Behavioral/Cognitive

The Network Structure of Cognitive Impairment: From Subjective Cognitive Decline to Alzheimer's Disease

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It was proposed that a reorganization of the relationships between cognitive functions occurs in dementia, a vision that surpasses the idea of a mere decline of specific domains. The complexity of cognitive structure, as assessed by neuropsychological tests, can be captured by exploratory graph analysis (EGA). EGA was applied to the neuropsychological assessment of people (humans) with subjective cognitive decline (SCD), mild cognitive impairment (MCI), and Alzheimer's disease (AD; total $N = 638$). Both sexes were included. In AD, memory scores detach from the other cognitive functions, and memory subdomains reduce their reciprocal relation. SCD showed a pattern of segregated neuropsychological domains, and MCI showed a noisy and less stable pattern. Results suggest that AD drives a reorganization of cognitive functions toward a less-fractionated architecture compared with preclinical conditions. Cognitive functions show a reorganization that goes beyond the performance decline. Results also have clinical implications in test interpretations and usage.

Key words: **cognitive impairment; dementia; exploratory graph analysis; MCI; neuropsychological assessment**

Significance Statement

The manuscript proposes an innovative vision for the study of the complex reorganization of cognition in people with dementia. We applied a sophisticated, reliable, cutting-edge statistical method (i.e., exploratory graph analysis) to the neuropsychological evaluations of 638 patients classified into subjective cognitive decline (SCD; $N = 155$), mild cognitive impairment (MCI; $N = 242$), and Alzheimer's disease (AD; $N = 241$). Patients with AD showed a simplified architecture as compared with subjects with SCD. The MCI group resulted in sharing specific aspects with the SCD and others with the AD. Recognizing the complexity of the cognitive organization is fundamental for properly understanding cognitive impairment and stimulates the discussion about the interpretation of neuropsychological profiles from a more systemic point of view.

Introduction

Cognitive functioning is a dynamic system where different cognitive processes interact with each other (Van Der Maas et al., 2006). This hypothesis is supported by studies showing that neuropsychological performances are associated with each other (Van Der Maas et al., 2006; Tosi et al., 2020; C. Ferguson, 2021). In this framework, changes in one cognitive function may influence the relationship between other functions. Indeed, cognitive impairment not only reduces the performance of cognitive tests but also alters the balance among them (Weintraub et al., 2012; Tosi et al., 2020).

Alzheimer's disease (AD) is one of the most frequent and studied neurodegenerative disorders. From a neuropsychological

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perspective, AD usually starts with memory decline, and additional cognitive symptoms emerge as pathology progresses (Weintraub et al., 2012). Mild cognitive impairment (MCI) is characterized by a cognitive impairment which does not affect a person's basic activities of daily living (Albert et al., 2011; Van Der Mussele et al., 2013). MCI can be divided into subtypes: amnestic (aMCI) with memory deficits and nonamnestic (naMCI) with cognitive decline other than memory; these subtypes can be further specified, based on cognitive impairment in single or multiple domains (Albert et al., 2011; Van Der Mussele et al., 2013). Patients with MCI show cognitive performances falling midway between normal aging and mild AD and progress to dementia at a rate of ∼12% per year (Petersen and Morris, 2005). Recent longitudinal studies (Reisberg et al., 2008; Jessen et al., 2010, 2014) have shown that subjective cognitive decline (SCD) represents the early clinical stage of the AD continuum.

In neuropsychological clinical practice, the quantitative data obtained during the assessment are integrated with a qualitative analysis of overall performance (Tosi et al., 2020). Defining the patient's cognitive profile, meaning the balance between cognitive performance, is important for a better diagnosis comprehension. Network analysis (NA) offers a quantitative method to characterize the complexity of cognitive assessment in a parsimonious and comprehensible way by showing the relationship between variables and their mutual importance. The complexity of the cognitive organization can be explored by using NA to evaluate changes in the relationships between the different cognitive functions, as assessed by neuropsychological tests (Tosi et al., 2020; C. Ferguson, 2021, Ferguson, 2023; Nevado et al., 2022). A network is a model composed of a set of nodes, representing the variables of interest, and a set of edges connecting the nodes, which represent their relations (de Nooy et al., 2011). A pioneering study applied NA to neuropsychological assessment of AD patients speculating that memory tests isolate from the rest of the neuropsychological performances showing a specific reorganization of the cognitive abilities (Tosi et al., 2020).

We suppose that different conditions may have specific reorganization of the balance between cognitive performances, a marker that goes beyond the mere decline of test scores. In the present paper, we tackled this issue with a quantitative approach by means of the innovative statistical tool exploratory graph analysis (EGA; H. F. Golino and Epskamp, 2017; H. Golino et al., 2020). EGA is a particular type of NA, which combines network estimation with community detection (Fortunato, 2010). Conceptually, a community is a set of nodes more strongly related to each other than with nodes out of the community (H. Golino et al., 2019), a sort of latent variable (H. F. Golino and Epskamp, 2017). We applied EGA to a new, relatively large, sample of patients with AD and extended the examination of the cognitive network to patients suffering from MCI and people with SCD. These entities align on a continuum of clinical severity, going from a less severe subjective memory complaint to a more severe cognitive decline. Besides community detection, we also compared the network architecture of the three groups with a robust methodology to further characterize differences in the network organization. This sophisticated statistical approach, applied to relatively large sample sizes, will bring impactful insights about the complexity of cognitive functioning and its reorganization in people with cognitive impairments.

Materials and Methods

Participants

We reviewed medical records of patients referred, between January 2017 and January 2021, for memory complaints to the Center for Neurodegenerative Diseases and the Aging Brain of the University of Bari Aldo Moro. According to the National Institute on Aging and Alzheimer's Association diagnostic guidelines (Albert et al., 2011; McKhann et al., 2011), we identified 242 MCI patients (130 females; 149 aMCI; mean age, 69.05 ± 7.80 years; mean years of education, 7.97 ± 4.45) and 241 probable AD patients (148 females; mean age, 72.2 ± 8.03 years; mean years of education, 7.69 ± 4.50). Moreover, we identified 155 subjects with SCD (93 females; mean age, 63.7 ± 7.83 years; mean years of education, 10.9 ± 4.31) according to Jessen et al. (2014; i.e., subjects perceiving decline in memory and/or other cognitive functions without objective neuropsychological deficits). Exclusion criteria included the presence of previously diagnosed psychiatric disorders and vascular brain injury. We did not include longitudinal data.

All patients underwent a complete clinical assessment including clinical history, neurological examination, and neuropsychological evaluation. All study participants gave written informed consent, and the study was approved by the Institutional Review Board (or Ethics Committee) of ASL Lecce (record number 6, 25 July 2017), according to the Declaration of Helsinki.

Neuropsychological assessment

The neuropsychological assessment comprised the following tests: mini-mental state examination (MMSE; Folstein et al., 1975); frontal assessment battery (FAB; Dubois et al., 2000); semantic fluency test (Capasso and Miceli, 2001); phonemic fluency test (Caltagirone et al., 1995); Boston naming test (Kaplan et al., 2001); digit span forward and backward (Monaco et al., 2013); Rey Auditory Verbal Learning Test (RVLT), immediate and delayed recall (Caltagirone et al., 1995); clock-drawing test (CDT; Freedman et al., 1994; Caffarra et al., 2011); and incomplete letters subtest of the visual object and space perception battery (VOSP; Warrington and James, 1991).

We selected tests with <10% missing values that covered the main cognitive domains (general cognition, executive functions, language, memory, praxis, and visual perception).

Statistical analysis

The analyses were done in RStudio, Version 1.4.1106 (R Core Team, 2017) and Jasp (JASP Team, 2021).

We imputed missing values using the random forest algorithm. This was done using the *rfImpute* function of the *randomForest* package (Liaw and Wiener, 2003) by setting the diagnosis as the predictor. Overall, the missing values were 7.5% of the entire dataset.

We compared the groups' age and education and the groups' performances in all the neuropsychological tests included in the NA with one-way ANOVAs or nonparametric counterparts (Table 1).

Network analysis. EGA has been developed to estimate the number of dimensions in multivariate data using NA. Thus, EGA is composed of two steps: (1) network estimation and (2) community detection.

For the network estimation, we used a Gaussian graphical model (GGM; Costantini et al., 2015), where nodes represent variables and edges correspond to partial correlation coefficients. This method employs the "least absolute shrinkage and selection operator" (LASSO; Tibshirani, 2011), a regularization technique that shrinks the partial correlation coefficients leading small connections to zero (McNeish, 2015; Epskamp and Fried, 2018). The LASSO uses a parameter called lambda (λ) to control the sparsity of the network. We set the ratio of the minimum and maximum λ to 0.001 and computed models across 1,000 values of λ. We selected the model that minimized the extended Bayesian Information Criterion (EBIC; Chen and Chen, 2008; Epskamp and Fried, 2018). The EBIC model selection uses a hyperparameter gamma (γ) to identify the most parsimonious model that best fits the data (Foygel and Drton, 2010). Larger values of γ lead to simpler models, which means fewer chances of false-positive edges (Type 1 error) and

Table 1. Groups comparison

					Post hoc		
	SCD (mean ± SD)	MCI (mean ± SD)	AD (mean ± SD)	ANOVA	SCD vs MCI	SCD vs AD	MCI vs AD
Age	63.72 ± 7.83	69.49 ± 7.80	72.16 ± 8.03	$F_{(2,635)} = 54.29$, $p < 0.001$	$t = -7.10$, $p < 0.001$	$t = -10.37$, $p < 0.001$	$t = -3.71$, $p < 0.001$
Edu	10.92 ± 4.31	7.97 ± 4.45	7.69 ± 4.50	$F_{(2,635)} = 28.72$, $p < 0.001$	$t = 6.47$, $p < 0.001$	$t = 7.07$, $p < 0.001$	$t = 0.68$, $p = 1.00$
MMSE	27.67 ± 2.31	24.43 ± 3.57	16.64 ± 5.43	$H_{(2)} = 371.12$, $p < 0.001$	$z = 7.39$, $p < 0.001$	$z = 18.61$, $p < 0.001$	$z = 12.71$, $p < 0.001$
FAB	15.39 ± 2.30	12.24 ± 3.14	8.51 ± 3.31	$H_{(2)} = 289.49$, $p < 0.001$	$z = 8.21$, $p < 0.001$	$z = 16.82$, $p < 0.001$	$z = 9.75$, $p < 0.001$
RVLTi	35.89 ± 7.98	25.28 ± 8.25	14.55 ± 6.46	$H_{(2)} = 358.75$, $p < 0.001$	$z = 8.58$, $p < 0.001$	$z = 18.62$, $p < 0.001$	$z = 11.36$, $p < 0.001$
RVLTd	7.01 ± 2.33	3.66 ± 2.77	0.60 ± 1.27	$H_{(2)} = 357.93$, $p < 0.001$	$z = 8.72$, $p < 0.001$	$z = 18.63$, $p < 0.001$	$z = 11.21$, $p < 0.001$
DSf	5.63 ± 0.86	4.94 ± 0.90	4.40 ± 1.10	$H_{(2)} = 126.17$, $p < 0.001$	$z = 6.62$, $p < 0.001$	$z = 11.23$, $p < 0.001$	$z = 5.23$, $p < 0.001$
DSb	3.78 ± 0.77	3.01 ± 1.04	2.19 ± 1.18	$H_{(2)} = 192.72$, $p < 0.001$	$z = 7.31$, $p < 0.001$	$z = 13.81$, $p < 0.001$	$z = 7.36$, $p < 0.001$
PhonF	29.36 ± 10.87	18.78 ± 9.91	12.58 ± 9.70	$F_{(2,635)} = 131.05$, $p < 0.001$	$t = 10.21$, $p < 0.001$	$t = 16.78$, $p < 0.001$	$t = 6.20$, $p < 0.001$
SemF	21.04 ± 10.80	17.75 ± 8.00	11.82 ± 5.01	$H_{(2)} = 159.67$, $p < 0.001$	$z = 3.83$, $p < 0.001$	$z = 11.88$, $p < 0.001$	$z = 9.11$, $p < 0.001$
BNT	30.13 ± 11.91	22.73 ± 9.75	15.58 ± 8.28	$H_{(2)} = 151.48$, $p < 0.001$	$z = 5.60$, $p < 0.001$	$z = 12.10$, $p < 0.001$	$z = 7.36$, $p < 0.001$
CDT	11.30 ± 1.71	8.79 ± 2.70	5.84 ± 2.86	$H_{(2)} = 271.42$, $p < 0.001$	$z = 8.06$, $p < 0.001$	$z = 16.30$, $p < 0.001$	$z = 9.33$, $p < 0.001$
Vsil	19.00 ± 1.88	17.16 ± 3.06	11.51 ± 6.22	$H_{(2)} = 253.97$, $p < 0.001$	$z = 6.71$, $p < 0.001$	$z = 15.55$, $p < 0.001$	$z = 10.01$, $p < 0.001$

The table shows the results of the one-way ANOVA or the Kruskal–Wallis test. In case of significant results, we reported the standard or Dunn's post hoc comparison. Bonferroni's correction was adopted. MMSE, mini-mental state examination; FAB, frontal assessment battery; RVLTi, Rey Auditory Verbal Learning Test, immediate recall; RVLTd, Rey Auditory Verbal Learning Test, delayed recall; DSf, digit span forward; DSb, digit span backwards; PhoF, phonemic fluency test; SemF, semantic fluency test; BNT, Boston naming test; CDT, clock-drawing test; VSil, incomplete letters subtest of the VOSP.

more chances of omitting a true edge (Type 2 error). We set γ to 0.5 to have a good balance between the two errors given our sample size (Epskamp, 2016). EGA then applies a Walktrap algorithm (Pons and Latapy, 2006), which uses the node strength to compute the probability of one node traversing to another. This transition matrix is then used to establish the probable destinations for four random steps. Using Ward's agglomerative clustering approach (Ward, 1963), each node merges with adjacent clusters thus minimizing the sum of squared distances between other clusters. Modularity (Newman, 2006) is then used to determine the optimal partition of clusters (i.e., communities).

After performing EGA, we evaluated the accuracy of edge weights (bootnet; Epskamp and Fried, 2018) and the dimensional structure (bootEGA; Christensen and Golino, 2019) via bootstrap procedures. In both cases, we generated 4,000 bootstrap samples with a nonparametric (resampling) procedure and obtained a sampling distribution of edge weights and EGA results. Moreover, we calculated centrality indices of each node, to inform about the relative role of the tests in the network. In particular, we focused on the betweenness (i.e., the number of shortest paths between any two nodes that pass through the focal node), the closeness (i.e., the inverse of the sum of the distances of the focal node from all the other nodes in the network), and the strength (i.e., the sum of the absolute weights of the connections with the focal node). Centrality stability was calculated by estimating network models based on subsets of the data (case-dropping subset bootstrap) via the bootnet function (Epskamp and Fried, 2018). We looked at the correlation stability coefficient (CS-coefficient), which shows the maximum drop proportions to retain a correlation of 0.7 in at least 95% of the samples (Epskamp and Fried, 2018). CS-coefficient values <0.2 suggest unstable measures (Epskamp and Fried, 2018). As an additional check, we correlated the strength of the nodes with their standard deviation, as suggested by Fried (2016), to check if nodes differential variability drive their centrality and the network structure.

EGA and bootEGA were applied using the *EGAnet* package (version 0.9.8; Christensen and Golino, 2021). bootnet was applied using the *bootnet* package (version 1.5.5; Epskamp and Fried, 2018). Centrality indices were calculated via the *centralityTable* function in the *qgraph* R package (version 1.9.5; Epskamp et al., 2012). The nodes of our EGA were the raw scores on the neuropsychological tests described above.

Network comparison test (NCT). To directly compare the three structures of the estimated networks, we applied the NCT, which evaluates the invariance between pairs of networks. The NCT computes the statistics of interest in each network and approximates their distribution through 1,000 permutations. After each permutation of the data, networks are reestimated, thus resulting in a reference distribution of the statistics under the null hypothesis. This reference distribution is then used to evaluate the extremeness of the observed test statistic.

We focused on the global strength invariance test, which compares the weighted absolute sum of all edges strength between the networks, and the edge invariance test, which compares the weight of each edge between the networks (applying Holm–Bonferroni's correction for multiple comparisons). We performed three comparisons: AD versus MCI, MCI versus SCD, and AD versus SCD.

NCT was applied using the *NetworkComparisonTest* package (van Borkulo et al., 2022).

Results

One-way ANOVAs between groups (AD vs MCI vs SCD) revealed significant differences in both age ($F_{(2,635)} = 54.29$; $p < 0.001$) and years of education ($F_{(2,635)} = 28.72$; $p < 0.001$). SCD subjects were younger than MCI patients, who were younger than AD patients. Moreover, SCD subjects had more years of study as compared with both AD and MCI patients. Significant differences were found in all neuropsychological tests as well. As expected, the cognitive performances significantly decreased along with the severity of the cognitive decline (Table 1).

EGA

We estimated the best-fitting network for each group and reported the following information: (1) the mean edge weight, as measuring the strength of the connections in the network; (2) the density of the network, as the proportion of existing edges in a graph compared to the total possible edges in a totally connected (i.e., dense) graph (Goswami et al., 2018; higher values of density indicate a higher proportion of existing edges on the total number of all possible edges); and (3) the centrality indices of the nodes, to inform about the relative role of the tests in the network: betweenness indicates the role of a node as a mediator between other nodes; closeness tells if a node is more directly or indirectly connected with the others; strength gives information about the direct interaction between nodes. In neuropsychological terms, these indices measure the importance of specific cognitive performance relative to general cognitive functioning. A central node will represent a cognitive performance associated with multiple cognitive domains. Such information can help plan cognitive training, indicating which cognitive task will more probably generalize to other functions.

We also reported the bootstrapped edge weights accuracy, the centrality stability, and the bootstrap results assessing the dimensional stability. In particular, we computed the median number of dimensions, the 95% confidence intervals (CI) around the

median, the number of times the structure replicated, and the number of times each node replicated in its dimension.

AD patients

The AD network showed a density index of 0.71, with a mean edge weight of 0.08 (the full list of weights and correlation is reported in Table 2; bootstrapped edge weights accuracy is reported in in Fig. 2). EGA identified two communities (Fig. 1*AD-A*) with semantic fluency and long-term memory subtests segregating from the other cognitive measures. The bootstrap confirmed a median number of dimensions of 2 [CI, (0.61; 3.39); replication frequency, 0.53], proving the best-fitting network as the most probable configuration. Looking at the replication rate of each item in its dimension (Table 3), most of the nodes showed a good replication rate (>0.70). Only the semantic fluency test showed a low replication frequency in its dimension (0.49) and a similar rate in the second dimension (0.42), suggesting that this node is likely to be a bridge between the two communities. The centrality indices revealed the immediate recall of the RVLT, the FAB, and the MMSE as the most central and influential nodes (Fig. 1*AD-B*; see Table 4 for centrality scores and stability). Differential variability may have influenced the network structure since the medium correlation between node strength and standard deviation ($r = 0.467$).

MCI patients

The MCI network showed a density index of 0.75, with a mean edge weight of 0.10 (the full list of weights and correlation is reported in Table 2; bootstrapped edge weights accuracy is reported in Fig. 2). EGA identified four communities (Fig. 1*MCI-A*): (1) long-term memory; (2) executive functions and short-term memory; (3) screening tests, working memory, and praxis; and (4) language. However, the bootstrap results showed a median number of dimensions of 3 [CI, (1.38; 4.62); replication frequency, 0.49). The best-fitting network had a replication frequency of 0.23, thus being the second most replicated structure. Table 5 shows the replication rate of each item in its dimension, considering the best-fitting network. As we can see, the first and the third communities' nodes showed good replication rates, higher than 0.67. On the contrary, the nodes comprised in the second and the fourth communities showed low replication frequencies (i.e., <0.57). Interestingly, the nodes in the second dimension showed moderate replication frequency (i.e., between 0.35 and 0.46) in the third community as well, suggesting fading boundaries between these dimensions. The item loadings are in line with these results (Table 5). The centrality indices revealed that the FAB was the most central and influential node (Fig. 1*MCI-B*; see Table 4 for centrality scores and stability). Differential variability may have influenced the network structure since the medium correlation between nodes strength and standard deviation ($r = 0.385$).

SCD subjects

The SCD network showed a density index of 0.62, with a mean edge weight of 0.08 (the full list of weights and correlation is

Table 2. Correlations and network edges of all the patients' groups

		MMSE	FAB	RVLTi	RVLTd	DSf	DSb	PhonF	SemF	Boston	CDT	VSil
AD	MMSE		0.663	0.549	0.315	0.440	0.561	0.601	0.388	0.564	0.546	0.525
	FAB	0.184		0.560	0.299	0.477	0.562	0.698	0.340	0.584	0.526	0.566
	RVLTi	0.115	0.109		0.430	0.414	0.402	0.550	0.376	0.550	0.360	0.394
	RVLTd	0.060	0.023	0.254		0.082	0.169	0.155	0.196	0.186	0.150	0.222
	DSf	0.043	0.061	0.072	0.000		0.431	0.525	0.201	0.434	0.283	0.286
	DSb	0.170	0.134	0.000	0.000	0.121		0.508	0.203	0.488	0.444	0.444
	PhonF	0.103	0.305	0.126	0.000	0.199	0.061		0.318	0.573	0.479	0.432
	SemF	0.127	0.022	0.143	0.000	0.000	0.000	0.021		0.176	0.260	0.306
	BNT	0.101	0.094	0.194	0.000	0.076	0.096	0.130	0.000		0.474	0.467
	CDT	0.167	0.081	0.000	0.000	0.000	0.076	0.069	0.000	0.099		0.506
	Vsil	0.104	0.191	0.000	0.001	0.000	0.076	0.000	0.070	0.087	0.196	
MCI	MMSE		0.504	0.390	0.435	0.303	0.342	0.311	0.228	0.255	0.405	0.429
	FAB	0.180		0.445	0.278	0.413	0.464	0.593	0.106	0.342	0.442	0.420
	RVLTi	0.000	0.186		0.668	0.248	0.234	0.235	0.266	0.194	0.217	0.259
	RVLTd	0.220	0.000	0.549		0.070	0.056	0.062	0.262	0.119	0.238	0.232
	DSf	0.069	0.124	0.057	−0.052		0.305	0.375	0.136	0.186	0.246	0.241
	DSb	0.068	0.212	0.031	−0.087	0.099		0.298	0.101	0.208	0.315	0.407
	PhonF	0.000	0.390	0.000	−0.063	0.156	0.000		0.028	0.395	0.263	0.296
	SemF	0.160	0.000	0.145	0.072	0.064	0.035	0.054		−0.453	0.049	−0.025
	BNT	0.099	0.035	0.102	0.000	0.013	0.000	0.224	−0.488		0.268	0.378
	CDT	0.129	0.159	0.000	0.031	0.028	0.048	0.000	0.000	0.043		0.439
	Vsil	0.161	0.056	0.000	0.030	0.007	0.202	0.000	0.000	0.188	0.215	
SCD	MMSE		0.562	0.330	0.256	0.262	0.487	0.370	0.264	0.021	0.254	0.569
	FAB	0.235		0.449	0.389	0.269	0.427	0.512	0.134	0.122	0.334	0.490
	RVLTi	0.029	0.158		0.708	0.262	0.242	0.180	0.111	0.205	0.242	0.318
	RVLTd	0.000	0.052	0.590		0.283	0.194	0.141	0.252	0.065	0.175	0.284
	DSf	0.032	0.038	0.037	0.098		0.092	0.103	0.101	0.006	−0.040	0.088
	DSb	0.210	0.083	0.000	0.000	0.188		0.333	0.049	0.178	0.133	0.445
	PhonF	0.054	0.320	0.000	0.000	0.010	0.103		0.184	0.050	0.155	0.282
	SemF	0.154	0.000	0.000	0.150	0.025	0.000	0.060		−0.641	0.052	0.075
	BNT	0.000	0.000	0.133	0.000	0.000	0.080	0.000	−0.599		0.156	0.210
	CDT	0.041	0.154	0.054	0.000	0.000	0.000	0.000	0.000	0.056		0.250
	Vsil	0.321	0.153	0.020	0.034	0.000	0.156	0.000	0.000	0.111	0.046	

The upper triangle shows the correlation between the nodes; the lower triangle shows the weights of the edges in the best-fitting networks. MMSE, mini-mental state examination; FAB, frontal assessment battery; RVLTi, Rey Auditory Verbal Learning Test, immediate recall; RVLTd, Rey Auditory Verbal Learning Test, delayed recall; DSf, Digit span forward; DSb, Digit span backwards; PhoF, phonemic fluency test; SemF, semantic fluency test; BNT, Boston naming test; CDT, clock-drawing test; VSil, incomplete letters subtest of the VOSP.

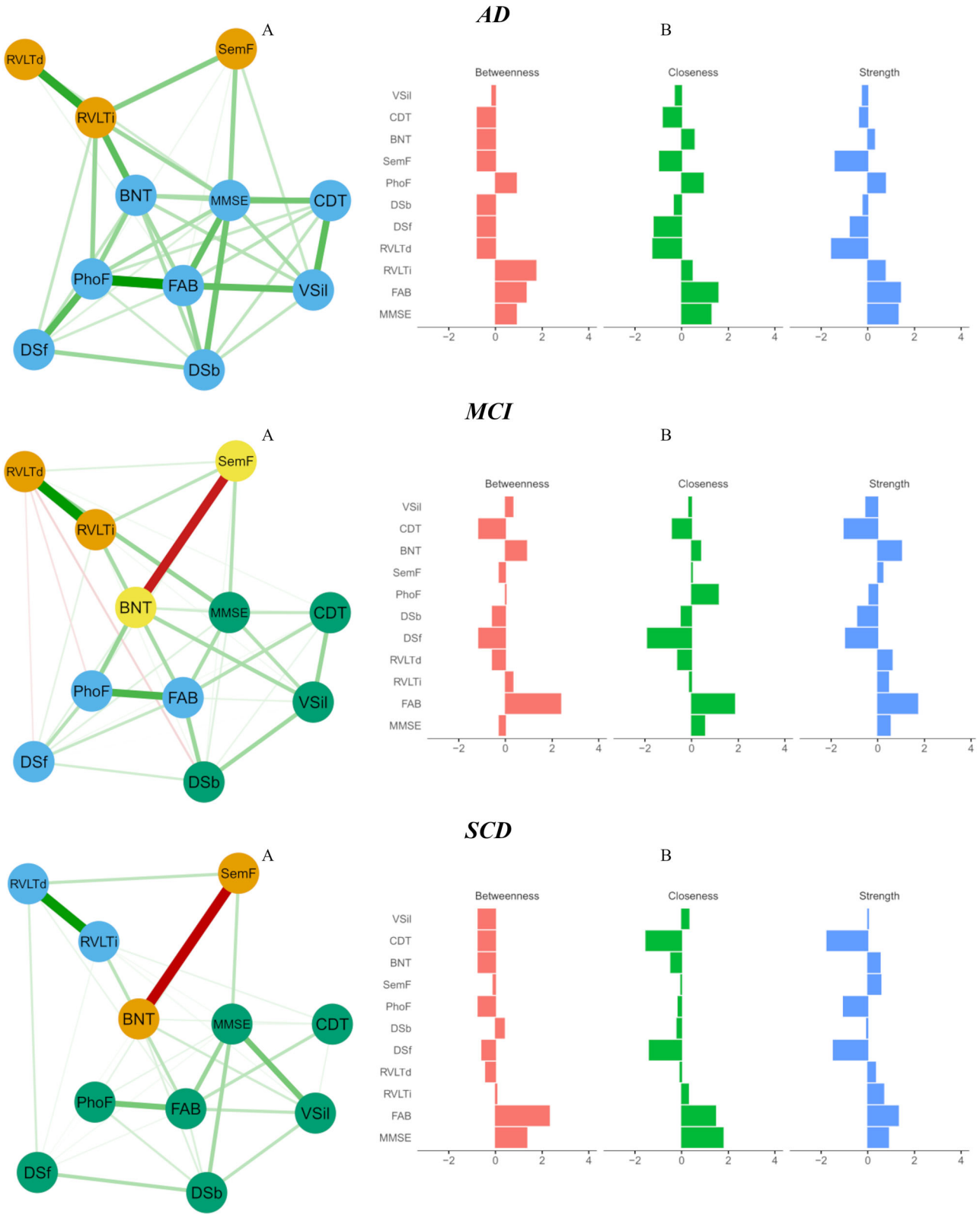

Figure 1. AD, MCI, and SCD networks, and centrality indices. Panel ***A*** represents the best-fitting network. Edges represent partial correlations as estimated by the GGM; red edges indicate negative relations; green edges show positive ones. The size and the color saturation of the edges represent the intensity of the relationships. The nodes' colors represent the communities (nodes with the same color belong with the same community). Network layouts were matched between groups to facilitate comparisons. Panel ***B*** reports the centrality indices. Betweenness is high if the node is part of many shortest paths connecting two different nodes. Closeness is high if the node is central in the network structure. Strength centrality is higher if a node has a large number of strong direct connections with other nodes. Centrality indices are standardized and expressed in *z*-scores. MMSE, mini-mental state examination; FAB, frontal assessment battery; RVLTi, Rey Auditory Verbal Learning Test, immediate recall; RVLTd, Rey Auditory Verbal Learning Test, delayed recall; DSf, Digit span forward; DSb, Digit span backwards; PhoF, phonemic fluency test; SemF, semantic fluency test; BNT, Boston naming test; CDT, clock-drawing test; VSil, incomplete letters subtest of the VOSP.

reported in Table 2; bootstrapped edge weights accuracy is reported in Fig. 2). EGA identified three communities (Fig. 1*SCD-A*): (1) memory; (2) executive functions, screening tests and praxis; and (3) language. The bootstrap results confirmed a median number of dimensions of 3 [CI, (2.09; 3.93); replication frequency, 0.78). Looking at the replication rate of each item in its dimension (Table 6), most of the nodes showed a good replication rate, higher than 0.70, suggesting a replicable structure. The digit span forward showed a moderate replication frequency in its dimension (0.64) but a low item loading. The centrality indices revealed the FAB and the MMSE as the most central and influential nodes (Fig. 1*SCD-B*; see Table 4 for centrality scores and stability). It is unlikely that differential variability have influenced the network structure since the small correlation between node strength and standard deviation ($r = 0.178$).

Table 3. AD patients' EGA item loadings and bootstrap replication frequency

	1		2	
	Loadings	Replication frequency	Loadings	Replication frequency
Digit span forward	0.102	*0.20*	**0.174**	***0.703***
Phonemic fluency	0.166	*0.175*	**0.298**	***0.734***
Boston naming test	0.154	*0.143*	**0.25**	***0.780***
Incomplete letters (VOSP)			**0.235**	***0.871***
MMSE			**0.331**	***0.875***
Clock-drawing test			**0.238**	***0.876***
FAB			**0.354**	***0.886***
Digit span backward			**0.239**	***0.933***
Semantic fluency	**0.132**	***0.492***	0.115	*0.428*
RVLT delayed recall	**0.187**	***0.711***	0.074	*0.279*
RVLT immediate recall	**0.306**	***0.713***	0.225	*0.277*

Replication frequency is highlighted in italic; loadings and replication frequency of nodes belonging to each community are highlighted in bold.

NCT

The global strength invariance test showed a nearly significant difference between the SCD and MCI networks ($s = 0.75$; $p = 0.07$). In particular, SCD subjects revealed a network characterized by weaker connections (global strength, 4.58) as compared with the MCI patients (global strength = 5.33). The other comparisons (AD vs MCI and SCD) did not show any significant differences (p values >0.10).

Table 4. Centrality scores and stability

	AD			MCI			SCD		
	Betweenness	Closeness	Strength	Betweenness	Closeness	Strength	Betweenness	Closeness	Strength
MMSE	0.894	1.305	1.301	−0.266	0.597	0.535	1.342	1.775	0.884
FAB	1.313	1.489	1.401	2.366	1.807	1.710	2.304	1.457	1.310
RVLTi	1.732	0.534	0.744	0.319	−0.064	0.462	0.058	0.291	0.681
RVLTd	−0.780	−1.237	−1.551	−0.558	−0.576	0.616	−0.423	−0.068	0.329
DSf	−0.780	−1.083	−0.751	−1.143	−1.890	−1.379	−0.583	−1.385	−1.477
DSb	−0.780	−0.375	−0.201	−0.558	−0.479	−0.859	0.379	−0.199	−0.050
PhoF	0.894	0.991	0.755	0.027	1.110	−0.372	−0.744	−0.155	−1.045
SemF	−0.780	−1.003	−1.397	−0.266	0.004	0.221	−0.102	−0.035	0.561
BNT	−0.780	0.490	0.286	0.904	0.502	1.017	−0.744	−0.466	0.530
CDT	−0.780	−0.781	−0.354	−1.143	−0.857	−1.441	−0.744	−1.529	−1.749
VSil	−0.152	−0.331	−0.232	0.319	−0.154	−0.509	−0.744	0.313	0.027
CS-coef (cor = 0.7)	0.207	0.593	0.593	0.360	0.360	0.285	0.206	0.052	0.284

The table shows standardized centrality indices and their stability (CS-coefficient). MMSE, mini-mental state examination; FAB, frontal assessment battery; RVLTi, Rey Auditory Verbal Learning Test, immediate recall; RVLTd, Rey Auditory Verbal Learning Test, delayed recall; DSf, Digit span forward; DSb, Digit span backwards; PhoF, phonemic fluency test; SemF, semantic fluency test; BNT, Boston naming test; CDT, clock-drawing test; VSil, incomplete letters subtest of the VOSP; CS-coefficient = correlation stability coefficient.

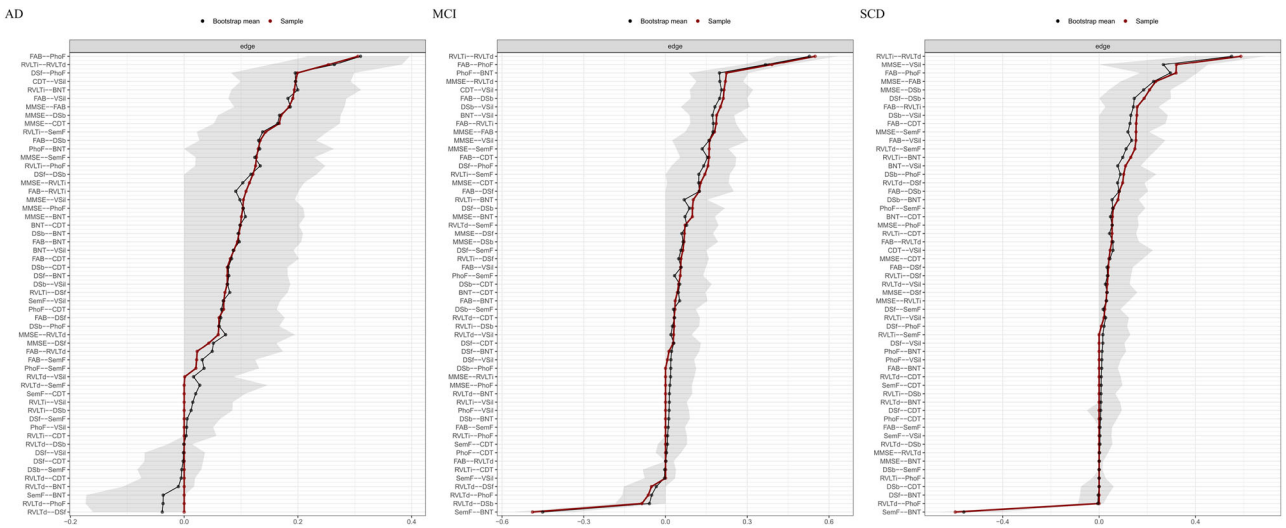

Figure 2. Bootstrapped confidence intervals of estimated edge weights. The figure shows the 95% bootstrapped CIs of edge weights in each sample. The black line indicates the bootstrapped mean values of the confidence interval, the red line indicates the sample values, and the gray area indicates the 95% confidence intervals.

Table 5. MCI patients' EGA item loadings and bootstrap replication frequency

	1		2		3		4	
	Loadings	Replication frequency	Loadings	Replication frequency	Loadings	Replication frequency	Loadings	Replication frequency
Boston naming test			0.117	*0.143*	0.077	0.201	**0.324**	***0.563***
Semantic fluency	0.068	*0.133*	0.080	*0.127*	0.059	0.176	**0.311**	***0.564***
MMSE			0.173	*0.124*	**0.244**	***0.665***	−0.013	*0.157*
Digit span backward			0.177	*0.233*	**0.213**	***0.749***		
Incomplete letters (VOSP)			0.118	*0.119*	**0.276**	***0.863***		
Clock-drawing test			0.129	*0.123*	**0.222**	***0.865***		
FAB			**0.348**	***0.538***	0.324	*0.459*		
Digit span forward			**0.190**	***0.550***	0.129	*0.395*		
Phonemic fluency			**0.289**	***0.569***	0.141	*0.35*		
RVLT delayed recall	**0.376**	***0.860***			0.128	*0.101*		
RVLT immediate recall	**0.378**	***0.860***						

Replication frequency is highlighted in italic; loadings and replication frequency of nodes belonging to each community are highlighted in bold.

Table 6. SCD patients' EGA item loadings and bootstrap replication frequency

	1		2		3	
	Loadings	Replication frequency	Loadings	Replication frequency	Loadings	Replication frequency
Clock-drawing test	0.042	*0.084*			**0.105**	***0.704***
Phonemic fluency					**0.211**	***0.894***
Digit span backward					**0.323**	***0.912***
FAB	0.151	*0.001*			**0.430**	***0.908***
Incomplete letters (VOSP)					**0.295**	***0.963***
MMSE			−0.110	*0.001*	**0.390**	***0.984***
Digit span forward					**0.116**	***0.637***
Boston naming test			**0.421**	***0.944***	−0.108	*0.001*
Semantic fluency	−0.108	*0.054*	**0.427**	***0.944***	−0.104	*0.001*
RVLT delayed recall	**0.424**	***0.968***	−0.107	*0.001*	0.128	*0.001*
RVLT immediate recall	**0.424**	***0.968***				

Replication frequency is highlighted in italic; loadings and replication frequency of nodes belonging to each community are highlighted in bold.

The edge invariance test showed that the AD patients differed from the other groups for the partialized correlation between the immediate and delayed recall of the RVLT. In particular, the correlation between the long-term memory subtests was weaker in the AD group ($r = 0.25$) as compared with those in both the MCI patients ($r = 0.55$; $p < 0.05$) and the SCD subjects ($r = 0.59$; $p < 0.05$). We found the same pattern between the semantic fluency test and the Boston naming test. In the AD network, the edge between the language tests was equal to zero, while we found a correlation between these nodes in both the MCI patients ($r = -0.49$; $p < 0.05$) and the SCD subjects ($r = -0.58$; $p < 0.05$). We did not find any significant differences in edge strength between the SCD and the MCI groups.

Discussion

It was proposed that dementia causes a reorganization of the cognitive system and not a mere decline of specific functions (Tosi et al., 2020). It was speculated that memory segregates from the other cognitive domains in a group of patients suffering from AD. Here, we investigated this speculation by systematically comparing the AD patients with two different populations potentially prodromic of AD (Albert et al., 2011; Jessen et al., 2014). In particular, we applied a network estimation procedure followed by a community detection algorithm to evaluate the relationships between cognitive tests in three groups of patients: AD, MCI, and SCD. NA allows to acquire information that cannot be provided through the analysis of simple correlations or item reduction procedure. We preferred NA over factor analysis because NA provides a node-level look into the associations between the nodes (i.e., the neuropsychological tests) and highlights the unique association between any two variables after conditioning on all others. Moreover, NA does not imply latent variables. On the contrary, communities are conceptualized as groups of variables more correlated between them then with the rest of the network. Lastly, we formally compared the network structures through an NCT.

SCD and MCI have been suggested to be the potential earlier manifestation of AD (Petersen and Morris, 2005; Reisberg et al., 2008; Jessen et al., 2010, 2014). We found increasing deficits in the neuropsychological tests going from the SCD to the MCI to the AD group. This result is in line with the literature, confirming MCI as interposed between normal aging and early dementia (Petersen, 2004). However, we intended to go beyond the description of lowering test scores in people with dementia. The working hypothesis is that different conditions have a specific architecture of the cognitive domains describable in terms of different correlations between tests.

In the SCD group, we found three replicable communities centered on memory, language, and general cognition, respectively. This network showed a lower sparsity as compared with the clinical groups. We previously suggested that low sparsity indicates that each test specifically captures one cognitive function, although it is not uniquely related to it (Tosi et al., 2020). Similarly, C. Ferguson (2021) observed more fractionated neurocognitive domains in a group of healthy older adults compared with those in the early clinical stages of AD. The MCI network partially overlapped with the SCD structure. The clusters centered on memory and language replicated in the MCI group.

The remaining nodes were split into two additional clusters. The MCI network structure was not stable, and these two communities are likely to be a unique, larger, cluster when considering bootstrap results. Interestingly, the number of edges in the MCI network is similar to the AD; thus while the community organization resembles the SCD, the network sparsity is similar to the AD.

A major finding regarding AD patients is that the communities centered on language and general cognition merged defining a unique cluster as opposed to memory, with semantic fluency bridging the two communities. In particular, the language cluster disappeared since the semantic fluency test and the Boston naming test did not show the strong correlation observed in the other groups. The structure is stable and reliable, considering the bootstrap replicability. Previous studies showed a similar segregation of memory tests (Tosi et al., 2020; C. Ferguson, 2021). Our results suggest that AD simplifies the cognitive architecture as compared with the other groups. The reduced fractionalization of the cognitive architecture might imply a simplification of the dimensionality of individual differences. Moreover, the NCT showed that the edge between the immediate and the delayed recall of the RVLT is weaker in the AD group as compared with the other populations. This result can be read as a reduced association between memory components. Although a node disconnection may emerge from a very specific deficit, the use of EGA can give a broader look at the phenomenon. First, we observed that there is not a mere memory decline but also a reorganization of the relationships between cognitive performance. Second, the immediate and the delayed recall significantly decrease their association in AD; thus also memory subcomponents are not declining in parallel.

In a recent preprint, Ferguson (2023) reanalyzed his data (C. Ferguson, 2021) with EGA and found high numbers of communities in all network models. These results contradict our hypotheses; however, Ferguson used a different cluster detection algorithm (i.e., the Louvain algorithm) and included in the network subjects' age, education, and premorbid intellectual functioning (American National Adult Reading Test; Gladsjo et al., 1999). The inclusion of demographic information and, more importantly, premorbid functioning may have strongly influenced the relationships between cognitive tests since the associations are estimated net to the contribution of these variables.

It is important to note that, because of the exploratory nature of NA, the examination of specific nodes and their edges can be performed on any specific node and connection. Here, we focused on memory functions and screening tests. If we look transversally at our populations, the MMSE, the CDT, the VOSP subtest, and the digit span backwards create a stable cluster that replicates across groups. We can reasonably add the FAB, the digit span forward, and the phonemic fluency test to this cluster, given the item loadings and replication frequency. The MMSE, the CDT, and the FAB are used as general screening tests, assessing more than one function to indicate the probability of cognitive impairment (Cullen et al., 2007). A stable cluster including these tests may confirm their transversal role as nonspecific assessment tools. Moreover, the FAB resulted as the most central and strong node in all the networks. No matter the specific impairment and the severity of the decline, this test appeared to have strong relations and intervene between the other functions. This result suggests that the screening of the frontal functions may play a pivotal role in the assessment of cognitive impairment because it captures a great amount of information. Conversely, it does not seem the best choice for the differential diagnosis from a network point of view since it has roughly the same role in all the networks. An alternative explanation could be that executive functions are assumed to regulate other cognitive functions and can be situated toward the top of cognitive hierarchy (C. E. Ferguson and Foley, 2023). Similar results were found by Nevado et al. (2022) who showed that the most central functions in three groups of healthy and cognitively impaired participants were executive functions. It is to note, as found by Ferguson (2023), that differential variability may have influenced the centrality measure so that strength differences between nodes might not indicate cognitive dissimilarities (Terluin et al., 2016).

The consideration of MCI as a homogeneous diagnosis is the principal limitation of this study. Our results confirm that MCI patients present mixed performances; a specific diagnosis (e.g., aMCI and naMCI) is thus needed to better understand this entity. We could not discriminate different types of MCI to maintain robust sample sizes. The second limitation is that we considered three groups and discussed the respective diagnoses as forming a continuum, but we lack longitudinal data to corroborate the hypothesis of a reorganization of the cognitive functions along the severity of the cognitive impairment. Future studies may focus on longitudinal data to directly assess the reorganization of cognitive performances in pathology evolution.

Despite these limitations, our study has also some important strengths. We used EGA to analyze different levels of complexity: the node level to reveal the unique associations between any two tests after conditioning on all the others and the community level to understand the structural organization. We considered three populations adopting the same test battery and with a relatively large sample size, allowing direct comparisons. We overcame previous studies' limitations (Tosi et al., 2020; C. Ferguson, 2021; Nevado et al., 2022) by applying a formal clustering algorithm and comparison test in the NA.

In conclusion, we had evidence of a specific cognitive reorganization taking place in dementia that goes beyond the well-known decreased cognitive performances. The MCI group resulted in sharing specific aspects with the other groups, a result useful to understanding the mixed nature of this clinical entity. Importantly, we enlightened the different architectures characterizing SCD and AD cognition. In particular, the latter group showed a simplified architecture, including the predicted unique feature of isolating memory function from the rest of the cognitive domains. Recognizing the complexity of neuropsychological performance and defining a patient's cognitive profile is essential for a correct diagnosis and patient care. NA and community detection provide a methodological basis for this clinical process by showing the relationship between variables and their mutual importance. NA is part of modern approaches to clinical neuropsychology and could be of help in multiple situations. On the assessment side, NA could be of help to overcome limitations in clinical assessments, such as the "impaired/spared" dichotomy. On the intervention/treatment side, NA can be of help in identifying the best function to treat in order to have generalized or local effects according to their network centrality and associations.

Data Availability Statement

The dataset and analysis codes supporting the conclusions of this article are available in the Open Science Framework repository at the following link: https://osf.io/8uxpd/?view_only=b9f9401477664289adc2e3dc9cb86843. No part of the study procedures or analysis was preregistered before the research was conducted.

References

Albert MS, et al. (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:270–279.

Caffarra P, Gardini S, Zonato F, Concari L, Dieci F, Copelli S, Freedman M, Stracciari A, Venneri A (2011) Italian norms for the freedman version of the clock drawing test. J Clin Exp Neuropsychol 33:982–988.

Caltagirone C, Gainotti G, Carlesimo GA, Parnetti L (1995) Batteria per la valutazione del deterioramento mentale: I. Descrizione di uno strumento di diagnosi neuropsicologica. [The mental deterioration battery: I. Description of a neuropsychological diagnostic instrument]. Arch Psicol Neurol Psichiatr 56:461–470.

Capasso R, Miceli G (2001) *Esame neuropsicologico per l'Afasia*. ENPA (Vol. 4). Springer Science & Business Media.

Chen J, Chen Z (2008) Extended Bayesian information criteria for model selection with large model spaces. Biometrika 95:759–771.

Christensen AP, Golino H (2019) Estimating the stability of the number of factors via bootstrap exploratory graph analysis: a tutorial. PsyArXiv. [Preprint].

Christensen AP, Golino H (2021) Estimating the stability of psychological dimensions via bootstrap exploratory graph analysis: a Monte Carlo simulation and tutorial. PsyCh 3:479–500.

Costantini G, Epskamp S, Borsboom D, Perugini M, Mõttus R, Waldorp LJ, Cramer AOJ (2015) State of the aRt personality research: a tutorial on network analysis of personality data in R. J Res Pers 54:13–29.

Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA (2007) A review of screening tests for cognitive impairment. J Neurol Neurosurg Psychiatry 78:790–799.

de Nooy W, Mrvar A, Batagelj V (2011) *Exploratory social network analysis with Pajek*. Cambridge: Cambridge University Press.

Dubois B, Slachevsky A, Litvan I, Pillon B (2000) The FAB: a frontal assessment battery at bedside. Neurology 55:1621–1626.

Epskamp S (2016) Regularized Gaussian psychological networks: brief report on the performance of extended BIC model selection

Epskamp S, Cramer AOJ, Waldorp LJ, Schmittmann VD, Borsboom D (2012) Qgraph: network visualizations of relationships in psychometric data. J Stat Softw 48:1–18.

Epskamp S, Fried EI (2018) A tutorial on regularized partial correlation networks. Psychol Methods 23:617–634.

Ferguson C (2021) A network psychometric approach to neurocognition in early Alzheimers's disease. Cortex 137:61–73.

Ferguson CE (2022) Network neuropsychology: the map and the territory. Neurosci Biobehav Rev 132:638–647.

Ferguson C (2023) Supplementary analyses to "A network psychometric approach to neurocognition in early Alzheimer's disease": Differential variability, community structure, and statistical tests.

Ferguson CE, Foley JA (2023) The influence of working memory and processing speed on other aspects of cognitive functioning in de novo Parkinson's disease: initial findings from network modelling and graph theory. J Neuropsychol 18:136–153.

Folstein M, Folstein S, McHugh P (1975) Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198.

Fortunato S (2010) Community detection in graphs. Phys Rep 486:75–174.

Foygel R, Drton M (2010) Extended Bayesian information criteria for Gaussian graphical models. In: Advances in Neural Information Processing Systems 23: 24th Annual Conference on Neural Information Processing Systems 2010, NIPS 2010

Freedman M, Leach L, Kaplan E, Winocur G, Shulman KI, Delis DC (1994) *Clock drawing: a neuropsychological analysis*. Oxford University Press.

Fried E (2016). New paper: differential variability of variables drives network structure. Psych Networks. Available at: https://psych-networks.com/new-paper-differential-variability-items-drives-network-structure/

Gladsjo JA, Heaton RK, Palmer BW, Taylor MJ, Jeste DV (1999) Use of oral reading to estimate premorbid intellectual and neuropsychological functioning. J Int Neuropsychol Soc 5:247–254.

Golino HF, Epskamp S (2017) Exploratory graph analysis: a new approach for estimating the number of dimensions in psychological research. PLoS One 12:1–26.

Golino H, Moulder R, Shi D, Christensen AP, Garrido LE, Nieto MD, Nesselroade J, Sadana R, Thiyagarajan JA, Boker SM (2020) Entropy fit indices: new fit measures for assessing the structure and dimensionality of multiple latent variables. Multivariate Behav Res 56:874–902.

Golino H, Shi D, Christensen AP, Garrido LE, Nieto MD, Sadana R, Thiyagarajan JA, Martínez-Molina A (2019) Investigating the performance of exploratory graph analysis and traditional techniques to identify the number of latent factors: a simulation and tutorial. Psychol Methods 25:292–320.

Goswami S, Murthy CA, Das AK (2018) Sparsity measure of a network graph: Gini index. Inf Sci 462:16–39.

JASP Team (2021). JASP (Version 0.15)[Computer software]. JASP - free and user-friendly statistical software

Jessen F, et al. (2010) Prediction of dementia by subjective memory impairment effects of severity and temporal association with cognitive impairment. Arch Gen Psychiatry 67:414–422.

Jessen F, et al. (2014) A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement 10: 844–852.

Kaplan EF, Goodglass H, Weintraub S (2001). *The Boston naming test*, Ed 2. Philadelphia: Lea and Febiger.

Liaw A, Wiener M (2003) Classification and regression by random forest. R News 2:18–22.

McKhann GM, et al. (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:263–269.

McNeish DM (2015) Using lasso for predictor selection and to assuage overfitting: a method long overlooked in behavioral sciences. Multivariate Behav Res 50:471–484.

Monaco M, Costa A, Caltagirone C, Carlesimo GA (2013) Forward and backward span for verbal and visuo-spatial data: standardization and normative data from an Italian adult population. Neurol Sci 34:749–754.

Nevado A, Del Rio D, Pacios J, Maestú F (2022). Neuropsychological networks in cognitively healthy older adults and dementia patients. Aging Neuropsychol Cogn 29:903–927.

Newman MEJ (2006) Modularity and community structure in networks. Proc Natl Acad Sci U S A 103:8577–8582.

Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. J Intern Med 256:183–194.

Petersen RC, Morris JC (2005) Mild cognitive impairment as a clinical entity and treatment target. Arch Neurol 62:1160–1163.

Pons P, Latapy M (2006) Computing communities in large networks using random walks. J Graph Algorithms Appl 10:191–218.

R Core Team (2017) R: a language and environment for statistical computing. Version 3.3.3. R Foundation for Statistical Computing

Reisberg B, et al. (2008) The pre-mild cognitive impairment, subjective cognitive impairment stage of Alzheimer's disease. Alzheimers Dement 4: S98–S108.

Terluin B, De Boer MR, De Vet HCW (2016) Differences in connection strength between mental symptoms might be explained by differences in variance: reanalysis of network data did not confirm staging. PLoS One 11:1–12.

Tibshirani R (2011) Regression shrinkage and selection via the lasso: a retrospective. J R Stat Soc 73:273–282.

Tosi G, Borsani C, Castiglioni S, Daini R, Franceschi M, Romano D (2020) Complexity in neuropsychological assessments of cognitive impairment: a network analysis approach. Cortex 124:85–96.

van Borkulo CD, van Bork R, Boschloo L, Kossakowski JJ, Tio P, Schoevers RA, Borsboom D, Waldorp LJ (2022) Comparing network structures on three aspects: a permutation test. Psychol Methods 28:1273–1285.

Van Der Maas HLJ, Dolan CV, Grasman RPPP, Wicherts JM, Huizenga HM, Raijmakers MEJ (2006) A dynamical model of general intelligence: the positive manifold of intelligence by mutualism. Psychol Rev 113:842–861.

Van Der Mussele S, Le Bastard N, Vermeiren Y, Saerens J, Somers N, Mariën P, Goeman J, De Deyn PP, Engelborghs S (2013) Behavioral symptoms in mild cognitive impairment as compared with Alzheimer's disease and healthy older adults. Int J Geriatr Psychiatry 28:265–275.

Ward JH (1963) Hierarchical grouping to optimize an objective function. J Am Stat Assoc 58:236–244.

Warrington EK, James M (1991) *The visual object and space perception battery*. Thames Valley Test Company.

Weintraub S, Wicklund AH, Salmon DP (2012) The neuropsychological profile of Alzheimer disease. Cold Spring Harb Perspect Med 2:1–18.