Empirical Article

Comparison of the symptom networks of long-COVID and chronic fatigue syndrome: From modularity to connectionism

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The objective was to compare the symptom networks of long-COVID and chronic fatigue syndrome (CFS) in conjunction with other theoretically relevant diagnoses in order to provide insight into the etiology of medically unexplained symptoms (MUS). This was a cross-sectional comparison of questionnaire items between six groups identified by clinical diagnosis. All participants completed a 65-item psychological and somatic symptom questionnaire (GSQ065). Diagnostically labelled groups were long-COVID ($N = 107$), CFS ($N = 254$), irritable bowel syndrome (IBS, $N = 369$), fibromyalgia ($N = 1{,}127$), severe asthma ($N = 100$) and healthy group ($N = 207$). The 22 symptoms that best discriminated between the six groups were selected for network analysis. Connectivity, fragmentation and number of symptom clusters (statistically related symptoms) were assessed. Compared to long-COVID, the symptom networks of CFS, IBS and fibromyalgia had significantly lower connectivity, greater fragmentation and more symptom clusters. The number of clusters varied between 9 for CFS and 3 for severe asthma, and the content of clusters varied across all groups. Of the 33 symptom clusters identified over the six groups 30 clusters were unique. Although the symptom networks of long-COVID and CFS differ, the variation of cluster content across the six groups is inconsistent with a modular causal structure but consistent with a connectionist (network, parallel distributed processing) biological basis of MUS. A connectionist structure would explain why symptoms overlap and merge between different functional somatic syndromes, the failure to discover a biological diagnostic test and how psychological and behavioral interventions are therapeutic.

Key words: Network, long-COVID, chronic fatigue syndrome, fibromyalgia, asthma.

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INTRODUCTION

The term medically unexplained symptom (MUS) is used to describe symptoms where there is no consensus about the biological cause or mechanism. Functional somatic syndromes such as irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS) are defined and diagnosed by MUS. MUS also feature in many diseases with or without formal diagnosis of a functional somatic syndrome (Nimnuan, Hotopf & Wessely, 2001).

People who have recovered from COVID sometimes experience long lasting symptoms described as long-COVID. Severe disabling fatigue is a primary symptom of long-COVID and a primary symptom of CFS. Two opposing positions have emerged: that long-COVID and CFS are the same and that they are different, based on evidence. Support for the position that they are the same comes from evidence that neither can be explained in terms of pathophysiology, that they are both polysymptomatic and the additional symptoms are similar, that infection is a risk factor for CFS, and that they share some similarities in systemic biological abnormalities (Ceban, Ling, Lui *et al*., 2022; González-Hermosillo, Martínez-López, Carrillo-Lampón *et al*., 2021; Tate *et al*., 2022; Wong & Weitzer, 2021; Yang, Chang, Yang, Pariante & Su, 2022). Importantly, psychological treatments such as mindfulness are helpful for both conditions (McKechnie, 2023).

Support for the position that long-COVID and CFS are different comes from evidence that infection is only a risk factor for CFS whereas COVID infection is a necessary (but not sufficient) condition for long-COVID, that there is evidence of organ damage in the case of long- only (Gyöngyösi, Alcaide, Asselbergs *et al*., 2023; Kersten, Baumhardt, Hartveg *et al*., 2021) and that studies on recovery suggest that the rate of recovery from long-COVID is better than that of CFS (Astin, Banerjee, Baker *et al*., 2023; Mizrahi, Sudry, Flaks-Manov *et al*., 2023; Nacul, O'Boyle, Palla *et al*., 2020; Vaes, Goërtz, Van Herck *et al*., 2021).

The similar versus different debate over CFS and long-COVID parallels a wider and longer debate over whether functional somatic syndromes should be considered the same because they have a common psychological cause (Wessely, Nimnuan & Sharpe, 1999; White, 2010) or whether they should be considered different because they have different biological causes. This wider debate is influenced by negative social attitudes toward syndromes because of their association with a psychological cause (Stone, Wojcik, Durrance *et al*., 2002). Long-COVID was originally termed post-COVID syndrome, but the name was changed in response to pressure from patients to have a label that did include the word "syndrome" (Byrne, 2022). The negative attitude to mental illness stems, in part, from an erroneous philosophy of dualism, the assumption that minds and bodies are distinct entities, and that mental illness is an illness of the mind entity and physical illness is an illness of the body entity (i.e., disease). Modern science rejects dualism in favor of a materialist and monist assumption according to which only the physical world exists, and mind is a property of the body. Suffering is a psychological phenomenon caused by mental or somatic symptoms that are properties of the physical body irrespective of

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the labels of mental illness, syndrome or disease. Psychological interventions alter the biology of the body through a neurological route. The difference between syndromes versus diseases is not that one is biological and the other is not, but that one has been explained in terms of biology and the other has not. There must be a reason why somatic symptoms can be explained only by psychology and not biology and why psychological interventions have a beneficial effect on the underlying biology. The data presented in this paper provides a possible explanation for the role of psychology in functional somatic syndromes.

Research into the biological basis of CFS and other functional somatic syndromes has been based on the assumption that they are diseases, for example, that CFS is caused by a persisting virus (Hanson, 2023), suppressed immune and metabolic activity (Uhde, Indart, Green *et al*., 2023), autonomic disfunction (Malkova & Shoenfeld, 2023) or central nervous system processing error (Boomershine, 2015). Diseases are defined by a biological abnormality, such as a pathophysiology, which is unique to the particular disease, and provides the basis for diagnosis. The science of nosology (Zachar & Kendler, 2017) and the disease concept are based on an assumption of modularity where each disease represents a different type of abnormality. Each disease is a different and distinct module. Diseases do not merge into each other. From this perspective, the body is modular like a car where different parts have different functions and, like a car, diseases are caused by faults that are specific to some part. The problem with functional somatic syndromes is that the observed biological abnormalities (immune, metabolic, autonomic, central nervous system) merge with other functional somatic syndromes and in many cases with diseases. None provide a unique defining pathophysiology. The disease concept of modularity has motivated the search for a biological basis of CFS based on the assumption that there must be some specific pathophysiology that is unique to CFS and can be used as a test of differential diagnosis from other functional somatic syndromes or diseases.

However, pathology does not have to be modular. In a network or connectionist system, information is encoded by the connection strengths between the nodes of the network. Informational error would therefore be distributed over the network (Ellis & Humphreys, 1999). If pathology was caused by informational error in a biological network, then pathology would be distributed and take the form of multiple small differences in the connection strengths between the nodes of the network represented by multiple pathophysiologies (Hyland, 2011). This distributed format would mean that different types of informational error would merge into each other as they share the same network. In this case pathology would not be modular and nor would it have the specificity assumed by the disease concept. Additionally, the distributed form of the pathology over the network would make biological explanation difficult because there would be multiple abnormalities that could be shared between different pathologies. However, the idea of network pathology is not well accepted, and this study was designed to examine the relationship between long-COVID and CFS within the conventionally accepted modularity paradigm, that is, that they are different types of unknown disease. The alternative was considered only when the data failed to conform to the assumption of modularity.

Symptom network analysis provides a way of comparing the relationship between symptoms rather the symptoms themselves (Borsboom & Cramer, 2013). Symptom clusters are formed from groups of symptoms that are statistically more highly related to each other than other symptoms, and based on the principle of common cause, each cluster can be considered a module of symptom causation. There are three causal factors that affect the statistical relationship between symptoms and therefore network structure and clusters. First, symptoms can cause other symptoms (e.g., sleep disturbance causing tiredness) which will produce clusters of conceptually related symptoms. Second, symptoms can be statistically related because they share a common biological mechanism, and which will tend to produce a modular structure consistent with the underlying biological mechanisms. For example, systemic inflammation (Kanbara, Fukunaga, Mutsuura, Takeuchi, Kitamura & Nakai, 2007; Penninx, Kritchevsky, Yaffe *et al*., 2003) has effects throughout the body and will tend to create a cluster of symptoms that result from systemic inflammation. Third, mood can have a generic effect on all symptoms reporting (Pennebaker, 2012) and this common factor would contribute to high inter-connectivity between all symptoms throughout the symptom network.

If long-COVID and CFS are the same as yet undiscovered diseases, they will have the same modular structure. If they are different undiscovered diseases, they may have different modular structures. If the same symptoms are used in the analysis for two different populations, then similar modular structures would indicate that they have the same disease-like pathology and different structures that the pathology is different in some way. Similar modular structures could also be explained by the psychosomatic model of functional somatic syndromes where different diagnoses are perceived as having the same cause (Wessely *et al*., 1999; White, 2010). Alternatively, if long-COVID and CFS have different modular structures then this could indicate that they are different types of disease.

The symptom network structures of long-COVID and CFS are compared in this study. However, more information is provided if that comparison is made in conjunction with groups having other theoretically relevant diagnoses. FMS and IBS are functional somatic syndromes and provide a theoretically relevant comparison with CFS. Asthma is a respiratory disease of the lung that involves both lung-specific and systemic inflammation (Rosenkranz, Esnault, Christian *et al*., 2016) and provides a theoretically relevant comparison with long-COVID. People with severe asthma experience extrapulmonary symptoms that are MUS and that have been shown to be similar to those of FMS (Hyland, Lanario, Wei, Jones & Masoli, 2019). In addition, FMS is a common comorbidity of asthma (Golino, Christensen & Moulder, 2020) as well as being a risk factor for poor asthma control (Martinez-Moragon, Plaza, Torres *et al*., 2017). A general public sample provides a theoretically relevant comparison as a healthy control. Our study therefore compares the symptom networks of six groups defined by clinical diagnosis, long-COVID, CFS, IBS, FMS, severe asthma and healthy in order to provide inference about underlying causal mechanisms, based on the assumption that statistically related symptoms have some form of common cause.

Groups identified through diagnosis are not mutually exclusive. Additionally, in the case of functional somatic syndromes different

diagnoses merge into each other and there is considerable overlap in symptoms (Barsky & Borus, 1999). Functional somatic syndromes are frequently underdiagnosed in relation to formal diagnostic criteria (Giral, Diaz-Manchay & Leon-Jimenez, 2021; Palacios, Fitzgerald, Komaroff & Ascherio, 2017), and this underdiagnosis also applies to comorbidity between functional somatic syndromes where diagnosis can be limited to the most troubling symptom (e.g., pain). In a survey of symptoms (Hyland, Bacon, Lanario & Davies, 2019), 95% of people who reported that they were diagnosed with FMS but not CFS, reported fatigue for no reason on at least a weekly basis. This issue of symptom and diagnostic overlap is relevant to any interpretation of results.

METHODS

Study populations and data collection

We analyzed data from six groups of people. The data for three of the groups were obtained from an online study (Hyland, Bacon, Lanario & Davies, 2019) where participants were recruited through IBS, CFS and FMS self-help organization websites and after consent indicated, before completing the questionnaire, whether they had any one or any combination of IBS, CFS and FMS. Those reporting only IBS formed the IBS sample. People with CFS were obtained from the same study and were included if they reported either CFS or CFS and IBS. People with FMS were obtained from the same study and were included if they reported FMS with or without either of the other two diagnoses. For these three groups, diagnosis was based on participant report only. People with severe asthma were obtained from a previous study of extra-pulmonary symptoms in severe asthma where patients attending a specialist asthma clinic completed paper versions of the questionnaire (Hyland, Lanario *et al.*, 2019). People attending such clinics would normally have a diagnosis of severe asthma. People with long-COVID were recruited for this study using an online questionnaire from an online group of people reporting long-COVID recruited through a self-help online forum. A healthy sample of people were recruited for this study from the general public through Prolific Academic (https://www.prolific.co/) and paid 2GBP for completing the questionnaire online. There was no restriction on the healthy sample so these may have included those with a disease or functional somatic syndrome.

Questionnaire

The general symptom questionnaire (GSQ) (Hyland, Lanario *et al.*, 2019; Hyland, Bacon *et al.*, 2019) is a 65-symptom questionnaire designed to measure the symptoms of people with IBS, CFS and FMS. For each symptom people respond on a six-point scale showing the frequency that the symptom is experienced, varying from 1 = never or almost never to 6 = every day. The questionnaire covers a wide range of psychological and somatic symptoms and is not restricted to those normally considered indicative of IBS, CFS and FMS.

Network analysis and statistics

The symptom severity for each participant was calculated as the mean of responses to the symptom items in the questionnaire. Network analysis was conducted on only those symptoms that discriminated between the six groups. These symptoms were identified using exponential mixed graphical models (Haslbeck & Waldorp, 2020; Yang, Baker, Ravikumar, Allen & Liu, 2014), which produces a binary classification of symptoms as either being or not being directly related to the categorical variable comprising the six groups. Only those symptoms that were directly related to the variable "group" were retained for further analysis. For this analysis we employed the "bootnet" package in R (Epskamp, Borsboom & Fried, 2018) which is described in detail in Haslbeck & Waldorp (2020).

Connectivity within the network for each group was calculated using mutual information (MI), (scores vary between 0 and no upper bound), a statistic assessing shared information between variables. For each symptom, MI between each possible couple of symptoms was calculated (Faes, Porta & Nollo, 2015; Kraskov, Stögbauer & Grassberger, 2004) producing the same number of values of MI as symptoms. The computation has been performed in MatLab environment with ITS toolbox (Faes *et al.*, 2015). The Kruskal–Wallis test was used to assess the overall differences between groups. *p*-values were adjusted for multiple comparisons of mean ranks across all groups. Subsequently, paired comparisons of ranks were performed to evaluate differences between specific pairs of groups. High values of connectivity indicate greater connectivity. The distributions of MI values are shown as violin plots with probability densities estimated using the kernel density estimator and the mean MI value shown for each group.

The fragmentation of the network was calculated using the fragmentation index (H_{frag}) which estimates the degree to which the networks are divided into smaller sub-networks (Wright, Parker & Lord, 2013) (high scores indicating low fragmentation). The fragmentation index is a single score so statistical comparison is not possible between groups.

Three different network parameters were calculated: connectivity, fragmentation and the number of clusters. Network connectivity expresses the overall extent to which a group of symptoms are statistically related. A highly connected network provides evidence of some common factor that explains the covariation between many of the symptoms in the network. A network low in connectivity provides evidence of weak causal relations between the different symptoms. Network fragmentation expresses the extent to which a network has clusters of strongly related symptoms but where there is a weak relationship between symptoms in different clusters. A network with high fragmentation indicates a network where a cluster has a separate cause, but where there is some common factor for symptoms within a cluster. A network low in fragmentation is a homogenous network which provides evidence that there are a few groups of symptoms each of which has a separate common cause. The number of clusters in a network is be related to fragmentation. The more numerous the clusters, the more evidence of causally unconnected causal mechanisms.

Symptom clusters were identified for each group by the walktrap algorithm using the MI values (Pons & Latapy, 2005) calculated using RStudio. The walktrap algorithm (Pons & Latapy, 2005) identifies closely connected communities by performing random walks, which tend to stay within communities rather than jumping to others, effectively capturing the inherent modularity in the symptom networks (Rosvall & Bergstrom, 2008). This process results in a sparse network for each group. At each statistically significant link was assigned the corresponding estimated value of MI. Otherwise, the link was set to zero. All the analyses were conducted using the R package "EGAnet" (Golino *et al.*, 2020). The selection of MI ensures the detection of both linear and non-linear associations, which are necessary to understand the complex relationships between symptoms (Antonacci, Astolfi, Nollo & Faes, 2020). The number of clusters for each group is shown and symptom clusters that are identical between groups described.

Bootstrap methods were applied to assess the accuracy and stability of estimated network structures. The stability of centrality indices was confirmed by estimating network models based on subsets of the data (Golino *et al.*, 2020). Since each matrix can be represented as a network, each edge can be interpreted differently, according to the type of variable it is connecting. The connection between two continuous variables is the typical pairwise interaction known from linear multiple regression. To assess the accuracy and stability of estimated network structures bootstrap methods have been applied. The stability of centrality indices was tested by estimating network models based on subsets of the data.

Ethics

New data collection received ethical approval from the University of Plymouth Human Research Ethics committee. Ethical approvals for data obtained from previous studies are reported in the cited publications.

Table 1. *Properties of the six groups*

Group	*N*	*n* (% female)	Age, mean (SD), range	Severity, mean (SD)	Fragmentation (H_{frag})	Number of clusters
Healthy	207	158 (76%)	31.4 (12.9), 18–74	2.6 (1.1)	2.61	4
Severe asthma	100	63 (63%)	51.9 (14.9), 16–79	2.90 (1.1)	2.36	3
Long-COVID	107	92 (86%)	47.7 (10.8), 19–76	3.21 (0.89)	2.56	4
CFS	254	221 (87%)	49.6 (14.3), 22–90	3.54 (0.81)	0.55	9
IBS	369	313 (85%)	55.3 (15.6), 23–92	2.84 (0.80)	1.31	7
FMS	1,127	1,057 (94%)	57.1 (11.5), 22–95	4.12 (0.78)	2.06	6

RESULTS

Table 1 provides demographic details of the six groups and the severity scores obtained from the mean of all items of the questionnaire. Twenty-two primarily somatic symptoms discriminated between diagnostic groups. The symptoms (as described in the questionnaire) are shown in Table 2.

Figure 1 shows the connectivity scores and distributions of the 22 MI values for each of the six groups. There are significant differences ($p < 0.001$) between the three functional somatic syndromes versus the other three group. Examination of Fig. 1 shows that the difference between the IBS, CFS and FMS versus the other groups is significant. IBS, CFS and FMS were not significantly different from each other. Healthy, severe-asthma and long-COVID were not significantly different from each other.

The fragmentation scores and number of clusters per group are shown in Table 1. The networks of CFS. IBS, and FMS are more fragmented and have more clusters than those of long-COVID, severe asthma and healthy.

We examined the symptoms within clusters to determine whether any clusters were identical between groups (see Fig. 2; note a color version of Fig. 2 is available in Figures **S1** and S2). A 2-symptom cluster of diarrhea and constipation was found in only the IBS, CFS and FMS groups. A 3-cluster of "Pain increasing the day after you are active," "Fatigue increasing the day after you are active" and "Fatigue increasing after a cold or sore throat" was found in only the CFS and FMS groups, and this cluster was similar though not identical to a 3-symptom one in the long-COVID group comprising "Pain increasing the day after you are active," "Fatigue increasing the day after you are active" and "Pain moving from one place of body to another on different days." The 22 symptoms formed the 33 symptom clusters spread over the six groups. Of these 33 clusters, 28 were unique to one group only. Of the remaining five clusters, one was shared between two groups and one between three groups. There were therefore 30 unique clusters spread over the six groups.

Figure 3 shows the results of the stability analysis. These results indicate that the symptom networks for each of the groups is stable and that differences between groups cannot be attributed to random factors.

Table 2. *The 22 symptoms used in the analysis*

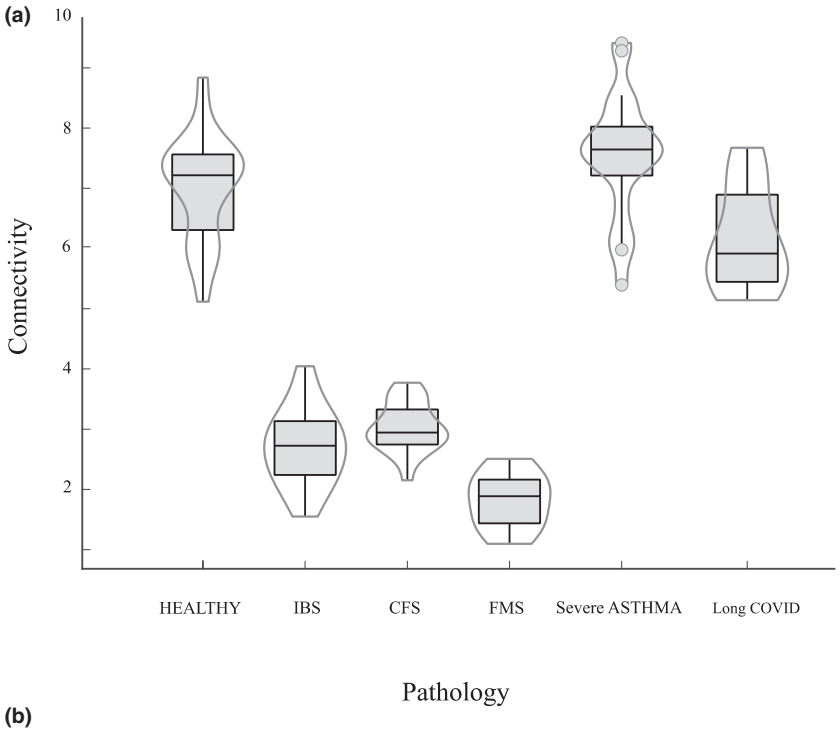
Symptom as written in questionnaire	
Pain moving from one place of body to another in different days	Racing heart
Stomach pain	Itchy skin
Sensitive or tender skin	Skin rash
Pain increasing the day after you are active	Twitching other than eye lid
Fatigue increasing the day after you are active	Choking sensations
Fatigue increasing after a cold or sore throat	Feeling faint
Thirsty all the time	Cramps in leg foot or bottom
Diarrhea	Numbness, tingling, pins and needles
Constipation	Feeling out of breath for no reason
Intolerant to some food	Backpain
Waking up often at night	Chest pain

DISCUSSION

The symptom networks of long-COVID and CFS are not the same. Network connectivity in the primarily somatic symptoms that were selected in this study is significantly greater in long-COVID which has less fragmentation and fewer clusters compared with CFS. There was partial overlap between a cluster in long-COVID and CFS relating to the "boom and bust" phenomenon where pain and fatigue is increased the following day, but otherwise there is little similarity between the networks of long-COVID and CFS. Connectivity was similar between the networks of long-COVID, severe asthma and healthy and between the networks of CFS, IBS and FMS but the content and number of clusters was different.

Based on a comparison of only long-COVID and CFS a possible conclusion might be that their symptoms are caused by different modular structures and that they are therefore different types of yet to be identified diseases. However, this conclusion is unsafe when the networks of the remaining four groups are also compared. Although the networks of CFS, IBS and FMS all share the property of low connectivity, the number and content of the clusters shows marked differences. From a clinical perspective, CFS and FMS are similar. Not only is there overlap in symptomatology but both are central sensitivity syndromes (Yunus, 2007). Additionally, these two groups of participants were not mutually exclusive. In our study the FMS group contains people diagnosed with CFS as well those who would meet the CFS diagnostic criteria due to underdiagnosis. The underlying modular structure should be similar if not the same. Yet only two of the nine CFS clusters are replicated in the six clusters of the FMS network. Over the six groups in our study, there were 30 different types of cluster out of a total of 33 clusters formed from 22 different symptoms.

Our finding was unexpected. Like others, we assumed that symptom clusters were caused by some kind of common biological factor (Kujawski, Słomko, Newton *et al.*, 2021; Liu, Epskamp,



(b)

	HEALTHY	IBS	CFS	FMS	S. ASTHMA	L. COVID-19
HEALTHY		**$<10^{-4}$**	**$<10^{-4}$**	**$<10^{-4}$**	1	1
IBS			1	0.678	**$<10^{-4}$**	**$<10^{-4}$**
CFS				0.07	**$<10^{-4}$**	**0.019**
FMS					**$<10^{-4}$**	**$<10^{-4}$**
S. ASTHMA						0.462
L. COVID-19						

Fig. 1. The violin plots (a) show the connectivity scores as a function of group. Middle horizontal line is the median of the 22 MI values (connectivity score), top and bottom horizontal lines are 5th and 95th percentiles, curved lines indicate distribution of MI values, vertical lines indicate estimated range. The estimated range is the same as the actual range for all groups except for the asthma group where outliers (shown as points) fall outside the estimated range. The table (b) shows the results of the paired comparisons of ranks to test differences between pairs of groups computed after Kruskal–Wallis test ($p < 10^{-4}$). Significant differences are in bold and the table reports *p*-values after multiple comparisons analysis.

Isvoranu, Chen, Liu & Hong, 2021). For example, Melidis, Denham and Hyland (2018) analyzed data from over 2000 participants and identified 11 symptom clusters that corresponded to 11 different pathogenic mechanisms, including small nerve fiber neuropathy, atopy, limbic system, and fatigue/cognitive. Each of the above studies examined the symptom network structure of a single population. Our study is unique in providing separate analysis of different populations, some of whom are closely related (e.g., CFS and FMS) and some are not. According to the disease concept, disease-causing mechanisms are modular. There should therefore be a limited number of symptom-causing mechanisms producing the 22 symptoms. The finding that there were 30 different types of symptom cluster is inconsistent with the assumption of modularity.

How our findings could be explained by network pathology

The variation in symptom clusters that we observed in our study could be explained by a pathology that is distributed over a biological network and where this distributed pathology encodes some form of informational error. The informational error then creates a disturbance in function that causes symptoms. A distributed pathology would explain the overlapping symptom presentation of functional somatic syndromes (Barsky & Borus, 1999) and the comorbidity between different diagnostic categories (van der Meulen, Bos, Bakker, Gans & Rosmalen, 2024). The distributed pathology would explain the observed multiple immune, metabolic, autonomic and central nervous system abnormalities of CFS (Boomershine, 2015; Malkova & Shoenfeld, 2023; Uhde *et al.*, 2023), and the non-identical overlap of these abnormalities with those of long-COVID (Ceban *et al.*, 2022; González-Hermosillo *et al.*, 2021; Tate *et al.*, 2022; Wong & Weitzer, 2021; Yang *et al.*, 2022). Importantly, this distributed form of pathology would explain why, despite considerable effort, there has been a failure to identify a specific pathophysiology that can be used to diagnose IBS, CFS or FMS. A theory of network pathology would show that although different diagnostic categories share biological abnormalities, the way these abnormalities are combined differs and the combination determines the precise presentation of symptomatology. In this case, the diagnostic categories are formed from the relationship between multiple pathophysiologies rather than having a specific pathophysiology.

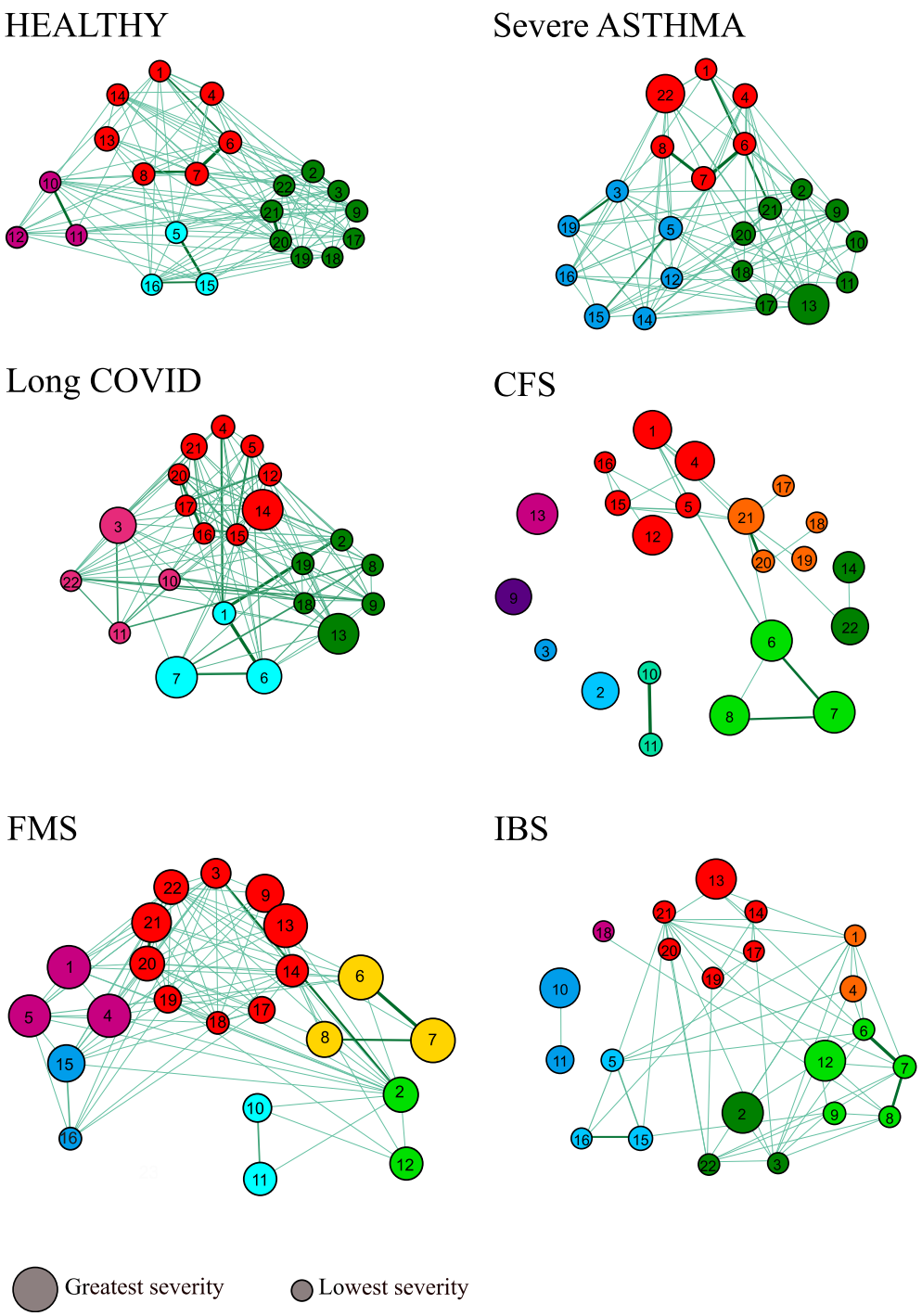


Fig. 2. Symptom networks of the six groups. The weight of the lines represents the MI values between the symptoms, no lines indicate the MI value is not significant. The size of the nodes shows the severity of the symptom. Node colors indicate clusters. Symptoms with no connecting lines are one item clusters. The symptoms correspond to the following numbers: 1 = pain moving from one place of body to another on different days; 2 = stomach pain; 3 = chest pain; 4 = back pain; 5 = sensitive or tender skin; 6 = pain increasing the day after you are active; 7 = fatigue increasing the day after you are active; 8 = fatigue increasing after a cold or sore throat; 9 = thirsty all the time; 10 = diarrhea; 11 = constipation, 12 = intolerant to some food; 13 = waking up often at night; 14 = racing heart; 15 = itchy skin; 16 = skin rash; 17 = twitching other than eye lid; 18 = choking sensations; 19 = feeling faint; 20 = cramps in leg foot or bottom; 21 = numbness, tingling, pins and needles; and 22 = feeling out of breath for no reason.

Mental illness versus functional somatic syndromes versus disease: A hypothesis

The structure of the brain is both modular and connectionist (Siegel, Shulman & Corbetta, 2022). Although some functionality is modular, information is encoded by the connection strengths between neurons rather than at a point location. If mental illness is considered a form of informational error, then the biological basis of mental illness is due to a malfunctioning biological network. If functional somatic syndromes are also the result of informational error, then network encoding that error is not

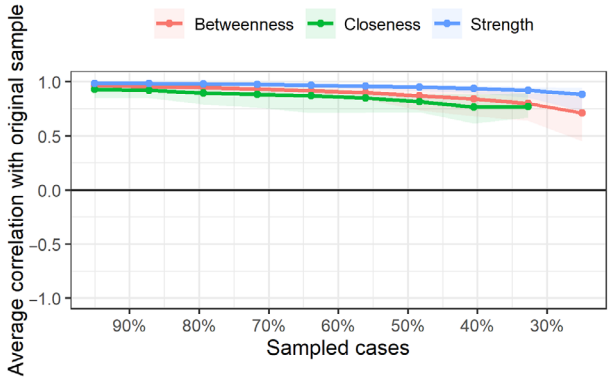


Fig. 3. The figure shows the average correlations between centrality indices of networks. Lines indicate the means, and areas indicate the range from the 2.5th quantile to the 97.5th quantile.

limited to the brain but extends throughout the body. The difference between mental illness (neurological network error) and functional somatic syndromes (more widespread network error) is therefore one of degree rather than a category difference. Mental illness, despite being primarily neurological, is associated with non-neurological abnormalities, such as raised pro-inflammatory cytokines (Lee & Giuliani, 2019) and functional somatic syndromes are associated with mood disturbance and central processing error (Boomershine, 2015). This leads to a possible conclusion. Mental illness is primarily neurological but with some non-neurological involvement, and functional somatic syndromes have less neurological and more non-neurological involvement, but both are due to informational error in a network system that extends throughout the body and includes immune, autonomic, endocrine, gastric and other systems.

Diseases are pathologies that are modular and have some of discrete form of biological of biological representation that makes them specific. However, the body has both modular and network functionality, so the specificity of a disease is within a network structure. Although the disease module forms a discreate area in the network, under some circumstances this specific form of pathology could leak out in the rest of the network and create the symptoms associated with functional somatic syndromes. Diseases are often associated with MUS as well as diagnosed functional somatic syndromes, and prevalence of MUS increases with severity (Nimnuan *et al*., 2001) suggesting that leakage from the localized disease pathology to the rest of the network increases with severity. Leakage across a network is also consistent with the explanation for comorbidities, for example, the explanation of the comorbidities of chronic obstructive pulmonary disease by the overspill hypothesis (Nishimura, Nakayasu, Mori, Sanda, Shibayama & Kusunose, 2021; Sinden & Stockley, 2010). A possible interpretation, therefore, is that diseases, mental illness and functional somatic syndromes are not entirely mutually exclusive categories of pathology but vary, to some extent, in the degree of specificity and distribution in a network system.

Hardware versus software

A biological network encodes information, and the distinction between specific and distributed pathology has some similarities to the distinction between computer hardware and software. The software in a computer provides information or a set of instructions called algorithms. However, there is one important difference. In a computer or other electronic device the hardware and software are physically separate. In a living system the software is encoded by the hardware: they are not separate, and this connection between the hardware and software is a defining feature of living intelligent systems in contrast to machines that only simulate intelligence (Ivanov, 2021). Psychological and lifestyle interventions provide information that alters the software of the body, but this alteration also changes the hardware. Therefore, although biological interventions will be the most effective for treating the modular pathology of disease, psychological factors can also influence disease processes. For example, there is some evidence that psychological state influences cancer survival (Fontesse, Fournier, Gérain *et al*., 2023; Okayama, Suzuki, Morishita *et al*., 2024; Roche, Cooper, Armstrong & King, 2023) these effects are small compared to those achieved by biological treatment. Similarly, psychological interventions that provide information to a biological network will be the more effective than biological intervention for network pathology, but biological interventions can have some effect. Antidepressants reduce depression, though more than 85% of the effectiveness of antidepressants in clinical practice is due to a placebo effect (Kirsch, 2010; Stone, Yaseen, Miller, Richardville, Kalaria & Kirsch, 2022). Placebos are psychological effects medicated through a neurological route that alters biology (Benedetti, Carlino & Pollo, 2011) thereby changing biological encoded information. Conversely, some biologically helpful pharmacological treatments for disease have adverse psychiatric consequences, for example, montelukast (Sansing-Foster, Haug, Mosholder, *et al*., 2021) and finasteride (Pompili, Magistri, Maddalena, Mellini, Persechino & Baldessarini, 2021).

Limitations

The study procedures and analytic plan were not preregistered. The diagnostic criteria for the six groups were based on self-report. The network analysis used a particular set of symptoms. The study was not designed to reach the conclusions that were drawn. Further research using other diagnostic groups and other symptoms is needed to determine whether the hypothesis proposed in this paper is correct. This study has not revealed the mechanisms that increase or decrease network pathology, nor has it revealed the algorithms that explain how informational input to the system alters the output of a psychological state.

CONCLUSION

The aim of this study was to determine whether CFS and long-COVID were the same or different diseases whose pathophysiology has not yet been elucidated. Our findings supported neither conclusion nor the conclusion deriving from psychosomatic theory that functional somatic syndromes are the same because they have the same psychological cause of stress. We have suggested an alternative interpretation that the body functions both as a modular and a connectionist system. Functional somatic syndromes are primarily connectionist

whereas diseases are primarily modular. The negative and often stigmatizing attitudes to mental illness and functional somatic syndromes are due to a misunderstanding that minds and bodies are separate. The symptoms of mental illness and functional somatic syndromes are both caused by a biological network structure that includes but extends beyond the brain. Correcting the informational error in that network is achieved by providing the network with new information that alters the "software" of the network thereby correcting the way the system functions. This new information can be provided by psychological and other behavioral interventions.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Figure S1. Symptom networks.
Figure S2. Symptom networks of the six groups.

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