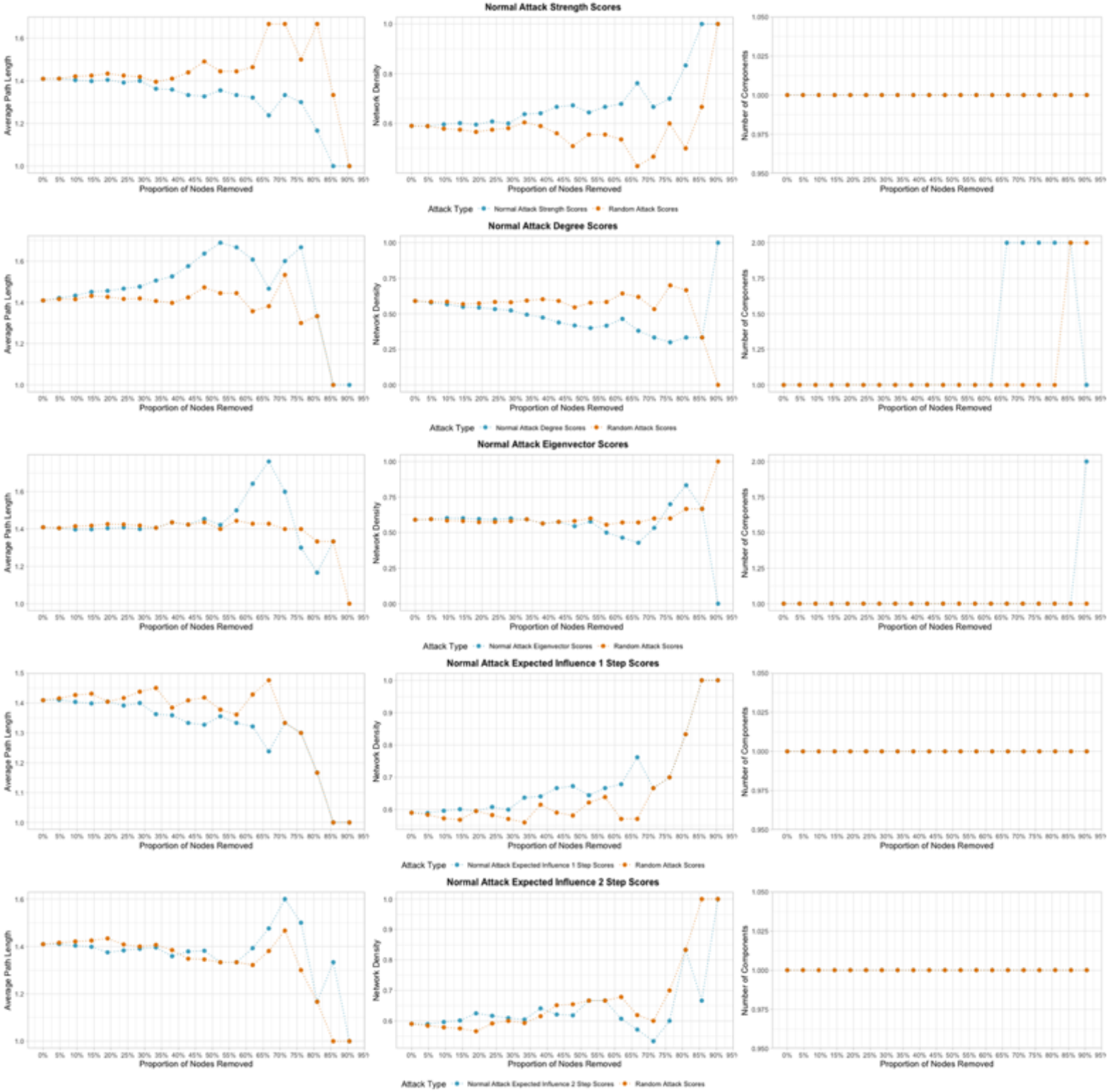
Plots displaying normal attack results for network 29



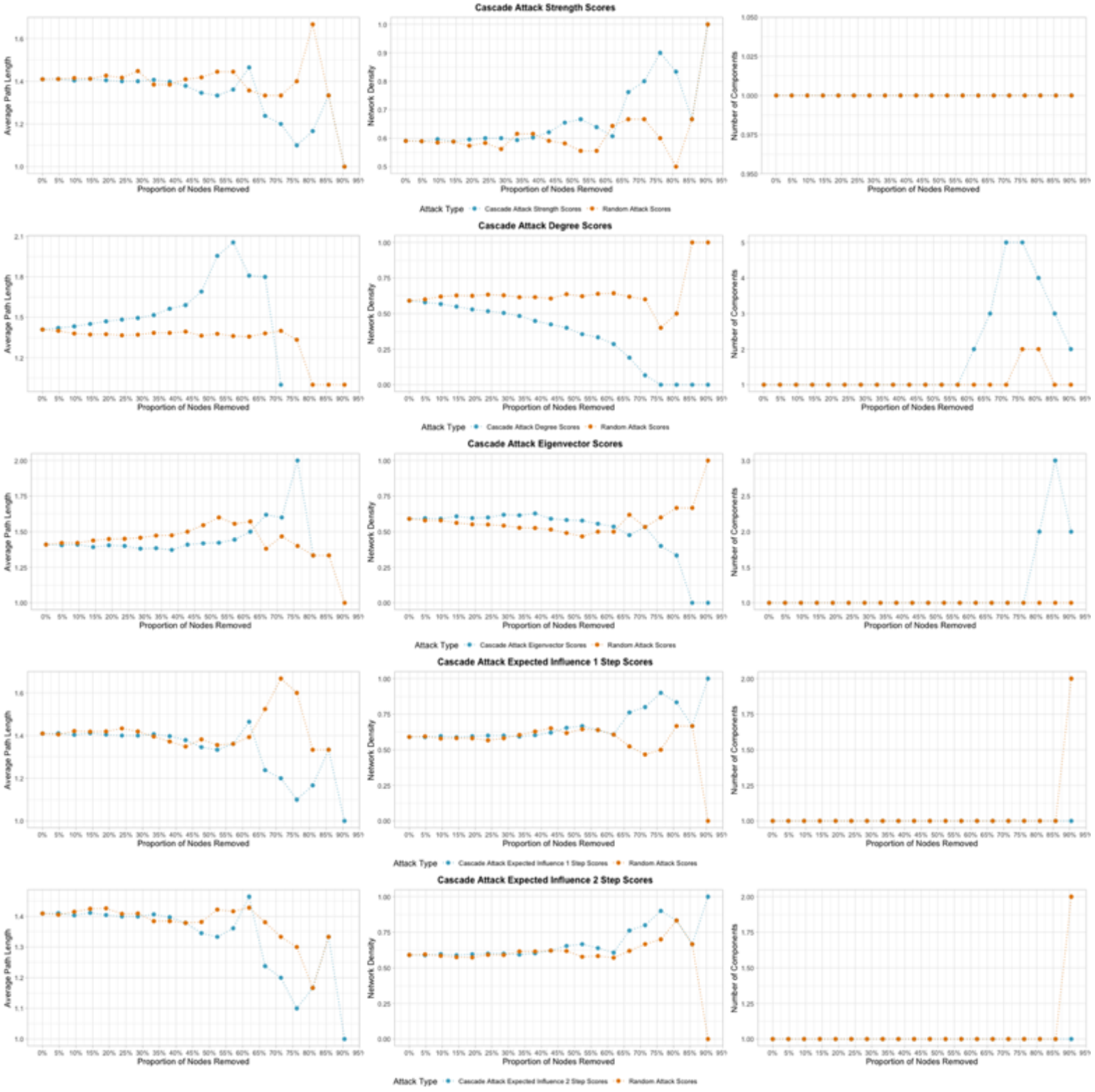
Plots displaying cascade attack results for network 29



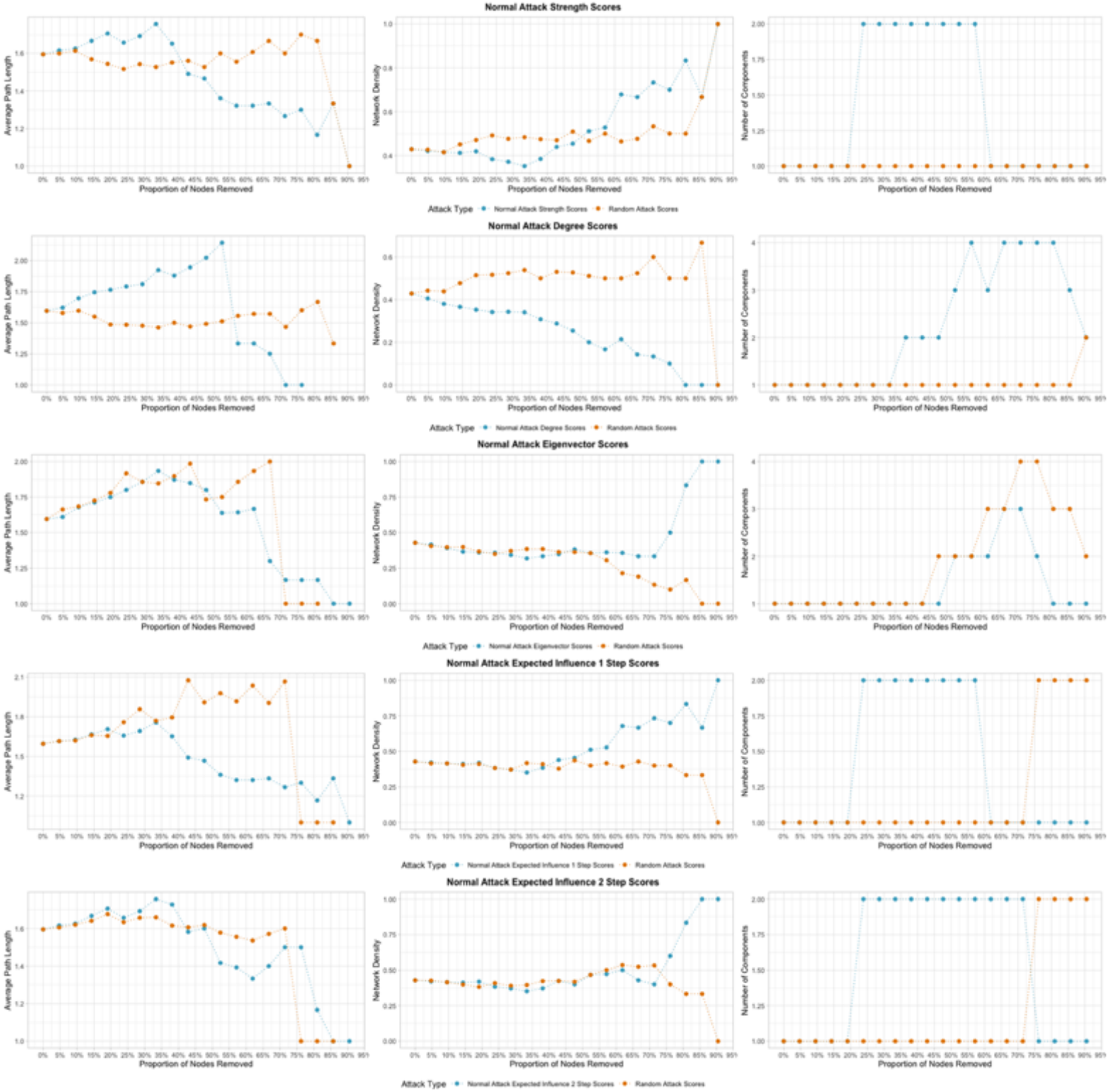
Plots displaying normal attack results for network 30



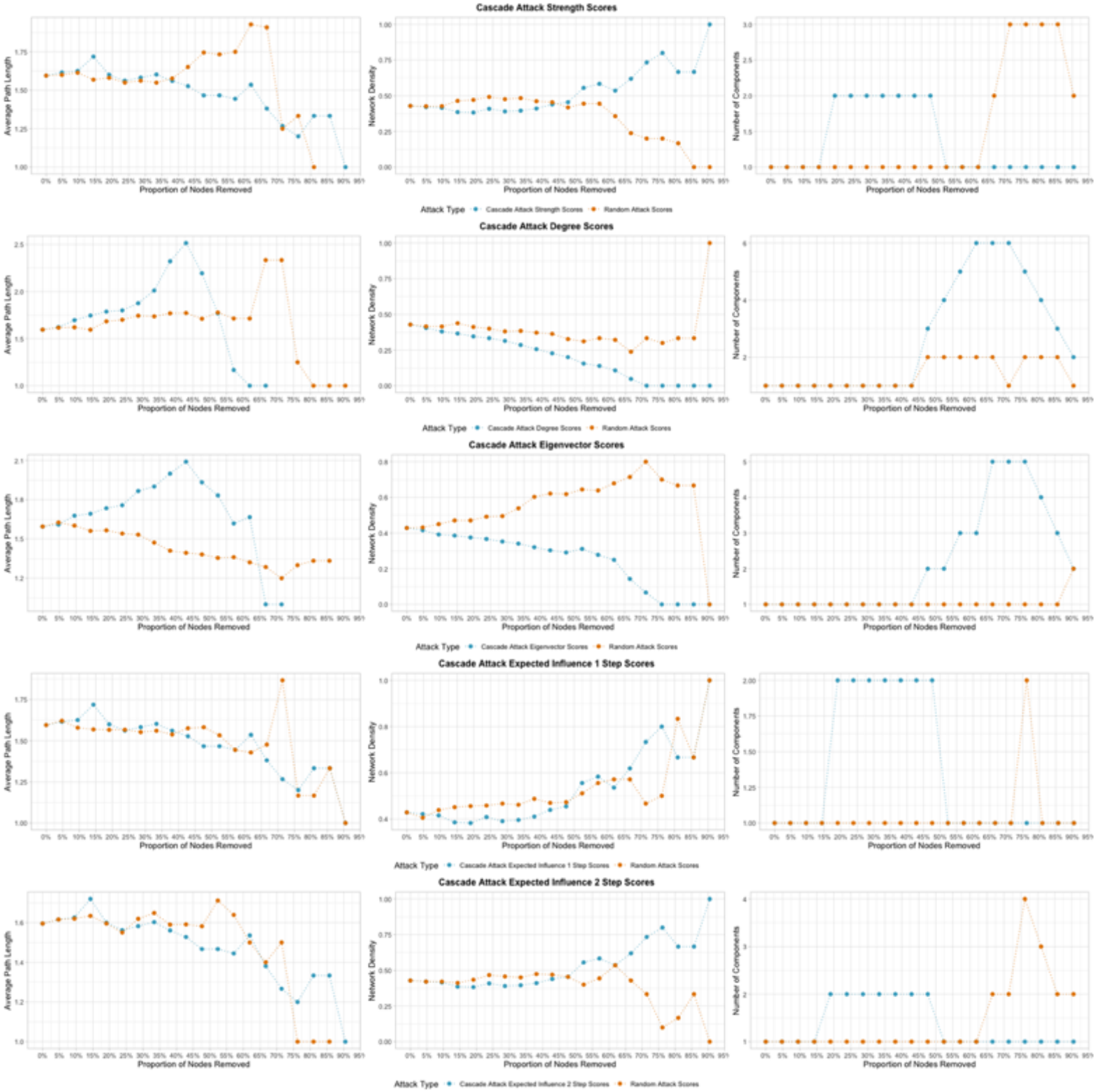
Plots displaying cascade attack results for network 30



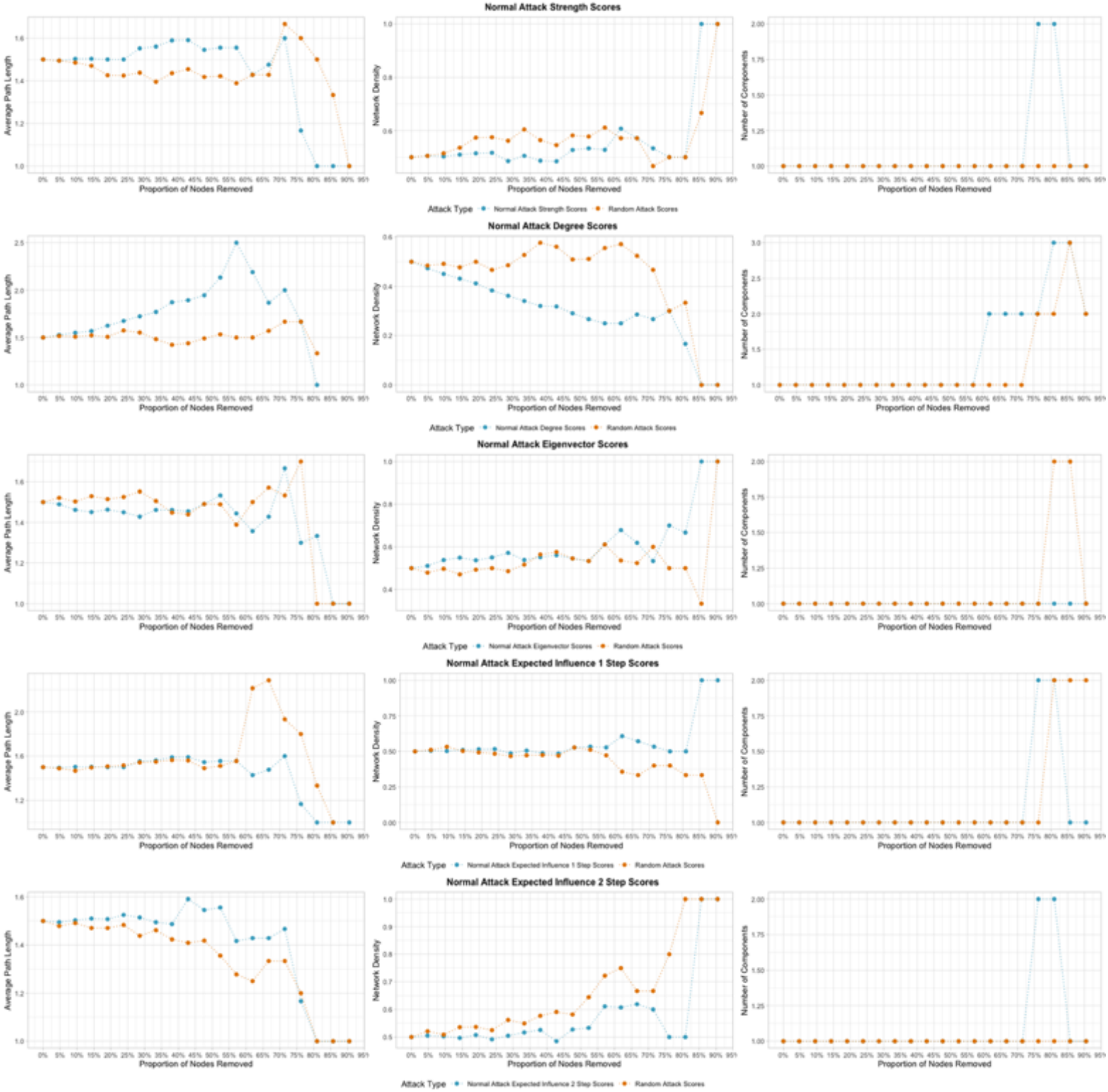
Plots displaying normal attack results for network 31



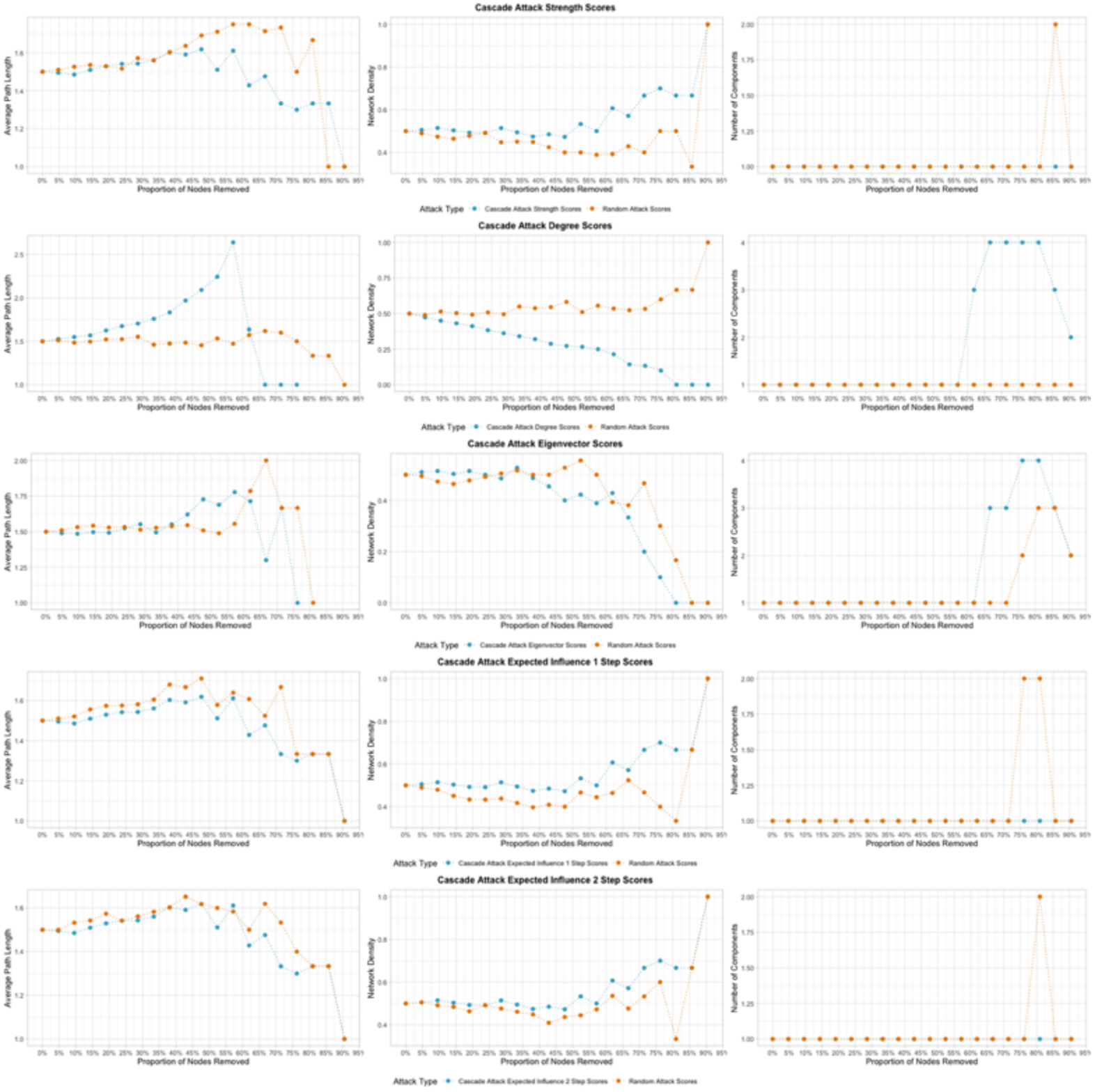
Plots displaying cascade attack results for network 31



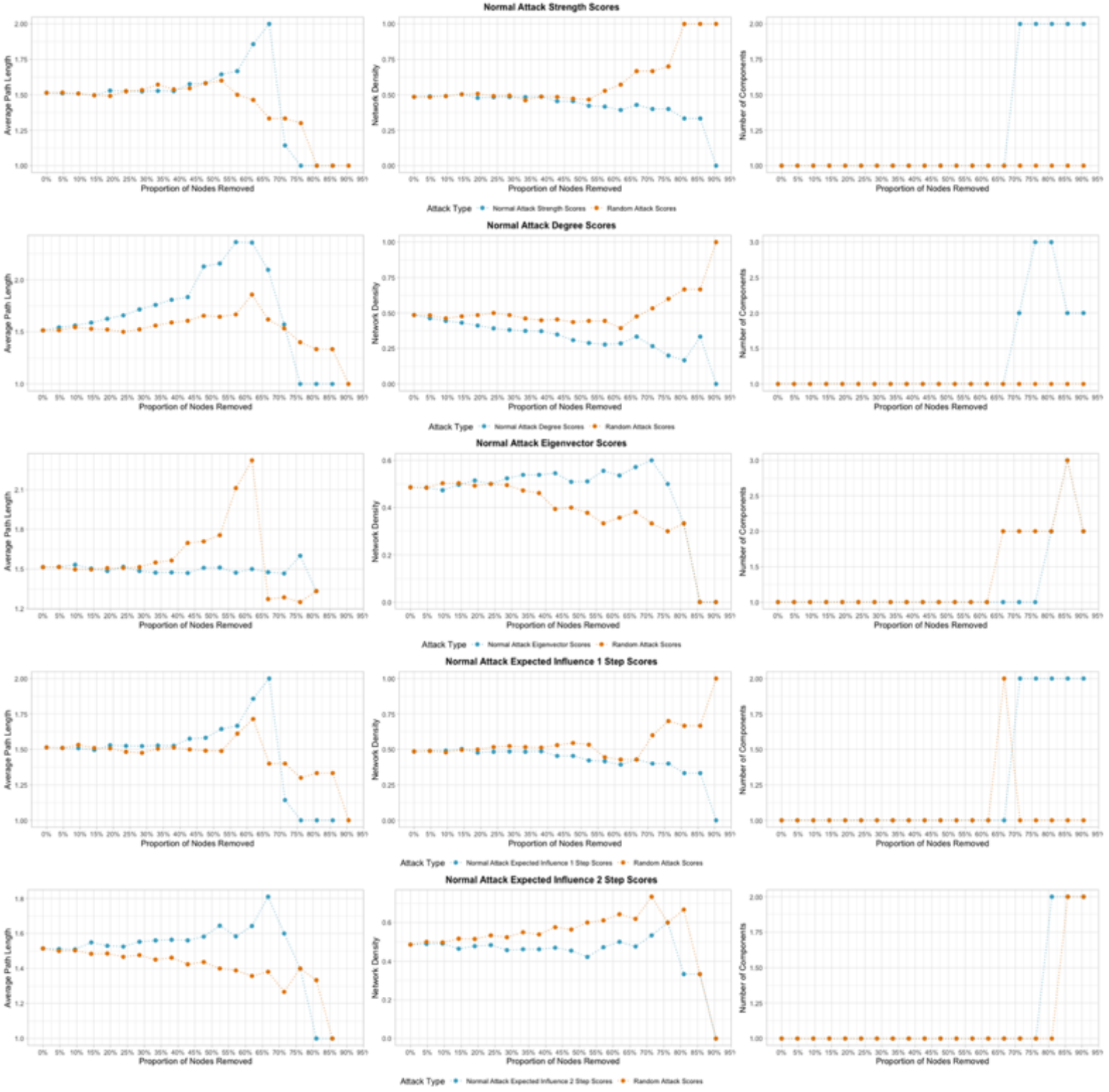
Plots displaying normal attack results for network 32



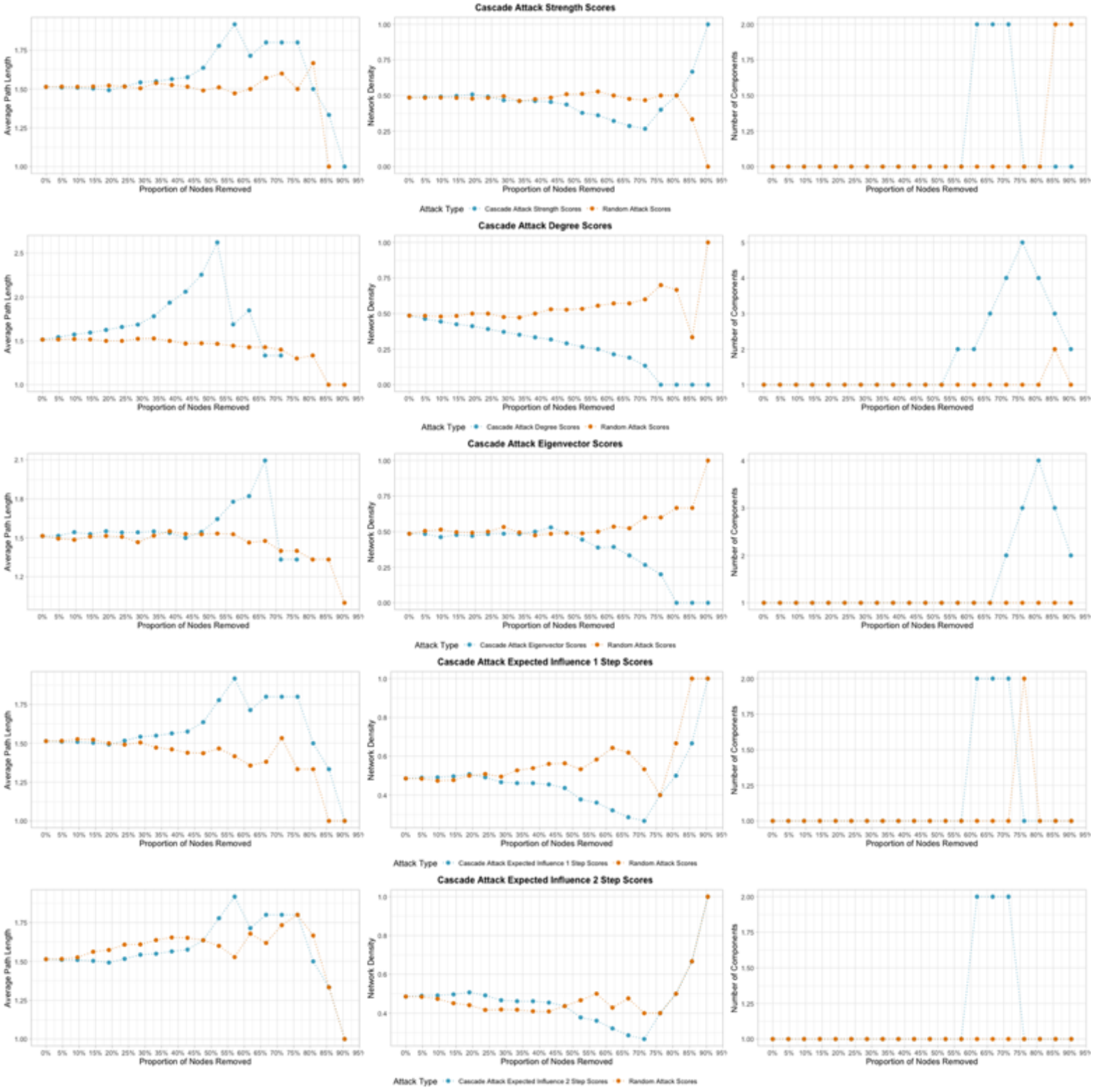
Plots displaying cascade attack results for network 32



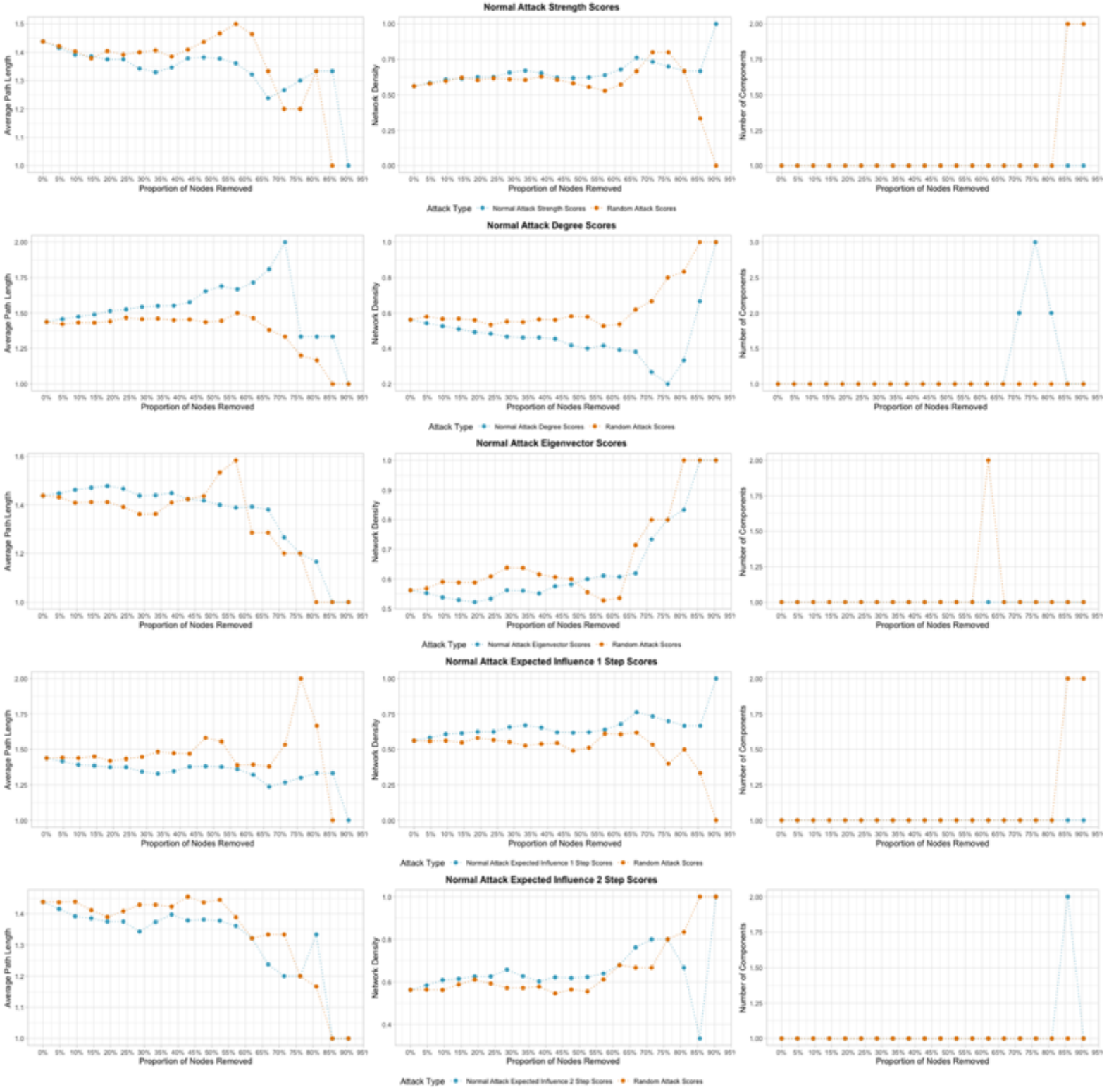
Plots displaying normal attack results for network 33



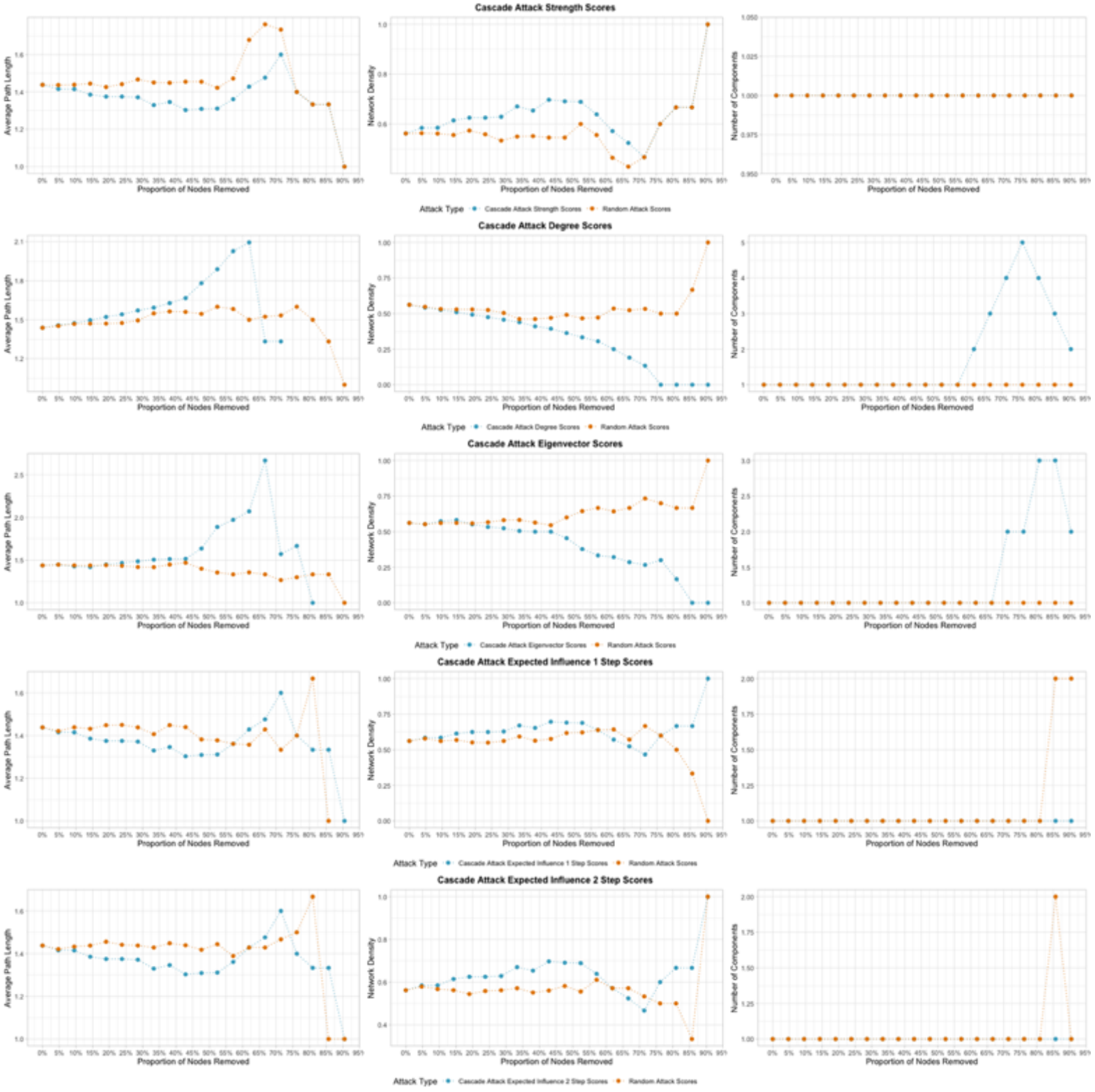
Plots displaying cascade attack results for network 33



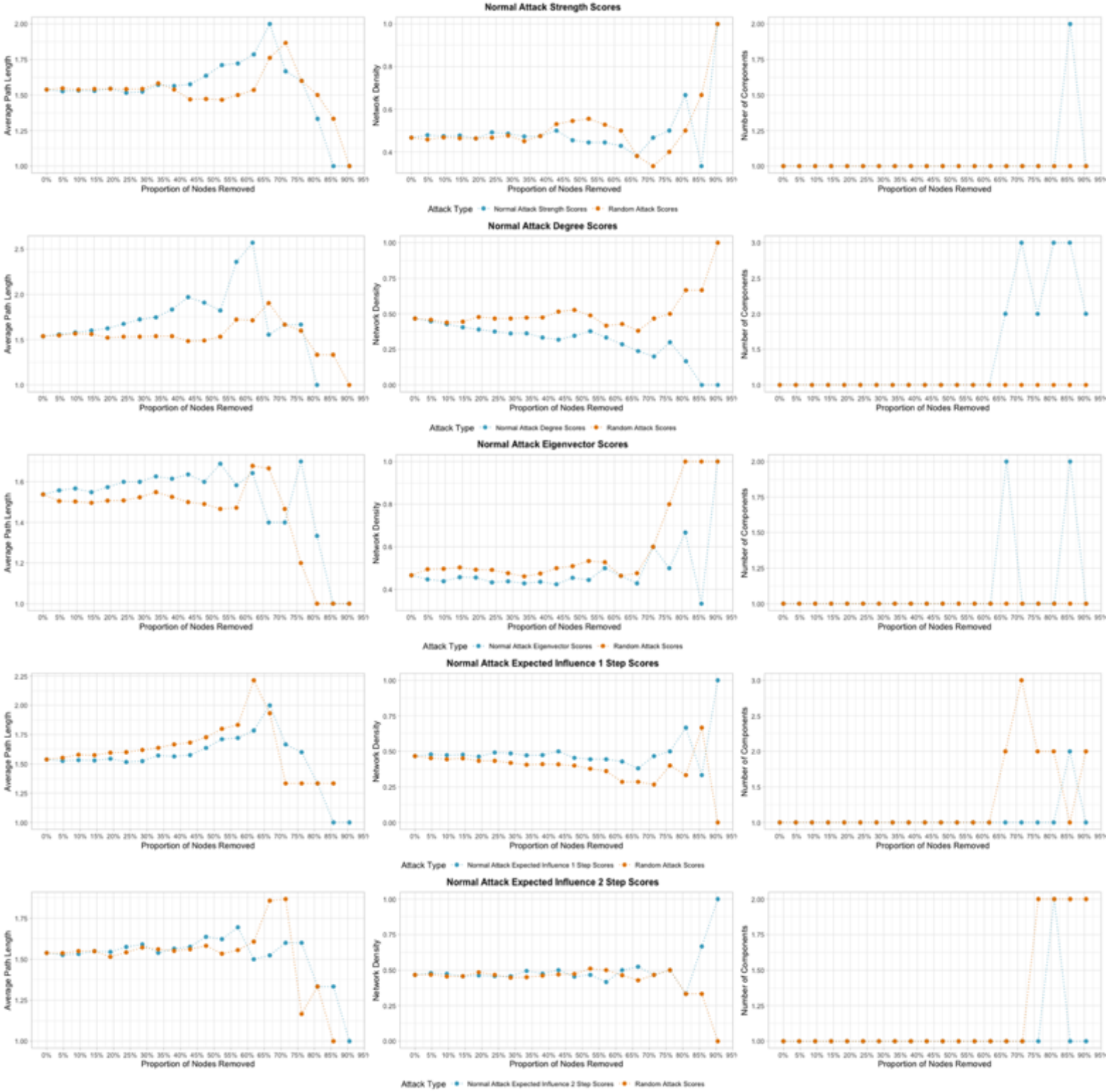
Plots displaying normal attack results for network 34



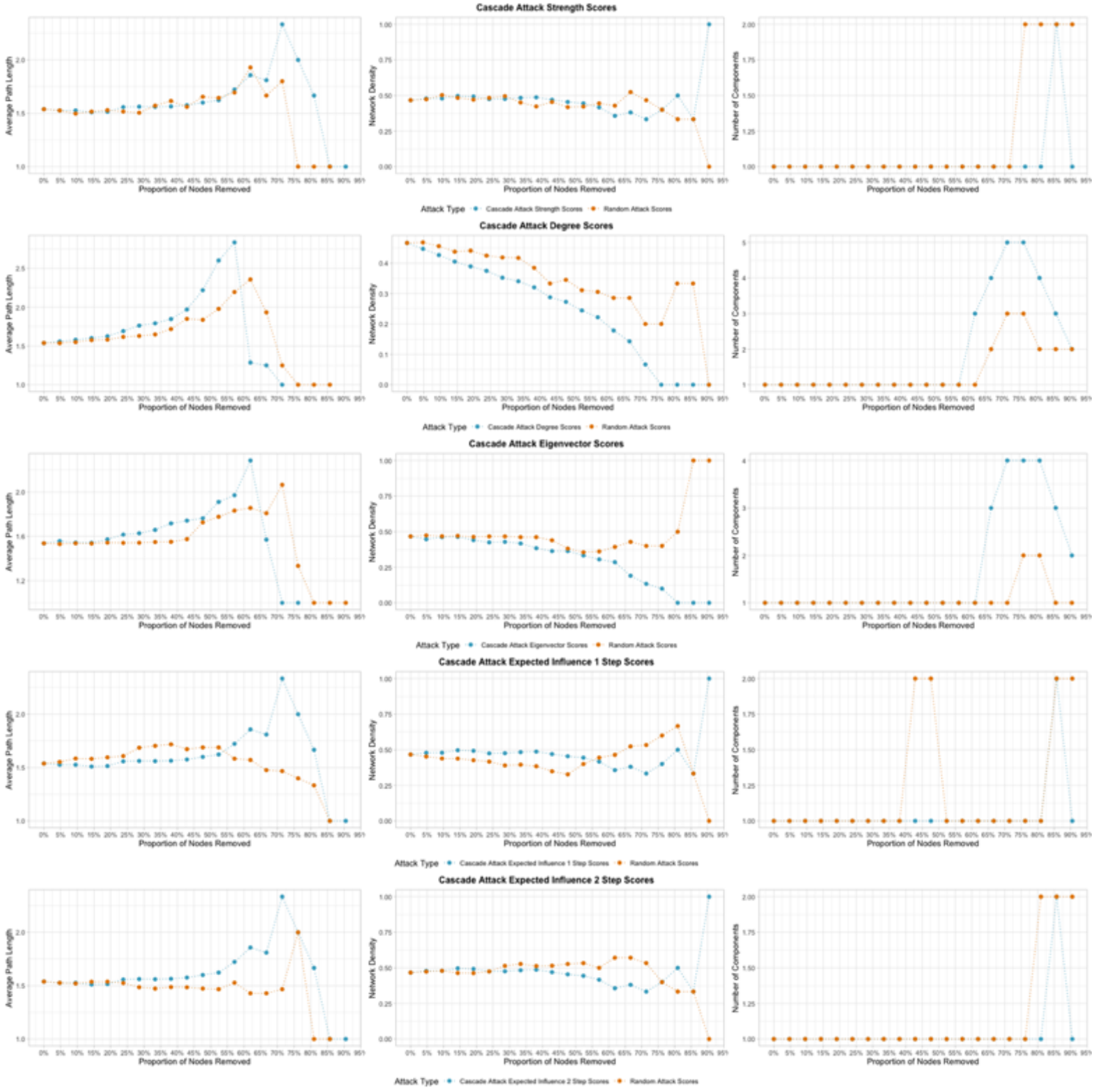
Plots displaying cascade attack results for network 34



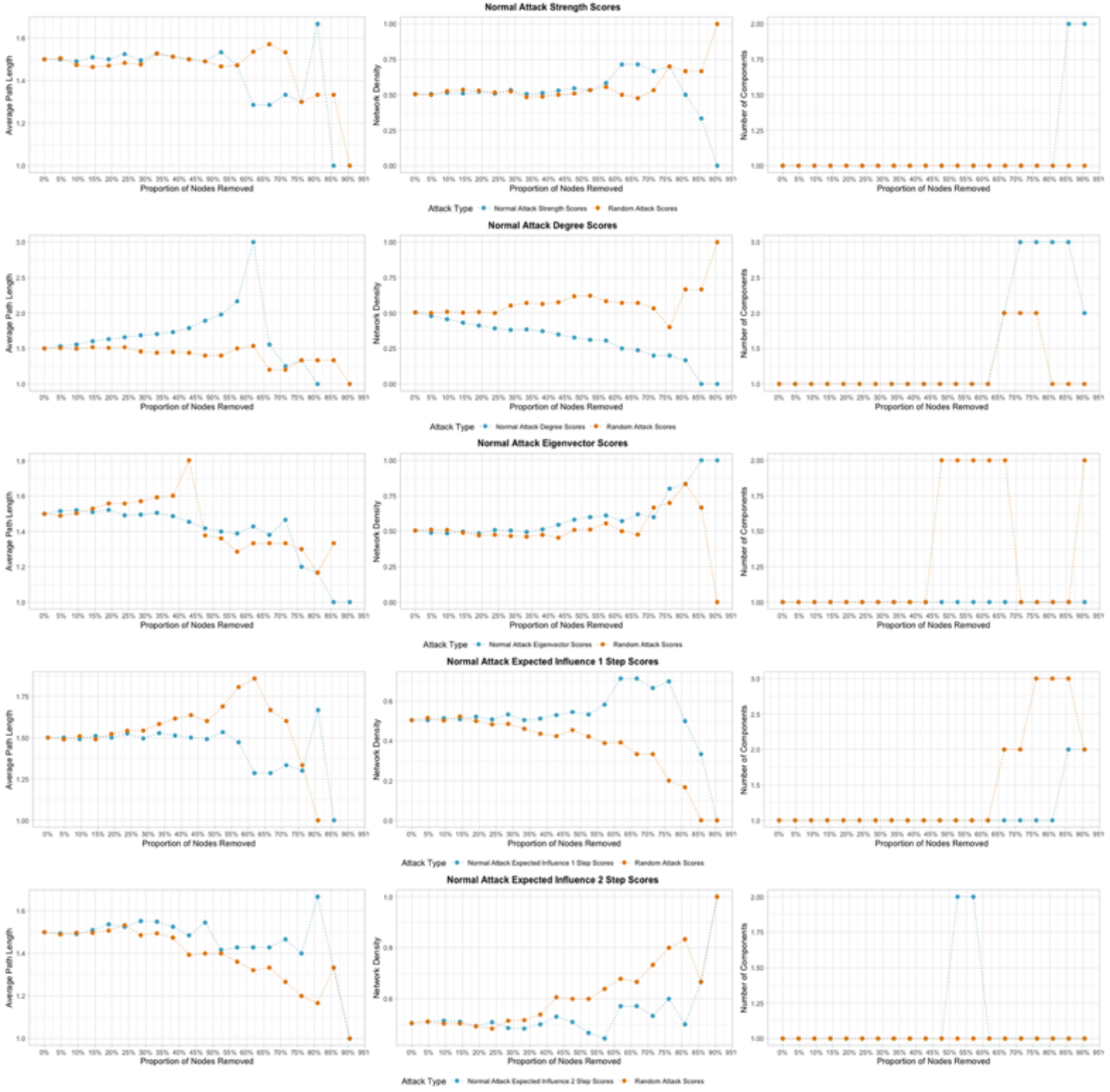
Plots displaying normal attack results for network 35



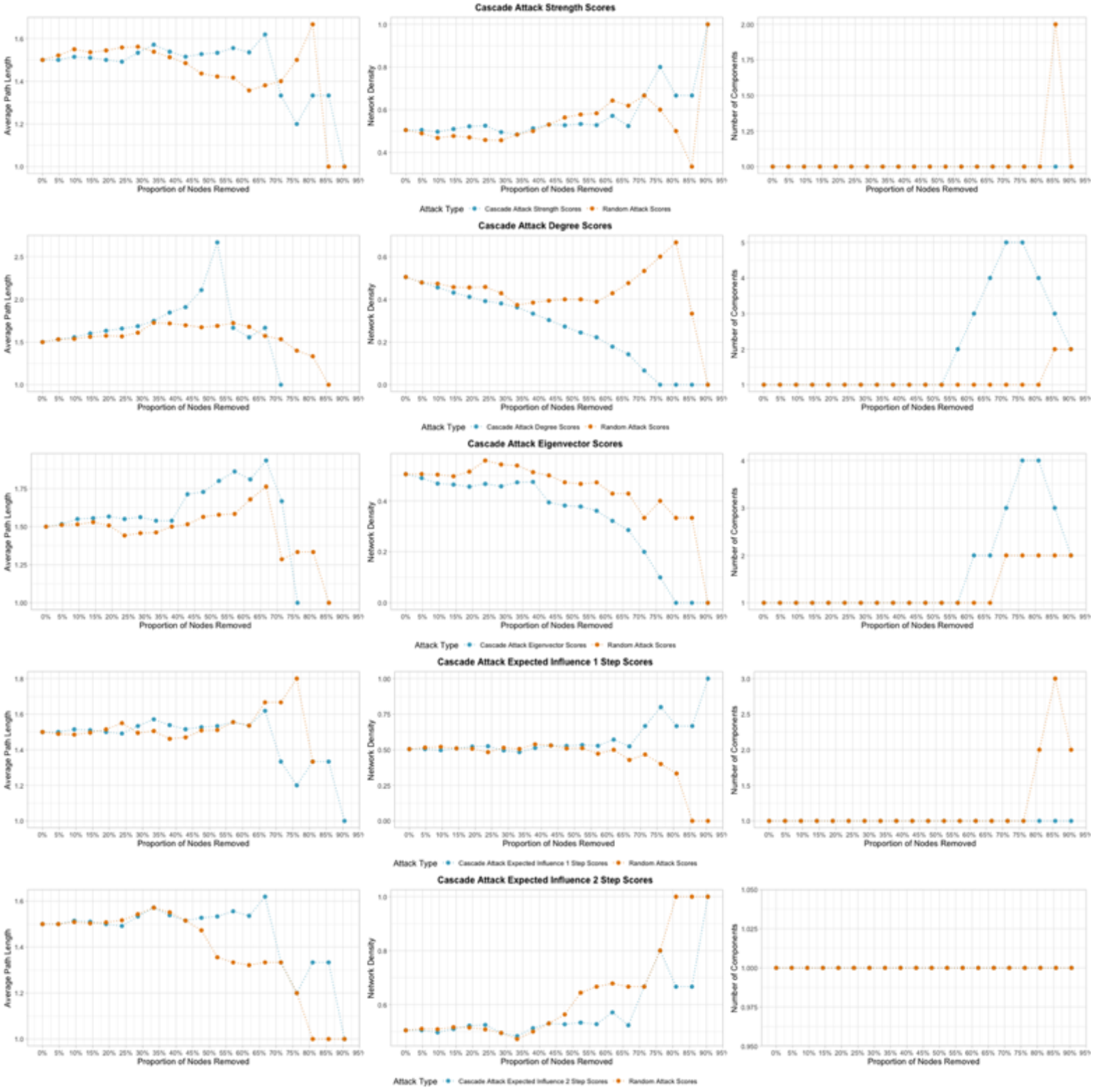
Plots displaying cascade attack results for network 35



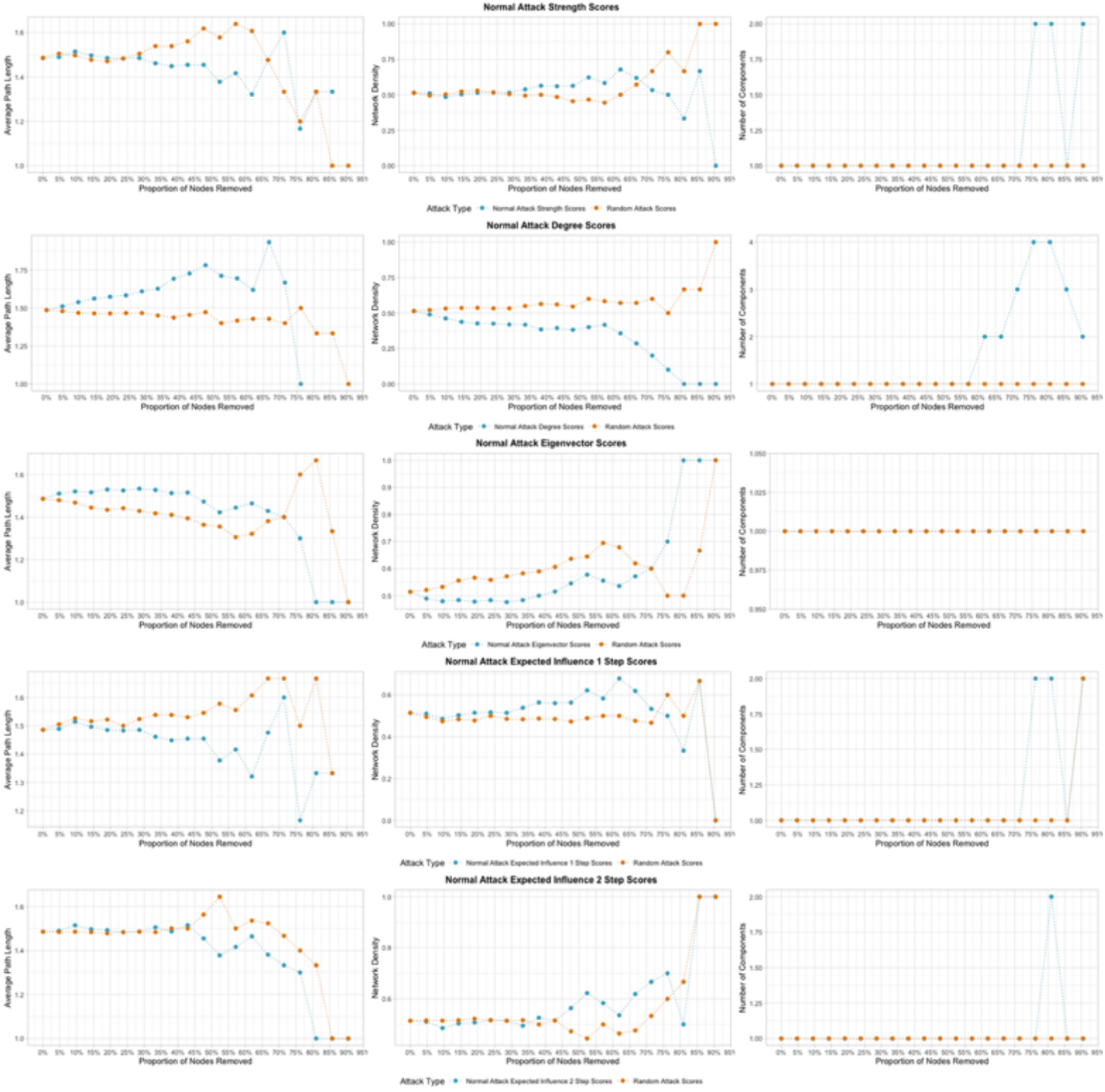
Plots displaying normal attack results for network 36



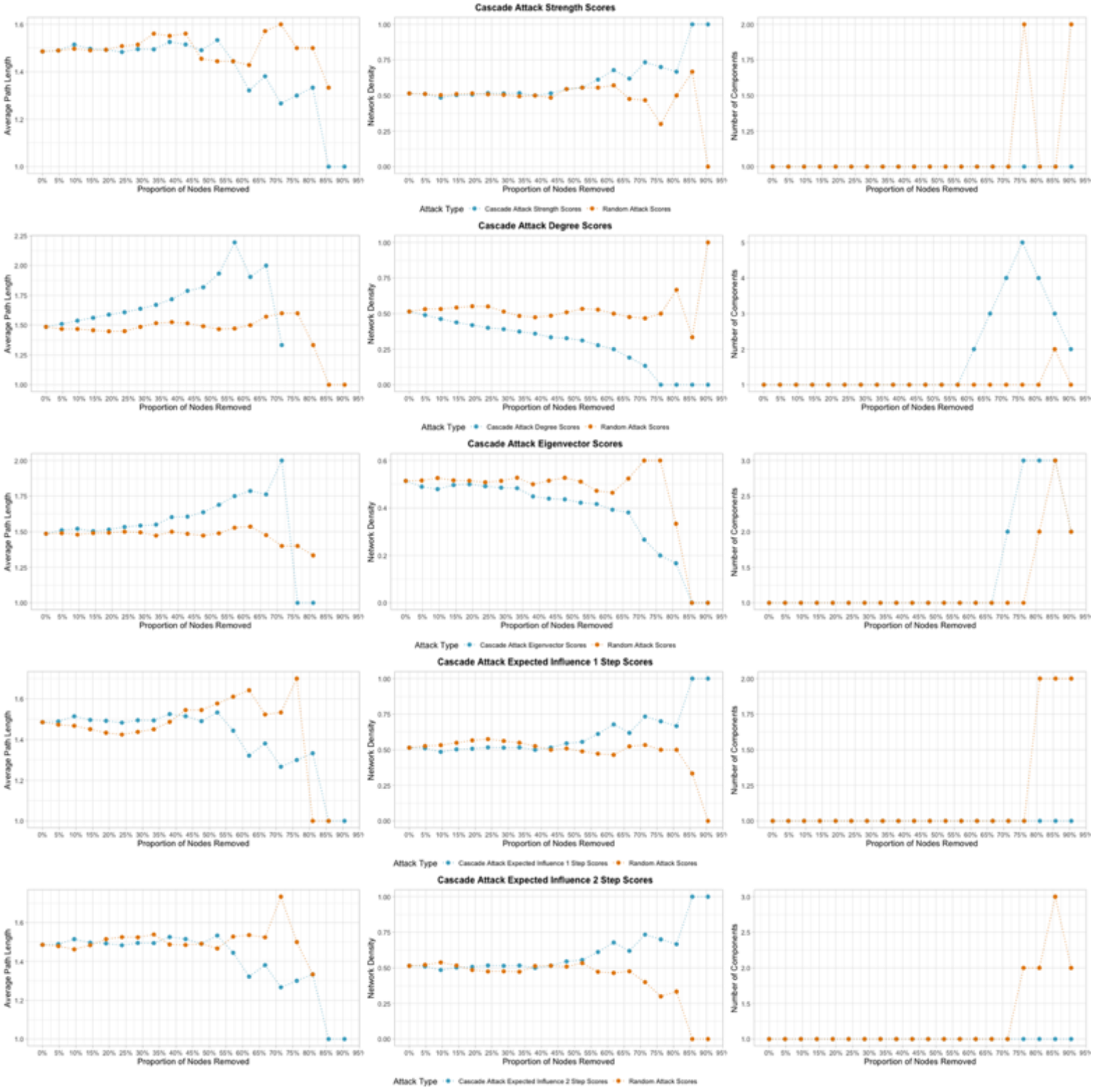
Plots displaying cascade attack results for network 36



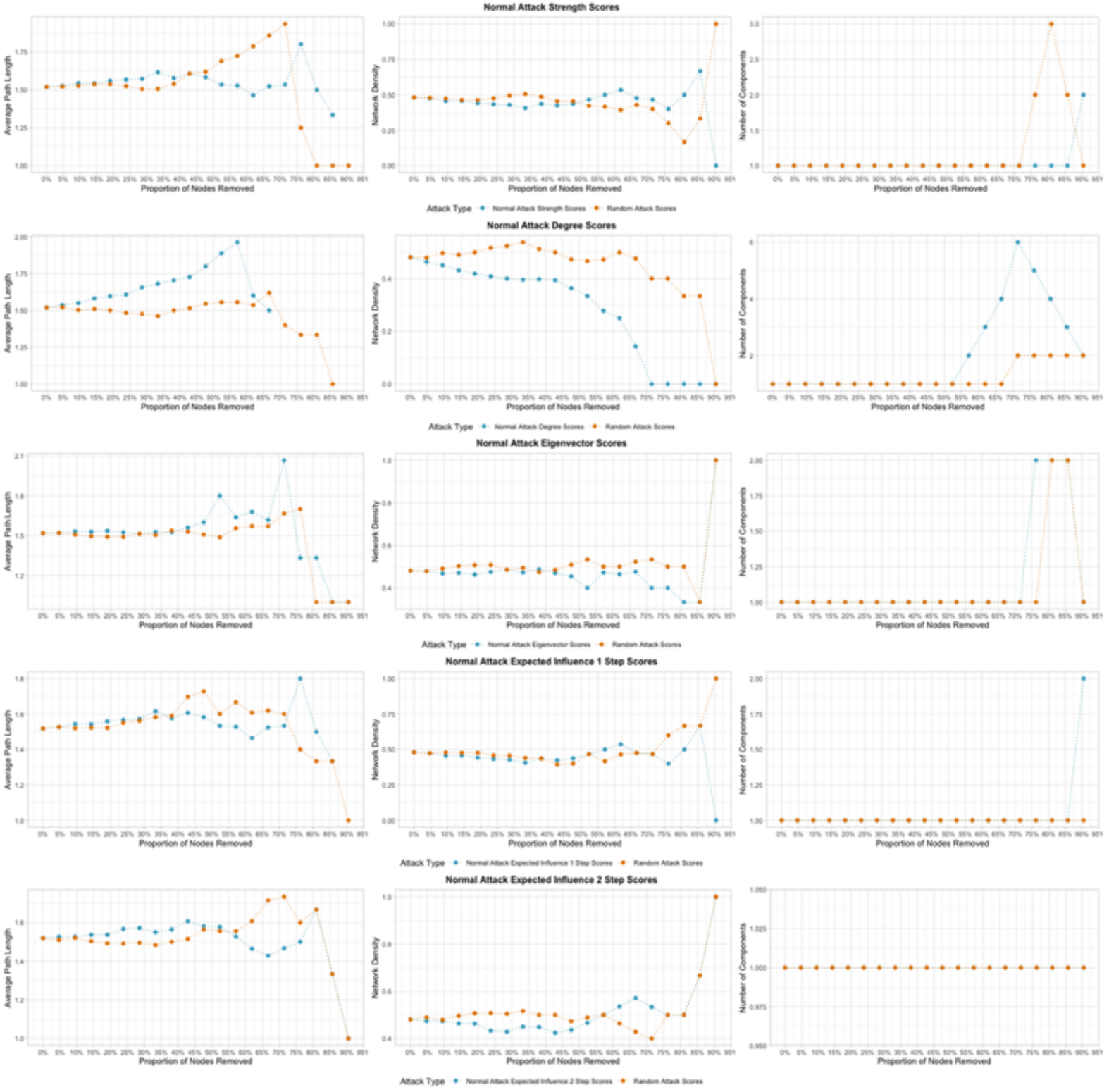
Plots displaying normal attack results for network 37



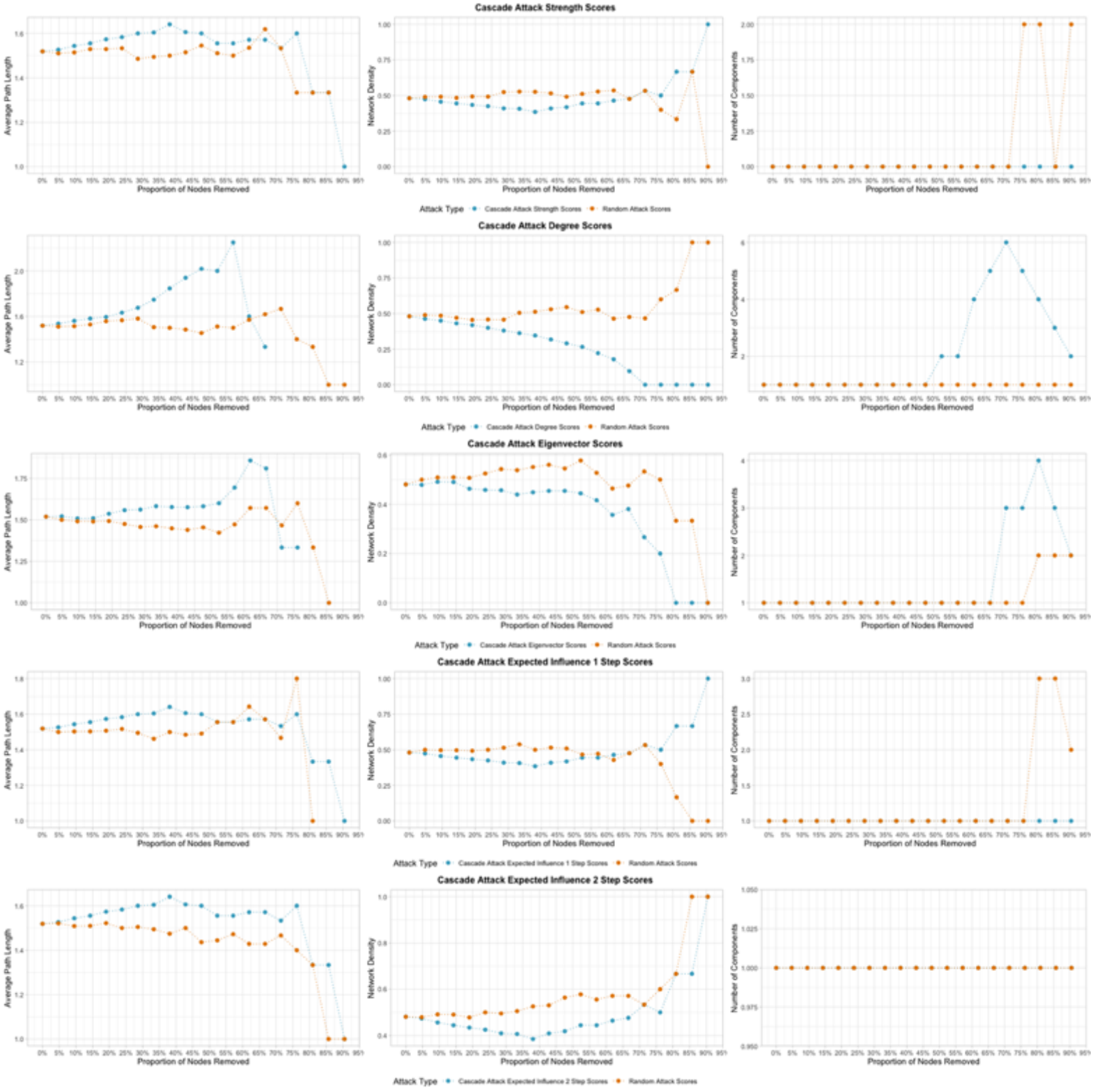
Plots displaying cascade attack results for network 37



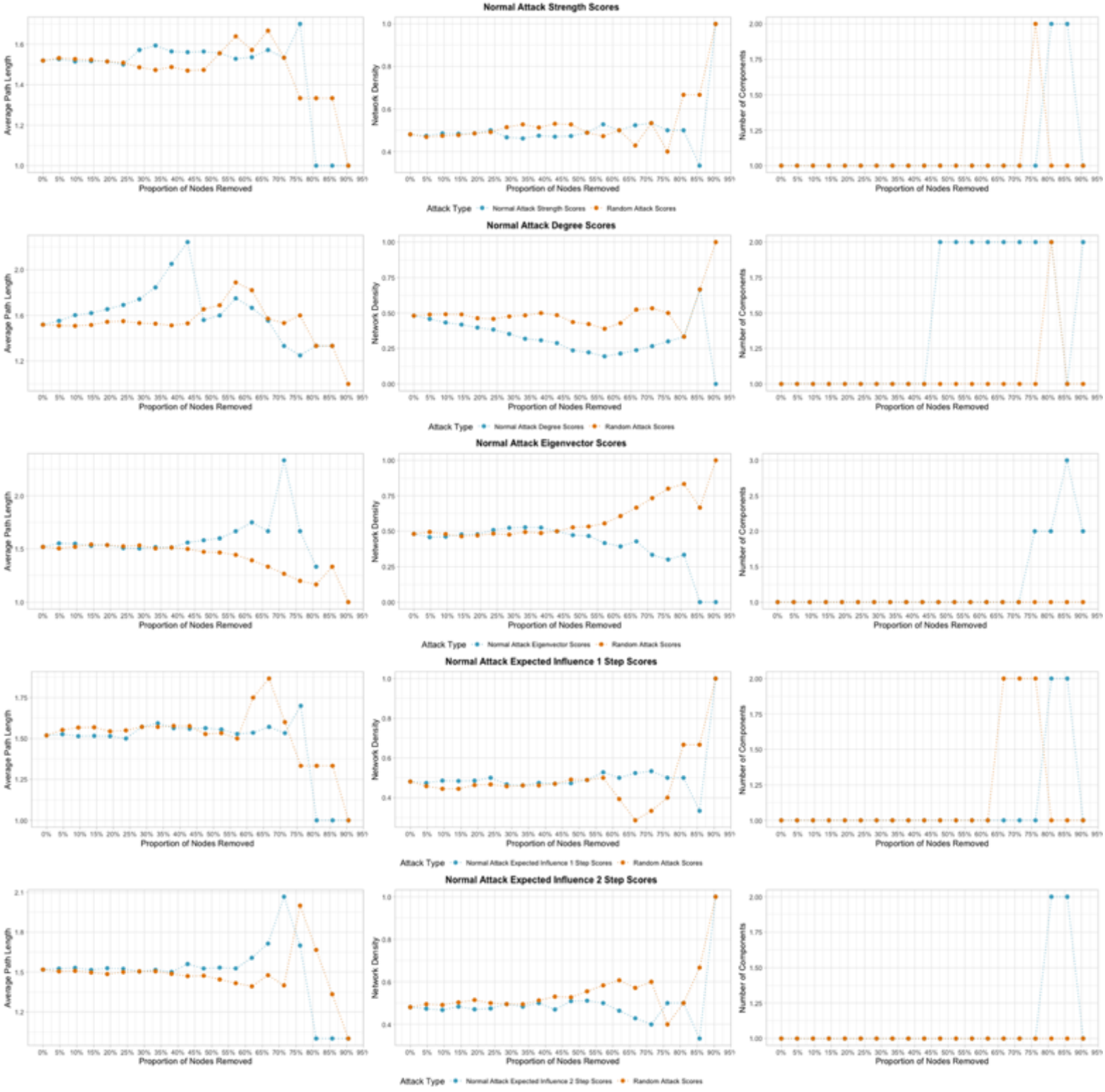
Plots displaying normal attack results for network 38



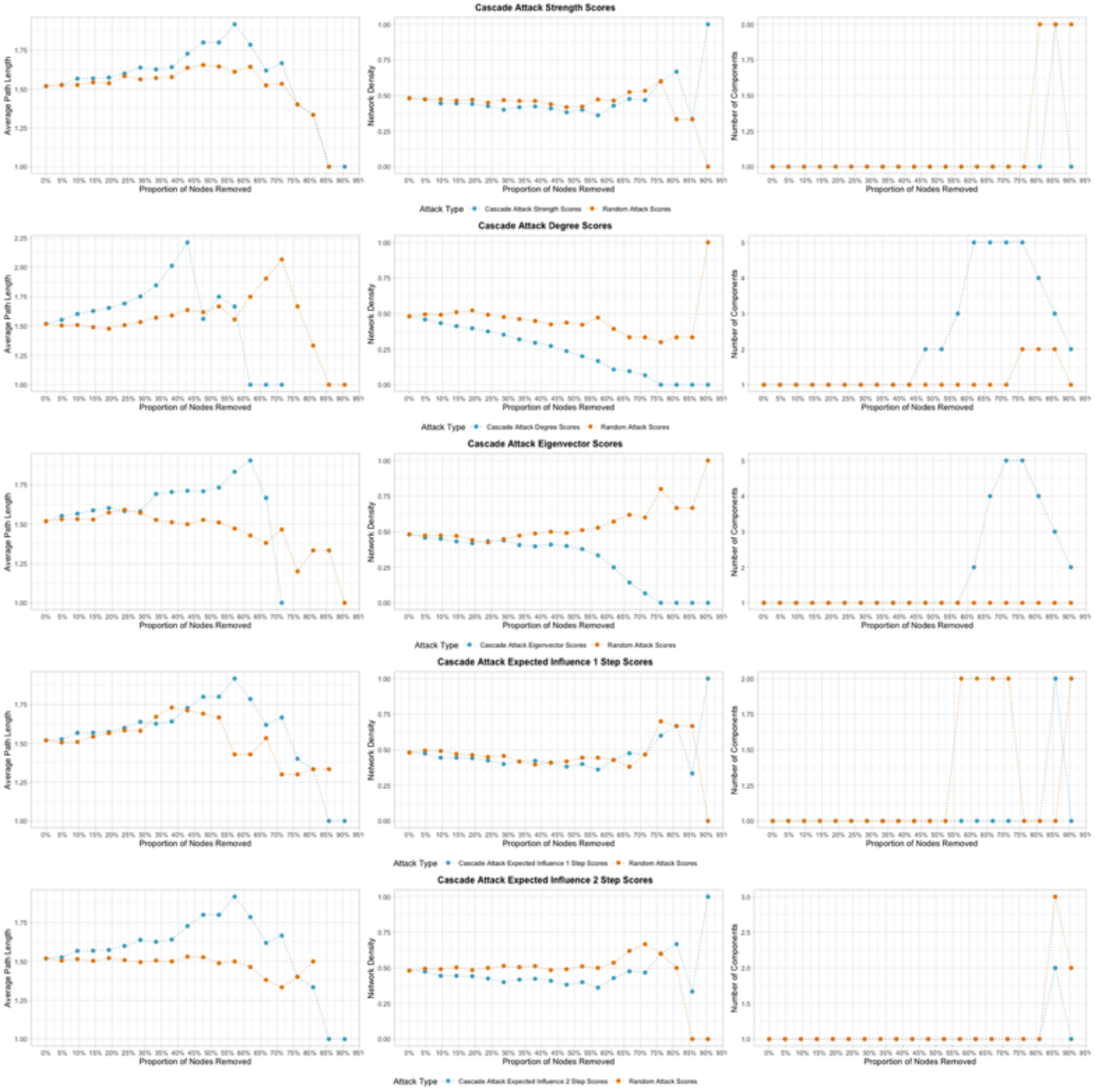
Plots displaying cascade attack results for network 38



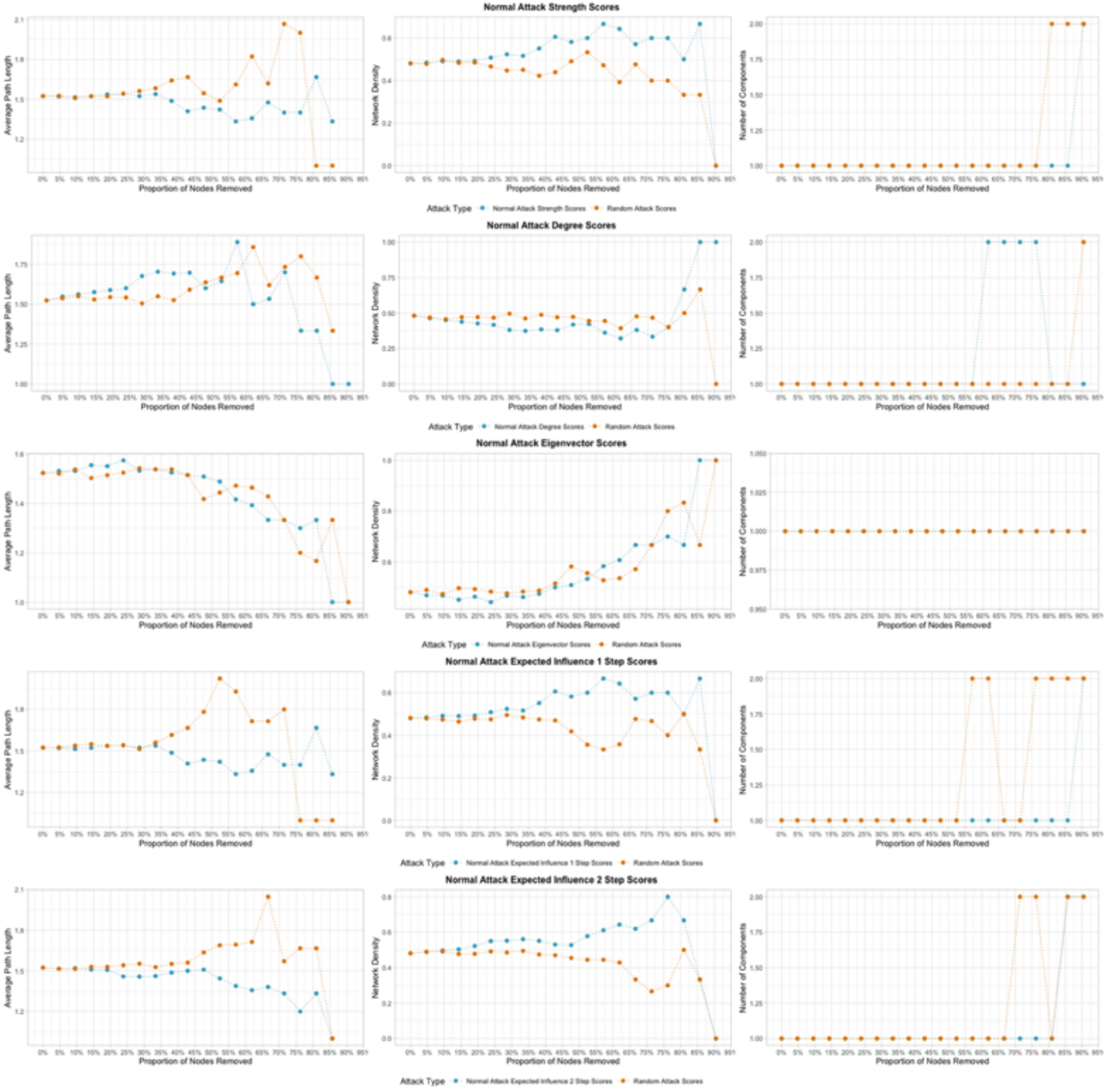
Plots displaying normal attack results for network 39



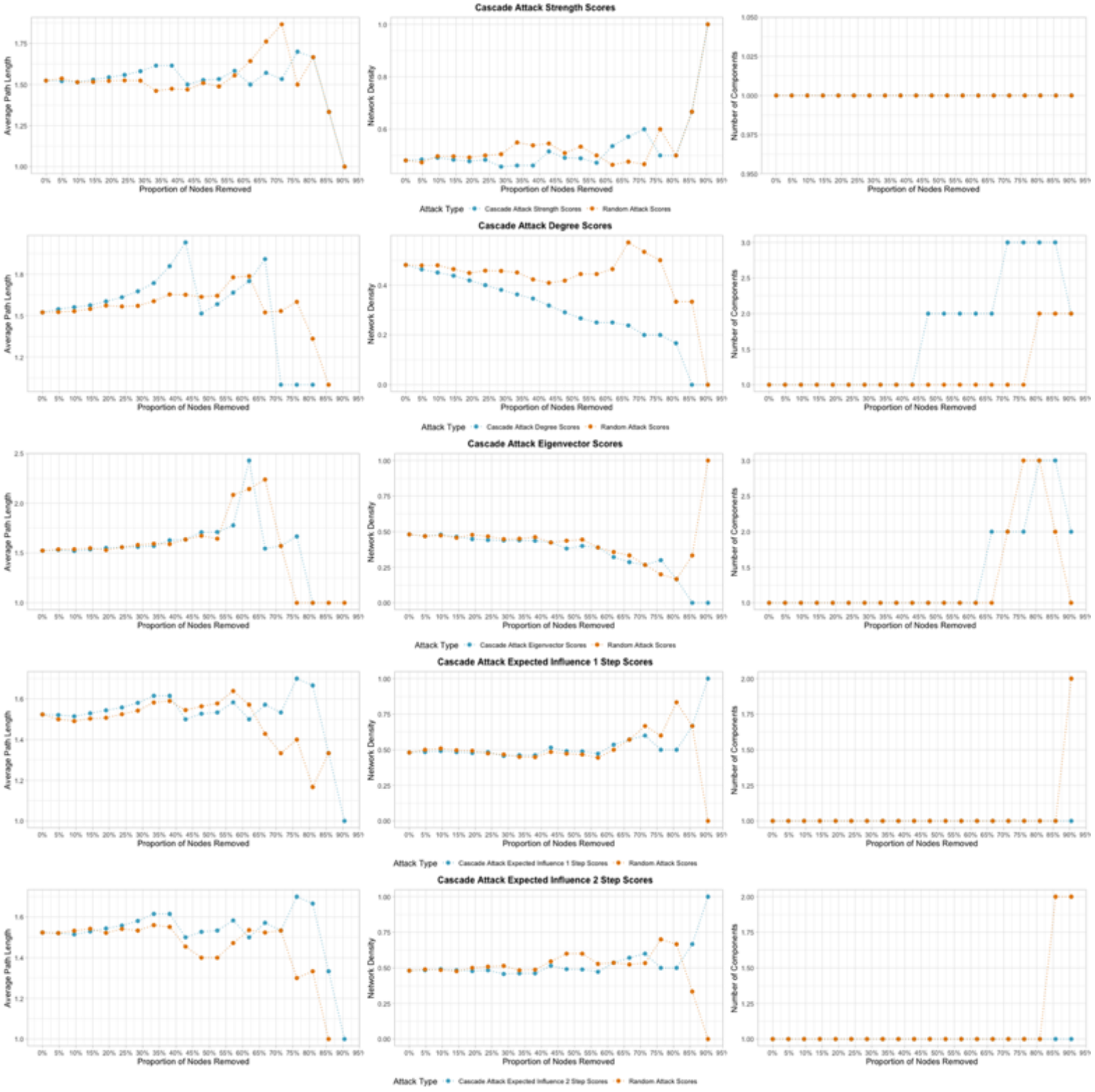
Plots displaying cascade attack results for network 39



Plots displaying normal attack results for network 40



Plots displaying cascade attack results for network 40



Supplementary Materials for Chapter III [1, 2, 3]

The Differential Impact of Processing Speed and Cognitive Flexibility on Cognitive Emotion Regulation Strategies and Depression

Note:

[1] This chapter has been submitted to *Cognition and Emotion* for publication:

Castro, D., Lopes, P., Araújo, A. S., Ferreira, F., Rodrigues, A. R., Cardoso, J., Ferreira-Santos, F., & Ferreira, T. B. (2023). The differential impact of processing speed and cognitive flexibility on cognitive emotion regulation strategies and depression [Manuscript submitted to publication].

[2] Supplementary materials of this paper are available in the Chapter III of the Appendix.

[3] Code to reproduce the analysis the analysis can be found at https://osf.io/c729f/

Index

1. Stability Plots Mixed Graphical Model

1.1. Edge-weight Accuracy

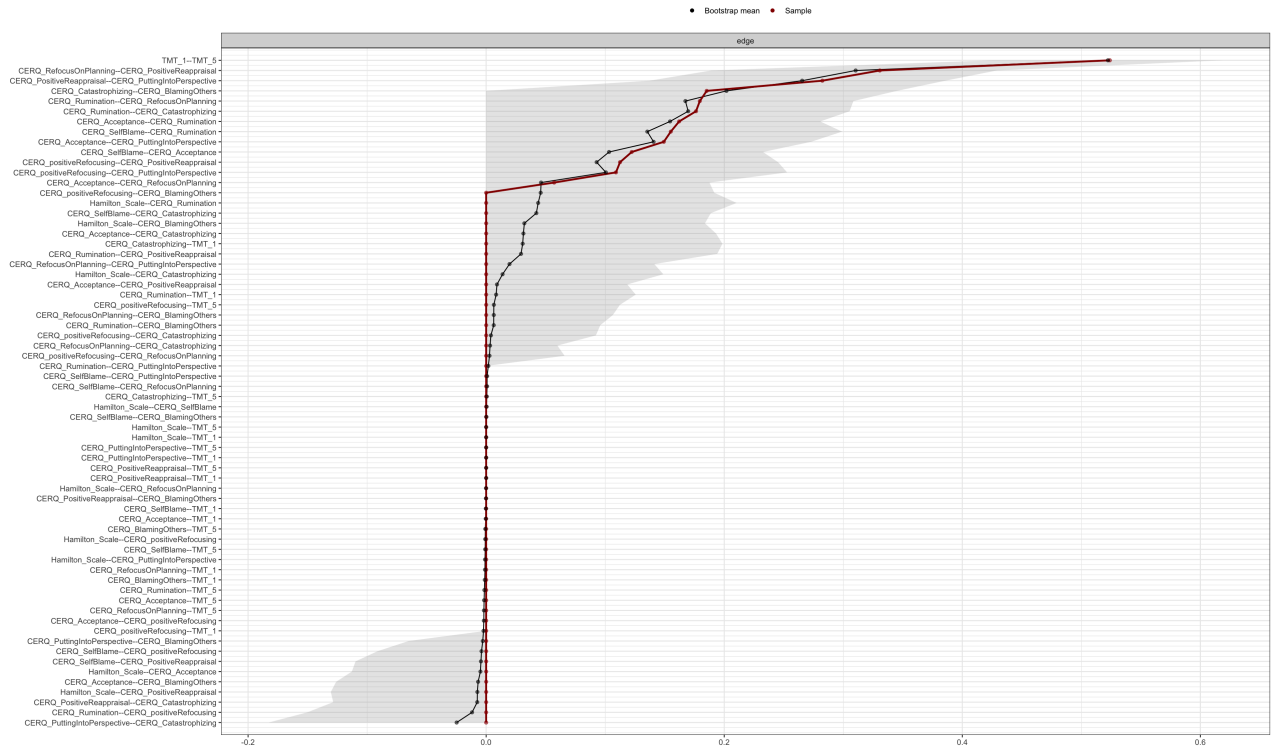


Figure S1. Bootstrapped confidence intervals calculated for the estimated edge-weights in the network. The red line represents the sample values, and the gray area denotes the bootstrapped confidence intervals. Each horizontal line corresponds to an edge in the network, ordered from the highest to the lowest edge-weight.

1.2. Centrality Stability

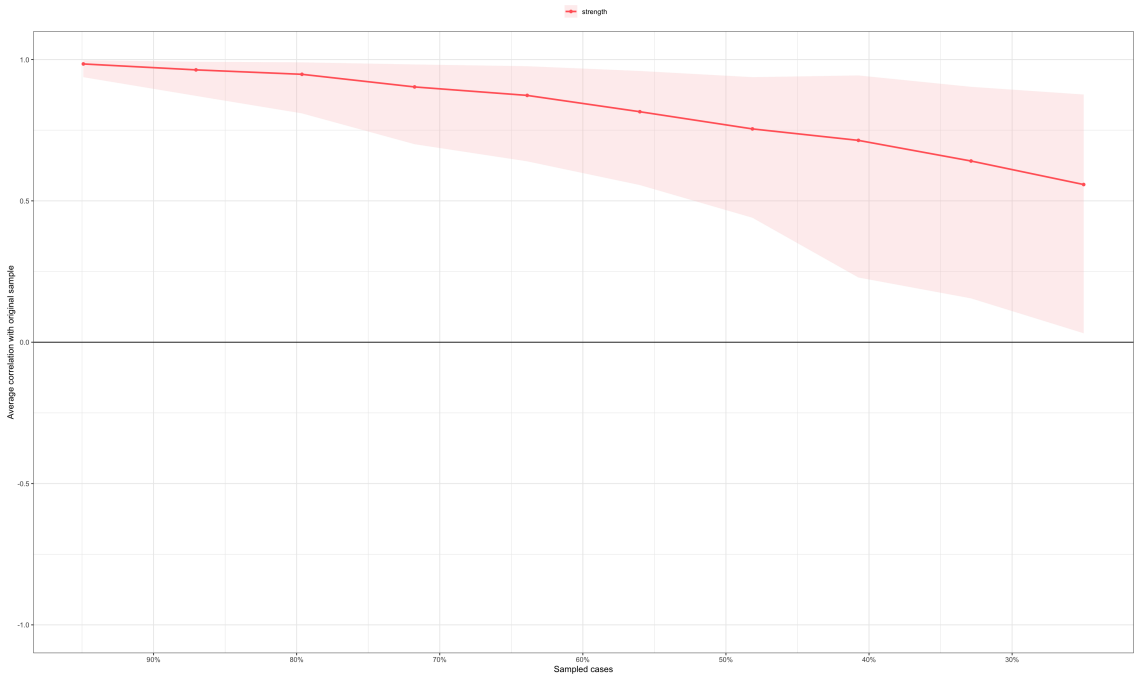


Figure S2. The mean correlations between centrality indices of networks obtained by sampling with individuals omitted and the original sample were computed. The lines depict the means, while the areas represent the range from the 2.5th quantile to the 97.5th quantile.

1.3. Bootstrapped difference tests

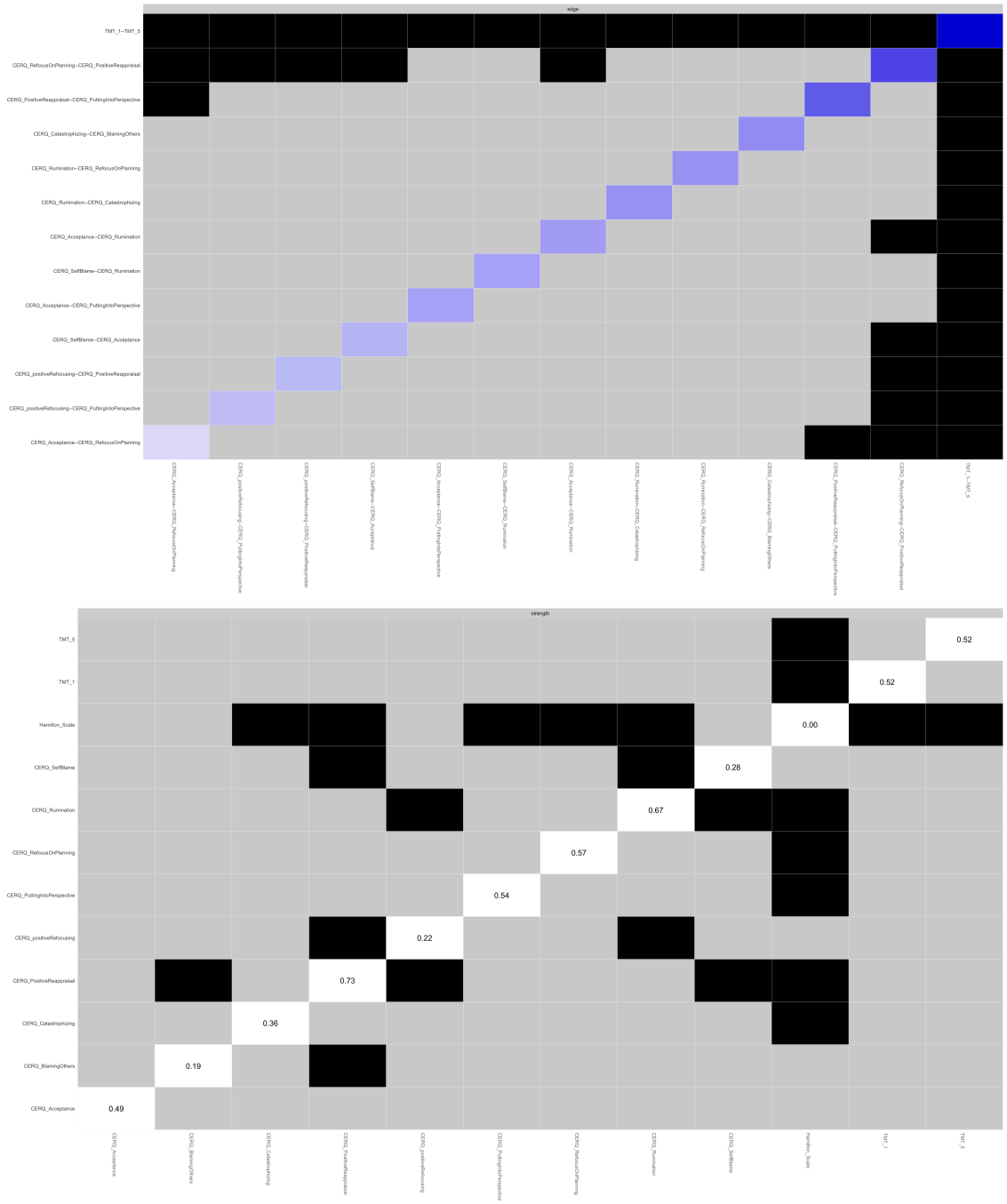


Figure S3. Bootstrapped difference tests (α = 0.05) were conducted between non-zero edge-weights in the estimated MGM network (above) and the node strength of the 12 network nodes (below). Nodes or edges enclosed in gray boxes signify no significant differences, while those in black boxes indicate significant differences.

2. Stability Plots Relative Importance Network

2.1. Edge-weight Accuracy

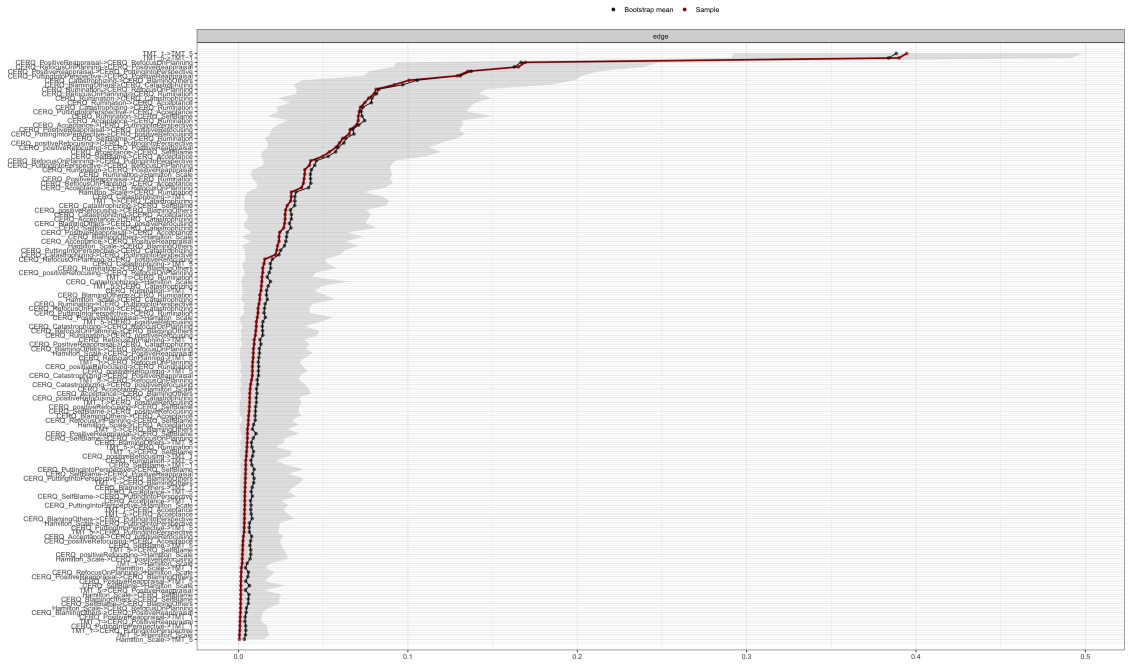


Figure S4. Bootstrapped confidence intervals calculated for the estimated edge-weights in the relative importance network. The red line represents the sample values, and the gray area denotes the bootstrapped confidence intervals. Each horizontal line corresponds to an edge in the network, ordered from the highest to the lowest edge-weight.

2.2. Centrality Stability

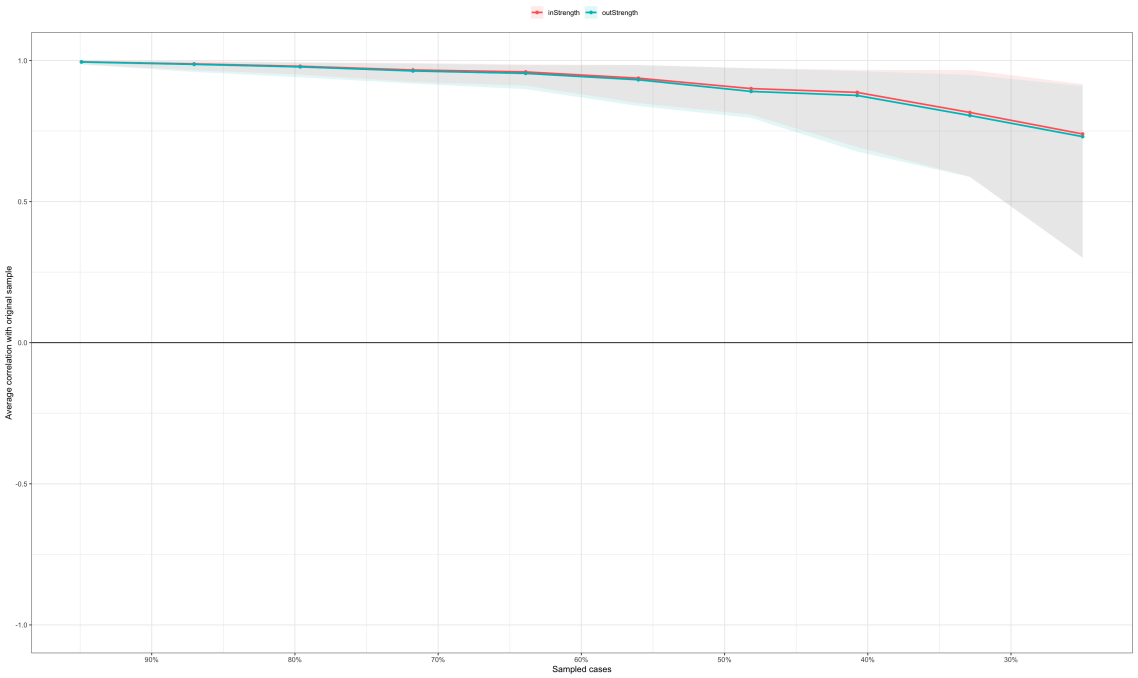
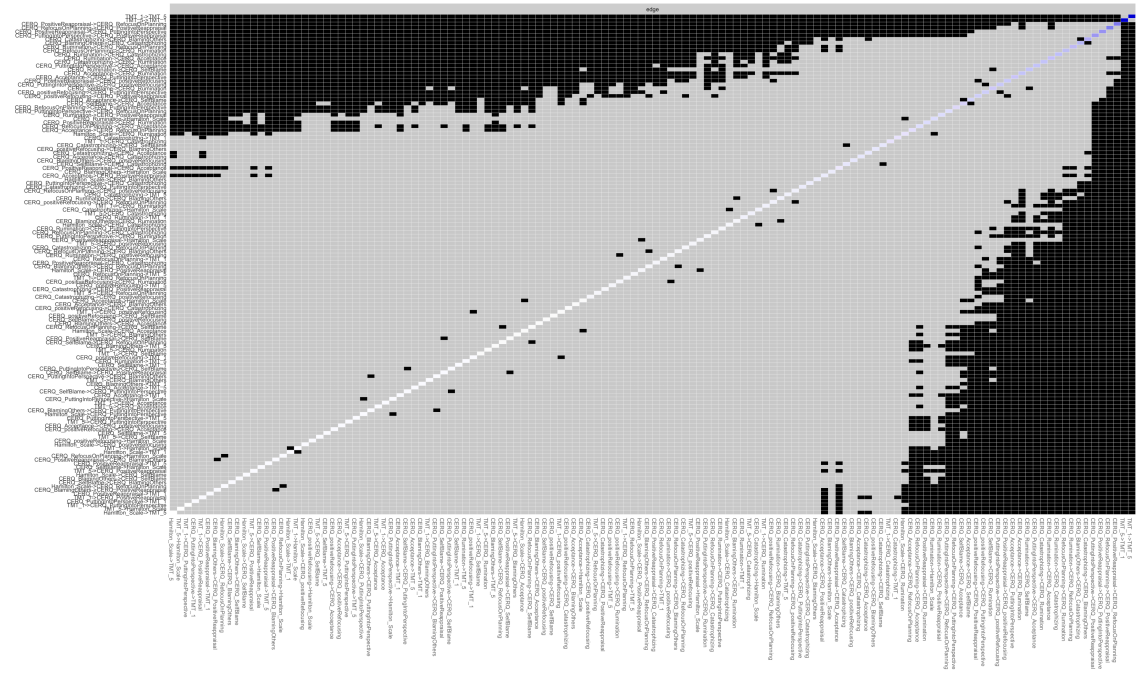


Figure S5. The mean correlations between centrality indices of networks obtained by sampling with individuals omitted and the original sample were computed. The lines depict the means, while the areas represent the range from the 2.5th quantile to the 97.5th quantile.

2.3. Bootstrapped difference tests

A)



B)

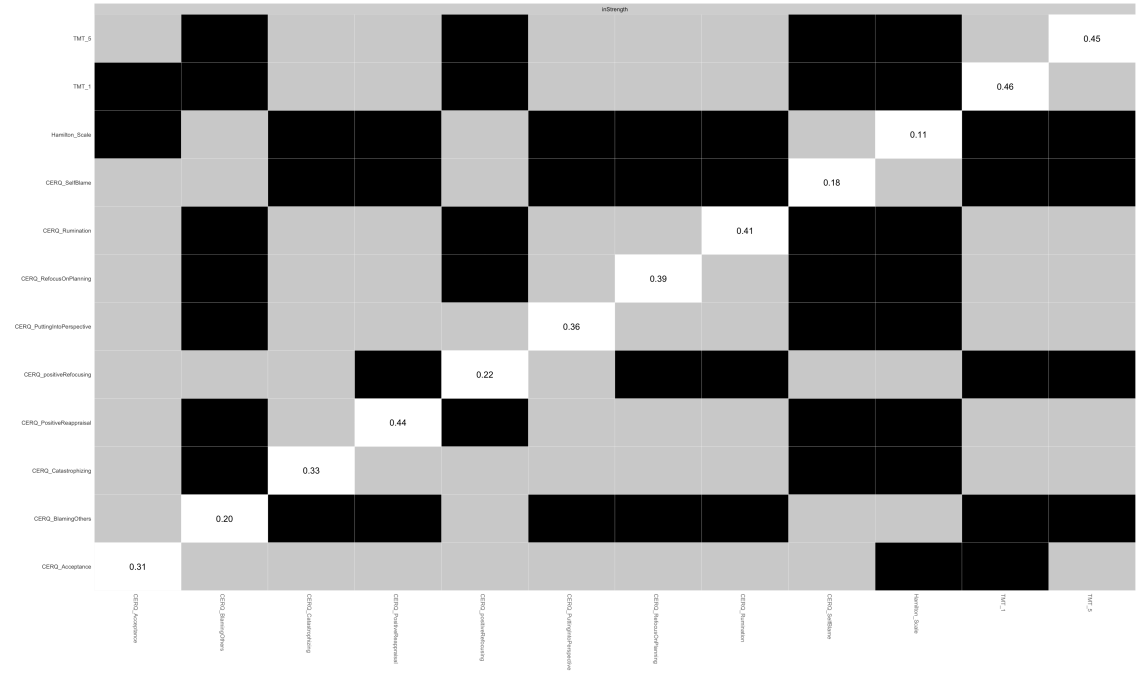


Figure S6. Bootstrapped difference tests (α = 0.05) between non-zero edge-weights in the estimated relative importance network (above) and the node in-strength of the 12 network nodes (below). Nodes or edges enclosed in gray boxes signify no significant differences, while those in black boxes indicate significant differences.

2.3. Bootstrapped difference tests

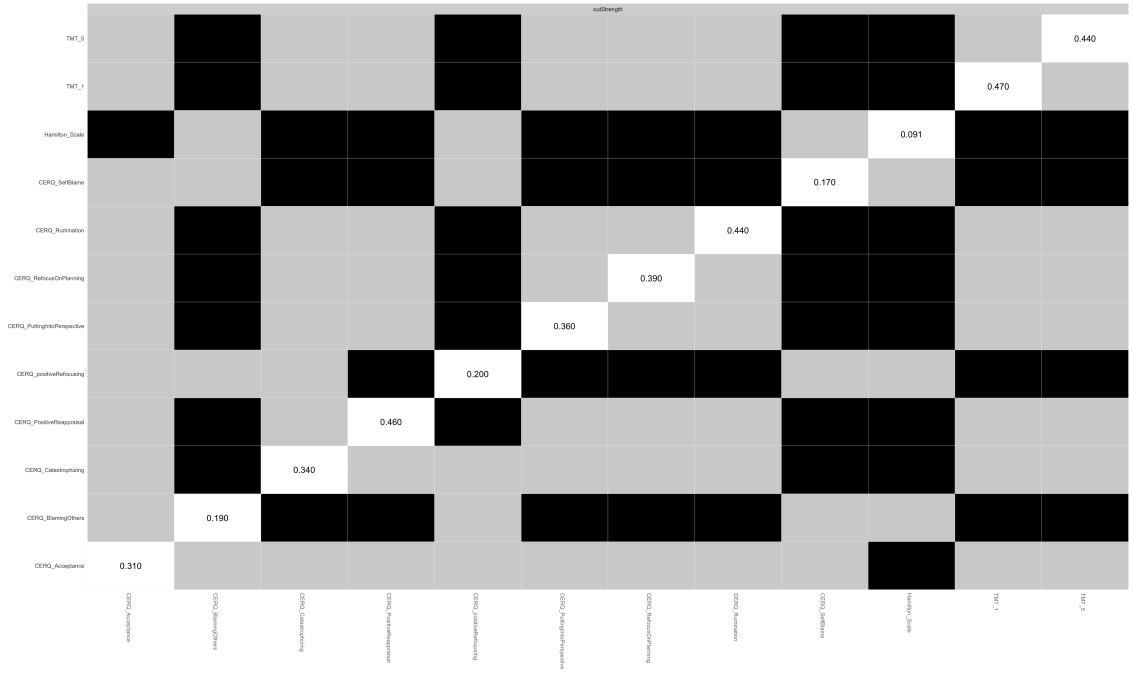


Figure S7. Bootstrapped difference tests (α = 0.05) between non-zero edge-weights in the estimated relative importance network (above) and the node out-strength of the 12 network nodes (below). Nodes or edges enclosed in gray boxes signify no significant differences, while those in black boxes indicate significant differences.