Research paper

Connectivity of depression symptoms before and after diagnosis of a chronic disease: A network analysis in the U.S. Health and Retirement Study

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ABSTRACT

Background: Many chronic diseases increase the risk of depressive symptoms, but few studies have examined whether these diseases also affect the composition of symptoms a person is likely to experience. As the risk and progression of depression may vary between chronic diseases, we used network analysis to examine how depression symptoms are connected before and after the diagnosis of diabetes, heart disease, stroke, and cancer.
Methods: Participants (N = 7779) were from the longitudinal survey of the Health and Retirement Study. Participants were eligible if they had information on depression symptoms two and/or four years before and after the diagnosis of either diabetes, heart disease, cancer or stroke. We formed a control group with no chronic disease that was matched on age, sex and ethnic background to those with a disease. We constructed depression symptom networks and compared the overall connectivity of those networks, and depression symptom sum scores, for before and after the diagnosis of each disease.
Results: Depression symptom sum scores increased with the diagnosis of each disease. The connectivity of depression symptoms remained unchanged for all the diseases, except for stroke, for which the connectivity decreased with the diagnosis.
Limitations: Comorbidity with other chronic diseases was not controlled for as we focused on the onset of specific diseases.
Conclusions: Our results suggest that although the mean level of depression symptoms increases after the diagnosis of chronic disease, with most chronic diseases, these changes are not reflected in the network structure of depression symptoms.

1. Introduction

Depression is a heterogeneous psychiatric disorder that is often associated with other diseases (Rush and Rush, 2007). These associations also appear to be bidirectional: people with depression have an increased risk of several chronic conditions, such as diabetes, cardiovascular disease, cancer, and stroke (Utzschneider et al., 2007, Schane et al., Ali et al., 2006, Williams et al., 2004, Anderson et al., 2001, Moussavi et al., 2007), but chronic diseases may also contribute to onset of depression (Ali et al., 2006, Anderson et al., 2001, Hackett and Anderson, 2005), as the psychological adjustment to chronic illnesses can be highly challenging (de Ridder et al., 2008). In addition, studies suggest that the co-occurrence of chronic disease and depression may incremental worsen health compared to having either disease alone (Moussavi et al., 2007), and such co-occurrence has been

associated with increased mortality (Williams et al., 2004, Pinquart and Duberstein, 2010). Depression involves several symptoms, including e.g. low mood, sleep disturbance, loneliness, lack of initiative, and anhedonia. However, little is known whether the pattern of symptoms might vary depending on the status of physical disease.

The severity of depression has been measured by counting how many depression symptoms are present for a given individual (Diagnostic and Statistical 2013), but it has been argued that such an aggregate measure might not adequately portray the complexity of depression (Fried and Nesse, 2015). An alternative approach is to examine the network structure and dynamics of specific depression symptoms, that is, how the symptoms are connected. A denser, more tightly knit network of symptoms, for example, may indicate a higher risk for developing depression (Cramer et al., 2016). A more strongly connected network structure of depression symptoms has also been

shown to characterize persistent depression compared to more transient depression (Van Borkulo et al., 2015). The network structure of depression symptoms might also be sensitive to changes in physical health.

In this study, we examined how depression symptoms were connected before and after the diagnosis of common chronic illness. As the pattern of symptoms can be specific to physical disease, we focused on multiple common chronic illnesses, including diabetes, coronary heart disease, stroke, and cancer. For each disease, we determined depression symptom networks before and after the diagnosis and examined how the overall connectivity of those networks compared against the traditional measure of depression scale sum score. Based on the findings from previous studies (Cramer et al., 2016, Van Borkulo et al., 2015) we hypothesized that the overall connectivity of depression symptom networks increases after the diagnosis of a chronic illness.

2. Methods

2.1. Study design and participants

The participants for this study were from the Health and Retirement Study (HRS) (Sonnega et al., 2014). HRS is a nationally representative longitudinal survey of people over age 50 in the USA that started in 1992. The survey is conducted every two years. The first wave includes a measure of depressive symptoms, but it is a version that features 11 items with a 4-point response scale, whereas all the other waves use a measure of depressive symptoms which includes 8 items with a 2-point response scale. The measures have been shown to be in disagreement and cross-wave analysis is not recommended (Steffick, 2000). Therefore, survey waves from 1994 to 2014 were used in this study.

Participants were eligible for this study if they had information on depression symptoms two and/or four years before and after the diagnosis of either diabetes, heart disease, cancer or stroke. Together with a control group that had none of the illnesses, our study included 7779 men and women.

HRS has been approved by the University of Michigan Institutional Review Board, and the study has been conducted according to the principles of the Declaration of Helsinki. HRS is described in more detail elsewhere (Sonnega et al., 2014).

2.2. Measurement of depression symptoms

Depression symptoms were measured using the Center for Epidemiologic Studies Depression (CES-D) scale (Radloff, 1977). The scale consists of eight indicators for depression: felt depressed, everything is an effort, sleep is restless, felt alone, felt sad, and could not get going, felt happy, and enjoyed life. Responses for each indicator were given as either yes or no. A summary score for the scale was computed for each participant by summing together all the answers. The answers for indicators "felt happy" and "enjoyed life" were reversed for the summary score.

2.3. Chronic diseases

In each wave, participants were asked whether a doctor had told them if they had one of the following conditions: 1) diabetes or high blood sugar, 2) heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems, 3) cancer or a malignant tumor of any kind except skin cancer, or 4) stroke or transient ischemic attack. The wave when participants first reported having been diagnosed with a disease was coded as year zero. The preceding two waves were coded as -2 and -4, and the two successive waves as 2 and 4.

2.4. Control group

A control group was formed of participants who did not have a

chronic disease at baseline and did not develop one during the follow-up period. The "diagnosis year" of zero was chosen randomly so that the mean age and age distribution at year zero of the control group and those with a disease matched. The control group was further matched to have the same distribution on gender and ethnic background as the participants with diseases.

2.5. Statistical analysis

In network analysis, the symptoms and their relations with each other are the main areas of focus. Network structures consist of nodes and edges. In the case of depression symptom networks, the symptoms represent the nodes, and the associations between symptoms represent the edges (Borsboom and Cramer, 2013). To construct the networks for depression symptoms before and after the diagnosis of each disease, we used Ising models which combine L1-regularized logistic regression with model selection based on Extended Bayesian Information Criterion (EBIC). The R package *bootnet* was used for this (Epskamp et al., 2018). We then compared the overall connectivity of the networks from before and after the diagnosis using the Network Comparison Test (NCT) (Van Borkulo, 2019). The NCT is a permutation-based test in which the network connectivity is calculated repeatedly – in our analysis 1000 times - for randomly regrouped participants. The resulting distribution of connectivity can be used to test for differences between two groups (Van Borkulo et al., 2015). The overall connectivity is defined as the sum of absolute values of the edges of a network and reflects how densely the symptoms are connected. We restricted the comparison for each disease to participants who had a full set of data for both before and after the diagnosis; otherwise, the differences in sample size could have biased the comparisons of connectivity measure. Apart from overall connectivity, the bootnet package allows the estimation of centrality indices for indirect networks. These include strength, closeness, and betweenness (Epskamp et al., 2018). Strength describes how strongly the node is directly connected with other nodes. Closeness describes how close a node is to other node or, in other words, how large of a capacity the node has for affecting all other nodes. Betweenness is an indicator for the importance of the node in the network. It represents the number of times a node acts as a bridge between two other nodes. The networks shown were estimated and drawn using bootnet package for R. Further, following the procedure of van Borkulo et al. (Van Borkulo et al., 2015) we used the Wilcoxon rank sum test to compare the CES-D sum scores before and after the diagnosis of each disease. The test can be used as an alternative to the t-test for dependent samples when the underlying distribution is not normal.

3. Results

The descriptive statistics for the participants at 4 and 2 years before the diagnosis of each disease, and the control group are presented in Table 1.

Table 2 shows CES-D sum scores and overall connectivity of depression symptom networks two and four years before and after diagnosis of each disease. As expected, the diagnosis of all diseases was associated with increasing CES-D sum scores when comparing two years before and after the diagnosis. Results for four years before and after were similar, although there was no difference in the sum score for diabetes.

Analyses of connectivity suggested no statistically significant changes in the overall connectivity of the symptom networks before and after the diagnosis of diabetes, heart disease or cancer (Table 2). For stroke, however, the symptoms became less strongly connected after the diagnosis compared to two years before the diagnosis (difference 3.63, $p = 0.01$; Fig. 1). Centrality indices for each disease, shown in **Supplementary A**, suggest that the composition of symptoms network alters in a heterogeneous way after diagnosis while changes in centrality indices, such as the strength, closeness, and betweenness of

Table 1
Baseline descriptive statistics for each diseases and control group 2 years and 4 before a diagnosis.

		Diabetes		Heart disease		Cancer		Stroke		Control	
		4 years before	2 years before	4 years before	2 years before	4 years before	2 years before	4 years before	2 years before	4 years before	2 years before
Sex												
	Men	571 (43)	779 (43)	675 (46)	1361 (48)	510 (53)	716 (54)	206 (47)	329 (49)	374 (44)	556 (52)
	Female	766 (57)	1021 (57)	787 (54)	1457 (52)	446 (47)	621 (46)	230 (53)	341 (51)	468 (56)	598 (48)
Age		64.59	66.71	65.42	65.87	65.63	67.78	66.17	68.56	67.05	69.76 (5.02)
		(6.44)	(6.76)	(6.49)	(7.28)	(6.23)	(6.70)	(6.99)	(7.61)	(4.68)	
Ethnicity												
	White	1058 (79)	1394 (77)	1238 (85)	2354 (84)	814 (85)	1129 (84)	345 (79)	516 (77)	713 (85)	975 (84)
	Black	207 (15)	311 (17)	172 (12)	369 (13)	126 (13)	179 (13)	75 (17)	128 (19)	99 (12)	142 (12)
	Other	72 (5)	95 (5)	52 (4)	95 (3)	16 (2)	29 (2)	16 (4)	26 (4)	30 (4)	37 (3)
Depression symptoms												
	Felt depressed	0.18 (0.39)	0.17 (0.37)	0.17 (0.37)	0.17 (0.37)	0.13 (0.33)	0.13 (0.34)	0.22 (0.41)	0.22 (0.42)	0.11 (0.31)	0.11 (0.32)
	Everything an effort	0.27 (0.44)	0.27 (0.44)	0.23 (0.42)	0.24 (0.43)	0.20 (0.40)	0.19 (0.40)	0.33 (0.47)	0.34 (0.47)	0.16 (0.37)	0.16 (0.36)
	Sleep was restless	0.31 (0.46)	0.32 (0.47)	0.30 (0.46)	0.34 (0.47)	0.27 (0.45)	0.29 (0.45)	0.36 (0.48)	0.39 (0.49)	0.24 (0.43)	0.22 (0.42)
	Was happy	0.86 (0.34)	0.86 (0.34)	0.86 (0.35)	0.87 (0.33)	0.90 (0.30)	0.89 (0.31)	0.83 (0.37)	0.83 (0.38)	0.91 (0.28)	0.92 (0.28)
	Felt lonely	0.17 (0.37)	0.16 (0.37)	0.15 (0.35)	0.15 (0.36)	0.13 (0.33)	0.12 (0.33)	0.21 (0.41)	0.21 (0.41)	0.11 (0.31)	0.12 (0.32)
	Felt sad	0.21 (0.41)	0.20 (0.40)	0.20 (0.40)	0.19 (0.39)	0.16 (0.36)	0.15 (0.36)	0.25 (0.43)	0.23 (0.42)	0.15 (0.36)	0.15 (0.35)
	Could not get going	0.23 (0.42)	0.22 (0.42)	0.20 (0.40)	0.23 (0.42)	0.18 (0.39)	0.18 (0.38)	0.27 (0.45)	0.29 (0.46)	0.14 (0.35)	0.15 (0.36)
	Enjoyed life	0.92 (0.27)	0.93 (0.26)	0.92 (0.27)	0.93 (0.26)	0.94 (0.23)	0.94 (0.25)	0.92 (0.27)	0.90 (0.30)	0.95 (0.23)	0.96 (0.20)

Frequency is given in parentheses for sex and ethnicity, and standard deviation for age and depressive symptoms.

symptom networks, are less marked.

4. Discussion

Using network analysis, we examined whether the strength of associations between different depression symptoms changed after compared to before the diagnosis of diabetes, heart disease, cancer, and stroke. Sum scores of depression symptoms increased with the diagnosis of all diseases. However, contrary to our hypothesis only stroke was associated with a change in symptom network connectivity so that the symptoms became less densely connected after compared to before the diagnosis of stroke.

Getting diagnosed with a chronic disease is distressing, and adjusting to functional limitations set by chronic diseases can be difficult (de Ridder et al., 2008). Thus, increases in depression symptoms are to be expected with the onset of chronic diseases. We found that for all the diseases included in our study, the depression symptoms sum scores were higher after the diagnosis of a disease. In contrast, the network structure of depression symptoms changed only for those diagnosed with stroke although no differences in the overall connectivity of the symptom networks were observed before diagnosis between participants with stroke, diabetes, heart disease, and cancer. In addition,

participants with stroke had a higher depression sum score before the diagnosis compared to participants with other chronic diseases. It is possible that the direct neurological damage induced by stroke is associated with some stroke-specific alterations in depression symptoms that are reflected in the symptom network structure. Further research is needed to determine whether other symptom network characteristics may distinguish stroke-related depressive symptoms from those related to other chronic conditions.

There are only a few previous longitudinal studies that have examined changes in symptom network structure associated with life events or other risk factors of depression. In a study of individuals in psychiatric care, hospital discharge was associated with a decrease in depression sum score and an increase in the overall depression symptom connectivity compared to assessment at hospital admission (Beard et al., 2016). In a study of adolescents' early responses to depression treatment, those who responded more positively to psychological treatment also showed an increase in the overall connectivity of depression symptoms (Mcelroy et al., 2019). By contrast, other studies have suggested that stronger network connectivity would be a marker of worse depression prognosis (Van Borkulo et al., 2015, Sonnega et al., 2014).

McElroy et al. (Mcelroy et al., 2019) hypothesized that changes in

Table 2
Comparison between network connectivity and CES-D sum scores before and after each diagnosis.

	n	Connectivity			CES-D Sum score (SD)		
		Before	After	p-value for difference	Before	After	p-value for difference
2 years before and 2 years after							
Diabetes	1800	20.15	19.76	0.67	**1.54 (2.04)**	**1.64 (2.04)**	**<0.01**
Heart disease	2818	19.88	19.89	0.99	**1.52 (2.02)**	**1.78 (2.13)**	**<0.01**
Cancer	1337	19.35	18.92	0.70	**1.24 (1.83)**	**1.46 (1.93)**	**<0.01**
Stroke	670	**19.53**	**15.90**	**0.01**	**1.96 (2.28)**	**2.13 (2.26)**	**0.02**
Control group	1154	18.01	20.25	0.35	0.95 (1.50)	0.99 (1.57)	0.39
4 years before and 4 years after							
Diabetes	1337	18.24	18.87	0.55	1.59 (2.03)	1.58 (2.01)	0.83
Heart disease	1462	19.97	18.46	0.17	**1.47 (2.03)**	**1.59 (2.06)**	**0.01**
Cancer	956	20.35	20.16	0.89	**1.22 (1.78)**	**1.37 (1.94)**	**0.03**
Stroke	436	16.96	15.36	0.41	**1.88 (2.25)**	**2.09 (2.20)**	**0.05**
Control group	842	20.23	18.44	0.46	0.91 (1.53)	0.98 (1.59)	0.17

P-values for the difference in connectivity are computed using Network Comparison Test, and for the difference in CES-D sum score using Wilcox Paired rank sum test. Statistically significant results are in bold.

Stroke -2 years   **Stroke 2 years**
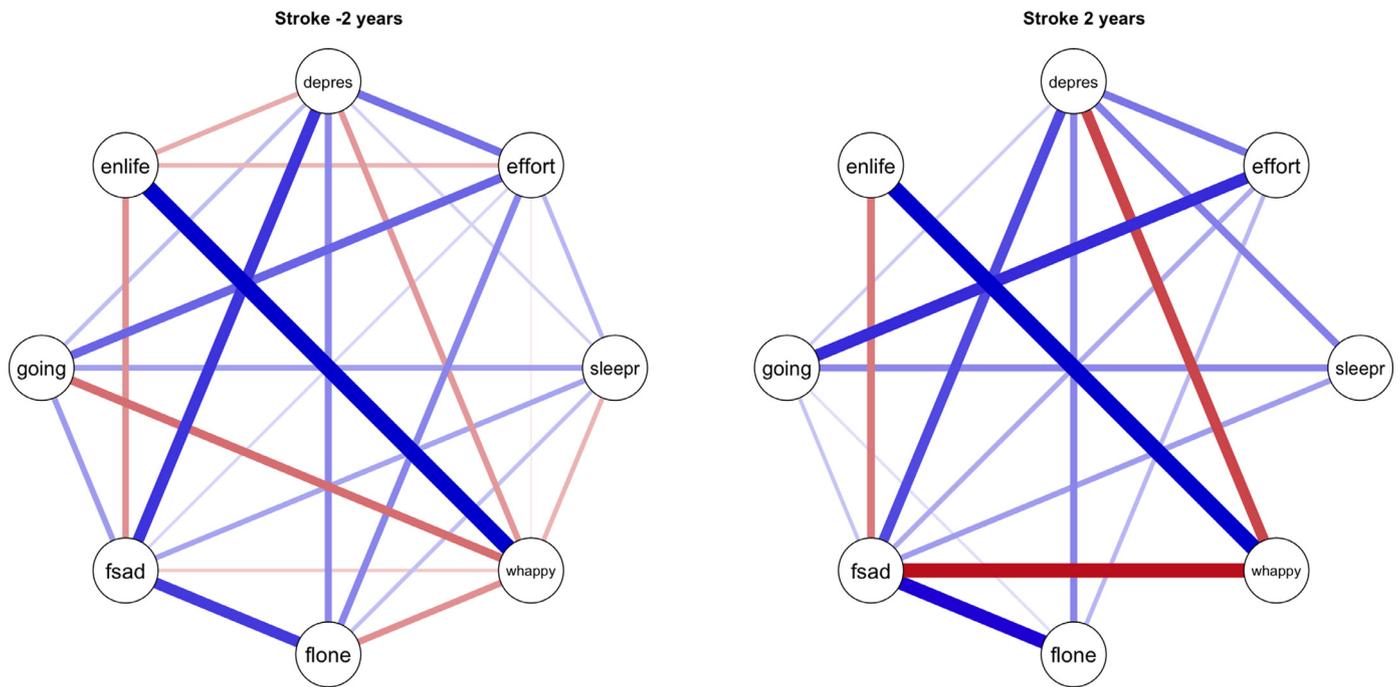
Fig. 1. Depression symptom networks two years before and after the diagnosis of stroke. Blue connections represent positive association and red connections represent negative associations between symptoms. Thicker lines represent stronger connections. fsad indicates felt sad; depress, felt depressed; effort, everything is an effort; sleepr, sleep is restless; flone, felt alone; fsad, felt sad; going, could not get going; whappy, felt happy; enlife, enjoyed life. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

symptom network connectivity may depend on the direction of change in depression symptoms scores. In a positive spiral of decreasing depression symptoms, an improvement in one symptom leads to improvements in other symptoms more strongly in a strongly connected symptom network. This in contrast to earlier explanations of negative spirals with the opposite effect in symptoms. Our study suggests that the connectivity in the network structure of depression symptoms may remain relatively unchanged even after the onset of chronic diseases that are known to increase the risk of depression symptoms. Similarly, we observed little systematic changes in centrality indices describing the strength of each symptom network node with other nodes, the likely capacity each node affects other nodes and the relative importance of each symptom in the symptom network. Further research beyond these indices is needed to examine the hypothesis that different chronic diseases or disease groups may induce specific changes in depressive symptom profiles.

4.1. Limitations

Some limitations of our study need to be considered. First, we did not control for having comorbid chronic illnesses because we wanted to focus on the onset of specific chronic diseases. Having more than one chronic illness could further exacerbate a person's depression symptoms (Barnett et al., 2012) and possibly change the symptom network structure differently than any individual disease. Second, the diagnosis of some diseases may not accurately match the actual onset of the disease—diabetes in particular—and the biannual assessments may have increased this variability. Some participants may have been diagnosed right after finishing one survey wave, and thus their diagnosis would only appear in the subsequent wave. These participants would have had up to two years to adjust to their diagnosis, which could have diluted the more short-term changes in depression symptoms. Furthermore, the diagnostic information used in the study is based on self-reports only. This could have introduced bias to the study as chronic conditions may not always be reported correctly by patients (Yasaitis et al., 2015).

5. Conclusions

Our results suggest that the overall connectivity of depression symptom network change little with the diagnosis of chronic diseases even when these diseases increase the mean level of depression symptoms. Further research is needed to test whether the network analysis of depression symptoms can help to better understand the effects of risk factors on the development of depression.

CRediT authorship contribution statement

Jaakko Airaksinen: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Kia Gluschkoff:** Conceptualization, Writing - review & editing. **Mika Kivimäki:** Conceptualization, Writing - review & editing. **Markus Jokela:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

All authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.01.170.

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