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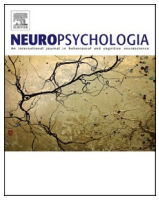

APOE ε4 positivity predicts centrality of episodic memory nodes in patients with mild cognitive impairment: A cohort-based, graph theory-informed study of cognitive networks

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ABSTRACT

As network neuroscience can capture the systemic impact of APOE variability at a neuroimaging level, this study investigated the network-based cognitive endophenotypes of ε4-carriers and non-carriers across the continuum between normal ageing and Alzheimer's dementia (AD). We hypothesised that the impact of APOE-ε4 on cognitive functioning can be reliably captured by the measurement of graph-theory centrality.

Cognitive networks were calculated in 8118 controls, 3482 MCI patients and 4573 AD patients, recruited in the National Alzheimer's Coordinating Center (NACC) database. Nodal centrality was selected as the neuro-functional readout of interest. ε4-carrier-vs.-non-carrier differences were tested in two independent NACC sub-cohorts assessed with either Version 1 or Version 2 of the Uniform Data Set neuropsychological battery.

A significant APOE-dependent effect emerged from the analysis of the Logical-Memory nodes in MCI patients in both sub-cohorts. While non-carriers showed equal centrality in immediate and delayed recall, the latter was significantly less central among carriers (v1: bootstrapped confidence interval 0.107–0.667, $p < 0.001$; v2: bootstrapped confidence interval 0.018–0.432, $p < 0.001$). This indicates that, in carriers, delayed recall was, overall, significantly more weakly correlated with the other cognitive scores. These findings were replicated in the sub-groups of sole amnestic-MCI patients ($n = 2971$), were independent of differences in network communities, clinical severity or other demographic factors. No effects were found in the other two diagnostic groups.

APOE-ε4 influences nodal properties of cognitive networks when patients are clinically classified as MCI. This highlights the importance of characterising the impact of risk factors on the wider cognitive network via network-neuroscience methodologies.

1. Introduction

A significant, yet intricate link appears to exist between variability in the expression of the Apolipoprotein E (APOE) genetic locus and susceptibility to neurofunctional changes in ageing and in Alzheimer's disease (AD) neurodegeneration. This is particularly visible in relation to the polymorphism at the basis of the differences between ε_3 and ε_4 alleles.

Evidence from genome-wide studies and from a systematic review of the literature indicates that the ε_4 isoform is significantly associated with increased likelihood of an AD diagnosis (Andrews et al., 2020; Hersi et al., 2017; Lambert et al., 2013). In addition, other genome-wide studies carried out in large cohorts of healthy adults highlight a link between ε_4-related variability and performance levels in episodic

Abbreviations: AD, Alzheimer's disease; ADRC, Alzheimer's Disease Research Centers; APOE, Apolipoprotein E; BNT, Boston Naming Test; CS, Correlation Stability; CATFL, Category Fluency Test; DIGITB, Digit Span Test; Backward, DIGITF; Digit Span Test, Forward; DSST, Wechsler Adult Intelligence Scale-Revised Digit Symbol Substitution Test; EBIC, Extended Bayesian Information Criterion; EI, Expected Influence; LASSO, Least Absolute Shrinkage and Selection Operator; LMTD, Logical Memory Test; Delayed Recall, LMTI; Logical Memory Test, Immediate Recall; MCI, Mild Cognitive Impairment; NACC, National Alzheimer's Coordinating Center; NIA, National Institute of Aging; TRAILA, Trail Making Test; Part A, TRAILB; Trail Making Test, Part B; UDS, Uniform Data Set; v1, Version 1; v2, Version 2.

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memory (Arpawong et al., 2017; Debette et al., 2015), but not general cognition (Trampush et al., 2017), processing speed and executive functioning (Ibrahim-Verbaas et al., 2016), or short-term memory (Papassotiropoulos et al., 2011).

Studies focussing on the sole APOE locus and investigating cross-sectional or longitudinal differences between ε_4 carriers and non-carriers have led to an inconsistent pattern of findings (O'Donoghue et al., 2018). Of the between-group cognitive differences described, episodic memory is the domain most frequently associated with lower performance among ε_4 carriers. Meta-analyses indicate that the effect of ε_4 among cognitively normal adults is linked to poorer performance in episodic memory, executive functioning, processing speed and general cognitive functioning, but not in other domains (Small et al., 2004; Wisdom et al., 2011).

Although limited evidence does suggest lower performance levels in ε_4 carriers, this area of research has only been investigated via analyses of single-test performance. As functional domains interact with each other to sustain overall cognitive functioning, cognitive profiles can be also described via levels of complexity that are based on network neuroscience and take into account the interplay across cognitive domains (Ferguson, 2022). Network neuroscience has been fruitfully applied to the study of ε_4-dependent neuroimaging profiles at the basis of cognition (Kuang et al., 2020; Li et al., 2020; Sanabria-Diaz et al., 2021). The current study expands this area of research and the application of these methods to characterise the differences in cognitive networks between ε_4 carriers and non-carriers, relying on the principles of graph theory, i.e., the mathematical framework at the basis of recent network-science-informed investigations of cognitive abilities in patients with mild cognitive impairment (MCI) and AD dementia (Ferguson, 2021; Nevado et al., 2022; Tosi et al., 2020; Wright et al., 2021). We hypothesised that network-related differences in cognitive profiles exist between ε_4 carriers and non-carriers across multiple diagnostic statuses associated with normal ageing and AD and that these, as inconsistently suggested by the literature, will be visible in the portions of the network responsible for episodic memory, executive functioning and processing speed, with differences in "centrality-based" expression of nodes between ε_4 carriers and non-carriers. Centrality indices describe the importance of variables by quantifying how influential these are within the whole network (Bringmann et al., 2019; Rubinov and Sporns, 2010). In this study, we focussed on two metrics known as *Expected Influence* (EI) and *Strength* to characterise the APOE-dependent, network-informed importance of individual cognitive test scores, in a way that is complementary to that offered by univariate statistical models. EI and Strength are two correlation-based indices that can be particularly informative to clinical profiles, as they can pinpoint those variables that show trends of "correlational isolation" (i.e., via overall weaker correlations) from the rest of the cognitive profile.

2. Material and methods

2.1. Participant datasets

To test the hypothesis of APOE-dependent differences in cognitive networks, baseline datasets of the National Alzheimer's Coordinating Center (NACC) database were scrutinised (https://naccdata.org/). NACC is a US-based clinical research enterprise coordinated by the National Institute of Aging (NIA) and the NIA Alzheimer's Disease Research Centers (ADRC) program. The NACC Uniform Data Set (UDS) includes "*prospective, standardized, and longitudinal clinical evaluation*" on thousands of participants recruited across multiple ADRCs (Morris et al., 2006). As of September 2021, this number was equal to 44,359, from 41 ADRCs.

Eligibility criteria (Fig. 1) were defined to shortlist a sub-database appropriate for addressing the study hypothesis. Datasets with no APOE information and ε_2 carriers were discarded, as the ε_2 isoform is associated with neurovascular mechanisms different from those of the ε_4 allele (Lumsden et al., 2020). The remaining 29,718 participants were classified according to the cognitive instrumentation used for clinical diagnostic procedures. Participants were assessed with one out of three versions of the standardised NACC UDS cognitive battery. While very little discrepancies exist between Version-1 (v1) and Version-2 (v2) (Weintraub et al., 2009), Version-3 includes a number of non-proprietary tests that are distinct from those of v1 and v2 (Stasenko et al., 2019), and administered via multiple routes (i.e., in-person, telephone and video-conference). As a consequence, only participants assessed with v1 and v2 were analysed in this study ($n = 23{,}009$).

Retained datasets were considered for inclusion if the primary aetiological diagnosis was one of AD or of normal control (i.e., no neurological diagnosis of concern). To maximise clinical translatability, clinical, rather than biological criteria were used to classify study participants. This is because in many countries, including the UK (Dunne et al., 2021), the majority of diagnostic settings do not routinely implement biological criteria to identify individuals with AD pathophysiology. In the case of MCI patients, relying on a non-biological routine can be helpful when screening for the presence of cognitive impairment (Frisoni and Coleman, 2011).

Medical exclusion criteria were thus defined. Firstly, datasets were discarded if associated with a primary diagnosis of neurological/neurodegenerative conditions (other than AD) causing cognitive impairment, (i.e., Lewy-body disease, frontotemporal-motor neurone disease continuum, a history of stroke, probable or possible vascular dementia and normal-pressure hydrocephalus); secondly, retained patients were excluded if presenting with other, more uncommon neurodegenerative conditions (e.g., cortico-basal degeneration, progressive supranuclear palsy, Huntington's disease, multiple system atrophy) or with rapidly-evolving forms of dementia or conditions of traumatic, psychiatric or other medical nature (e.g., prion disease infection, traumatic brain injury, central-nervous-system neoplasms, bipolar disorder, schizophrenia). Thirdly, patients were excluded if presenting with a systemic illness, a substance/alcohol abuse or other medically-relevant disorders that may compromise daily-life independence, or if treated with medications known to alter normal cognitive functioning. The application of this set of criteria resulted in 19,439 datasets. These were divided into the three main cognitive diagnoses: normal controls ($n = 8685$), MCI patients ($n = 3794$) and patients with AD dementia ($n = 6256$). The diagnosis of MCI was based on Petersen's criteria (Petersen and Morris, 2005), while the diagnosis of dementia was based on the DSM-IV or other clinical criteria, as routinely implemented in each individual ADRC. For the purposes of this study, participants diagnosed as "cognitively impaired/no MCI" ($n = 704$) were not further considered. The resulting database was finally inspected to quantify missing data (Supplementary Table S1). Only participants with a complete cognitive profile or with a single missing score were retained ($n = 18{,}168$). Ninety percent (i.e., 3153 out of the 3482 participants with a diagnosis of MCI completed at least one follow-up visit as part of the NACC initiative, at an average temporal distance of approximately 15 months. Although no longitudinal data was analysed in this study, follow-up diagnoses of these participants were reviewed for descriptive purposes. A total of 590 participants (equal to 16.94% of the cohort) received a clinical diagnosis of dementia at this follow up, and in 97.5% of cases the aetiology identified as the primary cause for cognitive impairment was a neurodegenerative condition: Alzheimer's disease (i.e., according to the NINCDS/ADRDA criteria): $n = 540$; Lewy Body disease: $n = 14$; frontotemporal dementia (behavioural variant): $n = 7$; frontotemporal dementia (primary progressive aphasia variants): $n = 7$; vascular dementia (i.e., according to the NINDS/AIREN criteria): $n = 7$; corticobasal degeneration: $n = 2$. For the remaining 13 MCI participants, the primary diagnostic contributors to dementia at follow up were other, non-neurological medical conditions.

APOE genotypes (reported in Table 1), were operationalised to address the study hypothesis: participants with an $\varepsilon_4\varepsilon_3$ or $\varepsilon_4\varepsilon_4$ genotype were grouped in a single category (i.e., "ε_4 carriers"), while participants

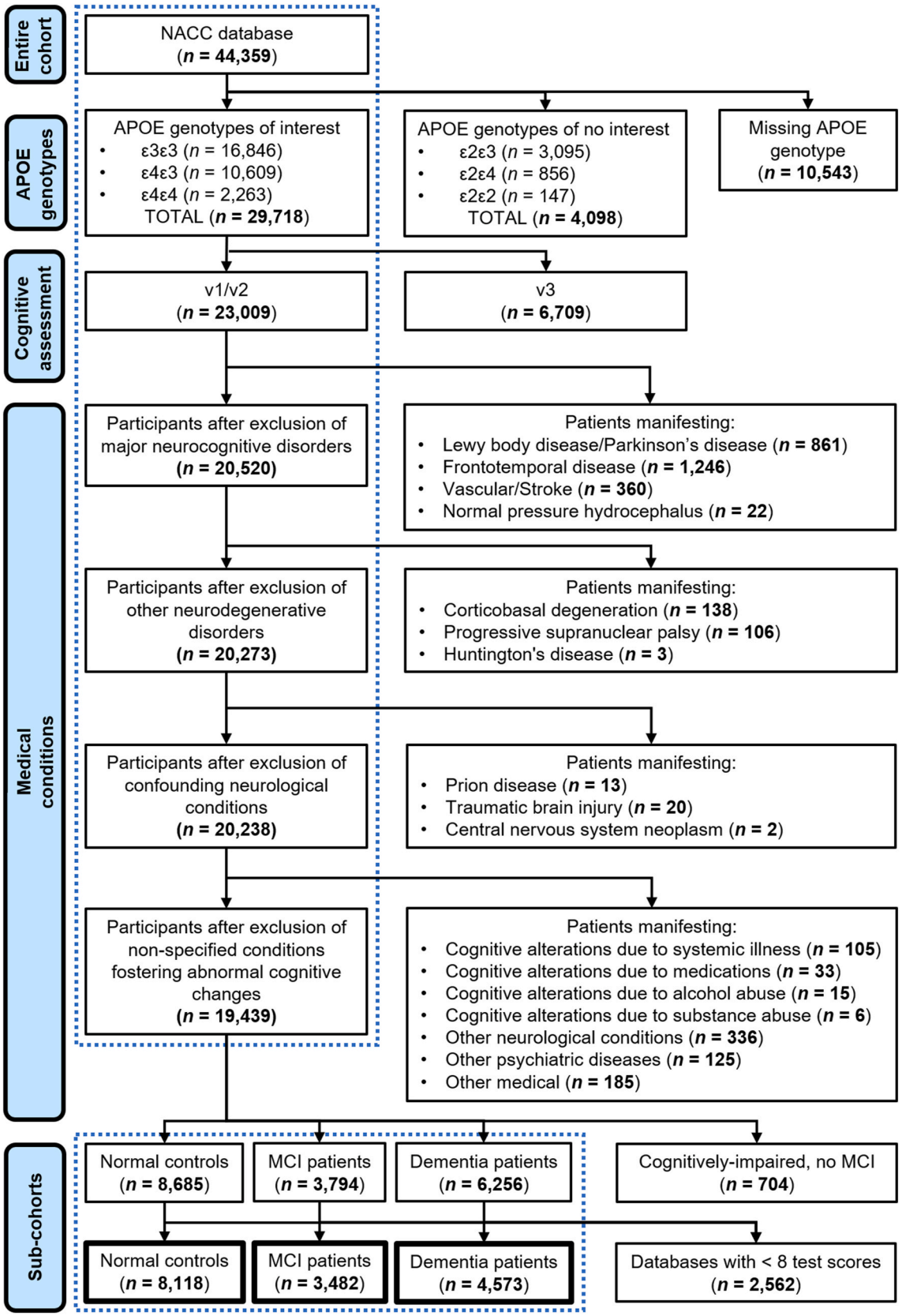

Fig. 1. *Flowchart illustrating the process of participant selection and all significant medical exclusion criteria.* Participants retained by the selection process at each step are framed by the dotted line.

Table 1
Main demographic characteristics and neuropsychological profiles of the cohort sub-groups.

	Controls			MCI Patients			AD Dementia Patients		
	ε4 non-carriers	ε4 carriers	*p*	ε4 non-carriers	ε4 carriers	*p*	ε4 non-carriers	ε4 carriers	*p*
	n = 5418	*n* = 2700		*n* = 1851	*n* = 1631		*n* = 1816	*n* = 2757	
Demographic Variables									
Age (years)	71.56 (10.68)	68.73 (10.39)	<0.001	74.81 (9.47)	72.33 (8.13)	<0.001	75.53 (10.43)	73.45 (8.98)	<0.001
Education (years)	15.73 (3.02)	15.65 (2.97)	0.237	14.86 (3.57)	15.35 (3.19)	<0.001	14.26 (3.69)	14.57 (3.40)	0.005
MMSE	28.93 (1.37)	28.87 (1.48)	0.138	27.23 (2.42)	26.95 (2.47)	<0.001	22.19 (4.51)	21.96 (4.42)	0.088
Gender (F/M)	3561/1857	1764/936	0.726	930/921	823/808	0.898	965/851	1540/1217	0.071
Handedness (L/R/AMB/ Unknown)	406/4869/ 126/17	218/2405/70/ 7	0.653	132/1677/ 39/3	135/1456/ 33/7	0.279	132/1647/ 32/5	187/2523/41/ 6	0.772
Neuropsychological Variables									
DIGIF	8.57 (2.03)	8.59 (2.06)	0.807	7.73 (2.07)	8.06 (2.05)	<0.001	6.90 (2.21)	7.07 (2.14)	0.008
DIGIB	6.84 (2.21)	6.80 (2.27)	0.414	5.82 (2.01)	5.94 (2.11)	0.091	4.52 (1.96)	4.66 (1.93)	0.015
TRAILA (seconds)	34.20 (15.62)	33.31 (15.86)	0.017	44.51 (23.12)	41.87 (19.91)	<0.001	70.20 (39.90)	67.25 (39.40)	0.014
TRAILB (seconds)	89.81 (49.66)	88.43 (50.48)	0.245	138.46 (77.86)	132.73 (73.48)	0.028	214.45 (87.22)	210.60 (87.79)	0.194
DSST	47.81 (12.69)	48.76 (12.75)	0.002	37.33 (12.02)	38.74 (11.84)	<0.001	24.99 (13.47)	25.89 (13.88)	0.032
CATFL (average)	17.56 (4.31)	17.71 (4.36)	0.144	13.52 (3.84)	13.69 (3.87)	0.209	8.97 (4.12)	9.52 (3.98)	<0.001
LMTI	13.65 (3.83)	13.32 (3.89)	<0.001	9.34 (4.16)	8.51 (4.18)	<0.001	4.61 (3.75)	4.12 (3.38)	<0.001
LMTD	12.37 (4.12)	12.03 (4.16)	<0.001	7.25 (4.61)	5.89 (4.66)	<0.001	2.45 (3.38)	1.74 (2.82)	<0.001
BNT	27.14 (3.21)	27.21 (3.17)	0.383	24.42 (4.74)	25.08 (4.44)	<0.001	19.70 (6.96)	20.62 (6.78)	<0.001
n	**v1** **v2**	**v1** **v2**		**v1** **v2**	**v1** **v2**		**v1** **v2**	**v1** **v2**	
	2574 2844	1162 1538		991 860	787 844		860 956	1266 1491	

AD: Alzheimer's disease; AMB: Ambidextrous; BNT: Boston Naming Test; CATFL: Category Fluency Test; DIGITB: Digit Span Test – Backward; DIGITF: Digit Span Test – Forward; DSST: WAIS-R Digit Symbol Substitution Test; F: Female; L: Left; LMTD: Logical Memory Test - Delayed Recall; LMTI: Logical Memory Test - Immediate Recall; M: Male; MCI: Mild Cognitive Impairment; MMSE: Mini Mental State Examination; R: Right; TRAILA: Trail Making Test – Part A; TRAILB: Trail Making Test – Part B; For DIGITF and DIGITB, the number of correct trials (rather than test scores) was used as part of the procedure. TRAILA and TRAILB are unconverted (i.e., not multiplied by −1) in this table.

with an $\varepsilon_3\varepsilon_3$ genotype were selected as the group of "ε_4 non-carriers". This analysis used data from 34 ADRCs, for NACC UDS visits conducted between June 2005 and June 2015. All procedures were carried out in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from all participants.

2.2. Cognitive profiles

Nine test scores were used to construct diagnosis-dependent and genotype-dependent cognitive networks. These are listed and described (including their abbreviated labels) in box 1. To safeguard the principle whereby higher scores indicate better performance, TRAILA and TRAILB scores were multiplied by −1. Furthermore, the sub-scores obtained in the two CATFL categories ("animals" and "vegetables") were averaged to obtain a single score for this test.

2.3. Definition of cognitive networks

Published methodological principles were applied to construct a popular network-based model of cognitive functioning known as *pairwise Markov random field* - also called *Gaussian graphical model* when the variables of interest show multivariate normal distribution (Epskamp et al., 2018). Each network was based on nine nodes (i.e., corresponding to the 9 cognitive scores) and 36 edges (representing conditional dependence) defined by the statistical pairwise association across all pairs of nodes.

The R open-source software environment (https://www.r-project.org) and the *qgraph* package were used to explore and analyse all study data (Epskamp et al., 2012). Partial correlation coefficients were

Box 1
Neuropsychological test measures used in this study

Test Name	Acronym	Target Cognitive Domain
Digit Span Test – Forward	DIGITF	Verbal short-term memory
Digit Span Test – Backward	DIGITB	Working memory
Trail Making Test – Part A	TRAILA	Visuospatial search
Trail Making Test – Part B	TRAILB	Set-shifting abilities
WAIS-R Digit Symbol Substitution Test	DSST	Attention and processing speed
Category Fluency Test	CATFL	Semantic memory
Logical Memory Test - Immediate Recall	LMTI	Verbal episodic memory
Logical Memory Test - Delayed Recall	LMTD	Verbal episodic memory
Boston Naming Test	BNT	Lexical-semantic abilities

calculated to define the raw statistical strength of each edge. As the majority of group-level test score distributions was skewed, nonparametric rank-based partial correlation coefficients (*Spearman's rho*) were computed, as this type of method makes no assumption on the underlying data distribution. Each correlational model was partialised for the remaining nodes and all edges represented weighted undirected associations.

The *Least Absolute Shrinkage and Selection Operator* (LASSO) regularisation technique was then applied. LASSO minimises the number of edges that account for the structure of data covariance via a "tuning parameter" (known as λ) that minimises the *Extended Bayesian Information Criterion* (EBIC) by imposing a penalty that reduces the strength of all correlation coefficients (with some becoming exactly zero), and thus controlling the degree of sparsity (Tibshirani, 1996). EBIC is, in turn, defined by a hyperparameter (known as γ) typically ranging between 0 and 0.5, with 0.5 indicating that more parsimonious (i.e., sparser) models are preferred. Simulation studies indicated that a $\gamma = 0.5$ conferred an optimal balance of sensitivity and specificity across diagnoses (Supplementary Figs. S1–S3).

2.4. Calculation of centrality metrics

Although multiple nodal and global metrics have been proposed in neuroscience research (Rubinov and Sporns, 2010), centrality is of particular interest as it quantifies how influential a node is within the entire network. This is important as it can help clinicians understand to what extent a single cognitive deficit can influence the entire clinical profile. *EI* (or "one-step *Expected Influence*") is a centrality metric consisting of the arithmetical sum of all standardised correlation coefficients (distinguishing between positive and negative values) between the target node and its immediate neighbourhood, i.e., the nodes linked to it with an edge surviving the sparsity-regularisation procedure (Robinaugh et al., 2016). A second form of EI, known as "two-step EI" also incorporates information about EI of a node's neighbours. In this study, however, we relied on one-step EI only, to capture and focus on "direct" aspects of nodes' centrality. While EI is a simple "summation-based" metric, *Strength* (or *Strength Centrality*) is a slightly more elaborate index that results from the arithmetical sum of the absolute values of all standardised correlation coefficients, thus not distinguishing between positive and negative values (Bringmann et al., 2019).

2.5. Data analysis

Group-level cognitive networks were finalised for each diagnostic and genotype-dependent level. First, a *Network Invariance Test* was run to test for the effect of genotype on the overall invariant network structure of the three diagnostic sub-cohorts (van Borkulo et al., 2022). This is a permutation-based test that compares metrics calculated on unpermuted data with the distribution of permuted metrics (with $n = 1000$ iterations). Second, a *Global Strength Invariance Test* was run to assess APOE-dependent differences in levels of *Global Strength*, i.e., the weighted absolute sum of all network edges (van Borkulo et al., 2022). Both these tests were run to assess the effect of genotype on global network metrics.

Third, as the *Network Invariance Test* is a "*generic procedure in which any relevant statistic that can be captured in a single value could be implemented*" (van Borkulo et al., 2022), the same principles were applied to address nodal centrality values. Specifically, as our experimental hypothesis proposed that ε_4 carriers would show differences in centrality in correspondence with episodic memory, executive functioning, and processing speed, *a priori* "ε_4 carriers-vs.-ε_4 non-carriers" between-group comparisons were defined for the following nodes: DSST, DIGITB, TRAILB, LMTI, and LMTD.

Although v1 and v2 of the NACC cognitive assessment only show minimal procedural differences, the two sub-cohorts were analysed separately, for a total of 12 networks (i.e., 3 diagnoses × 2 genotype levels × 2 versions). This gave us the opportunity to test the hypothesis in two independent sub-cohorts. As estimated models are inevitably subjected to sampling variation and estimated edges might not always coincide with the edges of the true model (Burger et al., 2023), replication of findings minimises the odds of imprecise centrality estimates.

3. Results

3.1. Overall network centrality structure

Findings are hereby reported following published guidelines (Burger et al., 2023). A sub-cohort-level characterisation of demographic indices and neuropsychological test scores is described in Table 1. The 12 cognitive networks are illustrated in Fig. 2. Most edges were supportive of a positive correlation, and the strongest conditional dependencies were consistently found in correspondence of pairs of tests that are methodologically similar (i.e., DIGITF-DIGITB; TRAILA-TRAILB, LMTI-LMTD) or known to be sustained by a shared set of skills (e.g., CATFL-BNT). All coefficients of simple correlation, coefficients of partial correlation and edge weights are reported in Supplementary Tables S2–S4. The process of partialisation resulted in an average drop of 0.250 ($SD = 0.08$) in the correlation coefficients across the entire cohort (sub-cohort drops: controls = 0.253 ($SD = 0.07$); MCI = 0.214 ($SD = 0.08$); AD Dementia = 0.253 ($SD = 0.09$)). Confidence intervals were calculated around each estimated edge weight (Supplementary Figs. S4–S6; please note that y-axis labels were not included to avoid cluttering) via 1000 nonparametric bootstrapping iterations (Epskamp et al., 2018).

The *Network Invariance Test* revealed no differences in the overall network pattern between ε_4 carriers and non-carriers (M "maximum statistics" are described in Table 2). Similarly, no differences in global strength were found (S "distances" are described in Table 2).

3.2. Nodal centrality metrics

Node EI and Strength were initially compared to define the impact of converting each edge weight to its absolute value. Correlation coefficients were calculated across the whole set of 108 nodes ($r = 0.89$), as well as within each diagnostic sub-set of 36 nodes (controls: $r = 0.98$; MCI: $r = 0.95$; AD Dementia: $r = 0.83$). These associations indicated that the conversion of edges weights into their absolute values led to minimal discrepancies only (see Supplementary Fig. S7 for a few examples of Strength-EI discrepancies). For this reason, the remainder of the analyses were run on EI only.

The between-group comparison of EI for the five nodes of interest revealed no significant differences between genotype groups. However, the graphical representation of node-by-node EI-informed centrality (globally illustrated in Fig. 3a) showed that LMTI and LMTD centralities had very different trends in MCI ε_4 carriers and non-carriers (Fig. 3b). A *Bootstrapped Difference Test* was thus run to compare LMTI and LMTD nodal centrality in each diagnostic and genotype-dependent sub-group (Epskamp et al., 2018). The results confirmed the significance of the trend (Fig. 3b; Table 2): no differences in centrality were found between LMTI and LMTD in MCI ε_4 non-carriers, while a statistically significant difference was found among MCI ε_4 carriers, in the analyses of both v1 and v2 sub-cohorts (at a $p < 0.001$). No comparable differences emerged from this contrast in controls or AD-dementia patients.

To corroborate these findings, the LMTI-LMTD difference in centrality found in the group of MCI ε_4 carriers was compared to the variability that emerged from differences between sub-cohorts tested with v1 and v2 of the cognitive assessment battery. A subtraction score (i.e., v1 minus v2) was calculated for each nodal centrality metric across all diagnoses. These differences (Fig. 3c) ranged between −0.80 and 0.93 (with mean ~ 0). A 3-*SD* confidence interval was built around the mean difference value (i.e., ±0.90): the differences between LMTI and LMTD found in the group of MCI ε_4 carriers were significantly larger (v1: 1.99;

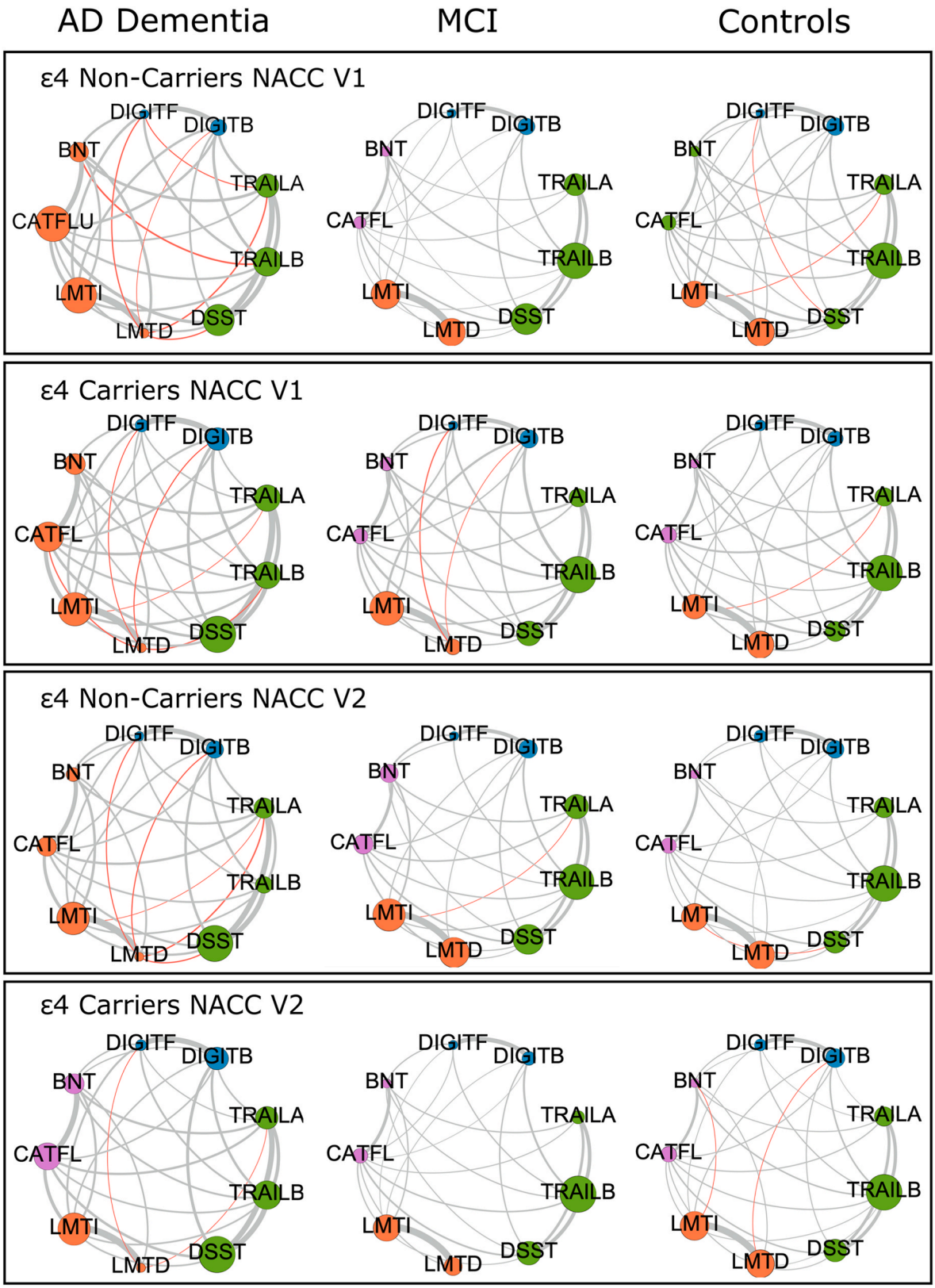

Fig. 2. *Cognitive networks emerging from each diagnostic class and in each APOE subgroup*. Networks associated with v1 and v2 are illustrated separately. Edges representing positive and negative correlations are coloured grey and red, respectively. Edge width is proportional to weight. Node size is proportional to EI. Node colour represents modularity class identified by the Louvain community detection algorithm.

Table 2
Between-group comparison of global and nodal network metrics.

Global Network Metrics					*Nodal Network Metrics*						
Diagnostic Group and Sub-cohort	Network Invariance Test: *M* (*p*)	Strength		Global Strength Invariance Test: *S* (*p*)	Centrality Invariance Test (*p*)					LMTI-LMTD Difference (Bootstrapped C.I.)	
		ε4 NC	ε4 C		DSST	TRAILB	DIGITB	LMTI	LMTD	ε4 NC	ε4 C
Controls - v1	0.068 (0.733)	3.982	3.903	0.079 (0.723)	0.717	0.303	0.994	0.769	0.192	[-0.127 - 0.081]	[-0.197, 0.130]
Controls - v2	0.053 (0.781)	3.756	3.787	0.031 (0.626)	0.772	0.472	0.960	0.313	0.485	[-0.137 - 0.045]	[-0.092, 0.165]
MCI - v1	0.109 (0.351)	3.849	3.866	0.018 (0.905)	0.087	0.434	0.112	0.076	0.773	[-0.083 - 0.231]	[0.107, 0.667] *
MCI - v2	0.073 (0.870)	3.786	3.672	0.114 (0.275)	0.114	0.107	0.826	0.901	0.239	[-0.115 - 0.169]	[0.018, 0.432] *
AD Dementia - v1	0.107 (0.429)	4.379	4.133	0.245 (0.164)	0.866	0.165	0.348	0.099	0.565	[0.430–0.776] *	[0.403, 0.721] *
AD Dementia - v2	0.110 (0.240)	4.181	3.916	0.265 (0.187)	0.392	0.016	0.203	0.124	0.502	[0.339–0.681] *	[0.392, 0.695] *
aMCI - v1	0.101 (0.569)	3.875	3.634	0.241 (0.166)	0.019	0.220	0.090	0.691	0.526	[-0.084 - 0.233]	[0.078, 0.638] *
aMCI - v2	0.073 (0.890)	3.740	3.674	0.066 (0.424)	0.091	0.056	0.977	0.741	0.373	[-0.170 - 0.174]	[0.023, 0.428] *

'*M*': "*maximum statistic*", i.e., the largest difference in edge weight between ε4 non-carriers and ε4 carriers across the entire network of 36 edges. '*S*': summed difference of all edge strength metrics between the two groups. aMCI: amnestic MCI; C.I.: confidence intervals; C: carriers; NC: non-carriers. *: $p < 0.001$. Bootstrapped confidence (indicated as ['lower limit', 'upper limit']) are significant when not including the zero.

v2: 0.93), indicating a discrepancy larger than those normally occurring from the analyses of distinct sub-cohorts (Fig. 3d).

We also measured the stability of network centrality by calculating the *correlation stability (CS) coefficient*. This assesses whether the order of nodal centrality metrics is unaltered when the network is re-estimated (via 1000 bootstrapped iterations; Supplementary Table S5) with fewer participants (i.e., a 5%-to-75% case drop) and there is a ≥0.7 correlation between the original and re-estimated networks in at least 95% of cases. The outcome indicated very strong stability ($CS(cor = 0.7) = 0.75$), which is above the recommended 0.5 cut-off (Epskamp et al., 2018).

Finally, we correlated the standard deviation of nodes with EI values for each group to investigate the impact of differential variability (Terluin et al., 2016). Correlations ranged between 0.37 and 0.73 and, although two of these were associated with significant *p*-values (Supplementary Table S6), these analyses were characterised by low power, i.e., there were only $n = 9$ data points.

3.3. Post-hoc analyses in the MCI sub-cohort

First, to test whether these findings might have been due to a difference in clinical sub-type frequencies, the analyses were rerun in the sole sub-cohort of amnestic MCI patients ($n = 2971$). The findings were replicated in both v1 and v2 sub-cohorts (Table 2).

Second, we tested the association between cognitive performance and three major demographic/clinical sources of variability: age, years of education and clinical severity estimated with the Mini Mental State Examination (this was done for each MCI sub-group; Supplementary Table S7). Almost all these associations (i.e., 98 out of 108) were significant at a $p < 0.001$, indicating that conditional dependencies calculated by the graphical model regressed out a very large portion of variability accounted for by these variables. This implies that the differences between ε_4 carriers and non-carriers cannot be attributed to differences in age, educational attainment, or clinical severity.

Finally, we inspected *network communities* in ε_4 carriers and non-carriers (Blondel et al., 2008). A community can be thought as a set of nodes that are highly interconnected and, when cognitive profiles are analysed, they broadly represent network-informed estimates of cognitive domains. The so-called "Louvain" community-detection method aims to maximise the graph's modularity. This is a metric that factors in within-community and between-community edge weights. The initial (and least parsimonious) solution allocates each node to its own community. Then, each node is moved to one of its neighbour's community and any gain in modularity is recorded. The node is then assigned to the community based on the maximum gain (or, if no gain is observed, it is maintained within its community). This process is repeated iteratively until no further gain is recorded (Blondel et al., 2008). The final solution indicated that both ε_4 carriers and non-carriers showed the same four sets (Fig. 2), ruling out the possibility that the results were due to "upstream" structural differences in network communities.

4. Discussion

This study investigated network-level differences in cognitive profiles between APOE ε_4 carriers and non-carriers across three diagnostic stages of the clinical "ageing-AD" continuum. As neuropsychological test performance relies upon multiple abilities interacting with one another, the study of cognitive functioning as informed by the principles of graph theory may provide a novel, higher-order view of how genetics influences cognitive profiles at the basis of clinical diagnoses. We hypothesised that carriers and non-carriers of the APOE ε_4 allele (i.e., the best-established risk factor for sporadic AD) would show differences in nodal centrality of cognitive networks.

EI is a centrality metric that quantifies the *correlation-based relevance* of a node within the network, while accounting for negative edges as well (Robinaugh et al., 2016). Overall, LMTD was significantly less central than LMTI in patients, regardless of APOE status. However, although between-group inferential models revealed no EI differences between ε_4 carriers and non-carriers, a significant within-group divergence emerged from the sub-analysis of episodic memory nodes in patients with MCI. Specifically, ε_4 carriers showed significantly lower centrality on the immediate compared to the delayed recall of the Logical Memory Test, while no such difference was found among non-carriers. This indicates that the ε_4 allele is associated with a significant shift of the normal pattern of network centrality in these patients, with a greater "isolation" of the LMTD node. Among MCI ε_4 carriers LMTD scores tend to be significantly less positively correlated than LMTI to the performance on the other cognitive tasks. In other words, while presence of the ε_4 allele is not linked to an *absolute* reduction in LMTD centrality in this sub-group, it is linked to a *relative* reduction of LMTD centrality, when compared to LMTI centrality. This statistical effect was independently replicated in both v1 and v2 large

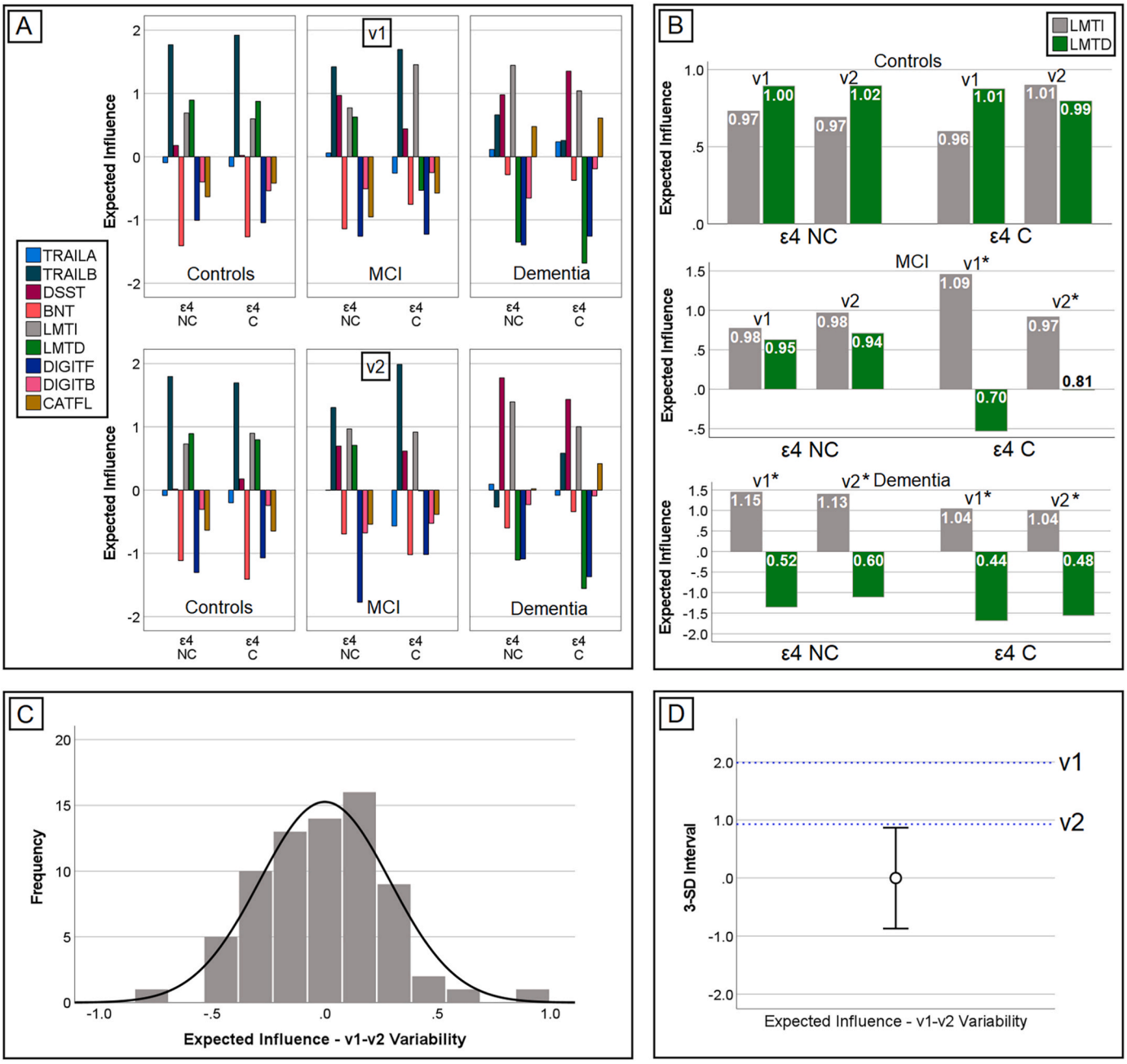

Fig. 3. *Summary of all nodal centrality metrics operationalised as EI.* (A) Bar graphs indicating nodal centrality calculated for each APOE genotype group and for each NACC sub-cohort (i.e., v1 and v2); (B) Memory centrality of the two nodes representing immediate and delayed recall (i.e., while bars indicate *z*-converted centrality scores, raw centrality scores were numerically superimposed); (C) Distribution of same-node v1-to-v2 variability of centrality measures; the ±3-SD interval constructed around the mean of this distribution is shown in (D). The distance in centrality between the two memory nodes at the basis of the group difference in the MCI sub-cohorts (i.e., v1 and v2) is indicated in this graph with the two dotted lines. C: ε_4 carriers; NC: ε_4 non-carriers. *: $p < 0.001$.

sub-cohorts of NACC MCI patients ($n = 1778$ and 1704, respectively), indicating reliability of findings. Moreover, the numerical difference in centrality found between LMTI and LMTD in MCI ε_4 carriers was more than 3-SD larger than the average "normal" test-retest variability indicated by the comparison of v1 and v2 within each node. Additionally, the outcome of a series of *post-hoc* analyses supports the conclusion that the difference between MCI ε_4 carriers and non-carriers was not due to difference in clinical sub-type distribution, age, education, clinical severity, or network community structure. In particular, the findings were confirmed even when limiting the analyses to participants with a diagnostic of amnestic MCI. This indicates that the effect of APOE on node centrality cannot be exclusively due to carriers having worse episodic memory performance: APOE genotype can also influence the extended cognitive profile by altering the relation between measures of episodic memory and other functions.

In experiencing memory alterations, patients with AD show degradation of recall abilities when they tackle the delayed phase of the Logical Memory Test retrieval (Albert, 1996). The ε_4 allele fosters hippocampal atrophy (Suh et al., 2021), and is associated with reduced cerebral metabolism in limbic and frontal regions normally deputed to episodic-memory processing (Liu et al., 2015). When the retention interval is taken into account, however, the ε_4 allele is associated only with worse delayed recall among MCI patients, while no similar genetic effect is found on immediate recall, nor among normal adults or patients with

AD dementia (Wang et al., 2019). Our findings expand this area of knowledge by characterising the statistical effect of the ε_4 allele in terms of its differential impact on immediate and delayed recall, and how this results in specific network effects.

At present, mechanisms explaining *why* these genotype-based differences in EI centrality occur are unknown. A number of neurological routes have been proposed to account for the cognitive differences observed between ε_4 carriers and non-carriers (Mahley et al., 2006). Recent evidence emerged from studies that have used neuromolecular PET radioligands indicates that ε_4 carriers show higher uptake of [^{18}F]-MK6240 (a tracer that binds to neurofibrillary tangles) in the entorhinal cortex and hippocampus, controlling for amyloid pathology, age, sex and clinical status (Therriault et al., 2020), and higher uptake of [^{11}C]-PBR28 (a tracer that binds to a translocator protein expressed in a range of neural components, including activated microglia) in the hippocampus, perirhinal and entorhinal cortex, controlling for amyloid and tau pathology (Ferrari-Souza et al., 2023). This suggests that a range of biological mechanisms linked to APOE variability (at least partially independent of AD pathophysiology) may concur in causing changes in memory function that can be captured by network analysis.

Node-to-node correlations (and, in turn, measures of centrality) may be affected by differences in node variability (Terluin et al., 2016). Although the association between EI and node variability was significant among v1 MCI non-carriers, the marginally significant *p*-value (i.e., = 0.05) suggests that, in all likelihood, this methodological aspect only had a minimal impact on the differences observed between genotypes. Moreover, similar variability across MCI patients was observed on both LMTI and LMTD, suggesting that differential variability between these two specific nodes did not bias the results. As the analysed data were cross-sectional, the variability associated with any node likely reflects a mixture of within- and between-subjects effects (Epskamp et al., 2022). It remains to be seen whether the decreased EI centrality of delayed episodic memory is reliably associated with APOE genotype in individual patients with amnestic MCI.

Previous research has indicated that the cognitive domains most often affected by APOE genotype variability are episodic memory, processing speed and executive functioning, with ε_4 carriers showing worse performance (Small et al., 2004; Wisdom et al., 2011). This pattern, however, is quite inconsistent across studies (O'Donoghue et al., 2018). This may be due to the insufficient level of "complexity" via which test scores are typically addressed by standard analytical procedures, as the independent analysis of multiple test scores only provides a partial description of cognitive profiles (Tosi et al., 2020). A network approach investigates the pattern of cognitive test performance scores in more depth, emphasising the role played by a specific test in relation to metrics that also account for the performance shown on other tests. These findings contribute to the understanding of the impact risk factors have on clinical profiles and are informative to the future design of comparable network-based investigations exploring the effect of other variables of clinical relevance. At the same time, they also expand the study of APOE-dependent neurofunctional systems informed by network neuroscience. When *eigenvector centrality* is investigated (a path-based centrality metric that, differently from *degree* and *betweenness*, factors in the low/high score of nodes), amnestic MCI ε_4 carriers show decreased centrality in the anterolimbic-medioprefrontal territory (Yuan et al., 2016), and episodic-memory impairment in this group is negatively correlated with functional connectivity between this region and the right middle-cingulate cortex (Wang et al., 2017). This suggests a wider and crossmodal effect of APOE variability on network-based neurocognitive organisation, in which neurofunctional and cognitive complexity are both influenced.

This study is not free from limitations. First, although we applied a robust set of exclusion criteria to minimise aetiological variability, we did not rely on biological criteria (e.g., Dubois et al., 2021). This is a methodological aspect that can be potentially improved by future studies, especially in the characterisation of MCI patients (Frisoni and Coleman, 2011). The current findings, however, may contribute to a pathway of clinical translation that is relevant to those settings where biological diagnoses are not possible due to lack of resources, or are not routinely implemented, e.g., in the United Kingdom (Dunne et al., 2021). A clinical diagnosis of MCI still retains its clinical validity and is regulated by dedicated guidelines (Petersen et al., 2018). In this respect, the findings described in the current study address the link between cognitive networks and the most important genetic risk factor for AD in a way that is independent of biomarker profiles. Second, although our graphs were defined by solid methodological principles, it must be recognised that networks may be constructed based on a multitude of procedural choices, such as the use of unweighted edges (Wright et al., 2021), the inclusion of demographic descriptors (Ferguson, 2021; Tosi et al., 2020), or the use of other (and/or more/fewer) neuropsychological tests. On this note, psychological tests often operationalise constructs that show a degree of mutual contiguity and, as a result, this can lead to large node-to-node correlations that can inflate centrality measures. Although the neuropsychological battery analysed in this study did include pairs of tests characterised by theoretical and methodological contiguity (e.g., DIGITF and DIGITB; TRAILA and TRAILB), node-to-node edges weighted only between 0.125 and 0.484 for these nodes (see Supplementary Tables S2–S4). The only edge with a consistent weight above 0.5 was that between LMTI and LMTD. This, however, did not contribute to any of our findings, as this edge contributed to centrality of both LMTI *and* LMTD. Nonetheless, it is important to be aware of the possibility that inflated centralities might arise from the use of multiple test measures that are excessively correlated to one another. Moreover, additional metrics beyond centrality (e.g., integration and segregation) may further contribute to an in-depth characterisation of cognitive profiles and the impact on these of APOE or other risk factors. These additional features deserve to be investigated in sufficient depth, and need to be accompanied by adequate hypotheses in support of their potential clinical role. In a previous exploratory study of cognitive profiles consisting of unweighted networks and relying on a range of metrics, for instance, we found that MCI individuals had higher level of *local efficiency* and *clustering* (two indices indicating how well integrated a node's neighbourhood is) than controls, but no differences in *global efficiency,* i.e., an index of global integration between the node and the rest of the network (Wright et al., 2021). Arguably, metrics that describe a node's neighbouring sub-graph are particularly sensitive to the selection of tests included in the cognitive battery. For this reason, it is important to rely on metrics that are methodologically compatible with the number and diversity of the available variables. A further aspect of relevance is the complexity of the inferential approach: at present, statistical tools are based on the comparison of two networks (van Borkulo et al., 2022). As, however, APOE genotypes result from the expression of three alleles (i.e., ε_3, ε_4 and ε_2), approaches that account for multinomial predictors would help provide a more accurate picture. In all likelihood, future studies will contribute to consolidating and fine-tuning a wide range of methodological gold-standards for network analysis of cognitive profiles and how these are influenced by the intricate mechanisms of clinical risk factors.

5. Conclusions

In conclusion, our study indicates that graph-theory-informed network-based cognitive profiles of MCI patients are significantly influenced by the presence of the APOE ε_4 allele. This is visible in nodes corresponding to episodic memory performance: delayed recall was less central than immediate recall regardless of APOE status, but ε_4 non-carriers showed comparable centrality in immediate and delayed recall, while ε_4 carriers showed instead a dissociation between the two forms of retrieval. This finding indicates that genetic variability is not only associated with variability in individual test performance, but also in the overall network-level cognitive profiles.

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CRediT authorship contribution statement

Matteo De Marco: Funding acquisition, Conceptualization, Methodology, Data curation, Visualization, Writing - original draft, Writing - review & editing. **Laura M. Wright:** Data curation, Methodology, Visualization, Writing - review & editing. **Jose Manuel Valera Bermejo:** Data curation, Methodology, Writing - review & editing. **Cameron E. Ferguson:** Data curation, Methodology, Software, Formal analysis, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

Data availability

Data used in this study was obtained from the National Alzheimer's Coordinating Center initiative (https://naccdata.org/).

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Appendix A. Supplementary data

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