Network structures and temporal stability of self- and informant-rated affective symptoms in Alzheimer's disease

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Background: Affective symptoms in Alzheimer's disease (AD) can be rated with both informant- and self-ratings. Information from these two modalities may not converge. We estimated network structures of affective symptoms in AD with both rating modalities and assessed the longitudinal stability of the networks.

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Methods: Network analyses combining self-rated and informant-rated affective symptoms were conducted in 3198 individuals with AD at two time points (mean follow-up 387 days), drawn from the NACC database. Self-rated symptoms were assessed by Geriatric Depression Scale, and informant-rated symptoms included depression, apathy and anxiety questions from Neuropsychiatric Inventory Questionnaire.

Results: Informant-rated symptoms were mainly connected to symptoms expressing lack of positive affect, but not to the more central symptoms of self-rated worthlessness and helplessness. Networks did not differ in structure ($p = 0.71$), or connectivity ($p = 0.92$) between visits. Symptoms formed four clinically meaningful clusters of depressive symptoms and decline, lack of positive affect, informant-rated apathy and anxiety and informant-rated depression.

Limitations: The symptom dynamics in our study could have been present before AD diagnosis. The lack of positive affect cluster may represent a methodological artefact rather than a theoretically meaningful subgroup. Requiring follow-up lead to a selection of patients with less cognitive decline.

Conclusions: Informant rating may only capture the more visible affective symptoms, such as not being in good spirits, instead of more central and severe symptoms, such as hopelessness and worthlessness. Future research should continue to be mindful of differences between self- and informant-rated symptoms even in earlier stages of AD.

Keywords: Network analysis, Alzheimer's disease, depression, apathy, anxiety, neuropsychiatric symptoms

Running head: Affective symptom networks in AD

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1. Introduction

Affective symptoms like apathy, depression, and anxiety are some of the most common psychological disturbances in Alzheimer's disease (AD; Zhao et al., 2016). While these symptoms may not be severe enough to warrant a formal diagnosis, they often co-occur (Cummings et al., 1994; Levy et al., 1998; Teri et al., 1999), persist or resurface later (Olin et al., 2002; Vik-Mo et al., 2018) and associate with worse quality of life (Hongisto et al., 2018) as well as performance of activities of daily living (Palmer et al., 2011). Affective symptoms are likely multifactorial (Lanctôt et al., 2017; Marin, 1991), for example, it has been postulated that depressive symptoms could reflect the individual's reaction to declining cognition (Fitz & Teri, 1994; Weintraub, Xie, Karlawish, & Siderowf, 2007), whereas apathy has been associated with neurobiological changes, such as disturbances in frontal circuitry (Rosenberg et al., 2015).

Both self-report and informant-report are used when assessing neuropsychiatric symptoms. The measures are often implicitly considered to reflect the same underlying construct, although the information derived from them may diverge (Georgi, Vlckova, Lukavsky, Kopecek, & Bares, 2018; Olin et al., 2002; Teri & Wagner, 1992), at least partially owing to anosognosia (Robert et al., 2018) and caregiver characteristics (de Vugt et al., 2004). Additionally, measures thought to reflect one construct, i.e. depression, may also include items relevant for another construct, i.e. apathy (Levy et al., 1998).

In addition to utilizing different sources of information, majority of the research on affective symptoms in AD is conducted using total scores of self- or informant-rated measures, masking the contribution of individual symptoms, such as feeling worthless, to the psychopathological picture of AD (e.g. Olin et al., 2002). Interpretation of summary scores is

challenging, as they may combine symptoms of varying etiologies and clinical importance. Therefore, it is valuable to examine the relationships between the individual symptoms themselves, instead of assuming them to be caused by any single construct, such as depression. It is also important to track individual symptoms to determine whether they predict developing, more widespread psychopathology (Robert et al., 2018).

Relationships between individual symptoms can be investigated using network analysis (Borsboom & Cramer, 2013), a method that has been widely adopted in psychopathology research covering psychiatric disorders (longitudinally, e.g. van Borkulo et al., 2015; von Stockert, Fried, Armour, & Pietrzak, 2018). Recently, network structures of depressive symptoms have been analyzed in a general geriatric setting (van Wanrooij et al., 2019) as well.

In this study, we use network analysis to investigate how both self- and informant-rated affective symptoms relate to one another in Alzheimer's disease in a longitudinal research design. By combining both sources of information and symptom-level data, we can examine the relative importance of individual affective symptoms in AD and estimate the extent to which these two information sources converge on a symptom level. Stability of symptom networks over two visits is also studied.

2. Methods

2.1 Participants and measures

Data for this study were obtained from the University of Washington's National Alzheimer's Coordinating Center (NACC) that aims to facilitate research in the field by sharing data. The NACC's Uniform Data Set (UDS), consisting of individuals with normal cognition, mild cognitive impairment or dementia stage neurodegenerative disorder (Weintraub et al.,

2018) was used in this study. Participants were recruited to Alzheimer's Disease Centers (ADCs), and underwent standardized comprehensive cognitive, behavioral and functional evaluation. Informed consent was acquired in written form from study patients and informants.

In this study, we used data from 39 ADC's, and the UDS visits were conducted between September 2005 and February 2019. From the UDS, we first selected individuals with a diagnosis of AD. The diagnosis of AD was made in accordance with the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable Alzheimer's disease (McKhann et al., 1984) criteria until a revision of the UDS protocol in 2015 (Morris et al., 2006). After the 2015 revision, the National Institute on Aging-Alzheimer's Association criteria for AD were used (McKhann et al., 2011; Besser et al., 2018).

In addition to a diagnosis of AD, age ≥ 65 years, and complete data on self- and informant-ratings of depression, anxiety and apathy at two visits were required. Of the initial sample of 7581 individuals with AD and self- and informant-rating data and at least 65 years of age, 3679 participants had follow-up data for the same measures and were further explored. State-of-the-art outlier removal method of median absolute deviation (MAD; Leys et al., 2013) was used to exclude participants clearly outside the approximately annual follow-up, leaving a final sample of 3198 individuals with AD. As a robustness check, all analyses included in this study have also been performed in the sample without outlier removal, and included in Supplementary Materials.

2.1.1 Self-rated affective symptoms

For self-reported affective symptoms, we used Geriatric Depression Scale (GDS; Yesavage et al., 1982; Yesavage & Sheikh, 1986), one of the most common depression screening instruments for aged populations. We further divided GDS to an apathy subscale, GDS-3A

(Adams et al., 2004; van Wanrooij et al., 2019), consisting of “dropped activities”, “feeling full of energy” (reverse-scored) and “prefer to stay at home”, and a depression subscale, GDS-12D, consisting of the remaining 12 items.

2.1.2 Informant-rated affective symptoms

For informant-rated affective symptoms, we used depression, apathy and anxiety questions of the Neuropsychiatric Inventory Questionnaire (NPI-Q, Kaufer et al., 2000). NPI-Q is an abbreviated version of the widely used Neuropsychiatric Inventory (Cummings et al., 1994), tapping into various psychopathological disturbances typically observed in neurodegenerative disorders. We included apathy and anxiety questions, as GDS has items related to these constructs. Additionally, NPI apathy and anxiety have loaded on the same factor as depression, although not consistently (Canevelli et al., 2013). Apathy should be conceptually distinct from depression (Levy et al., 1998), however, the previously identified GDS-3A suggests there are apathy items in the GDS (Adams et al., 2004; Kim et al., 2013; van Wanrooij et al., 2019). Anxiety is a common comorbidity with depression in AD (Teri et al., 1999), and factor analyses of GDS have demonstrated the presence of anxiety items (Adams et al., 2004), such as being afraid something bad might happen.

2.1.3 Cognitive and functional measures

Participants underwent standardized neuropsychological assessment designed to assess all major cognitive domains, although the specific tests in the protocol were updated during the study period (Morris et al., 2006; Weintraub et al., 2018). To characterize the study sample, we present data on only measures of global cognition. Global cognition was assessed using either Mini-Mental State Examination (MMSE; Folstein et al., 1975), a brief instrument for global cognitive screening, or Montreal Cognitive Assessment (MoCA;

Nasreddine et al., 2005), a similar instrument that has been favored over MMSE in recent years. Whether MoCA or MMSE was used depended on the form version used at the study visit; those with a more recent visit have undergone MoCA assessment. For more details regarding the revision of the neuropsychological assessment used in the UDS, see Weintraub et al. (2018). Disease severity was assessed with the CDR® Dementia Staging Instrument (CDR; Hughes et al., 1982), in which a score of 0.5 corresponds to mild cognitive impairment or very mild AD, 1 to mild, 2 to moderate and 3 to severe dementia. In our study, the CDR scores reflected AD severity.

2.2. Statistical analysis

All statistical analyses were conducted in R version 3.5.3 (R Core Team, 2019). Code for the analyses is included in the Supplementary Materials and at osf.io/njvsa/.

2.2.1 Differences related to follow-up

Differences between individuals who had only baseline data (n=3902) versus individuals who had also follow-up data, and differences between baseline versus follow-up data were analysed using t-tests and chi-square tests. As comparisons of large groups are prone to find statistically significant differences between many given variables (Meehl, 1990; Orben & Przybylski, 2019), Cohen's d was used as an effect size estimate of these differences.

2.2.2 Network estimation

Network analysis is used to reveal variable interactions within phenomena of interest, such as in psychiatric disorders (Borsboom & Cramer, 2013). Networks can serve as an alternative to factor analytic models (Bringmann & Eronen, 2018; Fried, 2015), which may carry with them problematic causal assumptions (Borsboom et al., 2003), i.e. latent entity

"depression" causing "worthlessness". In networks, symptom relationships are visualized as partial correlations, indicating the number and strength of unique associations (later, edges) any individual symptom, (later, node) has with other nodes. This framework allows for a thorough investigation of how symptoms interact, in line with clinical understanding of symptoms, and suggesting which symptoms may be the most crucial in psychiatric disturbances (Fried & Nesse, 2015).

Networks of 15 GDS symptoms and 3 NPI-Q symptoms were estimated using Ising models, a novel method for network analysis of binary data (van Borkulo et al., 2015). Briefly, the method uses logistic regressions of each variable regressed on all others, and Least Absolute Shrinkage and Selection Operator (LASSO; Tibshirani, 1996) to construct a sparse model, where small edges are set to zero. Ising models were constructed using R package *IsingFit* (van Borkulo, 2016), and visualized using *qgraph* (Epskamp et al., 2012). For a comprehensive introduction to Ising networks and their use in psychopathology research, see van Borkulo et al. (2015).

2.2.3 Network inference

We used *mgm* package (Haslbeck & Waldorp, 2016) to estimate how well other nodes in the network could predict the presence of a node. For binary data, the predictability estimate is normalized correct classification (nCC), indicated in our study by the blue circle around each node (Haslbeck & Waldorp, 2018). Nodes high in nCC are highly predictable based on the presence of the neighboring nodes, whereas low nCC indicates relative independence. In some instances, the nCC estimate may be negative due to over-fitting (Haslbeck & Waldorp, 2018). For graphical arguments the nCC of these near-zero nodes were set to exactly zero (no blue circle around the node).

Strength estimates of individual nodes were also analysed (Epskamp et al., 2018). Strength is a node centrality estimate, depicting how many and/or strong connections each individual node has. Instead of drawing inferences on the visual inspection of network structures themselves, centrality indices serve to quantify the relative importance of individual nodes. We used z-scores instead of raw scores in our study to facilitate comparison of strength estimates at two time points.

2.2.4 Network robustness

Bootstrapping methods were applied to edge weights and strength to estimate their robustness, using *bootnet* (Epskamp et al., 2018).

2.2.5 Network comparison

Invariance of the two network structures, global strengths and individual edges can be analysed using *NetworkComparisonTest* package (NCT; van Borkulo, 2016). However, if network structures do not differ significantly, examining individual edge differences may inflate the risk of type I error and should be avoided (Borkulo et al., 2017). Thus, only network structure and global strength invariances were analysed.

2.2.6 Community detection

Finally, we examined community structures of the networks at two time points. A community is a group of nodes that have dense connections inside the group, but sparse connections to other groups (Newman & Girvan, 2004). We used two community detection methods from *igraph* (Csardi & Nepusz, 2006), first of which is based on *walktrap* algorithm (Pons & Latapy, 2005), an agglomerative approach that detects the central nodes of a community with ease, but may be ambiguous in peripheral node detection (Newman &

Girvan, 2004). The second method is based on *spinglass* algorithm (Reichardt & Bornholdt, 2006) derived from principles of statistical mechanics. As *spinglass* produces slightly different results every time, 100 iterations were ran and a solution equivalent with the median number of communities in these iterations is presented. Results of *walktrap* community detection are presented in this paper, and *spinglass* results are located in the Supplementary Materials.

3. Results

3.1 Sample characteristics

Clinical and demographic data of participants is presented in Table 1. Of 3679 individuals, 481 were excluded due to them having a shorter than 259 or longer than 518 days of follow-up, as defined by MAD, leaving us the analytic sample of 3198 individuals. Participants with follow-up data were younger, more educated, had higher MMSE, MoCA, CDR and CDR-SOB scores and lower GDS scores than participants who had only baseline data (all p's < .05). However, the differences ranged from very small to medium in effect size (Cohen's d 0.04 – 0.37), highest for MMSE and lowest for age.

Table 1. Characteristics of the study sample.

	Baseline		Follow-up	
	Mean/%	SD	Mean/%	SD
Demographics				
Age, years	77.5	6.7		
Gender, female	52.8			
Ethnicity, Caucasian [a]	83.8			
Education, years[b]	14.4	3.7		
Clinical characteristics				
Cognitive Testing: MMSE (0-30)[c]	21.8	4.4	20.0	5.3
Cognitive Testing: MoCA (0-30)[c]	15.8	5.2	13.8	6.1
GDS Total Score (0-15)	2.3	2.4	2.1	2.4
CDR Sum of Boxes (0-18)	5.3	2.8	6.8	3.4
CDR Global Score (0-3)	0.9	0.5	1.2	0.6
Proportion positive for symptom				
NPI-Q Depression/Dysphoria	0.37	0.48	0.34	0.47
NPI-Q Anxiety/Nervousness	0.35	0.48	0.36	0.48
NPI-Q Apathy/Indifference	0.39	0.49	0.42	0.49
GDS Satisfied with Life*	0.11	0.31	0.10	0.30
GDS Dropped Activities and Interests	0.29	0.45	0.25	0.43
GDS Feel That Life is Empty	0.09	0.29	0.10	0.30
GDS Often Get Bored	0.17	0.37	0.17	0.37

GDS In Good Spirits Most of the Time*	0.06	0.24	0.05	0.22
GDS Afraid Something Bad is Going to Happen	0.09	0.29	0.07	0.25
GDS Feel Happy Most of the Time*	0.09	0.28	0.08	0.27
GDS Often Feel Helpless	0.14	0.34	0.13	0.33
GDS Prefer to Stay at Home	0.26	0.44	0.24	0.42
GDS More Memory Problems than Most	0.47	0.50	0.42	0.49
GDS Wonderful to be Alive*	0.04	0.20	0.04	0.20
GDS Feel Pretty Worthless	0.10	0.30	0.10	0.30
GDS Feel Full of Energy*	0.27	0.45	0.25	0.44
GDS Feel Situation is Hopeless	0.07	0.25	0.07	0.25
GDS Think Most People Are Better Off	0.08	0.28	0.08	0.28

Note. * Items have been reverse scored, a = missing data from 6 inviduals, b = missing data from 11 individuals. C, Participants were administered either MMSE or MoCA: MMSE for 2913 and 2844, MoCA for 237 and 300, cognitive data were missing from 48 and 51 participants, for baseline and follow-up, respectively. Ranges for clinical measures are included in parentheses. GDS = Geriatric Depression Scale, CDR = Clinical Dementia Rating, MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment, NPI-Q = Neuropsychiatric Inventory - Questionnaire

The mean time between visits was 386.74 (SD = 48.1) days. At follow-up, participants performed worse in cognitive testing on MMSE ($t(2834)= -28.63$, $p < .001$, $d = 0.39$) and MoCA ($t(231) = 8.55$, $p < .001$, $d = 0.35$), had higher CDR global score ($t(3179)= -38.01$, $p < .001$, $d = 0.43$) and CDR-SOB ($t(3179)= -38.01$, $p < .001$, $d = 0.48$), but scored slightly lower

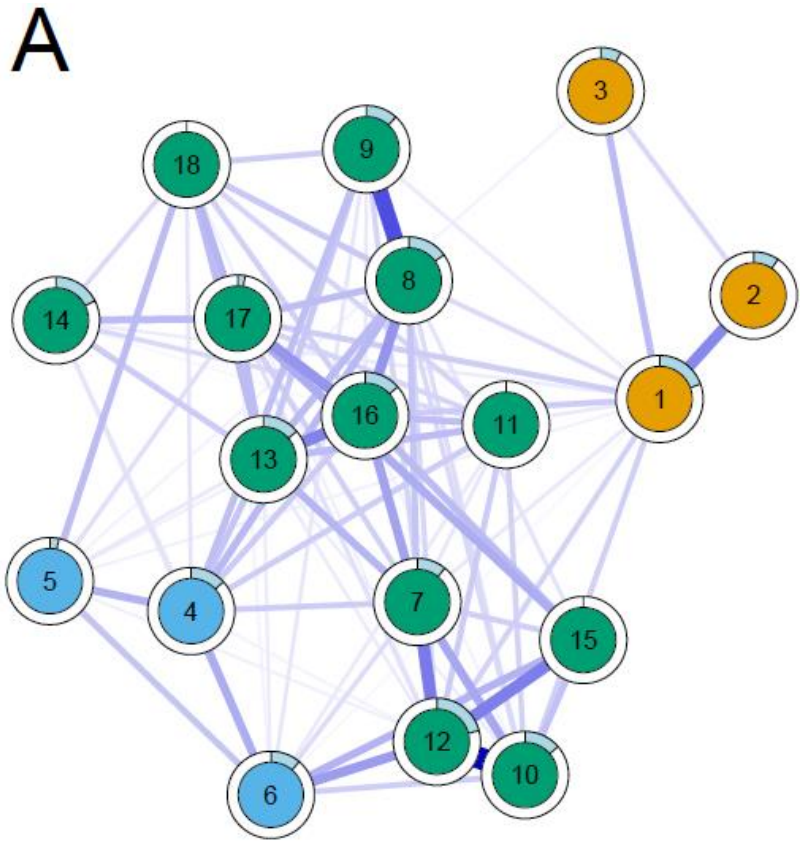
on GDS ($t(3179)=5.01$, $p < .001$, $d=0.08$) compared to baseline. At both time points, GDS item “More Memory Problems Than Most” was the most highly endorsed, whereas the item “Wonderful to Be Alive” (reverse-scored) was the least endorsed. Informant-rated affective symptoms, measured with NPI-Q, were for the most part more frequently observed than participant-rated symptoms.

3.2 Symptom networks

Figure 1 shows the networks at both time points. Relatively strong connections were observed between node 10 “In Good Spirits Most of the Time” and node 12 “Feel Happy Most of the Time”, as well as node 8 “Feel that Life is Empty” and node 9 “Often Get Bored”. Normalized correct classification, indicating how well a node is predicted by neighboring nodes, was highest for node 12 “Feel Happy Most of the Time” (0.2 and 0.21), but was relatively low averaged over all nodes ($M = 0.10$, $SD = 0.06$ and $M = 0.11$, $SD = 0.06$) at baseline and follow-up, respectively. For both networks, node 11 “Afraid Something Bad is Going to Happen” was not predicted by other nodes in the network, and node 18 “Think Most People are Better Off” was not meaningfully predicted by other nodes. Notable cross-modal connections were observed between informant-rated depression and (lack of) self-rated happy mood or being in good spirits.

Figure 2 indicates how many and/or strong connections each node had with other nodes. Highly similar strength estimates were observed at baseline and at follow-up, although satisfaction with life seemed to be more connected at follow-up. NPI-Q item for depressive symptoms was widely connected, however NPI-Q apathy item did not have strong connections with GDS-3A apathy questions despite conceptual resemblance. Additionally, NPI-Q anxiety item was not connected outside the NPI-Q triad. Self-reported memory

problem was also a relatively isolated node, as was staying at home and being afraid that something bad might happen. Feeling helpless or worthless, or not feeling happy, however, seemed to be more central symptoms.



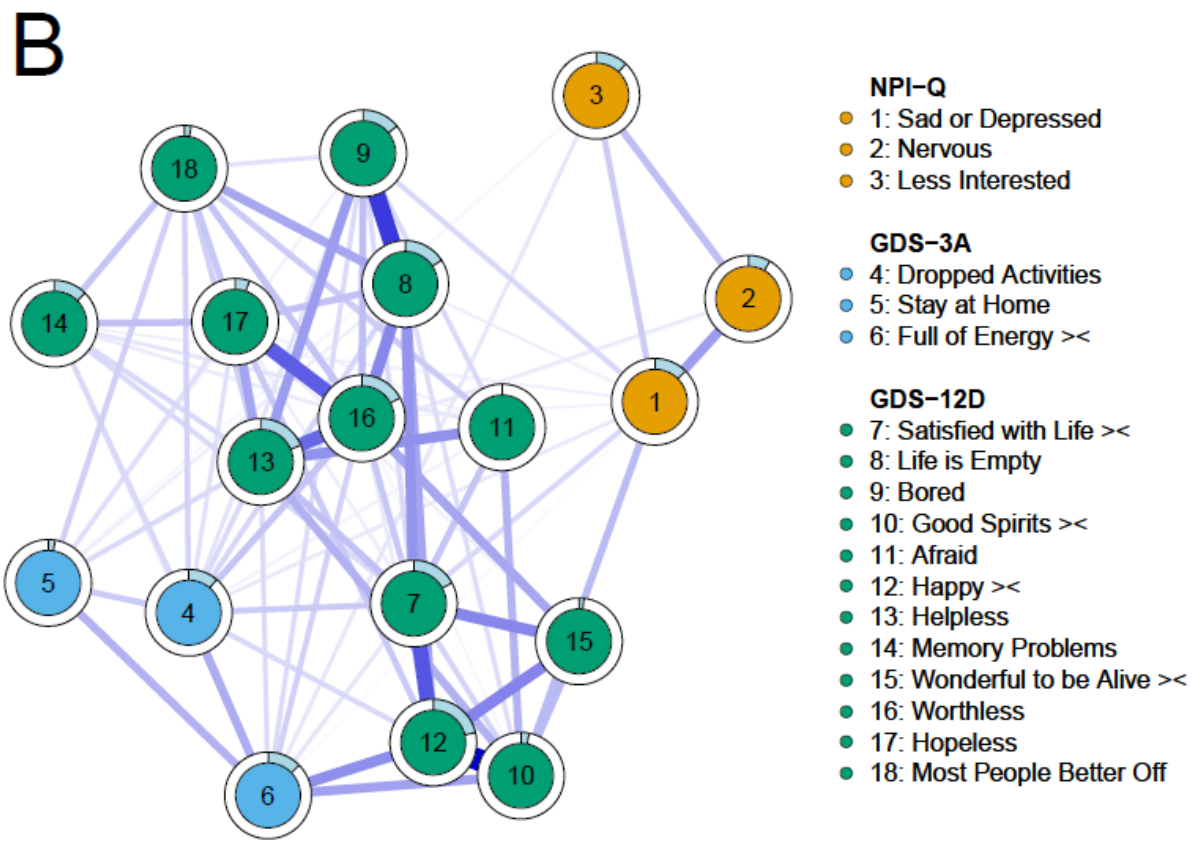


Figure 1. Network structures at baseline (A) and at follow-up (B). Orange nodes represent NPI-Q symptoms, as reported by an informant. Green nodes represent the twelve GDS items thought to assess depressive symptoms, and blue nodes correspond to the three GDS items related to apathy. Edges, or blue lines between the nodes, denote unique connections when conditioning for all other nodes in the network (van Borkulo et al., 2015)*, where thicker edges denote stronger connections. Blue circles around the nodes depict the degree of normalized correct classification, which is an index of predictability for binary data above what is trivially predicted by the relative probability of given condition (symptom present or not) irrespective of other nodes* (Haslbeck & Waldorp, 2018)*. Layout of the network is averaged over the two visits, and reverse-scored items are indicated by >< in the legend.*

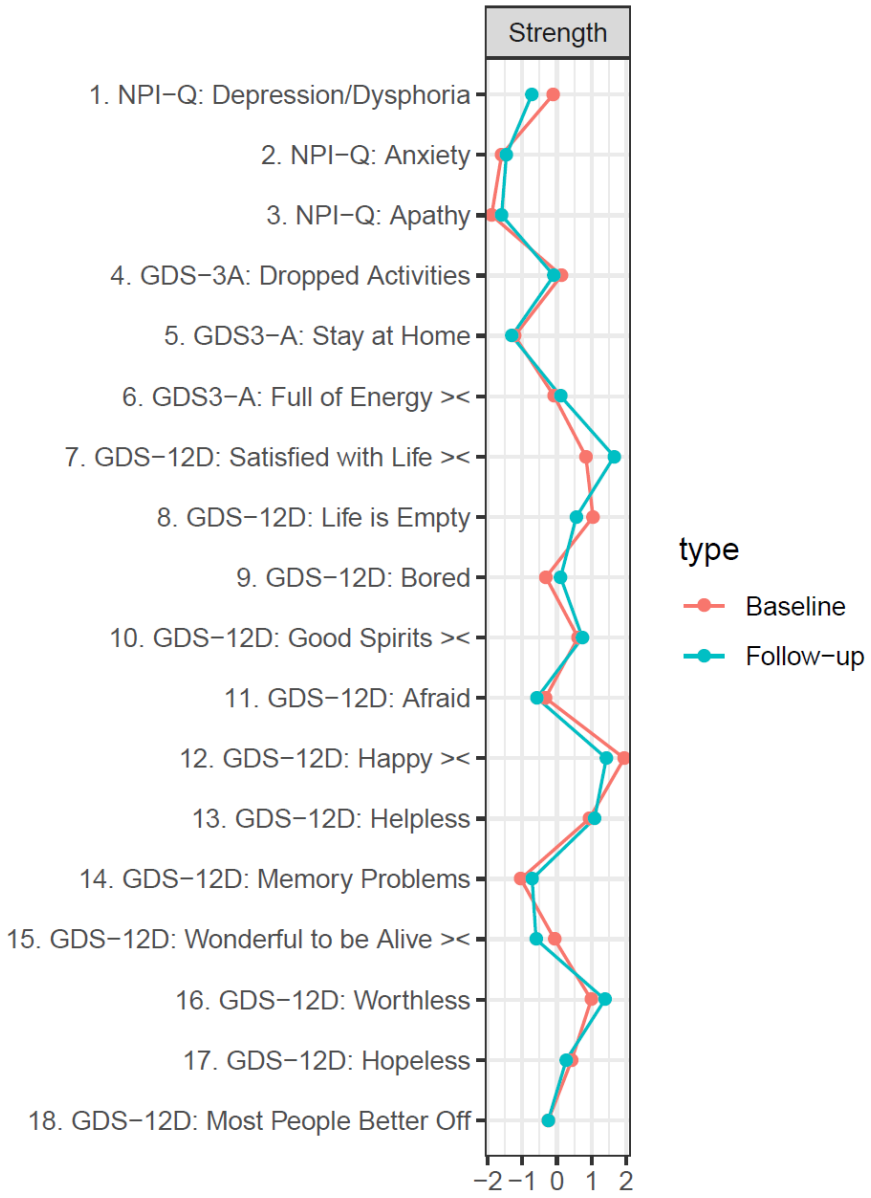
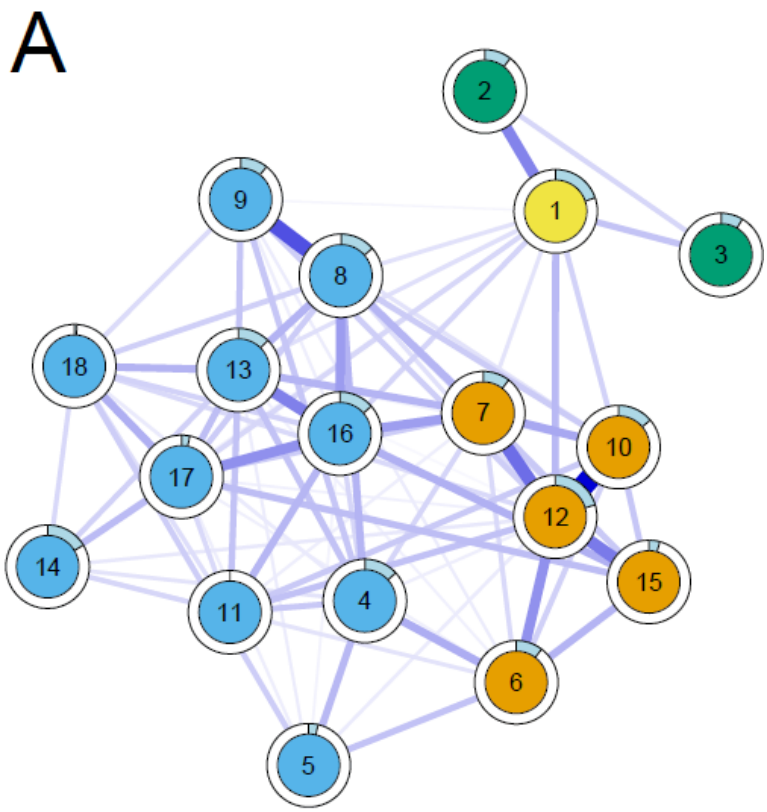


Figure 2. Standardized strength estimates of the nodes at baseline and at follow-up. Strength is a centrality measure for networks, which indicates the direct connectedness of a node (Epskamp et al., 2018)*. Strength values are the summary of edge weights connecting to a node, and these values were standardized for comparison in the figure.*

Bootstrapping methods were used to analyse whether networks, edge weights and strength estimates are robust and inferences justified (Supplementary Materials, Figures S1-S8). Of

note, correlation stability of the strength coefficient in Figure 2 were .67 and .75 at baseline and follow-up, respectively, indicating that the strength estimates are reliable (over the recommended cut-off of .5, Epskamp et al., 2018).

The networks were compared statistically to see if they differed between baseline and follow-up. No difference was found in network structure (0.71, p = 0.59), nor in global strength (0.92, p = 0.63).



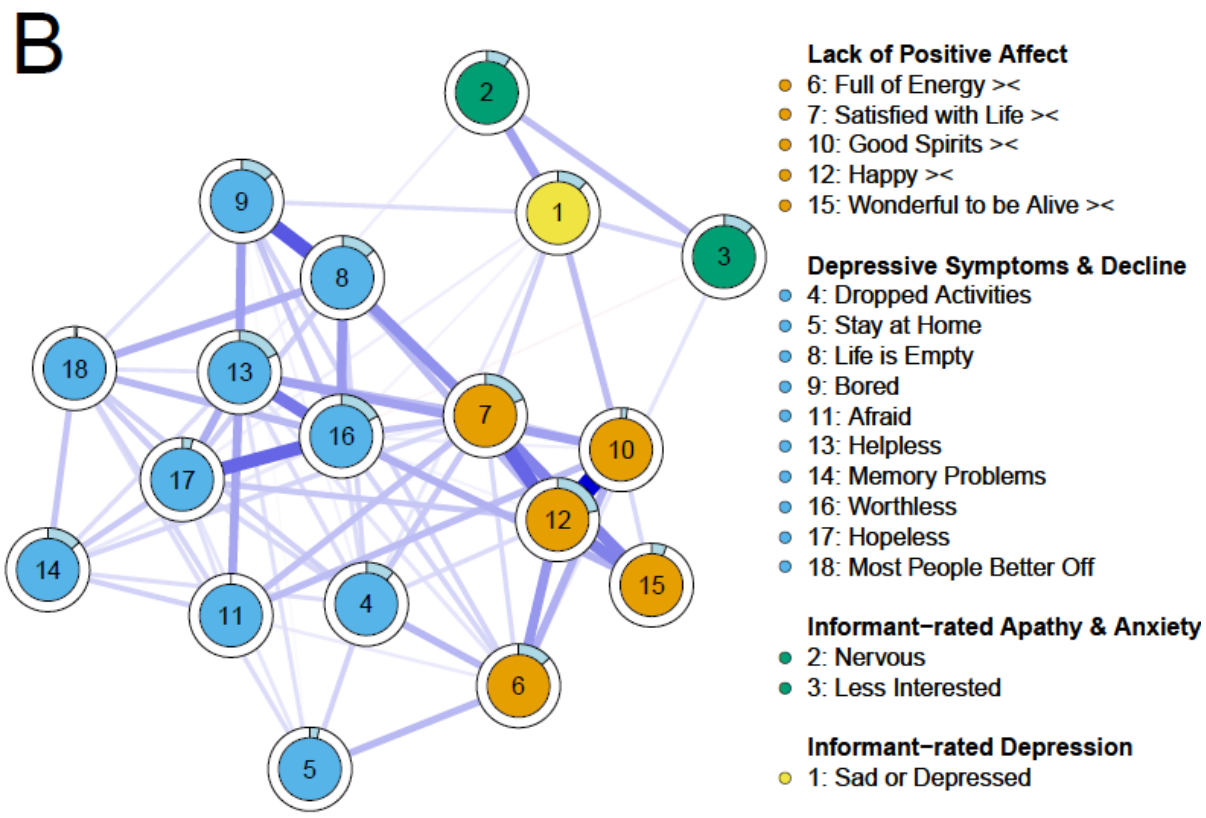


Figure 3. Community detection labelled networks using walktrap algorithm at baseline (A) and follow-up (B), where colors represent membership of communities. Note the discrepancies between a priori divisions in Figure 1 and this figure. Orange nodes represent the five reverse-scored items, interpreted as lack of positive affect. Blue nodes include depressive symptoms and symptoms that relate to decreasing capabilities, green nodes depict informant-rated apathy and anxiety, and the yellow node represents the one-node community of informant-rated depression.

Figure 3 demonstrates the results of community detection via *walktrap* algorithm. Notably, the community structures were identical at both time points (but not for *spinglass* method, see Figure S9, where a five-community structure was found for follow-up). Four communities were established, where the largest community represents depressive symptoms in combination with symptoms related to decreasing capabilities, a two-node

community includes informant-rated apathy and anxiety, and a five-node community denoting lack of positive affect. Finally, the last community is represented by just the informant-rated depression, bridging self-rated symptoms and other informant-rated symptoms.

None of the communities included a solution where informant-rated depressive symptoms would be included with self-rated depressive symptoms. Only *spinglass* results at follow-up supported the GDS-3A category.

All analyses were also performed without MAD outlier removal for time between visits, and highly similar results were found in terms of network structure, comparison between baseline and follow-up and centrality of individual nodes (Supplementary Materials). Community detection solutions were identical in the two samples.

4. Discussion

The aims of the study were to investigate network structures of affective symptoms in AD rated by the participant and an informant, and to examine whether the network structures were longitudinally stable. We found affective symptom networks to be stable across two visits in a large sample of elderly individuals with AD. Four communities of lack of positive affect, depressive symptoms and declining capabilities, informant-rated rated apathy and anxiety, and informant-rated depression were found. The most central symptoms in the first two large communities were not feeling happy for lack of positive affect, and feelings of worthlessness and helplessness for the depressive community. The informant-rated depression question had many, but relatively weak, connections to self-rated depression symptoms, perhaps capturing only the most visible, not necessarily the most central symptoms. Informant-rated symptoms of anxiety and apathy, also content represented in

the GDS questions, were mostly associated with informant-rated depression but not self-rated symptoms of similar content. Communities of self-rated symptoms differed slightly according to community detection method used, reflecting possible difficulties in assigning a symptom to just one community.

Stability of networks across the follow-up is in line with a recent study demonstrating that majority of the variance over time in GDS could be accounted for by a stable trait in elderly individuals (Gana et al., 2017). Network analytic research is just taking its first steps in neurodegenerative disease context, however the networks discovered in our study are markedly similar to those found recently in a sample of aged persons, largely without a diagnosis of dementia (van Wanrooij et al., 2019). Furthermore, a longitudinal study indicated that GDS-15 depressive symptoms, apart from memory problems, are similarly reported in individuals who reach CDR .5 and in those who remain at CDR 0 (Masters et al., 2015). Thus, there seems to be tentative evidence for symptom-level overlap in affective symptom dynamics in aged persons, with or without Alzheimer's disease.

Particularly, the similar connections between symptoms with a 'desperate quality' (Adams et al., 2004), such as helplessness, hopelessness and worthlessness, were found to be at the core of the symptom networks. We extended findings of van Wanrooij et al. by showing that informant-rated depressive symptoms are rather weakly connected to severe symptoms, such as hopelessness, which is a diagnosis-independent risk factor for suicide (Beck et al., 1990; Fried & Nesse, 2015). In line with van Wanrooij et al. (2019), we found anxiety (worry something bad might happen) and memory impairment to be weakly connected to other symptoms. Additionally, we found similar ambivalence regarding whether lack of energy was an indicator of absence of 'positive mood' (Kim et al., 2013) or apathy.

Furthermore, we found mixed evidence to support the GDS-3A apathy subscale, as both community detection methods would identify dropping of activities and preference to stay at home as part of broader depressive community, with the exception of *spinglass* method producing the apathetic symptom triad only at follow-up. This need not be controversial, as it may be reasonable to assume that one node can belong to multiple communities (Reichardt & Bornholdt, 2006): for example, having dropped activities may be related to several plausible causal chains, whether connected to depressive or apathetic symptoms (Marin, 1991). Hypothetically, we can formulate at least the following: dropping activities due to loss of interest, dropping activities due to burden of several depressive symptoms, or dropping activities due to cognitive impairment and being distressed by this loss. Based on symptom-level analysis, it is evident that the border between apathetic versus depressive disorders is fuzzy and the symptoms are perhaps more meaningfully modelled by networks, where sharp categories are not expected (Borsboom & Cramer, 2013; Fried, 2015; van Wanrooij et al., 2019).

The findings of this study may have clinical relevance. For example, it is acknowledged that informant reports may be biased in terms of severity, but our findings suggest that, owing to their nature, informant questionnaires could also be biased towards visible affective symptoms. Symptoms such as hopelessness or worthlessness could be crucial to understanding the patient's experience, yet these symptoms may be underappreciated in informant questionnaires (Mograbi & Morris, 2014). Notably, these are the same symptoms that are considered useful in differentiating apathy from depression (Tagariello et al., 2009).

In light of our data, research on affective symptoms in AD seems complex. Our findings highlight the limitations in using summary scores of GDS-15, GDS-12D or GDS-3A to denote

a symptom or a syndrome *a priori* (Marin, 1991; Fried, 2015; Fried & Nesse, 2015). Furthermore, it appears that informant-rated depressive symptoms only tap into some of the self-reported symptoms. Discrepancies between self- and informant ratings are likely influenced by several factors, such as differences in brevity and content of self and informant questions, anosognosia (Robert et al., 2018), biases in perceiving oneself versus others (Pronin, 2008; Allik et al., 2010), caregiver characteristics (de Vugt et al., 2004; Pfeifer et al., 2013) and variable representations of 'normal' age-related changes in mood (Georgi et al., 2018).

4.1 Limitations

Our study had some limitations. First, it is possible that the individuals enrolled in this study were already exhibiting similar patterns of affective symptoms before AD diagnosis, explaining similarities between networks found in this study and that found previously in predominantly cognitively healthy elderly (van Wanrooij et al., 2019). This issue could be further explored by constructing similar networks longitudinally in at-risk or MCI samples, who were later diagnosed with AD. However, as network analytic literature is still sparse in AD research, we considered characterization and temporal analysis of symptom dynamics to be a relevant opening for further studies. Second, a meta-analysis of the factor structure of GDS suggested that the language-invariant co-occurrence of the five reverse-scored items related to positive mood may simply reflect a methodological artefact, rather than a theoretically substantive clustering (Kim et al., 2013). However, network analysis allows us to demonstrate the connections inside and outside this five-node community, not just that they cluster together.

Third, our decision to remove individuals with very long or very short follow-up periods reduced the sample size. However, we consider this justifiable, as our analyses now represent more clearly an annual follow-up, and thus may generalize better to clinical contexts as well. It is also important to keep in mind that the network analytic methods here are considered to reveal the true network structure in sample sizes this large even with outlier removal (van Borkulo et al., 2015). Indeed, supplementary analyses revealed that our results are not dependent on outlier removal. Finally, the dropout rate was substantial and individuals who continued in the study were younger, more educated, cognitively and functionally less impaired and had lower total GDS-15 scores. These features, while not unusual in longitudinal studies of individuals with AD, may limit the external validity of our results.

4.2 Strengths

To our knowledge, this is the first, large-scale network analysis of affective symptoms in AD using data from two rating modalities. Our results complement factor analytic literature by showing that investigating detailed symptom relationships is a valid approach to model psychopathology in at least the early stages of AD. We were also able to demonstrate temporal stability of these symptom networks in a clinically relevant follow-up interval of one year. Furthermore, we demonstrated how informant-rated depressive symptoms align variably with self-rated symptoms, deepening the understanding of discrepancies between rating modalities. Finally, robustness analyses strengthened the validity of our models.

4.3 Conclusions

Networks of affective symptoms in individuals with AD were highly stable across a year of follow-up. Feelings of worthlessness and helplessness were central symptoms at both time

points, but they were relatively independent of informant-rated depressive symptoms. Informant-rated depressive symptoms were mostly connected to symptoms conveying lack of positive affect. No connections were found between informant-rated apathy and self-rated apathetic symptoms. Future research should continue to be mindful of differences between self- and informant-rated symptoms even in earlier stages of AD, and further utilize symptom-level data to increase precision in diagnostics and clinical intervention.

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