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Veränderungen der funktionellen Konnektivität bei der Alzheimer-Krankheit und ihre Abhängigkeit von Lebensstilfaktoren und kognitiver Reserve in der DELCODE-Studie

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zum Erwerb des Doktorgrades der Medizin
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Abkürzungsverzeichnis

AD Alzheimer's disease, dt. Alzheimer-Krankheit

ADD Alzheimer's disease dementia, dt. Demenz bei Alzheimer-Krankheit

APP Amyloid precursor protein, dt. Amyloid-Vorläuferprotein

ApoE Apolipoprotein E

Aβ Amyloid-β

BM Brain Maintenance, dt. Aufrechterhaltungskapazität des Gehirns

BR Brain Reserve, dt. Hirnreserve

BOLD Blood-Oxygen-Level-Dependent

CR Cognitive Reserve, dt. Kognitive Reserve

CSF Cerebrospinal Fluid, dt. Liquor cerebrospinalis

DAN Dorsal Attention Network, dt. Dorsales Aufmerksamkeitsnetzwerk

DMN Default Mode Network, dt. Default-Mode-Netzwerk

fMRT Functional Magnetic Resonance Imaging, dt. Die funktionelle Magnetresonanztomographie

FPN Frontoparietal Network, dt. Frontoparietales Netzwerk

LEQ Lifetime of Experiences Questionnaire

MCI Mild Cognitive Impairment, dt. Leichte Kognitive Störung

MRT Magnetresonanztomographie

NVC Neurovaskulären-Couplings

PET Positron-Emission-Tomographie

pTau Phosphoryliertes Tau-Protein

ROI Region of Interest, dt. Bereich von Interesse

RSN Resting-State Network, dt. Resting-State Netzwerk

SAL Salience Network, dt. Salience-Netzwerk

SCD Subjective Cognitive Decline, dt. Subjektive Kognitive Störung

SMN Sensorimotor Network, dt. Sensomotorisches Netzwerk

Publikationsliste

Die Artikel, die Bestandteil dieser kumulativen Dissertation sind, wurden gesondert (jeweils in eigenem Teil) aufgeführt.

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Ihr Beitrag zu den Veröffentlichungen

1.1 Beitrag zu Paper I

Der Beitrag des Doktoranden zu dem Paper „Lifelong Experiences as a Proxy of Cognitive Reserve Moderate of Association Between Connectivity and Cognition in Alzheimer's Disease“ umfasst folgende Leistungen:

Studienkonzept und -design, Methodologie, Zusammenstellung der Daten, statistische Analyse, Interpretation der Daten, Visualisierung, Manuskripterstellung und Überarbeitung des Manuskripts.

Eine geteilte Erstautorschaft erfolgte angesichts des gleichwertigen Beitrags beider Erstautoren zum Manuskript.

1.2 Beitrag zu Paper II

Zu der Studie „A Residual Marker of Cognitive Reserve Is Associated with Resting-State Intrinsic Functional Connectivity Along the Alzheimer’s Disease Continuum“ übernahm der Doktorand unten gezeigte Aufgaben, woraufhin eine geteilte Erstautorschaft aufgrund eines gleichwertigen Beitrags beider Erstautoren zum Manuskript erfolgte:

Studienkonzept und -design, Methodologie, Zusammenstellung der Daten, statistische Analyse, Interpretation der Daten, Visualisierung, Manuskripterstellung und Überarbeitung des Manuskripts.

1.3 Beitrag zu Paper III (Anhang)

Zu der Studie „Resting-State Network Alterations Differ between Alzheimer’s Disease Atrophy Subtypes“ leistete der Doktorand die Zusammenstellung der Daten, die Visualisierung und Überarbeitung des Manuskripts sowie Hilfe beim Design und Konzept der Studie und bei den statistischen Analysen und Manuskripterstellung.

2. Einleitung

Wie in den frühesten Lebensjahren erfährt das Gehirn im Laufe des Lebens signifikante Veränderungen, dabei nimmt die funktionelle Kapazität des Gehirns mit zunehmendem Alter im Erwachsenenalter tendenziell ab. Dieser Prozess hängt von einer komplexen Wechselwirkung zwischen Zeit, konstitutioneller oder genetischer Veranlagung eines Individuums und den kumulativen Auswirkungen stochastischer Begegnungen mit endogenen und exogenen Ereignissen zusammen (Mesulam, 2000). Manche Individuen sind dank einer hohen Reserve dabei resilienter als andere, sodass post-mortem-Untersuchungen zeigen konnten, dass Individuen mit höherer Reserve trotz ausgeprägten neuropathologischen Veränderungen keine kognitiven Einbußen aufweisen (Katzman et al., 1988; Yaakov Stern, 2002).

Die Zahl der Demenzkranken wird weltweit auf rund 50 Millionen Menschen geschätzt, wobei eine Verdreifachung bis zum Jahr 2050 zu erwarten sei (Patterson, 2018). Dieser Trend deutet darauf hin, dass die soziale und ökonomische Last durch Demenzerkrankungen weiter zunehmen wird, vor allem aufgrund der zunehmenden Behinderung, weniger durch die erhöhte Mortalität (Wolters & Ikram, 2018). Angesichts der alternden Bevölkerung und steigenden Prävalenz der Demenzen wurde vom *„Joint Programme on Neurodegenerative Disease Research“* der europäischen Union bereits im Jahr 2013 die Bedeutung von Studien zur Demenzprävention betont, mit besonderem Fokus auf die protektiven Wirkungen von bestimmten Lebensstilfaktoren (Livingston et al., 2017). Darüber hinaus definierte der globale Aktionsplan der Weltgesundheitsorganisation (engl. *World Health Organisation*) die Reduktion des Demenzrisikos als eine der Prioritäten (World Health Organisation, 2017). Zudem deutete die Studie der Lancet-Kommission für Prävention der Demenzen darauf hin, dass bis zu 40% des Demenzrisikos weltweit von modifizierbaren Faktoren wie u. a. Ausbildung, körperliche Aktivitäten und soziale Kontakten abhängt (Livingston, Selbaek, et al., 2020).

2.1. Alzheimer Demenz: Das Wichtigste in Kürze

2.1.1. Demenzielles Syndrom

Das „demenzielle Syndrom“ bzw. Demenzerkrankungen allgemein werden durch den Abbau und Verlust der kognitiven Leistungsfähigkeit definiert, welche meistens einen progressiven Charakter aufweisen und sich in einer Abnahme der Alltagskompetenzen sowie Orientierung zeigen, sodass besonders in späteren Stadien der Krankheit eine zunehmende Abhängigkeit von anderen Menschen auftritt (DGPPN & DGN, 2023). Studien berichten über eine Prävalenz der Demenz von 5-10% in der Bevölkerung über dem 65. Lebensjahr, mit einer altersbedingten Dynamik und Verdoppelung der Prävalenz alle 5 Lebensjahre (Hugo & Ganguli, 2014). Das demenzielle Syndrom kann auf verschiedenste Ursachen zurückgeführt werden, wobei die Symptomkonstellationen bezüglich der ätiologischen Zuordnung wegweisend ist. In der aktuellen S3-Leitlinie werden daher vor allem laborchemische und apparative Untersuchungen als erweiterte Diagnostik empfohlen (DGPPN & DGN, 2023). Die mit ca. 50-70% höchste Prävalenz weist die Demenz bei Alzheimer-Krankheit (engl. *Alzheimer’s disease dementia*, ADD) auf, gefolgt von der vaskulären Demenz mit ca. 15-20% (Qiu, De Ronchi, & Fratiglioni, 2007). Post mortem Studien ergaben eine Komorbidität beider (ADD und vaskuläre Genese) Formen von 4,7 bis 44% (Chui & Ramirez-Gomez, 2015). Im Allgemeinen ist gemischte Pathologie bei 20-50% der an einer Demenz Erkrankten zu erwarten, die auf die klinische Manifestation inklusive strukturelle Bildgebung beeinflussen kann (Mohanty et al., 2022; Qiu et al., 2007; Schneider, Arvanitakis, Bang, & Bennett, 2007).

2.1.2. Alzheimer-Krankheit „eine eigenartige Erkrankung der Hirnrinde“

Die Definition der Alzheimer-Krankheit (engl. *Alzheimer's disease*, AD) von Alois Alzheimer als „eine eigenartige Erkrankung der Hirnrinde“ (Alzheimer, 1911) kann weiterhin als zutreffend angesehen werden und begleitet uns weiterhin in der AD-Forschung bis heute. Ein eindeutiger Zusammenhang zwischen neuropathologischen und neuropsychiatrischen Merkmalen der AD wurde es vor etwa 40 Jahren hergestellt, wodurch die Erforschung der Erkrankung einen Schub erlebte (Robin G. Morris & Salmon, 2007). AD ist eine primär degenerative zerebrale Krankheit mit komplexen neuropathologischen und neurochemischen Merkmalen, sowie progredientem kognitiven Abbau. Typischerweise treten die Beeinträchtigungen der mnestischen Funktionen als erstes auf und sind im frühen Stadium das prominenteste Merkmal (D. Selkoe, 2002; Zhang et al., 2013). Die neuropathologischen Änderungen der AD gehen mit extrazellulärer Anhäufung der Amyloid-Plaques und intrazellulärer Ablagerung der Tau-Fibrillen (E. Braak et al., 1999) einher, wobei in den vergangenen Jahren deutlich wurde, dass Mechanismen wie Neuroinflammation sowie eine Störung der Blut-Hirn-Schranke eine wichtige Rolle bei der Pathogenese spielen (De Strooper & Karran, 2016; Heneka et al., 2015). Zusammenfassend deuten die Studien auf eine multifaktorielle Genese der AD hin (Armstrong, 2013).

Die bis heute bedeutendste Hypothese der Krankheitsentstehung ist die Amyloid-Kaskaden-Hypothese, der zufolge Plaquebildung durch Aggregation des Proteins Amyloid-β (Aβ) für die Erkrankung eine Schlüsselrolle spielt. In der Folge kommt es zur Akkumulation des Tau-Proteins, die in Neurodegeneration mündet (D. J. Selkoe & Hardy, 2016). Die Proteolyse des Amyloid-Vorläuferproteins (engl. *Amyloid precursor protein, APP*) durch β- und γ-Sekretasen ist der entscheidende Mechanismus der Aβ Aggregation, es werden Proteine wie $A\beta_{1-38}$ und $A\beta_{1-40}$, die nicht oder seltener aggregieren sowie häufig aggregierende Proteine wie $A\beta_{1-42}$ gebildet (Haass & Selkoe, 2007). Die potenziell neurotoxischen Aβ-Aggregate können pathologische Mechanismen wie Membran-Permeabilität und Neuroinflammation auslösen (Cras et al., 1991; De et al., 2019; Patel et al., 2005). Zudem werden unter den Aβ-Aggregaten die Oligomere und Protofibrille als besonders toxisch angesehen, die von Fibrillen und dann Plaques gefolgt werden (Hampel et al., 2021). Andererseits wurde vorgeschlagen, dass unlösliche Fibrillen die Oligomer-Formation katalysieren können (Törnquist et al., 2018). Neben der Amyloid-Kaskaden-Hypothese werden u. a. auch andere, teils komplementäre, Hypothesen wie die Tau-Hypothese (Arnsten, Datta, Del Tredici, & Braak, 2021; Takashima, 2010) und die vaskuläre Hypothese (Zlokovic, 2011) diskutiert. Die AD zeigt eine deutliche Heritabilität, wobei eine Variante im Apolipoprotein E *(ApoE)* Gen der wichtigste Suszeptibilitätsfaktor der sporadischen Variante ist. Die autosomal-dominanten familiären Formen sind deutlich seltener und gehen auf Mutationen in den Genen *APP*, *PSEN1* und *PSEN2* zurück (Corder et al., 1993; Goate et al., 1991; Hampel et al., 2021; Szaruga et al., 2017).

Die zeitlichen Zusammenhänge zwischen den unterschiedlichen Biomarkern wurden insbesondere in der Arbeit von Jack et al. beschrieben (Jack, Knopman, et al., 2013). Betrachtet man einzelne Individuen, so wird deutlich, dass es bezüglich des kognitiven Abbaus bei vergleichbarer pathologischer Krankheitslast deutliche Unterschiede gibt. Beginn und Verlauf der klinischen Manifestation variieren beträchtlich zwischen einzelnen Individuen, was durch die Reserve-Hypothese erklärt werden kann **(Abb. 1)**, die unten weiter eingeleitet wird. Erstaunlicherweise zeigten zudem Studien eine bestehende Aβ-Pathologie bei bis zu einem Drittel der Individuen ohne kognitive Einschränkungen in einer neuropathologischen Untersuchung (R. Sperling, Mormino, & Johnson, 2014) sowie in der Amyloid- Positron-Emission-Tomographie (PET) (R. A. Sperling et al., 2020).

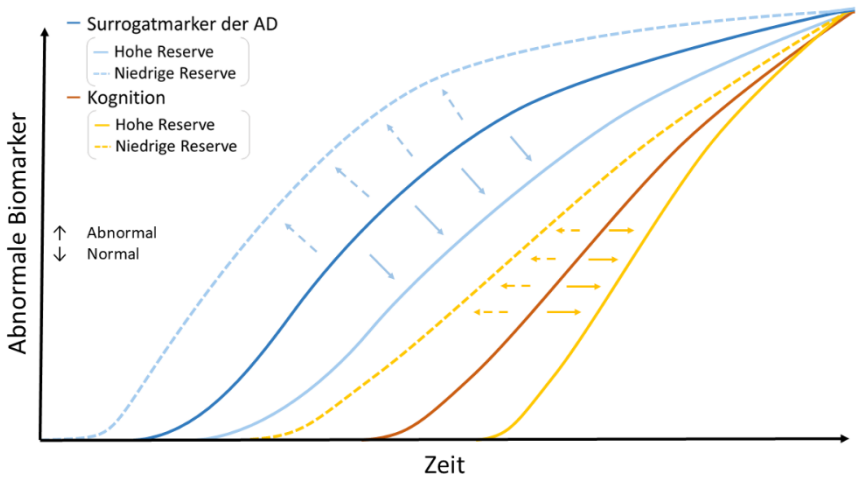

Abbildung 1: Hypothetisches Modell des zeitlichen Verlaufs der pathologischen Veränderungen bezüglich der Biomarkerveränderungen und des kognitiven Abbaus bei der Alzheimer-Krankheit. Kognitive Abnormalität wird im Hinblick auf die Reserve-Hypothese separat für Individuen mit hohen (durchgezogene Linie) und niedrigen Reservekapazitäten (gestrichelte Linie) dargestellt.

Der Verlauf der AD, als ein Kontinuum, lässt sich durch kontinuierliche Messungen der etablierten Biomarker abbilden. Es wird aus diesem Grund von einer kumulativen Progression der AD-Pathologie ausgegangen (Hansson, 2021; Jack et al., 2010). Diese Betrachtungsweise der Krankheitsstadien führte zu einer biologischen Klassifikation AT(N), die dazu dienen sollte, Individuen im Kontext der Beobachtung- oder Interventionsstudien hinsichtlich der Biomarker-Abnormalität identifizieren zu können: A für Amyloid, T für Tau und N für Neurodegeneration (Jack et al., 2018).

Viele Biomarker können bereits in dem präklinischen bzw. asymptomatischen Stadium festgestellt werden (Jack et al., 2018). Ein besonders langes präklinisches Stadium findet man bei der Aβ-Pathologie, mit signifikant erhöhten Messwerten bereits etwa 20 bis 30 Jahre vor Symptombeginn (Jansen et al., 2015). Im Verlauf kommt es zu einer Plateaubildung, die sich oft schon in frühen Krankheitsstadien zeigt (Jack, Wiste, et al., 2013). Der aktuelle Goldstandard, Aβ-Pathologie bei Patienten mit AD nachzuweisen ist die Messung einer verringerten $A\beta_{42}$ Konzentration, einer verringerten $A\beta_{42}/A\beta_{40}$-Ratio im Liquor cerebrospinalis (engl. *Cerebrospinal fluid*, CSF) (Bateman et al., 2012; Jack, Wiste, et al., 2013; R. A. Sperling, Karlawish, & Johnson, 2013), oder der Nachweis einer erhöhten Tracer-Aufnahme im Amyloid-PET (Jack et al., 2018). Ergänzend wird oft im Rahmen von Studien Tau-Pathologie über ein signifikant erhöhtes phosphoryliertes Tau-Protein (pTau) bestimmt (Ossenkoppele et al., 2015). pTau ist sowohl räumlich als auch zeitlich viel stärker mit einer Neurodegeneration und kognitiven Beeinträchtigungen als die Aβ-Pathologie assoziiert (van der Kant, Goldstein, & Ossenkoppele, 2020). Als weitere neuropathologische Kennzeichen im Verlauf der AD wurden ein verminderter zerebraler Glukose-Metabolismus sowie eine Hirnatrophie als Neurodegenerationsmarker definiert (Jack et al., 2018).

Die frühe Phase der AD wird in präklinische subjektive Gedächtnisbeschwerden (SCD, engl. *subjective cognitive decline*) ohne objektivierbare kognitive Auffälligkeiten, sowie in die klinisch relevante leichte kognitive Störung (engl. *mild cognitive impairment*, MCI) unterteilt (Jack et al., 2018; Jessen, 2014). Die Erkennung der frühen Phasen ist besonders für Präventionsstrategien

und therapeutische Interventionen entscheidend, da es in diesen Stadien noch nicht oder kaum zur irreversiblen Neurodegeneration gekommen ist (Morbelli et al., 2013; R. Sperling et al., 2014). Aus diesem Grund verdient eine Früherkennung eine erhebliche Aufmerksamkeit in der Alzheimerforschung (Jessen, 2014; Jessen et al., 2020; Molinuevo et al., 2017; Petersen et al., 2018; R. A. Sperling et al., 2011).

Neuropathologische Veränderungen durch Aβ- und Tau-Pathologien weisen ein charakteristisches zerebrales Verbreitungsmuster auf. Die Entwicklung der zerebralen β-Amyloidose zeigt sich mit einer klaren Abfolge der Ausbreitung der Aβ-Ablagerungen, bei der die Regionen hierarchisch involviert sind. Die Aβ-Ablagerungen sind nach den Thal-Phasen zuerst in dem Neocortex zu finden. Ab der zweiten Phase wird eine zusätzliche Beteiligung allocortikaler Hirnregionen beschrieben und danach folgen das basale Vorderhirn, mehrere Hirnstammkerne und das Cerebellum (Thal, Rüb, Orantes, & Braak, 2002). Tau Pathologie ist zudem nach Braak-Stadien im frühen Verlauf der AD vor allem in limbischen Regionen und dem medio-temporalen Lappen zu sehen (H. Braak & Braak, 1991; Heiko Braak, Alafuzoff, Arzberger, Kretzschmar, & Del Tredici, 2006). Aktuelle Studien wiesen dennoch darauf hin, dass Tau bereits während der prodromalen Phase der AD in unterschiedlichen räumlich-temporalen Mustern akkumuliert (Ten Kate et al., 2018; Vogel et al., 2020), die auf biologische Phänotypen (Subtypen) hindeuten kann (Ferreira, Nordberg, & Westman, 2020; Murray et al., 2011; Vogel & Hansson, 2022). Es wurde bereits in früheren Studien heterogene klinische Manifestationsformen der AD diskutiert (Snowden et al., 2007), die amnestisch und non-amnestische Formen umfassen. Auch ein multi-syndromaler Charakter wurde postuliert, welchem neben der Heterogenität in der klinischen Präsentation unterschiedliche neurobiologische Phänotypen zugrunde liegen (R. G. Morris, 2004). Sowohl die bildgebende Charakterisierung als auch Studien zu Genetik, Biomarker und molekularbiologische Untersuchungen haben dazu beigetragen, (Sub-)Phänotypen der AD zu identifizieren. Mit diesen Erkenntnissen könnten therapeutische Interventionen zukünftig noch präziser und individualisiert erfolgen (Graff-Radford et al., 2021). Mit unterschiedlichen klinischen Verläufen im Sinne des Symptombeginns, der Progressionsraten und des neuropsychologischen Charakters könnten Subtypen einen Zusammenhang zeigen (Vogel & Hansson, 2022).

Trotz einer exponentiell wachsenden Anzahl von Studien zur Aufdeckung zugrundeliegender Mechanismen der AD-Pathologie in den letzten Jahrzehnten waren bislang keine wirksamen kausalen Therapien in Europa verfügbar. Die aktuelle Standardbehandlung ist eine rein symptomatische pharmakologische Behandlung der kognitiven Auffälligkeiten und Verhaltensstörungen, beispielsweise mit den Acetylcholinesterase-Hemmern, (DGPPN & DGN, 2023), ohne über kausale den Krankheitsverlauf modifizierende Effekte zu verfügen (J. L. Cummings, Tong, & Ballard, 2019). Im Unterschied zu einer symptomatischen Behandlung wird bei einer kausal wirksamen Therapie das Fortschreiten der pathologischen Veränderungen verzögert und nicht auf symptomatischer Ebene eine Verbesserung erzielt (Grossberg, Tong, Burke, & Tariot, 2019). In Studien werden derzeit eine Vielzahl von potenziell krankheitsmodifizierenden Wirkstoffen ("disease modifying drugs") erprobt, u. a. Biologika oder *small-molecules* (J. Cummings, Lee, Zhong, Fonseca, & Taghva, 2021). Erste Vertreter dieser neuen Wirkstoffklasse haben bereits in den USA eine Zulassung erhalten. Den Anfang machte 2020 der Amyloid-Antikörper Aducanumab (Haeberlein et al., 2020), 2023 folgte die Zulassung von Lecanemab, eines weiteren Amyloid-Antikörper (van Dyck et al., 2023). Die Wirksamkeit dieser Medikamente, die in den Zulassungsstudien mäßige Effekte auf das Fortschreiten der klinischen Symptome zeigten, muss sich in der Praxis noch zeigen. Es wurden klinisch relevante Nebenwirkungen wie Hirnblutungen und Hirnödem als „*Amyloid-related imaging abnormalities*“ beobachtet, die besonders Anfang der Behandlung ein enges klinisches und bildgebendes Monitoring erforderlich machen. Die Therapie ist daher mit hohen Kosten verbunden (Fillit & Green, 2021; Thambisetty & Howard, 2023). Neben der Behandlung von Krankheitsursachen und Symptomen steht in letzter Zeit die Prävention als weitere Behandlungsmöglichkeiten mehr und mehr im Fokus. Präventive Maßnahmen können entweder durch eine Förderung der protektiven

Faktoren oder durch eine Hemmung von Risikofaktoren erzielt werden. Die Studien deuten hierbei darauf hin, dass ein Dutzend potenziell veränderbarer Faktoren, darunter Hörbehinderung, vaskuläre Gesundheit und lebenslange Erfahrungen wie kognitive, soziale und körperliche Aktivitäten, bis zu vierzig Prozent des Demenzrisikos in der Bevölkerung erklären (Livingston, Huntley, et al., 2020). Speziell für AD fehlen hierzu aktuelle Präventionsstrategien-übergreifende Meta-Analysen, wobei eine Meta-Analyse aus dem Jahr 2014 auf eine ähnliche Effektstärke hinweist (Norton, Matthews, Barnes, Yaffe, & Brayne, 2014). Für einzelne Faktoren wie Hörfähigkeit, Adipositas und körperliche Aktivität wurden hingegen bereits neuere Meta-Analysen in Bezug auf AD publiziert (Iso-Markku et al., 2022; Tarawneh, Menegola, Peou, Tarawneh, & Jayakody, 2022; Zhuang, Meng, Wang, Shen, & Ji, 2021).

2.1.3. Veränderungen der funktionellen Konnektivität im Ruhezustand bei Patienten mit Alzheimer-Krankheit

Untersuchungen der funktionellen Konnektivität im Ruhezustand mittels Magnetresonanztomographie (MRT) leisten einen wichtigen Beitrag zu einem besseren Verständnis der zugrundeliegenden Pathomechanismen der AD. Die funktionelle MRT (fMRT) ermöglicht die nichtinvasive Messung der Hirnaktivität und beruht auf dem Prinzip des Neurovaskulären-Couplings (NVC) (Lecrux & Hamel, 2011). NVC bezeichnet die Assoziation zwischen neuronaler Aktivität und lokalem Blutfluss. In aktiveren Hirnregionen kommt es aufgrund der neuronalen Aktivität lokal zu einem erhöhten Metabolismus und zu einem höheren Energiebedarf. Über den Mechanismus des NVC wird eine verstärkte Durchblutung der aktivierten Hirnregionen bewirkt, gleichzeitig kommt es zu einem überschießenden Angebot von oxygeniertem Hämoglobin, welches im Vergleich zu desoxygeniertem Hämoglobin eine andere magnetische Eigenschaft aufweist (Diamagnetismus) die in der MRT-Messung zur vom Blutsauerstoffgehalt abhängigen Kontrasterzeugung (engl. *Blood-Oxygen-Level-Dependent* (BOLD)-Kontrast) genutzt werden kann (Ogawa, Lee, Kay, & Tank, 1990). Unter funktioneller Konnektivität versteht man die Korrelation der BOLD-Signale zwischen unterschiedlichen Hirnregionen: Je höher die Korrelation zwischen zwei gepaarten Regionen (Voxels oder einzelne Regionen als ein vorbeschriebenes Areal bzw. ein „Bereich von Interesse" (engl. *Region of Interest, ROI*)) ist, desto höher ist die funktionelle Konnektivität (Hillman, 2014). Die synchronen BOLD-Signale bilden Module bzw. durch Komponentenanalysen definierten Clusters von Voxeln, die als *resting-state* Netzwerke (RSNs) bezeichnet werden (Damoiseaux et al., 2006). Die funktionelle Konnektivität zwischen den ROIs, die einem bestimmten Netzwerk oder unterschiedlichen Netzwerken angehören, wurde außerdem als ein alternativer Ansatz verwendet, um die Intra- sowie Internetwork-Konnektivität zu quantifizieren (Mathew R. Brier et al., 2012; Chhatwal et al., 2018; P. Wang et al., 2015). Die letzte Methode stellt somit eine weniger datengestützte Alternative dar als die Komponentenanalyse.

In einer Vielzahl von Untersuchungen konnten charakteristische Veränderungen in der Architektur der funktionellen Konnektivität bei Patienten mit AD gezeigt werden (Dennis & Thompson, 2014; Farahani, Karwowski, & Lighthall, 2019; Seeley, Crawford, Zhou, Miller, & Greicius, 2009). Die fMRT-Messungen im Ruhezustand legen darüber hinaus nahe, dass bei Patienten mit AD eine Assoziation zwischen der kognitiven Leistungsfähigkeit und Veränderungen der funktionellen Konnektivität im Default-mode-Netzwerk (DMN) besteht **(Abb. 2-A)** (Amaefule, Dyrba, Wolfsgruber, & Polcher, 2021; Binnewijzend et al., 2012; Dennis & Thompson, 2014; Jack et al., 2017; Matthews, Filippini, & Douaud, 2013; Palmqvist et al., 2017). Das DMN wird auch als *task-negatives Netzwerk* bezeichnet, das nur bei den nach innen fokussierten Aufgaben, wie dem Abruf des autobiografischen Gedächtnisses oder der Vorstellung der Zukunft aktiviert ist, jedoch nicht unter der Ausführung bestimmter zielgerichteter Aufgaben. Es lässt sich daher besonders gut im Ruhezustand untersuchen (Buckner, Andrews-Hanna, & Schacter, 2008; Fox et al., 2005; Greicius, Srivastava, Reiss, & Menon, 2004). Die Regionen des

DMN weisen zudem eine räumliche Überlappung mit Regionen der Aβ-Ablagerungen bereits in dem frühesten Stadium der AD auf (Palmqvist et al., 2017) und diese Überlappung ist auch schon bei Individuen ohne kognitive Auffälligkeiten zu finden (Ingala et al., 2021). Auch die Tau-Ablagerungen wurden bei Patienten mit AD verstärkt in DMN-Regionen identifiziert (Hoenig et al., 2018). Eine reduzierte funktionelle Konnektivität im DMN prädiziert zusammen mit Amyloid-Pathologie im posterior-cingulären Kortex eine schnellere Verschlechterung der mnestischen Funktionen in den folgenden zwei Jahren (Ingala et al., 2021). Außerdem wurden Zusammenhänge zwischen kognitiven Symptomen und veränderter funktioneller Konnektivität in sogenannten *task-positive* RSNs (Fox et al., 2005) wie dem *dorsal attention network* (DAN), *salience network* (SAL), *sensorimotor network* (SMN) und *frontoparietal network* (FPN) gezeigt (Agosta et al., 2012; Chhatwal et al., 2018; Elman et al., 2016; Gour et al., 2014; Putcha, Brickhouse, Wolk, & Dickerson, 2019; P. Wang et al., 2015). Diese task-relevanten Netzwerke wurden mit spezifischen extrinsischen Aktivitäten verbunden und zeigen eine starke Antikorrelation (Antagonismus) mit DMN in der *resting-state* fMRT (Fornito, Harrison, Zalesky, & Simons, 2012; Fox et al., 2005). Eine erhöhte Konnektivität zwischen den RSNs (im Sinne einer Internetzwerk-Konnektivität) wurde zudem bei Probanden mit AD identifiziert, was ebenfalls mit der Symptomausprägung eine Korrelation zeigte (Mathew R. Brier et al., 2012; P. Wang et al., 2015). Hierzu zählt u. a. die Konnektivität zwischen DMN und DAN, DMN und frontoparietalem Netzwerk (Palmqvist et al., 2017), sowie DMN und SMN (Mathew R. Brier et al., 2012; P. Wang et al., 2015). Neben der Ausprägung der kognitiven Beschwerden wiesen auch unterschiedliche neuropsychologische Profile auf spezifische Konnektivitätsveränderungen in RSNs (Amaefule et al., 2021; Pini et al., 2021).

Ein weiterer Ansatz zur Analyse der fMRT ist die Auswertung der Korrelationen zwischen unterschiedlichen Hirnregionen unter Verwendung der Graphentheorie-Analyse. Die Graphentheorie-Analyse ist ein auf Mathematik basierendes Verfahren, welches Hirnregionen als Knoten und die Verbindungen zwischen den Hirnregionen als Kanten (engl. *Edge*) untersuchen lässt **(Abb. 2-B)** (Farahani et al., 2019; Hallquist & Hillary, 2019). Die Graphentheorie-Analyse kann ermöglichen, die funktionelle Konnektivität auf einer globalen (gesamtes Gehirn betreffend) oder lokalen (regionalen) Ebene zu charakterisieren (Bullmore & Sporns, 2009; Dennis & Thompson, 2014). Auf globaler Ebene werden Netzwerkeigenschaften, d. h. Graphen-Metriken, wie Segregation („*clustering coefficient*“ und „*modularity*“), Integration („*global efficiency*“), Hubness und Zentralität („*strenght*“) definiert (Matthew R. Brier et al., 2014). Auf lokaler Ebene lassen sich zudem Hub-Regionen identifizieren, die die zentralen Schaltstellen im Gehirn darstellen und ein hoher Grad („*degree*“) sowie eine hohe Zentralität („*betweenness centrality*“) aufweisen (Farahani et al., 2019). Mit steigendem Alter weist das Gehirn auch bei Gesunden eine reduzierte Integration- und Segregation auf (Dennis & Thompson, 2014). Patienten mit AD zeigen ein reduziertes Gleichgewicht zwischen Integration und Segregation (small-worldness (Sporns, 2011)), sowie eine reduzierte Segregation wie *clustering coefficient* und *modularity* im Vergleich zu den gesunden Probanden (Dennis & Thompson, 2014; Weller et al., 2021). Die Graphen-Metriken sind mit Amyloid-Pathologie assoziiert, so wurde bei Menschen ohne objektivierbare kognitive Defizite eine negative Assoziation zwischen der Zentralität in den DMN-Regionen und der Amyloid-Pathologie berichtet (Ingala et al., 2021). Zudem legte eine Studie nahe, dass Aβ+ Individuen ohne objektivierbare kognitive Defizite eine positive Korrelation zwischen der Gedächtnisleistung und Graphen-Metriken wie *efficiency, modularity* und *small worldness* sowie *local efficiency* innerhalb des DMN zeigten, während Gruppenunterschiede zwischen Aβ- und Aβ+ Individuen nur bei *local efficiency* im Hippocampus nachweisbar waren (Adams et al., 2023). Somit fanden die Autoren mittels der Graphentheorie-Analyse Hinweise auf funktionelle Veränderungen in der Netzwerkeigenschaften bei Menschen mit erhöhtem AD-Risiko.

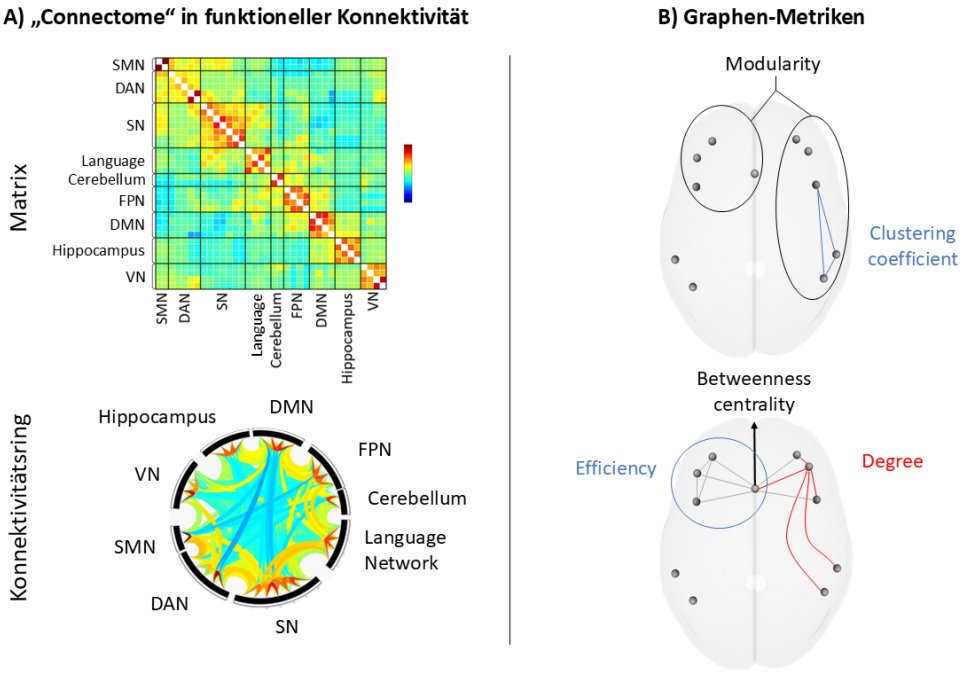

Abbildung 2: Theoretische Beispiele für **(A)** eine Analyse der funktionellen Konnektivität zwischen den Bereichen von Interesse, gezeigt in *Heatmaps* (Repräsentation der funktionellen Konnektivität auf einer Skala von Blau (gering) zu Rot (hoch)) sowie **(B)** eine Darstellung der daraus abgeleiteten Graphen-Metriken. Abkürzungen: DAN, Dorsal Attention Network; DMN, Default Mode Network; FPN, Frontoparietal Network; SN, Salience Network; SMN, Sensorimotor Network; VN, Visual Network.

2.2. Das Konzept der kognitiven Reserve

2.2.1. Theorie der Reserve

Das Konzept der „Reserve“ wurde geschaffen, um die interindividuelle Varianz in der Kognition relativ zur Ausprägung der lebensverlaufsbedingten Gehirnveränderungen und -verletzung oder Krankheit zu beschreiben (Perneczky et al., 2019). In einer bahnbrechenden Arbeit erkannte Stern et al. die unterschiedlichen Zusammenhänge zwischen dem Grad der pathologischen Änderungen und der kognitiven Leistungsfähigkeit (Yaakov Stern, 2002). Eine frühere Studie wies bei Patienten trotz der fehlenden kognitiven Einbußen auf erhebliche AD-typische neuropathologische Veränderung hin (Katzman et al., 1988). Weiterführende Untersuchungen zeigten, dass eine hohe Reserve mit einer bedeutend langsameren kognitiven Verschlechterung, insbesondere in prodromalen Stadien der Krankheit, sowie insgesamt mit einer geringeren Mortalität verbunden ist (Hall et al., 2007; Ossenkoppele et al., 2020; Reed et al., 2010; Soldan et al., 2017; Anna C. van Loenhoud et al., 2022; Zahodne et al., 2013). Anhand longitudinaler Studien wurde außerdem postuliert, dass es bei Individuen mit hoher kognitiver Reserve im späterem Krankheitsverlauf zu einer rascheren kognitiven Verschlechterung kommen kann (Hall et al., 2007; Scarmeas, Albert, Manly, & Stern, 2006; Y. Stern, Albert, Tang, & Tsai, 1999; Anna Catharina van Loenhoud et al., 2019).

Die kognitive Reserve (engl. *cognitive reserve* (CR)) wird als Anpassungsfähigkeit bezüglich der Flexibilität, Effizienz, Kapazität, sowie Kompensation der funktionellen Gehirnprozesse definiert (Yaakov Stern et al., 2020). Mit anderen Worten ist CR ein Moderator, der schädliche

Wirkungen der Pathologie auf die Kognition abschwächen kann (Chapko, McCormack, Black, Staff, & Murray, 2018) **(Abb. 3-A)**.

Weitere wichtige Begriffe der Reserve-Hypothese sind die Hirnreserve *(*engl. *brain reserve, (BR)*), und die Aufrechterhaltungskapazität des Gehirns *(*engl. *brain maintenance (BM))* (Yaakov Stern et al., 2020) **(Abb. 3-A)**. Unter Hirnreserve kann man ein bestimmtes neurobiologisches Kapital verstehen, welches von Studien beispielsweise anhand der intrakraniellen Volumina oder Integrität der weißen Substanz gemessen wurde (Guo et al., 2013; Perneczky et al., 2019; Anna C. van Loenhoud et al., 2022). BR repräsentiert Mechanismen einer passiven Reserve und kann als eine Schwelle angesehen werden, bis zu den Individuen das Ausmaß der pathologischen Änderungen kompensieren können (Arenaza-Urquijo & Vemuri, 2018; Katzman et al., 1988; Yaakov Stern et al., 2020). Lebensereignisse können die neurale Plastizität beeinflussen und es wurde vorgeschlagen, dass diese Plastizitätseffekte die Resistenz gegen Neurodegenerativen durch eine Erhöhung der Konnektivität zwischen Regionen bis zu einem gewissen Ausmaß abfangen können (Maguire et al., 2000; Valenzuela & Sachdev, 2006). BM wurde dagegen als die Aufrechterhaltung der Hirnstruktur während des Alterungsprozesses oder der pathologischen Neurodegeneration definiert. BM benötigt eine longitudinale Betrachtungsweise und kann synergistisch und kumulativ von genetischen und Umweltfaktoren beeinflusst werden, welche ebenfalls auf BR wirken (Nyberg & Lindenberger, 2020; Perneczky et al., 2019). BM bezieht sich darauf, wie sich die Hirnreserve mit der Zeit verändern bzw. erhalten lässt (Yaakov Stern et al., 2020).

Die genannten Begriffe sollten als sich dynamisch entwickelnde Konzepte verstanden werden, da die Definitionen gewisse Überlappung beinhalten und sich weiterentwickeln werden. In einer neueren Übersichtsarbeit wurde die Resistenz als Verzicht der Pathologie und die Resilienz als die Bewältigung der Pathologie als Oberbegriffe definiert (Arenaza-Urquijo & Vemuri, 2018) **(Abb. 3-B)**.

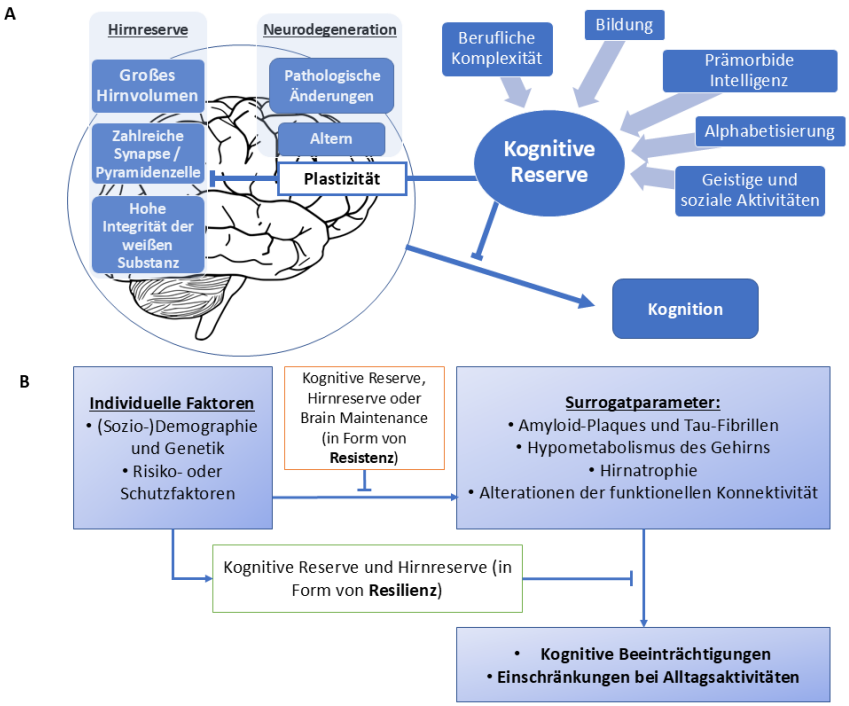

Abbildung 3: Darstellung der zwei theoretischen Modelle der Reserve mit Hinblick auf Kognition mit den ausgewählten Proxy-Faktoren als Beispiele: **(A)** Kognitive Reserve als Moderator der Wirkung von pathologischen Änderungen auf die Kognition und **(B)** Oberbegriffe „Resistenz und Resilienz“ einhergehend mit kognitiver Reserve und Hirnreserve.

2.2.2. Methoden zur Quantifizierung der kognitiven Reserve

Ansätze zur Quantifizierung und Messung der CR lassen sich in drei Kategorien unterteilen (Yaakov Stern et al., 2020): (i) **sozio-behaviorale Proxys von CR**, die lebenslangen Aktivitäten oder individuelle Faktoren wie sozio-ökonomischer Status; (ii) **Residual-Ansatz**, statistische Ansätze, die im Allgemeinen eine unerklärte Varianz in der Kognition im Verhältnis zur pathologischen Änderungen berechnen**;** und (iii) **Ansätze mit der funktionellen Bildgebung**, die Imaging-basierten Ansätze, beispielsweise anhand der funktionellen Konnektivität.

Studien legen nahe, dass **sozio-behaviorale Proxys von CR** in Form von lebenslangen Erfahrungen, einschließlich Bildungs- und Berufserfolge sowie Freizeitaktivitäten im späteren Leben, die Reserve erhöhen können (Yaakov Stern, 2012). Im folgenden Teil werden detaillierte Beschreibung und Beispiele dieses Ansatzes gesondert erläutert.

Der residuale Ansatz wurde entwickelt, um populationsbezogen, für jedes Individuum die Abweichung der pathologischen Veränderungen im Verhältnis zur kognitiven Veränderung zu definieren. Die Abweichung des einzelnen Teilnehmers wird als Residuum bezeichnet (Bocancea et al., 2021; Reed et al., 2010). Beim residualen Ansatz werden, im Großteil Teil der bisherigen Studien, demografische Faktoren wie Alter und verschiedene Surrogatparameter wie verschiedene Biomarker der AD im Verhältnis zur Kognition berechnet, wodurch CR als die ungeklärte Varianz der Kognition angesichts der geschätzten pathologischen Last zum Zeitpunkt der Untersuchung definiert wird (Lee et al., 2019; Reed et al., 2010; Anna C. van Loenhoud et al., 2017; Anna Catharina van Loenhoud et al., 2019; Zijlmans, Lamballais, Vernooij, Ikram, & Luik, 2021). Diese Abschätzung ist im Grunde genommen dynamisch und würde sich im Verlauf durch die entsprechenden Änderungen in Kognition sowie Prädiktoren verändern, was eine aufgebaute oder erschöpfte CR über den Krankheitsverlauf darstellen könnte. Ein solcher Marker kann als ein unmittelbares Maß der CR betrachtet werden (Yaakov Stern et al., 2020).

Durch verschiedene **Ansätze zur Definition der CR mittels funktioneller Bildgebung** wurden versucht, um die „neuronalen Korrelate“ der CR zu identifizieren. Beispielsweise wurde eine hohe Aktivität des frontoparietalen Netzwerkes (Neitzel, Franzmeier, Rubinski, & Ewers, 2019; Soldan et al., 2021), SAL sowie DMN im Ruhezustand (Buckley et al., 2017) als Surrogat für CR vorgeschlagen ebenso die globale Konnektivität des linken Frontalkortex (Cole, Yarkoni, Repovs, Anticevic, & Braver, 2012; Franzmeier, Duering, Weiner, Dichgans, & Ewers, 2017). Andere Forscher berichteten hingegen über lokale oder globale Netzwerkveränderungen in den Graphen-Metriken als ein potenzielles CR-Surrogat (Ewers et al., 2021; Lee et al., 2019; Marques et al., 2016; Soldan et al., 2021; Wook Yoo et al., 2015). Auch wenn die meiste Studien *resting-state* Konnektivität in diesem Kontext untersuchten, konnten Studien mit task-basierter fMRT, die überwiegend in gesunden Probanden durchgeführt wurden, funktionelle Konnektivitätsveränderungen identifizieren, die mit einer hohen CR wie eine hohe verbale Intelligenz oder hohe Resilienz (als Residuen) assoziieren (Boyle et al., 2023; Yaakov Stern, Gazes, Razlighi, Steffener, & Habeck, 2018; A. C. van Loenhoud, Habeck, van der Flier, Ossenkoppele, & Stern, 2020).

2.2.3. Lebensstil und kognitive Reserve – Was ist bekannt?

„We may not yet be able to cure dementia, but we can stop people getting it in the first place. “

- World Alzheimer report 2018 (Patterson, 2018)

Es wurde behauptet, dass ein intellektuell fordernder Lebensstil bezüglich der Bildung, des Berufs, des sozialen Netzwerkes, der Freizeitaktivitäten und anderer schützender Faktoren in den frühen, mittleren und späten Lebensabschnitten mit einem bedeutend niedrigeren Demenzrisiko verbunden sind (Chapko et al., 2018; Livingston, Selbaek, et al., 2020; Zheng, Cagney, & Choi, 2023). Eine Dosis-Wirkungs-Beziehung kann es zudem auch zwischen dem Ausmaß der geistig

fordernden Aktivitäten und Demenz geben (Valenzuela & Sachdev, 2006). Weitere Faktoren, die als gesunder Lebensstil betrachtet werden, wie zum Beispiel erhöhte körperliche Aktivität oder wenige chronische Krankheiten, u. a. Diabetes Mellitus und arterielle Hypertension, senken ebenfalls das Demenzrisiko (Mayeux & Stern, 2012; Pentikäinen et al., 2019; Rosenberg et al., 2018; C. Wang et al., 2014; Zijlmans et al., 2021).

Es ist allgemein anerkannt, dass sowohl Genetik- als auch Umweltfaktoren die Wahrscheinlichkeit für eine AD bestimmen, was sich im multifaktoriellen Modell der AD widerspiegelt (Perneczky, 2018). Es wurde außerdem vorgeschlagen, dass sich diese Faktoren auf die alterungs- und krankheitsbedingten Veränderungen der Kognition möglicherweise erst ab dem mittleren Erwachsenenalter auswirken (Pettigrew & Soldan, 2019). CR ist somit ein dynamisches Konzept und wird über die gesamte Lebensdauer hinweg von unterschiedlichen Faktoren beeinflusst. Es ist daher anzunehmen, dass jede Lebensstilkomponente einen eigenen Beitrag zur CR leistet (Yaakov Stern et al., 2020), zudem können auch diverse Lebensstilfaktoren eine gewisse Koexistenz haben (Perneczky, 2018). Um kausale Zusammenhänge zu untersuchen, wurden randomisierte Interventionsstudien mit verschiedenen Lebensstiländerungen durchgeführt, die in dem ersten Bericht der Lancet-Kommission anhand einer Metaanalyse untersucht wurden (Livingston, Huntley, et al., 2020). Insbesondere untersuchte die FINGER-Studie eine multi-domain Intervention mit Berücksichtigung der unterschiedlichen Lebensstilfaktoren wie Ernährung, Bewegung, kognitives Training und Überwachung von vaskulären Risiken. Die Autoren dieser Studie kamen zu der Schlussfolgerung, dass die Intervention zu einer Aufrechterhaltung der Kognition sowie einer Reduktion im CAIDE-Risikoscore (engl. *Cardiovascular Risk Factors, Aging, and Incidence of Dementia*) führte und dieser Effekt von der sozioökonomischen und -demographischen Faktoren sowie der Kognition und kardiovaskulären Risikofaktoren zu Beginn der Studie unabhängig war (Ngandu et al., 2015; Rosenberg et al., 2018; Solomon et al., 2021).

Zur retrospektiven Untersuchung der Lebensereignisse eignet sich in klinischen Studien u. a. der *Lifetime of Experiences Questionnaire* (LEQ) (Valenzuela & Sachdev, 2007). LEQ ist ein umfangreicher Fragebogen, der das gesamte Spektrum der geistig fordernden Aktivitäten im Laufe des Lebens eines Individuums abbilden soll. Je nach Lebensabschnitt werden unterschiedliche Aktivitäten erhoben. Im jungen Erwachsenenalter (13-30. Lebensjahr) werden u. a. die Art des Schulabschlusses und der Ausbildung(en), Reisen und das Spielen eines Musikinstruments erhoben; im mittleren Erwachsenenalter (31-65. Lebensjahr) werden u. a. der ausgeübte Beruf, Ausbildungen und Reisen und Hobbys, sowie die Lebenssituation (allein oder beispielsweise mit Partner oder Familienangehörigen lebend) abgefragt; im hohen Erwachsenenalter (über 65. Lebensjahr) werden ebenfalls die berufliche Aktivitäten, Ausbildungen sowie Reisen und Freizeitaktivitäten analysiert. Eine Verlangsamung des kognitiven Abbaus, sowie eine geringere Hippocampus-Atrophie ließen sich mit hohen LEQ-Scores in longitudinalen Untersuchungen vorhersagen (Valenzuela & Sachdev, 2006; Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008). Die Relevanz des LEQ-Scores für mittleren Erwachsenenalter wurden außerdem mit Hinblick auf CR untersucht und die Autoren schlugen vor, dass die anhand des LEQ gemessene Aktivitäten im mittleren Alter nicht nur zu einer besseren Kognition im hohen Alter führt, sondern auch zu einer reduzierten Wirkung der Dicke der grauen Substanz auf die Kognition (Chan et al., 2018).

Neben der Lebensereignisse legten Studien außerdem eine Assoziation zwischen einer hohen CR und der Genetik wie beim *brain-derived neurotrophic factor* (*BDNF*) Val66Met-Polymorphismus bzw. Vorhandensein eines BDNF-Met-Allels im Kontext der AD nahe (Buchman et al., 2016). Besonders relevant hierbei sind die Ergebnisse einer weiteren Studie mit gesunden Probanden im hohen Alter, die auf eine abgeschwächte Beziehung zwischen den exekutiven Funktionen und LEQ-Scores in gesunden Probanden mit *BDNF* Val66Met-Polymorphismus hinwiesen, welcher eine Rolle in u. a. neuronaler Aufrechterhaltung, der Neurogenese und synaptischer Plastizität spielt (Ward et al., 2015). Bezüglich des *ApoE*-Allels wies ferner eine

Studie mit einer longitudinalen Beobachtung der gesunden Probanden über ca. 10 Jahren darauf hin, dass eine hohe CR, definiert durch mehr Ausbildungsjahren und hohe kristalline Intelligenz, negative Effekte des ApoE-ε4-Allels auf globale Kognition und Mnestik abschwächen könnte (Pettigrew et al., 2023).

2.2.4. Kognitive Reserve und Biomarker für die Alzheimer-Krankheit

AD hat einen wichtigen Platz in der Literatur über CR, was möglicherweise neben einer hohen Prävalenz (Bocancea et al., 2021; Chapko et al., 2018) auch durch die wichtigen Erkenntnisse im Bereich des Surrogatbiomarkers erklärt werden kann, die die Untersuchungen ermöglichen (Yaakov Stern, 2002). Hypothese der CR bzw. kognitive Resilienz kann speziell mit Hinblick auf AD zu einem besseren Verständnis der kognitiven Trajektorien beitragen. So könnte eine individuelle Betrachtungsweise in Patienten mit AD-Pathologie im Sinne einer optimierten Präzisionsmedizin möglich sein. Die oben ausgeführten CR-fördernde Faktoren bezüglich des Lebensstils könnten auf die funktionellen Gehirnprozessen anhaltend wirken, sodass die Individuen mit hoher CR ein abgeschwächtes Verhältnis zwischen den pathologischen Änderungen im Rahmen der AD und kognitive Leistungsfähigkeit manifestieren (Perneczky et al., 2019). Hierfür untersuchten Studien die etablierten Biomarker der AD wie Aβ-Pathologie im CSF (Kleineidam et al., 2022; Roe, Xiong, Miller, & Morris, 2007), kortikale und hippocampale Atrophie (Pettigrew et al., 2016; Zijlmans et al., 2021), Hypometabolismus in PET-Untersuchungen (Carapelle et al., 2017; Ewers, Insel, Stern, & Weiner, 2013; Morbelli & Nobili, 2014) sowie Tau-Pathologie im PET (Ossenkoppele et al., 2020) und fanden entsprechende Hinweise auf hohe Reserve bei Patienten mit hoher Bildung sowie hoher kortikaler Dicke.

2.3. Zielsetzung und Hypothesen

AD stellt angesichts ihrer medizinischen sowie gesellschaftlichen Auswirkungen einer der größten Herausforderungen unserer Zeit. Während die Therapieansätze mit einer zunehmenden Dynamik studiert werden, nimmt gleichzeitig das Interesse an der Prävention im Sinne einer Primär- und Sekundärprävention kontinuierlich zu. Hierzu prägt die Hypothese der CR weiterhin die Alzheimerforschung zur Untersuchung der Resilienzfaktoren und ihren Mechanismen. Zugleich bleibt unser Verständnis der zugrunde liegenden neuronalen Mechanismen der CR derzeit noch sehr begrenzt (Perneczky et al., 2019). Den Einfluss der Lebensstilfaktoren auf die funktionellen Konnektivitätsveränderungen zu verstehen, könnte zu einer optimierten Stratifikation der Probanden in klinischen Studien im Sinne einer präziseren Phenotypisierung führen. Ebenfalls könnte die Varianz in den Atrophiemustern wie individuelle Unterschiede in räumlicher Suszeptibilität, die durch u. a. Komorbiditäten, genetischen Faktoren und Reserve entstehen kann (Ferreira et al., 2020), und das Verhältnis von verschiedenen Atrophiemustern zum funktionellen Connectome wichtige Hinweise auf eine bessere Charakterisierung der unterschiedlichen Sub(Pheno-)typen von AD geben. Denn neben einer gewissen Heterogenität in den strukturellen bildgebenden Ansätzen gewinnt auch die Variabilität in den funktionellen Netzwerken zunehmend an Bedeutung als ein potenzieller Biomarker (J. Cummings, 2019; Perovnik, Rus, Schindlbeck, & Eidelberg, 2023).

Zur Identifizierung der Auswirkungen von Lebensstilfaktoren auf AD-typische Konnektivitätsveränderungen in der *resting-state* fMRT führten wir explorative Analysen im Baseline-Datensatz aus der multizentrischen „DZNE multicenter observational study on predementia Alzheimer's disease“ (DELCODE-Studie) Kohorte durch. Der Datensatz aus DELCODE-Studie verfügt über eine bemerkenswert große Probandengruppe mit prodromaler AD, vor allem SCD, und stellt somit einen gut geeigneten Datensatz für die Fragestellung dar. Unserer Hypothese nach weisen die Individuen mit hoher CR funktionelle Netzwerkveränderungen auf, die in früheren Krankheitsstadien besonders wesentlich sind.

Hierfür fokussierten wir auf die RSNs, die von AD-Pathologie besonders stark betroffen werden: Intrinsische Aktivität im DMN sowie zwischen DMN und DAN (Mathew R. Brier et al., 2012; Chhatwal et al., 2018; Franzmeier, Buerger, et al., 2017). So kann die Auswirkung der CR auf die AD-relevanten Netzwerkveränderungen in verschiedenen Krankheitsstadien untersucht werden. Wir verwendeten hierzu neben der ausführlichen sozio-behavioralen Assessments (bzw. LEQ) einen residualen Ansatz als CR-Proxy, um die Assoziationen zwischen der funktionellen Konnektivität in *resting-state* und einem direkteren bzw. residualen CR-Marker zu untersuchen. Dieser wurde als von der eingeschätzten pathologischen Last abweichende globale Kognition (Residuum) definiert. Des Weiteren definierten wir hierbei die Studiengruppen nach biologischer bzw. AT(N)-Klassifikation der AD. Einen Fokus in der fMRT-Analyse lagen wir hierbei auf vier mit den kognitiven Fähigkeiten assoziierten RSNs (DMN, FPN, SAL und DAN). Unsere Hypothese lautete, dass die Probanden mit hohem Residuum bzw. hoher CR stärkere Kompensationsfähigkeiten in deren Netzwerk-Konnektivität zeigen.

In zwei voneinander unabhängigen multizentrischen Kohorten (DELCODE und Alzheimer's Disease Neuroimaging Initiative (ADNI)) testeten wir eine weitere Hypothese. Demzufolge assoziiert sich eine Subgruppierung nach räumlicher Variabilität in kortikaler Atrophie anhand der volumetrischen MRT-Bilder mit unterschiedlichen funktionellen Netzwerkeigenschaften im Ruhezustand. Ferner gibt es eine gewisse räumliche Überlappung zwischen den strukturellen und funktionellen Änderungen, die über demographische und *ApoE*-genotypische Unterschiede hinausgeht. Für einen Clustering-Ansatz (Louvain-Clustering) sowie Anzahl der Cluster (vier Clusters als „Atrophie-Subtypen") orientierten wir uns an den früheren Publikationen (Ferreira et al., 2020; Park et al., 2017). Zu diesem Zweck planten wir explorative Analysen der querschnittlichen Gruppenvergleiche hinsichtlich der Intra- und Internetzwerkaktivitäten sowie die lokalen und globalen Graphen-Metriken, die funktionellen Netzwerkeigenschaften abbilden lassen.

3. Zusammenfassung

Die Alzheimer-Krankheit (engl. *Alzheimer's disease*, AD) stellt die weltweit häufigste Ursache für Demenz bei älteren Erwachsenen dar. Aufgrund des demografischen Trends hin zu alternden Bevölkerungen in den Industrienationen steigt die Prävalenz von AD weltweit kontinuierlich an. Dies führt zur dringenden Notwendigkeit, wirksame Instrumente zur Früherkennung, Strategien zur Phänotypisierung sowie Prävention zu implementieren. Aktuelle Forschungsergebnisse unterstreichen das Potenzial präventiver Maßnahmen, insbesondere solcher, die einen geistig stimulierenden Lebensstil fördern und psychosoziale Schutzfaktoren wie ein höherer Bildungsgrad, die Ausübung anspruchsvoller beruflicher Tätigkeiten und intellektuell fordernde Freizeitaktivitäten stärken.

Die klinische Heterogenität im Verlauf der AD hat das Interesse an der Erforschung von Krankheitsvariabilität und insbesondere des Konzepts der kognitiven Reserve (engl. *cognitive reserve*, CR) intensiviert. Die CR beschreibt ein heuristisches Konzept, dem zufolge Individuen mit einer höheren CR in der Lage sind, trotz einer ausgeprägten neuropathologischen Belastung kognitive Funktionen länger aufrechtzuerhalten. Darüber hinaus scheint die CR durch Lebensstilfaktoren modifiziert zu werden, wobei die zugrundeliegenden neurobiologischen Mechanismen bislang nur unzureichend verstanden sind.

Fortschritte in der Neurobildgebung haben zur Identifizierung zuverlässiger Bildgebungs-Biomarker geführt, die strukturelle und funktionelle zerebrale Veränderungen abbilden. In der vorliegenden Arbeit wurden Daten aus zwei Kohortenstudien unter Anwendung vergleichbarer Bildgebungsprotokolle zur Datenharmonisierung analysiert – der AD Neuroimaging Initiative (ADNI) und der DZNE multicenter observational study on predementia AD (DELCODE). Es wurden anatomische Magnetresonanztomographie(MRT)-Aufnahmen und Resting-State Blood-Oxygen-Level-Dependent(BOLD)-MRT Bilder analysiert, um kortikale Atrophie und Veränderungen der funktionellen Konnektivität bei Individuen im AD-Kontinuum zu untersuchen.

In der ersten Studie wurden soziale und verhaltensbezogene Lebensstilfaktoren, welche die CR beeinflussen mit dem Lifetime Experiences Questionnaire (LEQ) erfasst. CR ist mit einer erhaltenen intrinsischen Netzwerkkonnektivität innerhalb des Default-Mode-Netzwerks (DMN), selbst bei Vorliegen von ausgeprägten mnestischen Symptomen, assoziiert. Darüber hinaus zeigten sich bei Menschen im Spektrum der Alzheimer-Krankheit, vor allem im präklinischen Stadium, eine positive Assoziation zwischen den LEQ-Werten und der funktionellen Konnektivität innerhalb des DMN. In einer zweiten Studie wurde die CR unter Verwendung eines Residualansatzes quantifiziert, wobei Residuen aus der Beziehung zwischen kognitiver Leistung und Surrogatmarkern der Krankheitslast abgeleitet wurden. Assoziationen zwischen CR und intrinsischer Netzwerkkonnektivität wurden bei Teilnehmern im AD-Kontinuum untersucht, die für Subgruppenanalysen nach ihren binären Amyloid-(A), Tau-(T) und Neurodegenerations-(N) Biomarker-Status stratifiziert wurden, die je nach Konstellation verschiedenen biologisch definierten Gruppen entsprechen. Menschen mit höherer CR wiesen intrinsische Konnektivitätsveränderungen in den Regionen innerhalb des DMN und des frontoparietalen Netzwerks (FPN) auf. Diese Veränderungen wurden vor allem bei Teilnehmern in frühen AD Stadien (d. h. A+T-N- und A+T/N+) identifiziert. Darüber hinaus zeigte die A+T+N+-Gruppe mit ausgeprägten pathologischen Veränderungen eine reduzierte intrinsische Netzwerkkonnektivität zwischen dem Salienz-Netzwerk und dem DMN. Unsere Ergebnisse stützen die Hypothese, dass AD-assoziierte Veränderungen der funktionellen Konnektivität durch CR moduliert werden und dass lebenslange Aktivitäten zur Förderung der CR dazu beitragen könnten, die funktionelle Netzwerk-Integrität in Abhängigkeit vom AD-Stadium zu erhalten.

Basierend auf der Beobachtung, dass Patienten mit AD unterscheidbare Atrophiemuster aufweisen, haben wir einen auf Ähnlichkeit basierenden und datengesteuerten Clustering-Ansatz angewandt, um vier Atrophie-Subtypen zu identifizieren. In Übereinstimmung mit früheren Studien ermittelten wir Gruppen mit Medial-temporal vorherrschendem (S-MT), limbisch vorherrschendem (S-L), diffusem (S-D) und minimalem (S-MA) Atrophiemuster. Hierbei wurden

ebenfalls die Unterschiede in der intrinsischen Netzwerk-Konnektivität und zusätzlich in Graphen-Metriken nach Graphentheorie untersucht. Unsere Ergebnisse zeigten weitreichende Netzwerkveränderungen zwischen den Subtypen, insbesondere Veränderungen innerhalb des DMN, des limbischen Netzwerks und des visuellen Netzwerks. Die Graphen-Metriken zeigten bei S-MT, S-D und S-MA eine reduzierte globale Integration (d. h. *efficiency*). Darüber hinaus wiesen lokale Graphen-Metriken wie eine reduzierte Zentralität (d. h. *degree*), der die Anzahl der verbundenen Verbindungen eines neuronalen Netzwerkknotens repräsentiert, räumliche Überschneidungen mit den gegebenen Atrophiemustern auf.

Unsere Studien beleuchten die Auswirkungen von AD-bedingten Störungen funktioneller Netzwerke und liefern wichtige Einblicke in das komplexe Zusammenspiel zwischen der Pathologie der AD, funktionellen Netzwerkveränderungen und kognitiven Beeinträchtigungen sowie den Einfluss der CR auf die Veränderungen dieser Netzwerke. Eine verbesserte Identifikation von Endophänotypen bei Individuen im AD-Kontinuum kann die Entwicklung und Optimierung zukünftiger Präventions- und Behandlungsstrategien für Demenzerkrankungen wesentlich vorantreiben. Darüber hinaus unterstreichen die Ergebnisse die Bedeutung der Implementierung von Ansätzen, die Resilienzfaktoren stärken und darauf abzielen, das Fortschreiten der AD zu verzögern.

4. Abstract (English)

Alzheimer's disease (AD) is the most prevalent cause of dementia among older adults globally. Owing to the demographic trend towards ageing populations in industrialised nations, the prevalence of AD is continuously increasing worldwide, underscoring the urgent need to implement effective tools for early detection, phenotyping strategies and prevention. Existing evidence highlights the potential of preventive strategies, particularly those promoting a mentally stimulating lifestyle and the optimization of psychosocial protective factors such as higher educational attainment, engagement in complex professional activities, and intellectually demanding leisure pursuits.

The variability in clinical progression observed among individuals with AD has promoted the investigations on disease heterogeneity and specifically cognitive reserve (CR). The CR is a heuristic construct that posits that individuals with higher CR are more likely to demonstrate preserved cognitive functioning despite higher degrees of neuropathological burden. Furthermore, CR is modulated by lifestyle factors, while the precise neurobiological underpinnings of CR remain poorly characterized.

Recent advances in neuroimaging have provided reliable imaging biomarkers related to structural and functional cerebral alterations. Here, we analysed data from two cohort studies using comparable imaging protocols for data harmonisation, i.e. AD Neuroimaging Initiative (ADNI) and DZNE multicenter observational study on predementia AD (DELCODE). Anatomical magnetic resonance imaging (MRI) images and resting-state blood-oxygen-level-dependent (BOLD) MRI images were analysed to investigate cortical atrophy and changes in functional connectivity in individuals along the AD continuum.

In the first study, social and behavioural lifestyle factors influencing CR, as assessed by the Lifetime Experiences Questionnaire (LEQ), were associated with preserved intrinsic network connectivity within the default mode network (DMN), even in the presence of pronounced amnestic symptoms. Moreover, individuals in the spectrum of AD, mainly in preclinical AD, revealed a positive association between LEQ scores and functional connectivity within the DMN. In a second study, CR was quantified employing a residual approach, whereby residuals were derived from the relationship between cognitive performance and surrogate markers of disease burden. Associations between CR and intrinsic network connectivity were investigated in participants along the AD continuum who were stratified for subgroup analyses according to their binary amyloid (A), tau (T) and neurodegeneration (N) biomarker statuses, which correspond to different biologically defined groups depending on the constellation. Individuals with higher CR exhibited intrinsic connectivity alterations in the regions within DMN and the frontoparietal network (FPN), mainly driven by the changes in participants in the early AD (i.e., A+T-N- and A+T/N+). Moreover, the A+T+N+ group with pronounced pathological changes displayed reduced intrinsic network connectivity between the salience network and DMN. Our findings support the hypothesis that AD-associated alterations in functional connectivity are modulated by CR and that lifelong activities promoting CR may help to maintain functional network integrity depending on AD stage.

Based on the observations that patients with AD exhibit distinguishable atrophy patterns, we employed a similarity-based and data-driven clustering approach to identify four atrophy subtypes. In line with the previous studies, we identified a group of patients exhibiting medio-temporal-predominant (S-MT), limbic-predominant (S-L), diffuse (S-D), and mild-atrophy (S-MA) atrophy patterns. Here, we explored also the differences in intrinsic network connectivity and, additionally, graph theoretical network features. Our results revealed widespread network differences among subtypes, including alterations within the DMN, limbic network, and visual network. Regarding the graph theoretical measures, the S-MT, S-D, and S-MA showed reduced global network efficiency. Moreover, nodal measures such as reduced degree, which represent

the number of connected links of a network node, exhibited spatial overlaps with the given atrophy patterns.

Our studies elucidate the impact of AD-related functional network disruptions, providing critical insights into the complex interplay between AD pathology, functional network alterations and cognitive impairment, together with the influence of CR on these network changes. Improved identification of endophenotypes among individuals with AD can optimize future prevention and treatment strategies for dementia. Additionally, they highlight the need to implement approaches that promote resilience factors and aim to delay the progression of AD.

5. Paper I - Lifelong experiences as a proxy of cognitive reserve moderate the association between connectivity and cognition in Alzheimer's disease (Neurobiol. Aging 2023)

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Lifelong experiences as a proxy of cognitive reserve moderate the association between connectivity and cognition in Alzheimer's disease

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Lifelong experiences

ABSTRACT

Alzheimer's disease (AD) is associated with alterations in functional connectivity (FC) of the brain. The FC underpinnings of CR, that is, lifelong experiences, are largely unknown. Resting-state FC and structural MRI were performed in 76 CSF amyloid-β (Aβ) negative healthy controls and 152 Aβ positive individuals as an AD spectrum cohort (ADS; 55 with subjective cognitive decline, SCD; 52 with mild cognitive impairment; 45 with AD dementia). Following a region-of-interest (ROI) FC analysis, intrinsic network connectivity within the default-mode network (INC-DMN) and anti-correlation in INC between the DMN and dorsal attention network (DMN:DAN) were obtained as composite scores. CR was estimated by education and Lifetime Experiences Questionnaire (LEQ). The association between INC-DMN and MEM was attenuated by higher LEQ scores in the entire ADS group, particularly in SCD. In ROI analyses, higher LEQ scores were associated with higher FC within the DMN in ADS group. INC-DMN remains relatively intact despite memory decline in individuals with higher lifetime activity estimates, supporting a role for functional networks in maintaining cognitive function in AD.

1. Introduction

Structural and functional brain alterations during aging and disease depend on interactions between individual genetic backgrounds and cumulative effects of lifestyle behaviors and other external influences (Mesulam, 2000; Sperling et al., 2011). Therefore, cognitive trajectories in neurodegenerative diseases such as Alzheimer's disease (AD) are highly variable between individuals (Perneczky et al., 2009; Reed et al., 2010; Valenzuela et al., 2009). Early-life education, good socioeconomic status, work complexity, midlife occupational attainment, and late-life leisure activities have been associated with lower dementia risk (Pettigrew and Soldan, 2019; Scarmeas et al., 2006; Wang et al., 2017). Lifetime experiences may influence individual functional brain processes, potentially moderating between pathology and clinical expression of disease (Perneczky et al., 2019).

The concept of cognitive reserve (CR) was introduced to explain inter-individual differences in cognitive performance related to brain aging or neurodegenerative changes (Stern, 2002). CR encompasses the concepts of neural reserve and neural compensation (Stern, 2017, 2012), referring to the ability of the human brain to maintain cognitive function and recruit compensatory networks in the face of deteriorating network function, respectively (Lee et al., 2019; Perneczky et al., 2019). Socio-behavioral proxies of CR, including education, IQ, occupational complexity, leisure and physical activity, and other protective factors across the lifespan, have been identified in epidemiologic research (Stern et al., 2020) and are reliably captured by the Lifetime of Experiences Questionnaire (LEQ) (Valenzuela and Sachdev, 2007). The LEQ measure can be subdivided into young adulthood, midlife and a late-life score; each period score comprises specific and non-period-specific questions. In younger years, education plays a major role; in midlife, occupation; and social and intellectual activities in later life. The separate analysis of these phases is suitable to reveal different aspects of cognitive reserve, with implications on how effective lifestyle modification for disease prevention could be in different life phases.

Using resting-state fMRI (rs-fMRI), the correlation of blood-oxygen-level-dependent (BOLD) signals between regions of interest (ROIs) can be measured, enabling the detection and analysis of resting-state networks (RSNs) (Biswal et al., 1995, 2010; Damoiseaux et al., 2006). It has been shown repeatedly that the default-mode network (DMN) is affected by disease progression in AD (Greicius et al., 2004), showing remarkable spatial overlap with amyloid pathology (Buckner et al., 2009), hypometabolism, and tau pathology in early disease stages (Hoenig et al., 2018; Reiman et al., 2001; Veitch et al., 2019). Functional connectivity (FC) changes in the DMN increase with disease progression (Brier et al., 2012; Chhatwal et al., 2018), even in prodromal and early AD stages (Sheline and Raichle, 2013; Verfaillie et al., 2018). A recent study showed activity disruption in resting-state networks and specific FC changes in patients with AD spectrum in the German Center for Neurodegenerative Diseases (DZNE)-Longitudinal Cognitive Impairment and Dementia Study (DELCODE) cohort (Amaefule et al., 2021). The anti-correlation between task-negative DMN and task-positive dorsal attention network (DAN) was found to be decreased, that is, closer to zero, in advanced stages of AD (Brier et al., 2012; Weiler et al., 2017). Intra- and internetwork FC of DMN, especially between the DMN and the DAN, is a major focus of interest in AD research (Elman et al., 2016; Palmqvist et al., 2017).

Early studies on CR proxies were conducted in patients in the dementia stage rather than subjects with prodromal disease (Garibotto et al., 2008). Although more recent studies also included preclinical and prodromal stages of AD (Franzmeier et al., 2017b; ; Garibotto et al., 2008; Lee et al., 2019; Mazzeo et al., 2019; Morbelli et al., 2013; Reed et al., 2010; Reijs et al., 2017), where beneficial effects of CR are most pronounced (Scarmeas et al., 2006; Stern, 2012), very few studies included subjects with subjective cognitive decline (SCD) (Du et al., 2021; Jia et al., 2021; Lee et al., 2020; Mazzeo et al., 2019; Reijs et al., 2017; Yang et al., 2020). However, the neural underpinnings of CR are still unclear, especially in the prodromal stage of AD, in which both pharmacologic and non-pharmacologic interventions are likely to be most effective (Morbelli et al., 2013).

Previous studies suggested that CR proxies such as years of education (Arenaza-Urquijo et al., 2013; Bozzali et al., 2015; Franzmeier et al., 2017b; Li et al., 2021; Marques et al., 2016; Stern et al., 2020; Weiler et al., 2018), IQ (Franzmeier et al., 2017a; Marques et al., 2016) and occupational activities in midlife (Suo et al., 2017) influence rs-fMRI changes due to neurodegeneration. In rs-fMRI studies, CR-associated changes in FC have been reported mainly in regions belonging to the DMN (Arenaza-Urquijo et al., 2013; Bozzali et al., 2015; Perneczky et al., 2006; Weiler et al., 2018), but also between the DMN and DAN (Franzmeier et al., 2017b). It is not clear how individual lifestyle differences influence rs-fMRI changes and cognitive decline in AD.

Here, we aimed to investigate the association between lifestyle at different life-stages and network alterations in patients with patients presenting pathological hallmark of AD and healthy controls (HC), focusing on the DMN. The biological mechanisms underlying CR variables' protective and compensatory effects in AD are still largely unknown; improving our mechanistic understanding of key interactions is crucial for developing effective therapies and preventive strategies (Perneczky et al., 2019).

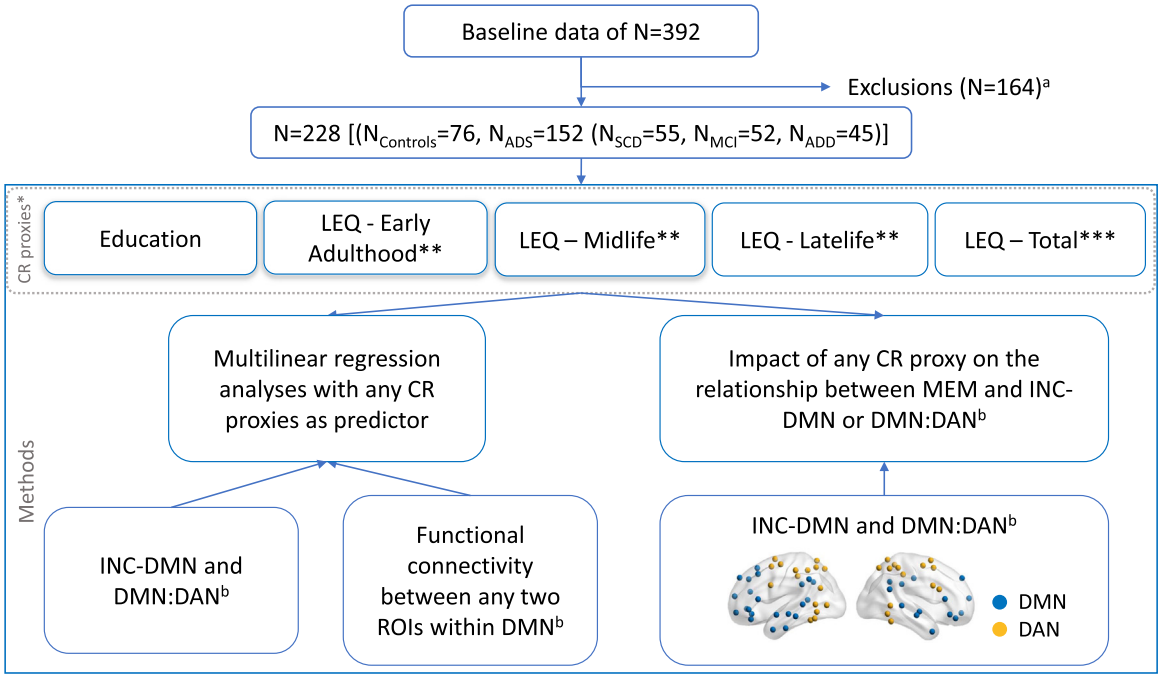

Fig. 1. Flow diagram of inclusions and/or exclusions and analyses. [a]Due to inappropriate ATN status and/or clinical status (N = 164). [b]Regions defined in Brainnetome-Atlas and segmentation of networks were made by using the resting-state networks (54) and resulted in 36 ROI in DMN and 30 ROIs in DAN (Table S1). *The CR proxies were tested separately. **Early adulthood corresponds with age 13 to 30 (LEQ-e), mid-life with 30 to 65, and late-life with 65 and above. ***Total LEQ score is calculated as the sum of the three LEQ subscores. Abbreviations: CR, cognitive reserve; MEM, memory composite cognitive score; ADS, Alzheimer's disease spectrum; SCD, subjective cognitive decline; MCI, mild cognitive impairment; ADD, Alzheimer's disease dementia; INC, intrinsic network connectivity; DMN, default mode network; LEQ, lifelong experiences questionnaire; INC-DMN, intrinsic network connectivity composite score of default mode network; DMN:DAN, inter-network connectivity of default mode network and dorsal attention network. ROI, region of interest.

2. Materials and Methods

The dataset analyzed in this study was obtained from the DELCODE, an observational brain imaging study initiated by the DZNE in 2014 (German Clinical Trials Register: DRKS00007966).

2.1. Standard protocol approvals, registrations, and patient consents

At each DELCODE site, the local institutional review boards approved the study protocol and the ethical committees issued local ethical approval. DELCODE is registered at the German Clinical Trials Register (DRKS00007966; 4/05/2015). The study protocol followed the ethical principles for human experimentation in accordance with the Declaration of Helsinki. All participants in the study provided written informed consent.

2.2. Participants

Eight hundred ninety-three participants were recruited for the DELCODE baseline dataset between May 2014 and August 2018, and 392 participants were eligible for the present analyses because of the availability of CSF biomarkers and appropriate structural and functional MRI data. To ensure that no participants with non-AD neurodegenerative disorders were analyzed, total of 164 individuals either diagnosed as healthy controls but with abnormal amyloid-β (Aβ) CSF concentrations (N = 34) or participants with a clinical diagnosis of SCD/MCI/ADD but normal Aβ CSF concentrations (N = 117) or participants with increased total-tau (t-tau) and/or phosphorylated-tau (p-tau) 181 but normal Aβ CSF concentrations (N = 13) were also excluded. The final cohort consisted of 228 participants, including Aβ negative 76 HC (mean age 68 ± 5, range 60–80, 41 female) and 152 Aβ positive patients with AD (mean age 73 years ± 6, range 61–90 years, 76 female) (Fig. 1). The detailed study design, including the inclusion and exclusion criteria and definitions of the diagnostic groups in DELCODE is reported elsewhere (Jessen et al., 2018). Aβ positive participants in the present study were defined as individuals with positive CSF Aβ42 status across the clinical AD spectrum, including individuals with SCD, MCI, and AD dementia (ADD). HC was defined as individuals without Aβ42 in CSF, no memory complaints, and a global score < 0.5 in Clinical Dementia Rating (CDR). Following CSF concentrations were defined in the CSF data of baseline cohort included number of 527 participants (sampling rate: 53%): ≤ 638.7 pg/ml for Aβ42, 510.9 pg/ml for t-tau and 73.65 pg/ml for p-tau, as reported elsewhere (Teipel et al., 2021).

2.3. MR Image acquisition and preprocessing

Imaging was performed at nine different DZNE sites on Siemens 3T MRI scanners (three Verio, three TimTrio, one Prisma and two Skyra) using synchronized acquisition parameters. The used MRI machines did not vary within any study site. T1 anatomical imaging was acquired in a 5 minutes scan (field of view, FOV: 256 × 256mm; isotropic voxel size: 1 mm; echo time, TE: 4.37 ms; flip angle, FA: 7; repetition time, TR: 2500ms; number of slices: 192). Rs-fMRI was acquired in a 7 minutes 54 seconds scan (180 volumes, FOV: 224 × 224 × 165 mm, isotropic voxel size: 3.5 mm, TE: 30 ms, TR: 2580ms, FA: 80, parallel imaging acceleration factor 2). Following a visual inspection by an experienced radiologist for completeness, cuts, subject motion, and other artifacts (such as blurring, echoes, and ghosting), images were classified as usable ($N_{structuralMRI}$ = 208, $N_{functionalMRI}$ = 185), questionable ($N_{structuralMRI}$ = 20, $N_{functionalMRI}$ = 43), or unusable (N = 0); only images classified as acceptable were included.

To correct the analyses for inter-individual differences in the degree of cortical atrophy, a meta score of cortical thickness

for AD-vulnerable regions was calculated, including the bilateral entorhinal cortices, temporal pole, inferior and middle temporal gyri, inferior and superior parietal cortices, precuneus, and posterior cingulate cortex (Pettigrew et al., 2016). All T1-weighted images were processed in FreeSurfer (version 6.0, http://surfer.nmr.mgh.harvard.edu) using the recon-all pipeline to derive estimations of cortical thickness in the aforementioned cortical regions (Fischl et al., 2002). Results were checked visually for accuracy and corrected as needed. By adjusting the analyses for cortical thickness levels, we aimed to identify FC changes independent of degree of atrophy, as brain structural characteristics were associated with brain and cognitive resilience before (Ossenkoppele et al., 2020; Perneczky et al., 2010). The mean cortical thickness of vulnerable regions in AD was moderately correlated with the mean global cortical thickness ($r = 0.32$, $p < 0.001$), whereas the correlation differed in study groups (r-ADS=0.31, p-ADS<0.001; r-HC=0.2, one-tailed-p-HC=0.04). Of note, cortical thickness values of participants were included in all analyses in the present study as the derived mean cortical thickness of the vulnerable regions in AD.

Functional connectivity analysis was performed using the CONN-fMRI Functional Connectivity Toolbox (v17, www.nitrc.org/projects/conn) and SPM12 (www.fil.ion.ucl.ac.uk/spm) in MATLAB (Release2017b, MATHWORKS). The default preprocessing pipeline for volume-based analyses was used, comprising realignment, slice-time correction, segmentation, and structural and functional normalization. The Artifact Detection Toolbox (ART)-based outlier detection and functional smoothing using a 6 mm kernel (Bastin et al., 2012) was applied. In the denoising step, linear regression of potential confounding effects was performed (Chai et al., 2012): Within each area (white matter and CSF), 5 potential noise components were estimated, and the blood oxygen level-dependent signal and all other potential confounding effects were averaged across the white matter and CSF. Moreover, residual head motion parameters (3 rotation and 3 translation parameters as well as 6 further parameters representing their first-order temporal derivatives) were regressed out (Chai et al., 2012). A band-pass filter (below 0.008 Hz or above 0.09 Hz) was applied. Consequently, the distribution of correlation between mean motion and FC correlation values were directly compared to an associated null-hypothesis (NH) distribution: 96.8% match with NH (95% or higher match with NH indicate lack of noticeable QC-FC associations) (Ciric et al., 2017).

2.4. Clinical characteristics, cognitive testing, and assessment of CSF biomarkers

Dementia severity was quantified using the CDR-sum of the boxes (CDR-sob). Memory function was assessed using a validated cognitive domain composite score for memory (MEM) (Jessen et al., 2018) derived from the AD Assessment Scale-cognitive subscale word list, Free and Cued Selective Reminding Test immediate recall, Wechsler Memory Scale Logical Memory 1 and 2, Consortium to Establish a Registry for AD neuropsychological assessment battery figure savings, Symbol-Digit Modalities Test incidental learning, and Face Name Test. CSF biomarkers were measured using established commercially available analysis kits, including V-PLEX Aβ Peptide Panel 1 (6E10) Kit (K15200E), V-PLEX Human Total Tau Kit (K151LAE) (Meso Scale Diagnostics LLC, Rockville, MD, USA), and Innotest Phospho-Tau (181P) (Fujirebio Germany GmbH, Hannover, Germany) (Jessen et al., 2018). *APOE* ε4 were genotyped using commercially available TaqMan SNP Genotyping Assay (ThermoFisherScientific) (Jessen et al., 2018), and allele carrier status was dichotomized into carriers of one or two alleles vs. non-carriers.

2.5. Assessment of lifestyle parameters

Individual lifestyle differences were assessed using years of formal education and LEQ total and subscores for different stages of life (early adulthood (LEQ-e, age 13 to 30 years), midlife (LEQ-m, age 30 to 65 years), and latelife (LEQ-l, age 65 and older). LEQ was assessed using the validated German version (Roeske et al., 2018). The LEQ scores mirror educational, occupational, and managerial history, social and intellectual activity, and non-specific mental activities (Valenzuela and Sachdev, 2007). The questionnaire was provided to the subjects, who were encouraged to answer to the best of their knowledge and without omissions in the space provided for ticking or in the details of the professions practiced. The latter also enables the so-called motivational reserve to be recorded by using a category system (Forstmeier et al., 2012). We acknowledge that in some patients with dementia, cognitive impairment may have affected the LEQ results. However, the severity of cognitive deficits in this cohort is mild and recall of events from the past should be preserved relatively well.

2.6. Assessment of within- and between- network functional connectivity

Composite scores for intrinsic network connectivity within the DMN (INC-DMN) and for the anti-correlation between DMN and DAN (DMN:DAN) were calculated by averaging fisher-z-transformed bivariate correlation coefficients of FC between pairs of ROI BOLD time-series belonging to the networks, accordingly. Higher levels of ICN indicate higher FC in the corresponding network measured in rs-fMRI. We used definitions of RSNs, obtained as 36 ROIs in DMN and 30 ROIs in DAN (Yeo et al., 2011), defined as anatomical ROIs from the brainnetome atlas (Fan et al., 2016) (Fig. 1 and Table S1). The DMN:DAN anti-correlation was calculated as the internetwork connectivity between DMN and DAN, averaging the fisher-z-transformed correlation values between every two nodes from both networks (only inter-network connections).

2.7. Statistical analysis

The statistical analyses were performed using SPSS, version 25.0 (IBM Corp., Armonk, NY), while graphics were made in SPSS or RStudio, v2021.09.1. All tests were two-sided, with $p < 0.05$ considered significant. Kruskal-Wallis tests and Chi-square tests were used to compare the baseline sociodemographic, and genetic variables between the study groups. Analysis of covariance (ANCOVA) was conducted to compare differences in clinical and neuropsychological assessments, DMN INC and DMN:DAN anti-correlation between the groups, adjusting for age, sex, years of education, and imaging site, as appropriate. Normal distributions within each group were tested using the Kolmogorov-Smirnov-Test without Lilliefors correction. Variables deviating from the normal distribution were transformed using Rankit's formula (Chambers, 2018).

The multilinear regression models were conducted, testing the CR-proxies separately as the independent and the INC-DMN or DMN:DAN anticorrelation as the dependent variables. Next, the associations between any two CR-Proxies (years of education, LEQ sub- and total scores) were tested using multilinear regression models. The models were tested in the entire sample and the ADS subgroup and adjusted for age, sex, cortical thickness, MEM, diagnostic group, and study site.

To test our central hypothesis that CR proxy measures moderates the relationship between network deterioration and memory performance, we constructed general linear models (GLMs) with unstructured covariance matrix independently in the entire ADS cohort and the diagnostic subgroups, including interaction

Table 1
Demographic and clinical characteristics of the study cohort

	Healthy controls (N = 76)	SCD (N = 55)	MCI (N = 52)	ADD (N = 45)	*p* value
Age, mean (SD) [a], range	68 (5), 60 - 80	71 (5), 61 - 83†	73 (6), 61 – 84†	75 (6), 64 – 90†,‡	<0.001
Sex, N (% female) [b]	41 (54)	20 (36.4)	27 (51.9)	29 (64.4)	0.04
Years of education, mean (SD) [a], range	14 (3), 9 - 20	15 (3), 10 - 20	14 (3), 8 - 20	13 (3), 8 - 19	0.04
APOE ε4-status, N (% carriers) [b]	13 (17)	30 (54.5) †	31 (59.6) †	28 (62.2) †	<0.001
CDR-SoB, mean (SD) [a]	0.07 (0.17)	0.35 (0.52)	1.81 (1.38) †,‡	4.03 (2.3) †,‡,††	<0.001
Memory composite score, mean (SD) [a+]	0.54 (0.42)	0.32 (0.53)	-0.99 (0.64) †,‡	-1.91 (0.55) †,‡,††	<0.001
Cortical Thickness, mm mean (SD)* [c]	2.7 (0.01)	2.67 (0.11)	2.56 (0.13) †,‡	2.46 (0.15) †,‡,††	<0.001
Binary CSF biomarker profiles					
Aβ42, N (% positive)	0 (0)	55 (100) †	52 (100) †	45 (100) †	<0.001
p-tau, N (% positive)	0 (0)	17 (31) †	27 (52) †	33 (73) †,‡,††	<0.001
t-tau, N (% positive)	0 (0)	15 (27) †	22 (42) †,‡	30 (67) †,‡,††	<0.001
INC composite scores					
DMN, mean [c+] (SD)	0.233 (0.062)	0.228 (0.07)	0.213 (0.071)	0.214 (0.062)	0.54
DMN:DAN, mean [c+] (SD)	-0.036 (0.042)	-0.035 (0.057)	-0.021 (0.051)	-0.031 (0.05)	0.56
LEQ subscores [d]					
LEQ-early adulthood, mean (SD) [a]	37.4 (8.9)	37.2 (7.5)	34.8 (9.7)	33.5 (8.5)	0.13
LEQ-midlife, mean (SD) [a]	44 (11)	45.1 (9.9)	39.1 (13.4)	39.8 (13.2)	0.053
LEQ-late life, mean (SD) [a]	38.2 (9.4)	38.9 (11.1)	36.3 (11.5)	30.7 (7.5) †,‡	0.001
LEQ-total, mean (SD) [a]	119.1 (26.8)	122.6 (24.7)	111.7 (30.6)	106.4 (24.1)	0.08

Key: SCD, subjective cognitive decline; MCI, mild cognitive impairment; ADD, Alzheimer's disease dementia; CDR-sob, Clinical dementia rating-sum of boxes; LEQ, lifetime experiences questionnaire; LEQ-e, LEQ for early adulthood; LEQ-m, LEQ for midlife LEQ-l, LEQ score for late life; LEQ-t, total LEQ score, Aβ42, Amyloid-β 42; t-tau, total tau; p-tau: phosphorylated-tau.

[a] Kruskal-Wallis-test

[b] Chi-Square-test

[c] Analysis of Covariance test, adjusted for age, sex and years of education; adjusted mean values are shown. [+]Adjusted additionally for imaging sites.

[d] LEQ-e available for N_{HC}=58, N_{SCD}=47, N_{MCI}=43, and N_{ADD}=35; LEQ-m for N_{HC}=60, N_{SCD}=44, N_{MCI}=43, and N_{ADD}=29; LEQ-l for N_{HC}=41, N_{SCD}=41, N_{MCI}=35, and N_{ADD}=31; LEQ-t for N_{HC}=40, N_{SCD}=36, N_{MCI}=34, N_{ADD}=26. Cortical thickness was calculated as the averaged thickness values of the bilateral vulnerable regions in AD (see methods). † Bonferroni-$p < 0.05$ versus HC, ‡ Bonferroni-$p < 0.05$ versus SCD, †† Bonferroni-$p < 0.05$ versus MCI.

terms between continuous CR proxies and FC measures, adjusted for age, sex, cortical thickness, and imaging site. GLMs conducted in the entire AD sample were adjusted for clinical diagnosis. The following two-way interactions were tested in separate models: (1) INC-DMN or DMN:DAN x years of education, (2) INC-DMN or DMN:DAN x LEQ-e, (3) INC-DMN or DMN:DAN x LEQ-m, (4) INC-DMN or DMN:DAN x LEQ-l, and (5) INC-DMN or DMN:DAN x LEQ-t. Participants with missing data of LEQ-scores or -subscores (LEQ-e available for N_{HC}=58, N_{SCD}=47, N_{MCI}=43, and N_{ADD}=35; LEQ-m for N_{HC}=60, N_{SCD}=44, N_{MCI}=43, and N_{ADD}=29; LEQ-l for N_{HC}=41, N_{SCD}=41, N_{MCI}=35, and N_{ADD}=31; LEQ-t for N_{HC}=40, N_{SCD}=36, N_{MCI}=34, N_{ADD}=26) were excluded from the analyses in the respective models. The p values from models with LEQ-t and years of education were presented as uncorrected *p* values given the exploratory character of the study, while the models including LEQ-subscores were corrected for multiple testing using FDR.

General linear models conducted in ROI-level analyses were adjusted for age, sex, cortical thickness, MEM, diagnostic group, and study site. False-discovery-rate (FDR) correction implemented in CONN was applied to adjust p values for multiple ROI-level comparisons.

3. Results

Characteristics of the study sample are presented in Table 1. As expected, the study groups differed in age, years of education, LEQ-l, *APOE ε4*-status, CDR-sob, MEM, and cortical thickness. HC was the youngest group and had the lowest ratio of *APOE ε4*-carriers and showed the highest LEQ-l subscore. Moreover, MEM and cortical thickness levels were highest in HC, followed by MCI and ADD. The patients with ADD had the highest CDR-sob scores, followed by MCI. Interestingly, LEQ-l subscore was lower in ADD than HC and SCD. The groups within ADS differed from HC in their CSF biomarker profiles. ADD had the highest increase of t-tau and p-tau levels compared to HC, SCD and MCI, while t-tau levels were higher in MCI compared to SCD.

3.1. The impact of education and LEQ on the association between functional connectivity and memory performance

We explored whether the CR proxies predict the INC composite scores or other CR proxies (Table 2). CR proxies were associated with each other, as expected. LEQ subscores revealed a moderate association with years of education levels, while LEQ-e had the strongest association with educational years among LEQ subscores. However, no significant associations between INC composite scores and CR proxies were found in the regression analyses, neither in the entire sample (including HC) nor in the HC or ADS groups alone (Table 2).

The GLMs revealed a significant attenuating effect of CR proxies on the relationship between MEM and functional network connectivity (Table 3 and Table S2). A median split of the CR proxies was performed to visualize the differences between participants with high and low CR-proxy values (Fig. 2, only significant interactions are shown). LEQ-t (b=-0.25, $p < 0.001$) and LEQ subscores (p-FDR < 0.05 for LEQ-e, LEQ-m, and LEQ-l; b=-0.18, b=-0.13 and b=-0.22, respectively) moderated the association between MEM and INC-DMN in SCD (Fig. 2B), whereas only LEQ-t (b=-0.13, p=0.04) and LEQ-l (b=-0.12, p-FDR=0.03) showed a moderation in the entire AD group (Fig. 2A). Participants in ADS and SCD groups with high LEQ scores showed higher MEM scores for low INC-DMN, while participants with low LEQ scores showed higher MEM scores for high INC-DMN (Fig. 2A and B). In patients with MCI, years of education moderated the relationship between DMN:DAN and MEM (b=0.26, p=0.01), suggesting a closer association between MEM and DMN:DAN in participants with higher years of education (Fig. 2C). In contrast, no significant effects of LEQ-t or LEQ subscores on the relationship between INC-DMN or DMN:DAN and MEM score were found in MCI.

In contrast to observed interaction of LEQ scores, participants with higher years of education tended to show higher MEM scores for high DMN:DAN in MCI (Fig. 2C), while ADS group did not reveal any interaction between years of education education

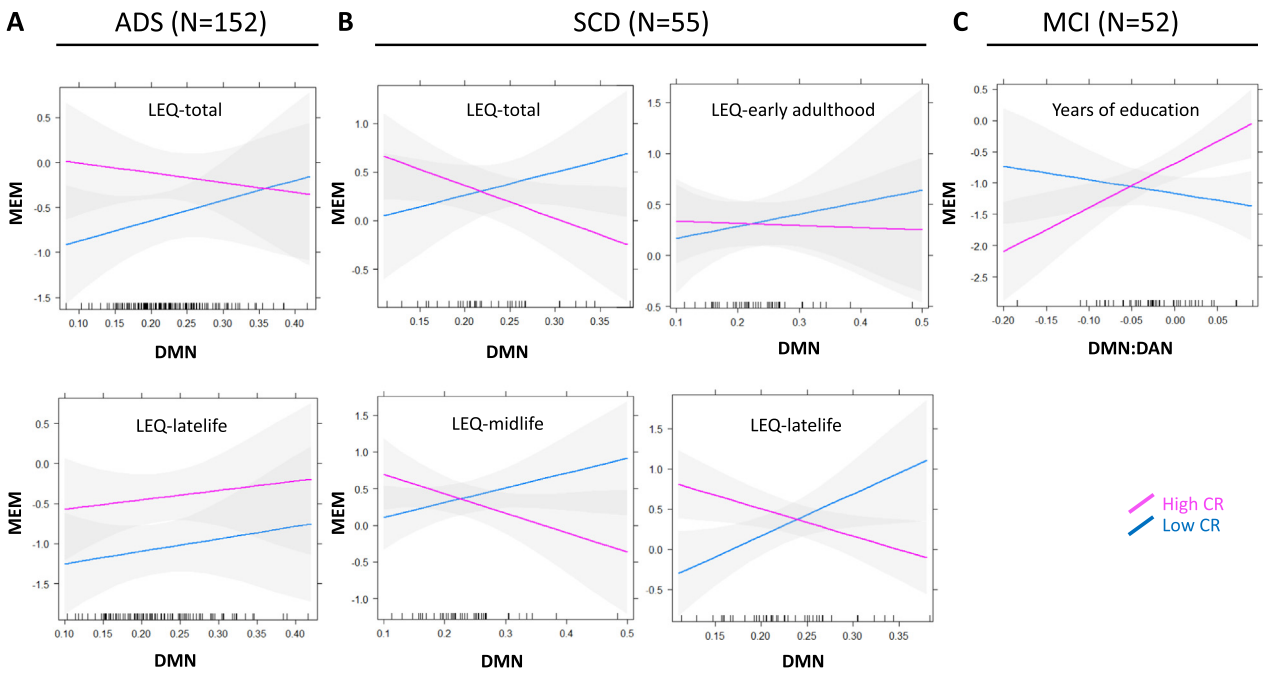

Fig. 2. Line plots with 95% confidence interval lines representing the impact of CR proxies, that is, LEQ scores and years of education, on the association between memory cognitive domain composite score and within- and between-network connectivity scores via median split of CR proxies, separately for A) ADS, B) SCD and C) MCI. In the models in which statistical tests were conducted with interaction terms, the continuous CR proxy measures were included (Table 3). Binarization of the groups is shown here made for visualization, where significant interactions were found. Abbreviations: CR, cognitive reserve; ADS, Alzheimer's disease spectrum; SCD, subjective cognitive decline; MCI, mild cognitive impairment; LEQ, lifelong experiences questionnaire; LEQ-e, LEQ for early adulthood; LEQ-m, LEQ for mid-life LEQ-l, LEQ score for late-life; LEQ-t, total LEQ score; MEM, memory composite score; DMN, intrinsic network connectivity composite score of the default mode network; DMN:DAN, inter-network connectivity composite score of default mode network and dorsal attention network.

and DMN:DAN. CR proxies did not show any significant interactions in ADD. Using a median split may not convey all relevant information on the interaction between continuous variables. Therefore, we also present plots of MEM scores at various levels of CR proxies in supplementary material which show the associations at different levels of the moderators (Figure S1). Of note, the HC group revealed no significant impact of CR proxies on the associations between MEM and INC composite scores (Table S3).

3.2. The associations between CR proxies and functional connectivity on ROI analyses

After the moderating effects of LEQ were revealed, we tested the associations between LEQ-t and ROI analyses, which showed that higher LEQ-t scores were associated with increased connectivity between the left anterior cingulate cortex and right superior temporal gyrus and between the right anterior cingulate cortex (ACC) and bilateral temporal areas in the entire ADS cohort (Fig. 3A). SCD revealed more regions with higher connectivity than the entire ADS cohort, mainly between the ACC and temporal areas. More, in patients with SCD, higher LEQ-t levels were associated with an increased FC between temporal areas and inferior frontal gyrus and inferior parietal lobule and between the middle frontal and cingulate cortices (Fig. 3B). In contrast, we found both lower and higher FC between the inferior parietal lobule and both temporal regions and inferior frontal gyrus (Fig. 3C). In ADD, LEQ-t was associated with higher FC between the right middle temporal gyrus and the ACC and superior frontal gyrus (Fig. 3D). We found no significant associations between any CR proxy and ROI-level FC within the DMN in the HC group.

4. Discussion

Years of education and LEQ are socio-behavioral CR proxies, reflecting the degree of mental enrichment during different periods of life. In the present study, we tested their associations with functional network connectivity and their impact on the relationship between functional network connectivity and cognitive performance in individuals across the AD spectrum and HC, focusing on DMN intranetwork connectivity and DMN-DAN internetwork connectivity. We found that a higher level of CR attenuated the association between cognitive function and network deterioration in DMN in the entire ADS cohort, suggesting inter-individual differences in neural reserve that is most prominent in SCD. Interestingly, MCI patients with higher years of education revealed a closer positive association between DMN:DAN and MEM, suggesting a possible neural compensation. MCI patients with higher CR might display such compensation as the neuropathological changes, that is, tau pathology, become relevant in this clinical stage. In contrast to AD dementia, the compensation capacity is possibly present in MCI. Higher connectivity between inferior parietal and middle frontal regions observed in MCI at a given level of clinical severity might suggests neural compensation. Thus, we provide evidence on potentially modifiable determinants of CR related to active and stimulating lifestyles, going beyond the effects of education and occupation. To the best of our knowledge, this is the first report on the neural underpinning of CR in SCD regarding the rs-fMRI connectivity of DMN.

While the LEQ subscores included in our analyses assess social, academic, occupational, and cognitive lifestyle activities at different stages throughout life (Valenzuela and Sachdev, 2007), we assume that total LEQ-t scores may provide the most comprehensive picture of these lifestyle events, as LEQ scores reflect not only educational and occupational attainment but also leisure activities,

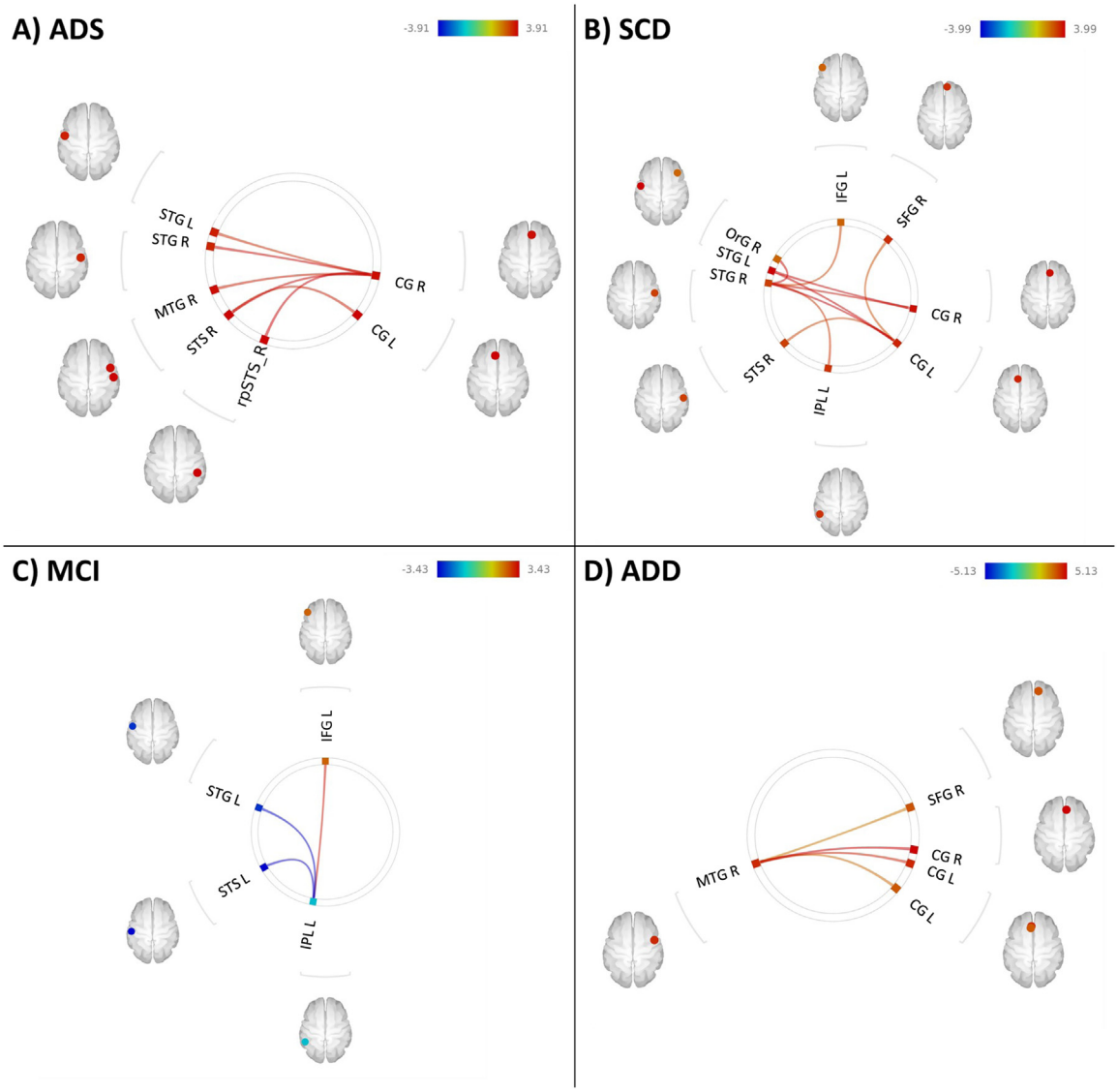

Fig. 3. Functional connectivity between ROIs belonging to the DMN showing significant associations with the LEQ-t in ADS (A), SCD (B), MCI (C), and ADD (D). Edges are represented as a connectivity ring when two-tailed-*p-FDR* < 0.05, adjusted for age, sex, cortical thickness, imaging sites, and MEM. The general linear model conducted in ADS was adjusted additionally for diagnosis groups. The T values presented in the color bar. Exact Atlas-ROI definitions are provided in supplementary material (Figure S2). Abbreviations: ADS, Alzheimer's disease spectrum; SCD, subjective cognitive decline; MCI, mild cognitive impairment; ADD, Alzheimer's disease dementia; MEM, memory composite score; LEQ, lifelong experiences questionnaire; LEQ-t, total LEQ score; FDR, False Discovery Rate; STG, Superior Temporal Gyrus; MTG, Middle Temporal Gyrus; STS, Superior Temporal Sulcus; CG, (anterior) Cingulate Gyrus; OrG, Orbital Gyrus; IFG, Inferior Frontal Gyrus; SFG, Superior Frontal Gyrus; IPL, Inferior Parietal Lobule; SFG, Superior Frontal Gyrus; L, left, R, right.

which are associated with CR (Perneczky et al., 2011). Higher levels of LEQ-t attenuated the association between memory and DMN connectivity in ADS. At the same time, only LEQ-l revealed a significant interaction in ADS. This may suggest that LEQ-t is a better overall representation of CR than single subscores, in line with a recent expert consensus suggesting a global nature of socio-behavioral proxies of CR (Stern et al., 2020). Considering the interaction of LEQ-l in ADS, LEQ-l may have a more specific value compared to other LEQ subscores while identifying higher neural reserve. However, reverse causation may interfere with the observations on the LEQ subscore for late life, possibly reflecting early AD symptoms rather than lifestyle choices (Stern et al., 2020); such reverse causation might also explain the lower LEQ-l levels observed in ADD in the present study. Moreover, participants in the SCD group demonstrated a relatively strong interaction between LEQ, MEM and FC within DMN. The SCD group may exhibit the highest neural reserve because of the mild pathological changes present in this particular population allowing reserve mechanisms to occur. In contrast, in later AD stages the effect of CR might be diminished by disease progression.

The LEQ subscore for early adulthood may be a more comprehensive measure of CR compared to years of formal education, most frequently used in research as a CR proxy. Education is likely associated with lifelong activities that is, intellectual, social, and physical activities (Perneczky et al., 2009). The moderate associations between years of education and LEQ subscores or LEQ-t in our results support this notion partly. However, the absence of a moderating effect of education in contrast to LEQ on the association between network connectivity and cognition suggests a closer relationship between LEQ and neural reserve. It was previously reported that the moderating effect on anti-correlation is inconsistent when comparing years of education tested in different

Table 2
Separately tested multilinear regression models with CR proxies as predictors and intrinsic network connectivity composite scores or CR proxies as dependent variables

		All (N = 228)					HC (N = 76)					ADS (N = 152)				
Dependent Variables		Predictors					Predictors					Predictors				
		Education	LEQ-e	LEQ-m	LEQ-l	LEQ-t	Education	LEQ-e	LEQ-m	LEQ-l	LEQ-t	Education	LEQ-e	LEQ-m	LEQ-l	LEQ-t
DMN	b	-0.05	-0.02	0.1	0.01	0.08	-0.14	-0.15	0.06	0.15	0.1	0.004	0.06	0.15	-0.05	0.07
	p	0.44	0.81	0.24	0.87	0.34	0.27	0.34	0.69	0.38	0.59	0.97	0.56	0.14	0.65	0.53
DMN:DAN	b	0.08	0.07	0.1	0.05	0.03	0.17	0.23	0.13	0.21	0.27	0.04	0.03	-0.03	0.03	-0.02
	p	0.29	0.39	0.87	0.56	0.77	0.2	0.14	0.37	0.21	0.14	0.68	0.8	0.8	0.75	0.89
Education	b	n.a.					n.a.					n.a.				
	p															
LEQ-e	b	0.66**	n.a.				0.63**	n.a.				0.66**	n.a.			
	p	<0.001					<0.001					<0.001				
LEQ-m	b	0.6**	0.71**	n.a.			0.55**	0.76**	n.a.			0.59**	0.67**	n.a.		
	p	<0.001	<0.001				<0.001	<0.001				<0.001	<0.001			
LEQ-l	b	0.4*	0.51**	0.58**	n.a.		0.29	0.75**	0.74**	n.a.		0.44**	0.42**	0.52**	n.a.	
	p	0.001	<0.001	<0.001			0.09	<0.001	<0.001			<0.001	<0.001	<0.001		
LEQ-t	b	0.64**	0.84**	0.92**	0.8**	n.a.	0.56**	0.92**	0.94**	0.9**	n.a.	0.67**	0.8**	0.9**	0.77**	n.a.
	p	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	

Multilinear regression models were adjusted for age, sex, study sites, diagnosis groups, MEM and cortical thickness. Two-tailed p values are shown. $^{*}p < 0.05$, $^{**}p < 0.001$.
Abbreviations: CR, cognitive reserve; ADS, Alzheimer's disease spectrum; LEQ-e, LEQ for early adulthood; LEQ-m, LEQ for midlife LEQ-l, LEQ score for late life; LEQ-t, lifetime experiences questionnaire total score; MEM, memory cognitive domain composite score; DMN, intrinsic network connectivity composite score of default mode network; DMN:DAN; anti-correlation between DMN and DAN; b, standardized Beta value; p, p value.

Table 3
General linear models for testing the interactions between intrinsic network connectivity composite score (intra-network connectivity of DMN or anti-correlation of DMN and DAN) and any given CR proxy on composite memory score

	ADS (N = 152)					SCD (N = 55)					MCI (N = 52)					ADD (N = 45)				
	Parameter	b	SE	p	p-FDR	Parameter	b	SE	p	p-FDR	Parameter	b	SE	p	p-FDR	Parameter	b	SE	p	p-FDR
DMN	**DMN * LEQ-t**	-0.13	0.06	0.04	n.a.	**DMN * LEQ-t**	-0.25	0.06	<0.001	n.a.	DMN * LEQ-t	0.09	0.22	0.68	n.a.	DMN * LEQ-t	0.22	0.14	0.12	n.a.
	DMN * LEQ-e	-0.02	0.06	0.68	0.68	**DMN * LEQ-e**	-0.18	0.06	0.01	0.01	DMN * LEQ-e	0.08	0.15	0.59	n.a.	DMN * LEQ-e	0.16	0.09	0.07	n.a.
	DMN * LEQ-m	-0.06	0.05	0.26	0.26	**DMN * LEQ-m**	-0.13	0.05	0.01	0.01	DMN * LEQ-m	-0.03	0.14	0.84	n.a.	DMN * LEQ-m	0.13	0.12	0.26	n.a.
	DMN * LEQ-l	-0.12	0.05	0.01	0.03	**DMN * LEQ-l**	-0.22	0.06	0.001	0.003	DMN * LEQ-l	-0.12	0.20	0.53	n.a.	DMN * LEQ-l	0.06	0.08	0.45	n.a.
	DMN * Education	-0.04	0.04	0.33	n.a.	DMN * Education	-0.14	0.08	0.07	n.a.	DMN * Education	0.01	0.11	0.93	n.a.	DMN * Education	0.01	0.08	0.91	n.a.
DMN:DAN	DMN:DAN * LEQ-t	0.05	0.07	0.45	n.a.	DMN:DAN * LEQ-t	-0.02	0.08	0.79	n.a.	DMN:DAN * LEQ-t	0.13	0.19	0.50	n.a.	DMN:DAN * LEQ-t	0.08	0.10	0.46	n.a.
	DMN:DAN * LEQ-e	0.02	0.06	0.73	n.a.	DMN:DAN * LEQ-e	0.06	0.07	0.41	n.a.	DMN:DAN * LEQ-e	0.01	0.12	0.92	n.a.	DMN:DAN * LEQ-e	0.15	0.08	0.06	n.a.
	DMN:DAN * LEQ-m	0.07	0.05	0.19	n.a.	DMN:DAN * LEQ-m	0.03	0.05	0.54	n.a.	DMN:DAN * LEQ-m	0.08	0.13	0.54	n.a.	DMN:DAN * LEQ-m	0.07	0.08	0.38	n.a.
	DMN:DAN * LEQ-l	0.07	0.06	0.25	n.a.	DMN:DAN * LEQ-l	-0.04	0.10	0.68	n.a.	DMN:DAN * LEQ-l	0.26	0.18	0.16	n.a.	DMN:DAN * LEQ-l	0.11	0.06	0.09	n.a.
	DMN:DAN * Education	0.05	0.05	0.26	n.a.	DMN:DAN * Education	-0.03	0.06	0.60	n.a.	**DMN:DAN * Education**	0.26	0.10	0.01	n.a.	DMN:DAN * Education	-0.01	0.08	0.89	n.a.

The models with each CR proxy were tested separately. All models were adjusted for age, sex, imaging sites and cortical thickness. The general linear models conducted in ADS were adjusted additionally for diagnosis groups. The models with significant interaction terms with two-tailed $p < 0.05$ values are indicated in bold. The results are presented with all terms included in Table S2.
Abbreviations: CR, cognitive reserve; ADS, Alzheimer's disease spectrum; SCD, subjective cognitive decline; MCI, mild cognitive impairment; ADD, Alzheimer's disease dementia; b, standardized beta value; SE, standard error; p, p value; p-FDR, false discovery rate corrected p value; LEQ, lifelong experiences questionnaire; LEQ-e, LEQ for early adulthood; LEQ-m, LEQ for midlife LEQ-l, LEQ score for late-life; LEQ-t, total LEQ score; DMN, intrinsic network connectivity composite score of default mode network; DMN:DAN; anti-correlation between DMN and DAN; n.a., not applicable.

cohorts (Franzmeier et al., 2017b). Education, but not LEQ, moderates FC in MCI, suggesting a stronger education-related association between DMN:DAN and MEM, possibly occurring due to neural compensation. This may be explained by a more specific effect of education as CR proxy, while LEQ-e may represent more general aspects of reserve. In line with this notion, LEQ-e shows the same directionality as education in the interaction term (DMN:DAN x LEQ-e).

FC mainly in the ACC and the bilateral superior temporal cortices and multimodal association areas are typically affected by AD pathology (Ingelsson et al., 2004; Maass et al., 2017). Higher connectivity in these areas was associated with higher LEQ-t scores, as a neural correlate of CR in the AD spectrum, pronounced in SCD and possibly sparing the MCI subgroup. Education was suggested to reinforce resting-state FC of the ACC with frontal, temporal, and parietal cortical areas, suggesting mechanisms underlying education-related reserve in healthy older individuals (Arenaza-Urquijo et al., 2013). Similarly, neuropathological and neuroimaging examinations revealed two comparable findings, including (1) higher cortical volume and higher von Economo neuron density in the ACC in individuals with a higher resilience against the effects of age-related cortical atrophy (Gefen et al., 2015; Harrison et al., 2012); and (2) higher intrinsic connectivity of ACC, maintained by so-called "supernormals," presenting remarkably better memory performance than age-matched peers (Lin et al., 2017), suggesting an involvement in reserve-related mechanisms (Perneczky et al., 2019). Of note, these studies have focused on cognitively normal elderly participants, which might explain the differences compared with our findings. Previous work also reported a closer association between FC of cingulate cortexand global cognition in Aβ positive group compared to participants without pathological Aβ levels and suggested a cingulate cortex-involved neural function as a protective FC alteration against AD pathology (Lin et al., 2017). Furthermore, studies suggested CR-associated higher connectivity revealed using latent CR estimations in the right temporal pole (Lee et al., 2019) and right inferior temporal gyrus (Marques et al., 2016). Differences between the studies can be explained by our focus on the DMN vs. whole-brain analyses, additional analysis methods, that is, graph theory in these studies and the use of different CR proxy measures.

Another important finding of our study is the asymmetry in FC changes related to CR proxies, namely higher FC in bilateral temporal (right>left) and cingular cortices in AD spectrum, in right superior frontal and left inferior parietal cortices in SCD and the right middle temporal gyrus in AD. Interestingly, lower FC of left inferior parietal FC was associated with higher LEQ-t in MCI. These findings support the observations in patients with prodromal AD, suggesting modifications in FDG-PET due to both neural reserve and neural compensation in prodromal AD (Morbelli et al., 2013). Similar to our findings, the authors concluded that the higher metabolic activity in the left middle temporal and left middle occipital gyri underlie neural reserve. Authors have also suggested higher metabolic activity in the dorsolateral prefrontal cortex, a cortical region not included in the DMN, as neural compensation can explain the difference between studies. A recent systematic review indicated that FC of medial temporal regions and DMN - mainly in the anterior and posterior cingulate cortex- are associated with neural reserve (Anthony and Lin, 2018). The authors also concluded that the FC in frontal and DAN regions are related to neural compensation.

Utilizing a relatively large cohort with rs-fMRI data in different AD stages, including SCD, considering pathological confirmation of AD, and using a comprehensive measure of lifestyle choices across the lifespan are major strengths of our approach. At the same time, we must also acknowledge a few limitations of our study, including the cross-sectional design. Further research is warranted to validate and extend our observations in studies with a longitudinal design. Furthermore, the application of different rs-fMRI analysis methods, such as graph theory, and the further investigation of resting-state networks will help shed light on various neural features of CR. Other relevant future research aims include extending our approach to potentially modifiable lifestyle factors not reflected with enough detail by LEQ, such as physical activity and nutritional habits, and relevant risk factors, including vascular risk. Other CR proxies, among others latent CR marker approaches, should be tested in association with socio-behavioral CR proxies. These could have fewer limitations considering the indirect and retrospective nature of socio-behavioral CR proxies.

In summary, our results contribute to a better understanding of the brain functional underpinning of CR. They may help to fine-tune future dementia prevention and treatment strategies, for example, by defining specific endophenotypes amenable for disease modification to reduce sample size. Our findings emphasize the possible effectiveness of implementing prevention approaches in AD beginning early in life and demonstrate that healthy lifestyle choices might still be effective in mid- and late-life.

Verification

The data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging. Appropriate approval and procedures were used concerning human subjects.

Disclosure statement

Ersin Ersoezlue, Boris-Stephan Rauchmann, Thomas Schneider-Axmann, Michael Wagner, Tommaso Ballarini, Maia Tatò, Julia Utecht, Carolin Kurz, Boris Papazov, Selim Guersel, Lena Burow, Gabriele Koller, Sophia Stöcklein, Daniel Keeser, Oliver Peters, Lukas Preis, Arda Cetindag, Eike Jakob Spruth, Anja Schneider, Klaus Fliessbach, Jens Wiltfang, Claudia Bartels, Franziska Maier, Emrah Düzel, Coraline D. Metzger, Katharina Buerger, Daniel Janowitz, Stefan Teipel, Ingo Kilimann, Christoph Laske, Matthias H. Munk, Annika Spottke, Nina Roy, Michael T. Heneka, Frederic Brosseron, Ingo Frommann, Laura Dobisch, Alfredo Ramirez, Michael Ewers, Peter Dechent, John Dylan Haynes, Klaus Scheffler, Steffen Wolfsgruber, Luca Kleineidam, Renat Yakupov, and Sandra Roeske report no disclosures. Frank Jessen received fees for consultation from Eli Lilly, Novartis, Roche, BioGene, MSD, Piramal, Janssen, Lundbeck. Josef Priller received fees for consultation, lectures, patents from Neurimmune, Axon, Desitin, Epomedics. Robert Perneczky received fees for consultation from Janssen, Roche, Biogen, Eli Lilly, and Grifols.

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Supplementary materials

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6. Paper II - A residual marker of cognitive reserve is associated with resting-state intrinsic functional connectivity along the Alzheimer's disease continuum (JAD 2023)

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A Residual Marker of Cognitive Reserve Is Associated with Resting-State Intrinsic Functional Connectivity Along the Alzheimer's Disease Continuum

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Abstract.
Background: Cognitive reserve (CR) explains inter-individual differences in the impact of the neurodegenerative burden on cognitive functioning. A residual model was proposed to estimate CR more accurately than previous measures. However, associations between residual CR markers (CRM) and functional connectivity (FC) remain unexplored.
Objective: To explore the associations between the CRM and intrinsic network connectivity (INC) in resting-state networks along the neuropathological-continuum of Alzheimer's disease (ADN).
Methods: Three hundred eighteen participants from the DELCODE cohort were stratified using cerebrospinal fluid biomarkers according to the A(myloid-β)/T(au)/N(eurodegeneration) classification. CRM was calculated utilizing residuals obtained from a multilinear regression model predicting cognition from markers of disease burden. Using an independent component analysis in resting-state fMRI data, we measured INC of resting-state networks, i.e., default mode network (DMN), frontoparietal network (FPN), salience network (SAL), and dorsal attention network. The associations of INC with a composite memory score and CRM and the associations of CRM with the seed-to-voxel functional connectivity of memory-related were tested in general linear models.
Results: CRM was positively associated with INC in the DMN in the entire cohort. The A+T+N+ group revealed an anti-correlation between the SAL and the DMN. Furthermore, CRM was positively associated with anti-correlation between memory-related regions in FPN and DMN in ADN and A+T/N+.
Conclusion: Our results provide evidence that INC is associated with CRM in ADN defined as participants with amyloid pathology with or without cognitive symptoms, suggesting that the neural correlates of CR are mirrored in network FC in resting-state.

Keywords: Alzheimer's disease, cognition, cognitive reserve, functional MRI, intrinsic network connectivity, resting-state functional connectivity

INTRODUCTION

The concept of cognitive reserve (CR) refers to the capacity and flexibility of cognitive and brain processes that help to attenuate the impact of brain aging or pathology on cognitive function or daily activities, for example, in Alzheimer's disease (AD) [1]. Key mechanisms underlying CR include the brain's ability to maintain neural functions, recruit compensatory networks, or use existing networks more efficiently [2]. The related concepts of brain reserve [3] and brain maintenance describe different, complementary aspects of resilience [2].

Years of formal education [1, 4] and occupational complexity [5] are used frequently as CR proxy measures [6]. Still, they only reflect selected aspects of intellectual attainment. The residual estimation of cognitive reserve (i.e., residual CR marker (CRM)) has been obtained by quantifying the discrepancy between the observed cognitive performance and the performance estimated based on the neuropathological burden of a person using a multiple linear regression analysis. The neuropathological burden included demographical data, genetic predisposition, and disease surrogates, i.e., cerebrospinal fluid (CSF) biomarkers. This approach may offer more granular data resulting in more detailed insights into the nature of CR [2]. Residual approaches were shown to be relatively reliable and were studied in cross-sectional [7, 8] and longitudinal studies [9–11]. A residual CR measure considers demographical and disease-related confounders multidimensionally and may be more comprehensive and informative at the individual level than traditional markers such as education [2].

Resting-state networks (RSNs) such as the default mode network (DMN), which is involved in cognition, self-reference, social cognition, or autobiographical memory (i.e., inwardly directed cognition) [12–14], and networks associated with externally directed cognitive processing, including the dorsal attention (DAN), salience (SAL), and frontoparietal network (FPN) [12, 15–18], are affected by AD pathology and correlate with disease progression. Spatial links exist between AD pathology and functional connectivity (FC) changes, particularly in the posterior DMN and FPN [19]. Moreover, the inter-network connectivity among RSNs is also affected in AD, especially between DMN and DAN [12] as well as SAL [20]. As AD progresses, functional network changes affect predominantly intra-network connectivity and to a lesser extent inter-network connectivity [15].

The inter-individual variances in FC using various functional imaging approaches are increasingly the focus of studies of the neural implementation of CR that might contribute to functional neural processes to preserve a relatively better cognition [2, 21]. Previous studies showed positive associations between residual markers of CR and the graph-theoretical measurement of network efficiency and FC [7, 8]. FC was also associated positively with CR measured as educational attainment in DMN regions [22, 23] and between DMN and FPN [24]. In contrast, CR was associated with lower metabolic activity in the DMN and the DAN [1, 25]. Furthermore, increasing evidence suggests a crucial role of the FPN in CR, regarding global connectivity of the left frontal cortex (LPC) in resting-state functional magnetic resonance imaging (fMRI), a hub region within the FPN [26–28]. Unlike node-to-node connectivity analyses, whole network intrinsic connectivity analysis following the data-driven independent component analysis (ICA) [29] allows FC analysis more broadly within and across networks [15].

A biologically-based definition of the AD diagnosis has been proposed in a recent research framework using a binary biomarker status (presented or absent) for (A)myloid-β (Aβ), (T)au and (N)eurodegeneration (i.e., the ATN classification) as biomarker-based diagnostic profiles, prompting the switch from a symptom-based to a biological definition of AD [30]. Considering the various stages of AD, FC alterations appear already in the preclinical and early clinical stages of AD [31], showing meaningful effects of CR on the individual clinical progression trajectories [27]. Nevertheless, the characterization of residual approaches is improving in individuals at-risk of dementia and dementia populations [32]; there is a need to operationalize them in early disease and explore their associations with intrinsic network connectivity (INC) of cognitive RSNs.

In this study, we aimed to examine the associations of a residual CRM with FC alterations within and between network connectivity, focusing on the disease-susceptible RSNs, in the AD neuropathological continuum (ADN), using a biomarker-based approach for diagnosis and staging. Furthermore, we defined memory function-related functional network connectivity of the DMN and the FPN to test their associations with the CRM to provide insights into the function of CRM in cognitive decline.

MATERIALS AND METHODS

Data from the prospective, observational German Center for Neurodegenerative Diseases (Deutsches Zentrum für Neurodegenerative Erkrankungen, DZNE)-Longitudinal Cognitive Impairment and Dementia Study (DELCODE) [33] was used for the present analyses, an observational brain imaging study initiated by the DZNE in 2014 (German Clinical Trials Register: DRKS00007966).

Participants

All eligible DELCODE participants were included if they had available Clinical Dementia Rating (CDR), neuropsychological tests, CSF biomarker analyses and apolipoprotein E (*APOE*) genotyping results and relevant structural and functional MRI data. We classified each participant following the A/T/N classification scheme using binarized CSF biomarker measurements of Aβ for A, total tau (tTau) for N, and phosphorylated-tau181 (pTau) for T [34]. To restrict the cohort to participants in the ADN and healthy controls, we excluded participants classified as A–T/N+ (A–T+N– and A–T–N+) (i.e., suspected non-AD pathology) and A–T–N– with a global CDR rating of higher than 0 (i.e., non-AD cognitive impairment). The final cohort of 318 participants included 112 A–T–N– individuals with global CDR = 0 as healthy controls (HC, mean age 69 ± 6, 52 females) and 206 A+ patients as ADN regardless of the cognitive status or clinical diagnosis (mean age 72 ± 6, 101 females), encompassing 106 A+T–N–, 28 A+T/N+ (A+T+N– and A+T–N+), and 72 A+T+N+ individuals. The detailed inclusion and exclusion criteria and study procedures of the DELCODE study are reported elsewhere [33]. The following CSF biomarker cut-off values were obtained by Gaussian mixture modeling using the R package flexmix (version 2.3–15) in the DELCODE dataset included 481 participants with CSF biomarker data (sampling rate among entire baseline cohort: 48%): $A\beta_{42}$: <= 638.7 pg/ml, tTau: >510.9 pg/ml, and pTau181: >= 73.65 pg/ml, as reported elsewhere [35]. The maximum time lag between study visit with clinical and neuropsychological assessment and CSF draw and fMRI scan was four weeks.

MR image acquisition and preprocessing

Imaging was performed at nine different DZNE sites on 3T MRI scanners (Siemens Healthineers, Erlangen, Germany; three Verio, three TimTrio, one Prisma, and two Skyra) using synchronized acquisition parameters. T1-weighted anatomical imaging was acquired in a 5-min magnetization-prepared rapid gradient echo (MPRAGE) scan with the following parameters: field of view (FOV) 256×256 mm, isotropic voxel size: 1 mm, echo time (TE) 4.37 ms, flip angle (FA) 7°, repetition time (TR) 2500 ms, number of slices 192. Resting-state functional MRI was acquired in a 7-min 54-s run (180 volumes, FOV: $224 \times 224 \times 165$ mm, isotropic voxel size: 3.5 mm, TE: 30 ms, TR: 2580 ms, FA: 80, parallel imaging acceleration factor 2). In the DELCODE study, participants consistently in all study centers were instructed to keep their eyes closed and not fall asleep before the resting state scan. All scans were visually inspected for completeness, cuts, subject motion, and other artifacts (such as blurring, echoes and ghosting). Images were classified as usable, questionable, or unusable and only images that were classified as usable were included.

All T1-weighted images were processed in FreeSurfer (v6, https://surfer.nmr.mgh.harvard.edu/) using the recon-all pipeline, including registration to Montreal Neurological Institute (MNI) standard space, intensity normalization, brain extraction, tissue type classification, surface reconstruction and probabilistic anatomical labeling [36]. Cortical thickness was estimated in FreeSurfer (Desikan-Killiany) atlas segmentations. A mean cortical thickness score in a composite region comprising the most vulnerable regions to atrophy in AD was calculated. This composite score was used to adjust the subsequent analyses throughout the manuscript for inter-individual differences in the degree of cortical atrophy. The composite region included the entorhinal cortex, temporal pole, inferior and middle temporal gyri, inferior and superior parietal cortices, precuneus, and posterior cingulate cortex [37].

Functional connectivity analysis was performed using the CONN-fMRI Functional Connectivity Toolbox (v19c, https://www.nitrc.org/projects/conn) and SPM12 (www.fil.ion.ucl.ac.uk/spm/), implemented in MATLAB (Release2017b, https://de.mathworks.com/products/new_products/release2017b.html). The default preprocessing pipeline for volume-based analyses was used, comprising realignment, slice-time correction, segmentation, and structural and functional normalization. The Artifact Detection Toolbox (ART)-based outlier detection (https://web.mit.edu/swg/software.htm) and smoothing using a Gaussian kernel of 6 mm at FWHM

[25] was applied. Denoising was performed using the default pipeline based on linear regression of potential confounding effects of white matter and CSF [38], estimated subject-motion parameters [39], outlier scans and scrubbing [40], followed by applying a band-pass filter (below 0.008 Hz or above 0.09 Hz) [41]. Afterward, the distribution of FC correlation values was directly compared to the null-hypothesis distribution that showed a 95.5% match with the null-hypothesis, indicating a lack of noticeable associations between quality control measures and FC [42].

Clinical characteristics, cognitive testing, and assessment of CSF biomarkers

The clinical severity of dementia symptoms was quantified using the CDR-sum of boxes (CDR-sb). Cognitive performance was assessed using the Mini-Mental State Examination (MMSE), given its clinical relevance. Moreover, cognitive domain-specific (learning and memory (MEM), executive functions and mental processing speed, visuo-spatial abilities, language ability and working memory) composite scores were derived by using confirmatory factor analysis of a larger neuropsychological assessment battery (DELCODE-NP), while the global cognitive composite score was calculated by averaging all five domain-specific cognitive composite scores [43]. DELCODE-NP comprised established neuropsychological tests such as MMSE, The Alzheimer's Disease Assessment Scale-Cognitive Subscale 13, the Free and Cued Selective Reminding Test and Wechsler Memory Scale revised version Logical Memory (Story A) and Digit Span, Boston Naming Test, two semantic fluency tasks (animals and groceries), the Boston Naming Test, the oral form of the Symbol-Digit-Modalities Test, Trail Making Test A and B, Clock Drawing and Clock Copying, and a recall task of previously copied figures and two newly developed computerized tests, i.e., the Face Name Associative Recognition Test and a Flanker task to assess executive control of attention [43]. The details of the confirmatory factor analysis procedures are reported in the previous studies [35, 43], while a complete overview of individual test scores that were assigned to the five different cognitive domains is reported in the Supplementary Material. A trained neuropsychologist performed the neuropsychological tests at all sites [33]. CSF biomarkers were assessed using established commercially available analysis kits: V-PLEX Aβ Peptide Panel 1 (6E10) Kit (K15200E), V-PLEX Human tTau Kit (K151LAE) (Meso Scale Diagnostics LLC, Rockville, MD, USA) and Innotest Phospho-Tau(181P) (Fujirebio Germany GmbH, Hannover, Germany) [33].

Assessment of static parameters of cognitive reserve

Individual lifestyle differences defined as CR proxies were assessed using the total years of formal education and a validated German version [44] of the Lifetime Experiences Questionnaire (LEQ) total score, reflecting activities across the lifespan (educational, occupational, managerial history, social and intellectual activities) [45]. The LEQ total score was derived as a mean score of three sub-scores for different stages of life (early adulthood (LEQ-e, age 13 to 30 years), mid-life (LEQ-m, age 30 to 65 years), and late-life (LEQ-l, age 65 and older)). Participants with missing data (also provided in Supplementary Table 1) of $N_{All} = 132$ ($N_{HC} = 49$, $N_{ADN} = 83$) for LEQ total, $N_{All} = 63$ ($N_{HC} = 23$, $N_{ADN} = 40$) for LEQ-e scores, $N_{All} = 73$ ($N_{HC} = 22$, $N_{ADN} = 51$) for LEQ-m scores and $N_{All} = 118$ ($N_{HC} = 47$, $N_{ADN} = 71$) for LEQ-l scores were excluded from the analyses that had included these variables. Of note, one participant with an outlier LEQ-l value (z-score>3) was excluded from the analyses included LEQ-l. Moreover, the mean values and standard deviations of LEQ subscores by study groups are provided in Supplementary Table 1.

Quantitative residual cognitive reserve marker

In order to estimate a residual CRM for each participant, we calculated a stepwise regression model including the global cognitive composite score as the dependent variable and demographic (age and sex), genetic risk and neurodegenerative burden as predictors [7], adjusting for study sites and estimated total intracranial volume. Estimates of neurodegenerative burden included binarized *APOE* ε4 allele carrier status, CSF biomarker levels ($A\beta_{42}$, tTau, and pTau181), mean cortical thickness of predefined brain regions vulnerable to atrophy in AD and mean bilateral hippocampal volume (Supplementary Figure 1A, adjusted $R^2 = 0.54$). While the variables male sex ($b = 0.04$, $p = 0.85$ and $VIF = 1.2$), *APOE* ε2 allele carrier status ($b = 0.02$, $p = 0.95$ and $VIF = 1$) and estimated total intracranial volume ($b = 0.04$, $p = 0.85$ and $VIF = 1$) did not improve the model, p-tau lev-

els showed high collinearity (b = –0.05, $p = 0.16$ and VIF = 6.4). The high multicollinearity for p-tau was considered to be caused by t-tau, as the p-tau related variance in global cognition is fully predicted by individual differences in t-tau, e.g., very high collinearity between t-tau and p-tau, which is explained in the Supplementary Material in detail. Of note, age revealed shared effects of 10% with total-tau and 7% with phospho-tau on global cognition. Therefore, the stepwise method removed these variables from the multilinear regression model. We utilized a stepwise approach in the multilinear regression model, aiming for the best-fitted model and less subjectivity for covariables selection. Of note, the stepwise multilinear regression utilizes both forward selection and backward elimination methods according to the defined criteria (Probability-of-F-to-enter <= 0.05, Probability-of-F-to-remove >= 0.1).

The linearity of the regression model was approved by the normally distributed residuals (Kolmogorov-Smirnov $p > 0.05$ under Lilliefors Significance Correction).

Independent component analysis of functional MRI

We applied ICA to determine the spatial extent of the RSNs [29] and to test the intrinsic network connectivity on preprocessed resting-state fMRI data using the CONN toolbox [46]. We calculated ICA-maps, representing a measure of different networks expression and connectivity at each voxel, following the group-ICA methodology implemented in CONN. The CONN toolbox uses a temporal concatenation of blood-oxygen-level-dependent (BOLD) signal data across participants, as described previously [47, 48]. Following group-ICA, subject-specific independent component maps of the DMN, SAL, DAN, and FPN were back-reconstructed using the GICA3 algorithm [49]. Participant-level spatial maps were estimated through back projection, which was attained by performing dual regression with univariate spatial regression and multivariate temporal-regression steps [48]. The number of independent components to extract was set *a priori* to 20 [50]. To identify RSNs from the ICA components, the obtained group ICA components were spatially compared to templates derived from the resting state network templates of the network cortical ROIs defined by ICA in 497 healthy subject from the human connectome project (HCP) dataset including FPN, DMN, DAN, and SAL (dice coefficients indicating a spatial overlap: 0.37, 0.49, 0.6, and 0.2, respectively) [46].

Intrinsic network functional connectivity analysis of resting-state networks

Using the first-level ICA data, a second-level analysis was performed using the identified resting-state functional connectivity networks on the subject level: Separate general linear models were calculated for MEM and CRM. The results were presented using the Harvard-Oxford Atlas labels [51]. Additionally, we identified the network regions using binarized masks as group component maps at an intensity threshold of >2 from ICA for each of the four RSNs, through which we identified overlapping network regions.

Seed-to-voxel functional connectivity of memory-related seed regions

Using the associations between FC and MEM (see below for statistical description), we identified regions of interest using binary masking based on regions with significant MEM-related FC changes for each RSN (identified as the significant associations of the corresponding network with MEM, as described above), separately. Masked regions were used as seed regions for every voxel in the brain. Seed-based connectivity analyses were computed using the Fisher-z-transformed bivariate correlation coefficients between a seed region's BOLD time series and any individual voxel BOLD time-series.

Statistical analyses

All statistical analyses were performed using SPSS, version 25.0 (IBM Corp., Somers, NY). The Bonferroni method was used to adjust for multiple comparisons in the assessment of demographical and clinical data. False discovery rate (FDR) [52] correction was applied to FC analyses. Kruskal-Wallis and Chi-square tests were used to compare the study groups' baseline sociodemographic, clinical, and genetic variables. Analysis of Covariance (ANCOVA) was used to compare cortical thickness composite scores and hippocampal volumes, INC of each cognitive RSN, CSF biomarkers, and CRM between the groups, adjusting for age and sex (additional adjustments were made for years of education in comparisons of cognitive assessments and for imaging sites in comparisons of INC), as appropriate.

The associations of CRM with CR Proxies (i.e., years of education and LEQ-total) were tested using separate multilinear regression models, adjusting for age, sex, study sites, and A/T/N diagnostic subgroups. Results were reported with standardized beta coefficients (b) considered significant when $p < 0.05$, corresponding to the multiple testing corrected significance level for p-Bonferroni<0.05 (one-tailed).

The associations between FC and MEM as well as CRM were tested separately on voxel-level using general linear models (see above for ICA). Likewise, the associations between CRM and any MEM-related connectivity seeds for each RSN were tested using general linear models (see above for Seed-to-voxel analysis). Statistical models were adjusted for age, sex, site, cortical thickness composite score, and the A/T/N group. Results were considered significant when $p < 0.05$ in Gaussian random field theory [53] for INC, indicating a significance when cluster-level FDR-corrected $p < 0.05$ and voxel-level $p < 0.001$.

RESULTS

The characteristics of the study groups are shown in Table 1. The severity of cognitive decline and the clinical status of the ADN group and the healthy controls is presented in terms of MMSE and CDR mean scores. The ADN group was defined using a biomarker-informed stratification approach in which all participants with underlying Aβ pathology were combined into one group consisting of a spectrum from cognitively normal participants to participants with early AD and revealed significantly lower MMSE and higher CDR-sb compared to controls. Aβ positive individuals were more frequently *APOE* ε4 allele carriers and less frequently *APOE* ε2 allele, had lower mean hippocampal volumes and mean cortical thickness, lower CSF $A\beta_{42}$, higher CSF tTau, and pTau181, as well as lower global cognitive composite scores, as expected. HC was younger than ADN participants, while the groups did not differ in years of education or CRM.

Associations between CRM and educational attainment and lifetime experiences

CRM was predicted by years of education when analyzing the entire cohort (Supplementary Figure 1B, $b = 0.28$, $p < 0.001$, adjusted-$R^2 = 0.06$) and ADN subgroup separately ($b = 0.34$, $p < 0.001$, adjusted-$R^2 = 0.09$), but not in the HC ($b = 0.07$, $p = 0.52$, adjusted-$R^2 = 0.04$). Furthermore, higher CRM was associated with higher LEQ-total scores in the entire sample (Supplementary Figure 1C, $b = 0.26$, $p < 0.001$, adjusted-$R^2 = 0.05$) and ADN subgroup ($b = 0.29$, $p = 0.002$, adjusted-$R^2 = 0.05$), but not in the HC ($b = 0.15$, $p = 0.27$, adjusted-$R^2 = 0.03$).

Associations between functional network connectivity and MEM

We tested the associations between INC of each RSN and MEM. The whole cohort revealed a positive association between DMN INC and MEM. Furthermore, MEM score was negatively associated with inter-network connectivity between DMN and SAL (Table 2, Fig. 1B, and Supplementary Figure 2A). However, in the FPN and the SAL, MEM scores were negatively associated with INC in frontal and parietal brain regions (Table 2, Fig. 1B, and Supplementary Figures 2B and 2C).

Associations between CRM and intrinsic network connectivity in cognitive networks

CRM was positively associated INC within the DMN, particularly in the posterior cingulate cortex and the precuneus (Table 3, Fig. 1C, and Supplementary Figure 3A). In a subgroup analysis, CRM was positively associated with anti-correlation between the FPN and medial prefrontal cortex in the entire cohort and the A+T–N– group (Table 3, Fig. 1C, and Supplementary Figure 3C) and between the SAL and the DMN in the A+T+N+ group (Table 3, Fig. 1C, and Supplementary Figure 3C). We found a negative association of SAL in occipital regions in the A+T/N+ group, showing no spatial overlap with the cognitive RSNs. Notably, no associations were found in the ADN.

To test the specific effects of CRM on network FC, we adjusted the models additionally for years of education. CRM revealed positive associations with INC of the DMN and FPN only in the entire cohort when accounted for years of education (Supplementary Table 2 and Supplementary Figure 4A, B). Moreover, years of education revealed no association with INC of any RSN in the general linear model, even after CRM was excluded. Like education, LEQ-total score did not show any association with FC with and without CRM as covariable. We found no significant associations between the CRM and INC of any networks when the number of edu-

Table 1
Demographic and clinical characteristics of the study cohort. Mean values are presented if not indicated otherwise

	HC (N = 112)	ADN (N = 206)	p (HC versus ADN	ADN			p (overall)
				A+T–N– (N = 106)	A+T/N+ (N = 28)	A+T+N+ (N = 72)	
Age (SD)[a]	69 (6)	72 (6)	<0.001	70 (6)[h]	71 (6)	74 (6)[e,f]	<0.001
Sex (female, N/%)[b]	52 (46.4)	101 (49)	0.66	49 (46)	14 (50)	38 (53)	0.81
Years of formal education (SD)[a]	15 (3)	14 (3)	0.16	14 (3)	14 (3)	14 (3)	0.22
APOE ε4-allele (carrier, N/%) [b]	18 (16)	113 (55)	<0.001	44 (42)[e,h]	17 (61) [e]	52 (72)[e,f]	<0.001
APOE ε2-allele (carrier, N/%)[b]	20 (18)	20 (10)	0.04	12 (11)	3 (11)	5 (0.07)	0.16
MMSE (SD)[a]	29 (1)	27 (3)	<0.001	28 (2)[h]	28 (2)[h]	26 (3)[e,f,g]	<0.001
CDR-sb (SD)[a]	0 (0.1)	2 (2)	<0.001	1 (1)[e]	2 (2)[e]	3 (2)[e,f]	<0.001
Mean hippocampal volume (mm^3, SD)[c]	3149 (30)	2820 (32)	<0.001	2944 (42)[e,h]	2807 (87)[e]	2584 (49)[e,f]	<0.001
Mean cortical thickness (cm, SD)[c]	2.71 (0.1)	2.6 (0.01)	<0.001	2.64 (0.1)[e,h]	2.62 (0.3)[e]	2.53 (0.02)[e,f]	<0.001
CSF biomarkers							
$A\beta_{42}$ (pg/ml, SE)[c]	898 (18)	428 (13)	<0.001	450 (12)[e]	419 (23)[e]	415 (14)[e]	<0.001
tTau (pg/ml, SE)[c]	299 (8)	524 (22)	<0.001	302 (11)[g,h]	584 (20)[e,f]	904 (33)[e,f]	<0.001
PTau (pg/ml, SE)[c]	43 (0.7)	68 (3)	<0.001	42 (1)[g,h]	68 (2)[e,f]	113 (5)[e,f]	<0.001
Global cognitive composite (Z-score, SE)[d]	0.4 (0.04)	–0.44 (0.06)	<0.001	–0.19 (0.09)[e,h]	–0.19 (0.17)[e,h]	–0.97 (0.1)[e,f,g]	<0.001
MEM (Z-score, SE)[d]	0.51 (0.04)	–0.56 (0.07)	<0.001	–0.12 (0.09)[e,h]	–0.34 (0.19)[e,h]	–1.29 (0.11)[e,f,g]	<0.001
CRM (Residuals, SE)[c]	–0.007 (0.05)	0.004 (0.67)	0.83	–0.04 (0.06)	0.25 (0.14)	–0.03 (0.08)	0.15
LEQ-total[a*†] (SD)	120 (25)	115 (27)	0.38	115 (25)	115 (28)	114 (28)	0.74

[a]Kruskal-Wallis-test, [b]Chi-Square-test, [c]Analysis of Covariance tests were conducted, adjusting for age, sex, and sites. Means and frequencies are shown, [d]Analysis of Covariance tests were conducted, adjusting for age, sex, years of education, and site, [e]Bonferroni-$p < 0.05$ versus HC, [f]Bonferroni-$p < 0.05$ versus A+T–N–, [g]Bonferroni-$p < 0.05$ versus A+T/N+, [h]Bonferroni-$p < 0.05$ versus A+T+N+. [†]LEQ-total values are available for $N_{HC} = 63$, $N_{ADN} = 123$, $N_{A+T-N-} = 63$, $N_{A+T/N+} = 17$ and $N_{A+T+N+} = 46$ participant. HC, healthy controls; ADN, Alzheimer's disease neuropathological-continuum; $A\beta_{42}$, Amyloid-beta 42; tTau, total tau; pTau, phosphorylated tau 181; CRM, cognitive reserve marker; MEM, memory cognitive composite score; MMSE, Mini-Mental State Examination; CDR-sb, Clinical Dementia Ratio – sum of boxes; LEQ, lifetime experiences questionnaire; SD, standard deviation; SE, standard error. *Total score of LEQ was available in $n = 186$ ($n = 63$ in HC, $n = 123$ in A+) participants.

Table 2
Associations between memory cognitive composite score and intrinsic network connectivity on whole brain level. *Network regions identified through the independent component analysis. **Atlas regions in the Harvard-Oxford Atlas

RSN	Cluster (x,y,z)	Cluster size (voxels)	p-FDR	Overlapping network ROI* (x,y,z)	Main atlas region** (voxel size)
DMN	–04 –74 +40	483	<0.001	DMN, $n = 7675$ (0,–51,34)	Precuneus (453)
	–52 +28 +14	257	0.002	SAL, $n = 3433$ (–44,12,20)	l tri-IFG (176)
	+58 +34 +04	212	0.006		r tri-IFG (153)
	–04 –26 +32	180	0.01		PC (153)
	–04 –42 +46	122	0.03		Precuneus (98)
FPN	–04 +52 +36	127	0.042		l SFG (60)
					Precuneus (56)
SAL	–04 –46 +56	165	0.046		r PostCG
DAN	n.s.				

RSN, resting-state network; DMN, default mode network; FPN, frontoparietal network; SAL, salience network, DAN, dorsal attention network; FDR, false-discovery rate; tri-IFG, inferior frontal gyrus, pars triangularis; PC, cingulate gyrus, posterior division; SFG, superior frontal gyrus: PostCG, postcentral gyrus; l, left; r, right.

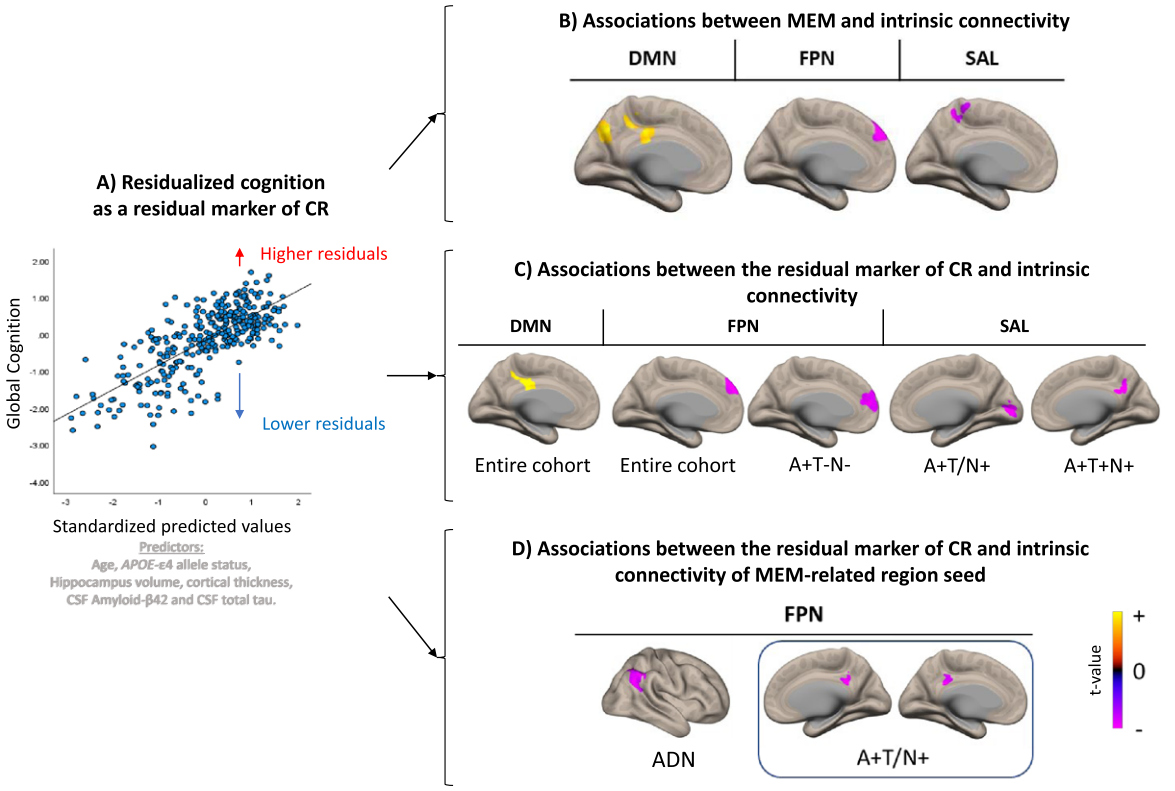

Fig. 1. A) Estimation of cognitive reserve marker as residuals in a multilinear regression model. B) Associations between memory cognitive composite score and intrinsic network connectivity to derive MEM-related seed regions. C) Associations between CRM and intrinsic connectivity of resting-state networks in whole brain in the entire cohort and A/T/N subgroups. D) Associations between CRM and functional connectivity of seeds of MEM-related regions in each resting-state network in the entire cohort and A/T/N subgroups. The color bar represents *t*-values. MEM, memory cognitive composite score; DMN, default mode network; FPN, frontoparietal network; SAL, salience network; DAN, dorsal attention network; FDR, false-discovery rate; CRM, cognitive reserve marker; ADN, Alzheimer's disease neuropathological-continuum; p-FDR, FDR-corrected *p*-value.

Table 3
Associations between CRM and intrinsic connectivity of resting-state networks on whole brain level in the entire cohort and in the A/T/N groups. *Network regions identified through the independent component analysis. **Atlas regions in the Harvard-Oxford Atlas

	RSN	Cluster (x,y,z)	Cluster size (voxels)	p-FDR	Overlapping network ROI (x,y,z)*	Main atlas region (voxel size)**
Entire cohort	**DMN**	–04 –26 +32	170	0.02	DMN, size = 7675 voxels (0,–51,34)	PC (103) Precuneus (38)
	FPN	–04 +56 +32	217	0.003	–	l SFG (100) l FP (51)
	SAL	n.s.				
	DAN	n.s.				
A+T–N–	DMN	n.s.				
	FPN	–10 +56 +14	293	<0.001	–	l FP (112)
	SAL	n.s.				
	DAN	n.s.				
A+T/N+	DMN	n.s.				
	FPN	n.s.				
	SAL	+10 –84 +04	115	0.02	–	r ICC (81)
	DAN	n.s.				
A+T+N+	DMN	n.s.				
	FPN	n.s.				
	DMN	n.s.				
	SAL	+04 –50 +28	120	0.04	DMN, size = 7675 voxels (0,–51,34)	PC (60)

CRM, cognitive reserve marker; DMN, default mode network; FPN, frontoparietal network; SAL, salience network; DAN, dorsal attention network; ROI, region of interest; FDR, false discovery rate; p-FDR, FDR-corrected *p*-value; SFG, Superior Frontal Gyrus; FP, Frontal Pole; PC, Cingulate Gyrus, posterior division; ICC, Intracalcarine Cortex; l, left; r, right.

cation years was replaced with LEQ-t (available data of participants $n = 186$).

Associations between CRM and FC of mem-related seed regions

A seed-to-voxel analysis revealed a negative association of CRM with FC of MEM-related region seed of the FPN with the right angular gyrus, a lateral DMN region (Table 4, Fig. 1D, and Supplementary Figure 5B) in the ADN group. More, CRM was associated with lower FC of the FPN seed region with the DMN (posterior cingulate cortex) in the A+T/N+ group (Table 4, Fig. 1D, and Supplementary Figure 5B).

DISCUSSION

The present study provides further evidence on the neural underpinnings of CR, i.e., neurobiological changes associated with the resting-state functional connectivity alteration estimated using residualized cognitive performance in INC of the RSNs of interest. The CRM was associated with commonly used socio-behavioral CR proxies, including years of education, and the LEQ total score, assessing mental activity levels over the lifespan. Our experiment extends previous research by including the aspect of biomarker-defined A/T/N groups, revealing neural associations of residual CRM, especially in the earlier AD stages (A+T/N– and A+T/N+). In ADN, higher CRM is associated with INC changes within and between cognitive RSNs, particularly the DMN, the FPN and the SAL. Our findings support previous findings suggesting that reserve has its most considerable impact in the transitional stage between physiological aging and advanced neurodegeneration [3, 54].

The observed positive associations between INC changes and memory scores align with the literature, showing similar associations in the DMN, particularly in the posterior cingulate cortex and precuneus [50, 55]. We found increased network connectivity in the DMN and FPN with higher performance in the memory domain and increased connectivity between networks of the posterior DMN regions and the FPN. We also found negative associations between memory composite scores, between-network connectivity for SAL-DMN and SAL-FPN and between the FPN and the anterior DMN. In contrast, no association was observed between memory and INC in the DAN.

We found higher INC in the DMN in subjects with higher CR when tested in the entire cohort. Here, A/T/N groups revealed different associations between INC and CRM, with a higher anti-correlation between DMN and SAL only found in the A+T+N+

Table 4
Associations between CRM and seed-to-voxel functional connectivity of memory domain score related regions for each resting-state network in the ADN and in A/T/N groups. *Network regions identified through the independent component analysis. **Atlas regions in Harvard-Oxford Atlas

	RSN with MEM-related seed connectivity	Cluster (x,y,z)	Cluster size (voxels)	p-FDR	Overlapping network ROI (x,y,z)*	Main atlas region (voxel size)**
ADN	DMN	n.s.				
	FPN	+52 –46 +50	779	<0.001	FPN, $n = 2321$ voxels (44,–53,46) DMN, $n = 1140$ voxels (49,–58,30)	r AG (525) r sLOC (132) r pSMG (94)
	SAL	n.s.				
	DAN	n.s.				
A+T–N–	DMN	n.s.				
	FPN	n.s.				
	SAL	n.s.				
	DAN	n.s.				
A+T/N+	DMN	n.s.				
	FPN	0 –42 +32	120	0.01	DMN, $n = 7675$ voxels (0,–51,34)	PC (111)
	SAL	n.s.				
	DAN	n.s.				
A+T+N+	DMN	n.s.				
	FPN	n.s.				
	SAL	n.s.				
	DAN	n.s.				

CRM, cognitive reserve marker; ADN, Alzheimer's disease neuropathological-continuum; DMN, default mode network; FPN, frontoparietal network; SAL, salience network; DAN, dorsal attention network; AG, angular gyrus; sLOC, lateral occipital cortex, superior division; pSMG, supramarginal gyrus, posterior division; PC, cingulate gyrus, posterior division; ROI, region of interest; FDR, false discovery rate; p-FDR, FDR-corrected *p*-value.

group. Higher INC in the DMN might contribute to CR when disruptions in the functional network due to AD-related neurodegenerative changes occur. Therefore, the associations between CRM and INC within the DMN may suggest inter-individual variability in network properties, pointing towards a possible neural representation of CR. More, the INC of the FPN showed a lower FC in the medial frontal region, also part of the DMN [55], suggesting a possible association between CRM and DMN-FPN anti-correlation. Also the seed-to-voxel analyses in the present study revealed associations of CRM with FC of MEM-related seed region in FPN anti-correlations between FPN and DMN in ADN and A+T/N+ subgroups in right lateral regions and medial regions of DMN, respectively. In line with these findings, a previous study suggested a CR-related higher anti-correlation between DMN and the left frontal cortex (i.e., Brodmann area 6/44), a hub region of FPN [26]. Previous studies also proved that more efficient networks are associated with higher CR, particularly involving regions in the DMN [22, 23, 56] and FPN [27, 57].

Our findings support the major role of the FPN in CR and, more precisely, in neural compensation. In previous work, an association between CR proxies such as education and functional connectivity of FPN was found in preclinical AD, i.e., mild cognitive impairment [54]. However, another study suggested no association between the activity of FPN and increased compensation, as no temporary changes in FPN activity were observed with disease progression [27]. Besides their role in CR, FPN and FPN-DMN connectivity coupling might also play a more general protective role, with proven associations for CR and other lifestyle factors such as sleep [58]. Similarly, the results of the present study show differences between the entire cohort and individuals in ADN, suggesting compensatory changes.

Interestingly, the association between CRM and FC remained significant for INC of the DMN after analysis was accounted for education in contrast to the anti-correlation between DMN and FPN in the entire cohort. Additionally, CRM was associated with higher INC within the FPN when the general linear model was adjusted for education. However, all associations between CRM and FC were no longer significant when LEQ-t was accounted for. This finding might suggest that the CRM can predict inter-individual FC differences beyond education, while LEQ-t removed the associations between CRM and FC. Therefore, we speculate that LEQ-t can more effectively estimate the residualized cognition than

years of education alone. In line with this observation, we reported in our previous study that LEQ predicts FC changes within DMN, while years of education revealed no association with DMN connectivity [59]. An alternative explanation can be the potential loss of statistical power for LEQ due to missing data.

The socio-behavioral proxies revealed no significant associations with INC in any RSN, even when CRM was excluded from the statistical model. These findings might indicate a unique effect of residualized cognition, i.e., CRM, while capturing the FC alterations related to CR. These findings align with a previous report defining residual approaches as a resilience measure apart from socio-behavioral proxies [60]. However, the residualized cognitive reserve approach can estimate the inter-individual variance possibly partly due to the lifetime experiences [32] and, therefore, might be not only unique but also more suitable. Future studies are needed to identify the relationship between both approaches to measuring CR.

Our data suggest also that FC in the pre-supplementary motor area and the anteromedial prefrontal cortex are associated with the cognitive reserve in ADN, considering the ICA results for FPN. The first region has been described in the cognitive motor control network. It is involved in complex processes such as learning and cognitive functions [61], while the latter was identified as critical for specific components of social interpretation and behavioral interactions [62].

A recent interventional study identified the effects of cognitive intervention, showing improved FPN activity and better maintenance of DMN activity in amnestic mild cognitive impairment after a vision-based speed of processing training [63]. This pilot study provides an approach to explaining the functional neural alterations associated with CR and demonstrates the practical value of the concept for developing effective intervention strategies against cognitive decline. Other non-invasive stimulation techniques, such as transcranial magnetic stimulation and focused ultrasound pulse stimulation, may have similar beneficial effects on RSNs [64, 65].

A limitation of our work is the cross-sectional study design, precluding firm conclusions on causality. Moreover, an important cohort-relevant limitation is that the participants grouped as AD continuum might underrepresent participants with moderate and severe AD dementia. However, due to relatively large group sizes, our results are sufficiently powered to support the validity of the observed associations. Future studies with longitudinal datasets are needed to examine causal relationships between functional network measures and residual CRM. We recommend a further characterization of residual CRM in biomarker-stratified cohorts in future studies. As the residual approach has been studied using different statistical approaches and modalities [26], it is less established compared to socio-behavioral proxies of CR; this shortcoming should be addressed in future studies. However, we conducted regression analyses to validate the residual approach to investigate the associations between CRM, education, and lifelong experiences.

To conclude, our results advance the understanding of the neurobiological substrates of CR by delineating mechanisms of neural implementation in functional RSNs. The detailed characterization of CRM-related network differences among individuals with AD pathology and controls will be relevant for designing future clinical trials and preventive strategies in AD.

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CONFLICT OF INTEREST

Ersin Ersoezlue, Boris-Stephan Rauchmann, Maia Tatò, Julia Utecht, Carolin Kurz, Jan Häckert, Selim Guersel, Lena Burow, Gabriele Koller, Sophia Stöcklein, Daniel Keeser, Boris Papazov, Marie Totzke, Tommaso Ballarini, Frederic Brosseron, Katharina Buerger, Peter Dechent, Laura Dobisch, Michael Ewers, Klaus Fliessbach, Wenzel Glanz, John Dylan Haynes, Michael T Heneka, Daniel Janowitz, Ingo Kilimann, Luca Kleineidam, Christoph Laske, Franziska Maier, Matthias H Munk, Oliver Peters, Alfredo Ramirez, Sandra Röske, Nina Roy, Klaus Scheffler, Anja Schneider, Björn H Schott, Annika Spottke, Eike Jakob Spruth, Stefan Teipel, Chantal Unterfeld, Michael Wagner, Xiao Wang, Jens Wiltfang, Steffen Wolf-

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Robert Perneczky and Stefen Teipel are Editorial Board Members of this journal but were not involved in the peer-review process nor had access to any information regarding its peer-review.

DATA AVAILABILITY

The data supporting the findings of this study are available on reasonable request for any qualified investigator for purposes of replicating procedures and results by the corresponding author. The data are not publicly available due to legal, privacy or ethical restrictions.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-220464.

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Anhang A: Paper III - Resting-state network alterations differ between Alzheimer's disease atrophy subtypes (Cereb. Cortex 2021)

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ORIGINAL ARTICLE

Resting-State Network Alterations Differ between Alzheimer's Disease Atrophy Subtypes

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Abstract

Several Alzheimer's disease (AD) atrophy subtypes were identified, but their brain network properties are unclear. We analyzed data from two independent datasets, including 166 participants (103 AD/63 controls) from the DZNE-longitudinal cognitive impairment and dementia study and 151 participants (121 AD/30 controls) from the AD neuroimaging initiative cohorts, aiming to identify differences between AD atrophy subtypes in resting-state functional magnetic resonance imaging intra-network connectivity (INC) and global and nodal network properties. Using a data-driven clustering approach, we identified four AD atrophy subtypes with differences in functional connectivity, accompanied by clinical and biomarker alterations, including a medio-temporal-predominant (S-MT), a limbic-predominant (S-L), a diffuse (S-D), and a mild-atrophy (S-MA) subtype. S-MT and S-D showed INC reduction in the default mode, dorsal attention, visual and limbic network, and a pronounced reduction of "global efficiency" and decrease of the "clustering coefficient" in parietal and temporal lobes. Despite severe atrophy in limbic areas, the S-L exhibited only marginal global network but substantial nodal network failure. S-MA, in contrast, showed limited impairment in clinical and cognitive scores but pronounced global network failure. Our results contribute toward a better understanding of heterogeneity in AD with the detection of distinct differences in functional connectivity networks accompanied by CSF biomarker and cognitive differences in AD subtypes.

Key words: Alzheimer's disease, brain structure, graph theory, independent component analysis, resting-state connectivity

Introduction

Alzheimer's disease (AD) shows considerable heterogeneity in central disease characteristics among individual patients, who may differ in their cognitive profiles (Scheltens et al. 2017) and biomarker patterns (Mitelpunkt et al. 2020). Postmortem studies separating groups with distinguishable atrophy patterns and histopathological features (Murray et al. 2011; Janocko et al. 2012) suggest the existence of biologically distinct AD subtypes, supported by evidence from magnetic resonance imaging (MRI), tau positron-emission-tomography (PET) (Whitwell et al. 2018), and clinicopathological research (Whitwell et al. 2012).

An MRI-based classification of subtypes can be achieved by visual atrophy ratings (Persson et al. 2017; Ferreira et al. 2019) or data-driven methods (Noh et al. 2014; Hwang et al. 2016; Zhang et al. 2016; Dong et al. 2017; Park et al. 2017). Most studies, including those in prodromal disease (Ten Kate et al. 2018), subdivide AD atrophy patterns into 1) a typical subtype with accentuated pathology of the hippocampus and association cortex; 2) a limbic predominant subtype with atrophy comprising the limbic system, including the hippocampus; 3) a hippocampal sparing subtype; and 4) a minimal atrophy subtype (Ferreira et al. 2020). These AD subtypes differ in their clinical progression rate, neurocognitive scores, years of education, disease duration, genotype, and cerebrospinal fluid (CSF) biomarker profiles (Ten Kate et al. 2018; Ferreira et al. 2020); further research is warranted to better characterize the underlying pathophysiological differences. To our best knowledge, differences in functional connectivity of resting-state networks (RSNs) between AD subtypes together with neurocognitive and biomarker data have not been explored yet. Furthermore, most previous studies classified patients based on clinical data rather than biomarker information, resulting in heterogeneous datasets. Here, we minimized heterogeneity and potential misdiagnoses by using a biomarker-based classification scheme informed by clinical diagnoses (Jack Jr et al. 2018).

The widespread loss of cortical neuronal connections in AD causes disruptions of brain connectivity (Braskie et al. 2010). Resting-state functional MRI can quantify the degeneration of the cerebral functional architecture and is widely used to investigate intrinsic large-scale neural networks (Biswal et al. 2010). Coherent patterns in spontaneous fluctuations of the blood oxygen level depended (BOLD) signal represent temporarily stable and reproducible intrinsic brain networks, overlapping with individual cognitive and behavioral characteristics (Yeo et al. 2011). The decline in functional connectivity is associated with disease progression and is found typically in AD in the default-mode network (DMN), linked to episodic memory processing (Greicius et al. 2004) and covering hotspots of amyloid-β (Aβ) and tau pathology (Buckner et al. 2005).

Graph theory is a framework used to characterize the behavior of complex brain networks (Bullmore and Sporns 2009). Connectome-based analyses allow measuring network

segregation (i.e., "clustering coefficient," "modularity," and "transitivity") and integration (i.e., "global efficiency" and "degree"). Global efficiency, modularity, and transitivity relate to large-scale networks, whereas clustering coefficient and degree characterize network properties at a local level (Watts and Strogatz 1998; Supekar et al. 2008). On a nodal level, highly connected regions, referred to as hub regions, are of primary interest. Regions with a high number of connections can be detected by calculating the degree (Farahani et al. 2019). Previous studies in AD revealed decreased network segregation measures (Supekar et al. 2008) and decreased measures of network integration compared with controls (Sanz-Arigita et al. 2010). In addition, clustering coefficient and modularity are decreased in AD (Brier et al. 2014).

Recently, differences in structural connectivity (Ferreira et al. 2019) and cognitive performance (Ten Kate et al. 2018) between different AD subtypes have been characterized. However, alterations in functional connectivity remain to be explored. Here, we aimed to explore heterogeneity in network properties in the DMN and other RSNs between distinct AD subtypes to investigate how cognitive and AD biomarker differences are associated with these functional network alterations.

Methods and Materials

Data included in this study originate from datasets of two independent study cohorts. The first dataset was obtained from the AD neuroimaging initiative (ADNI) launched in October 2004 (ClinicalTrials.gov IDs: NCT02854033, NCT01231971). The second dataset was obtained from the Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE)-longitudinal cognitive impairment and dementia study (DELCODE), an observational brain imaging cohort (German Clinical Trials Register: DRKS00007966). Per ADNI and DELCODE protocols, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. Experiments were undertaken with the understanding and written consent of each subject. All local institutional review boards and ethical committees approved the study protocol (Lancichinetti and Fortunato 2012).

Participants

The AD and control groups were defined considering Aβ status and clinical dementia rating (CDR) score. Participants were included based on the availability of T1-weighted structural MRI, resting-state functional MRI, and Aβ status information.

The participants in the ADNI dataset were recruited for the ADNI2, ADNI-go, and ADNI3 convenience cohorts, details about the general ADNI inclusion and exclusion criteria can be found in the ADNI procedures manual available online (https://adni.loni.usc.edu/wp-content/uploads/2008/07/adni2-procedures-manual.pdf). Aβ-positivity in ADNI was defined according to established cut-points as CSF Aβ1–42 concentration < 980 pg/mL (Galasko et al. 2019), or 18F-AV-45 or 18F-Florbetaben Aβ-PET normalized composite score with a cutoff > 1.11 or > 1.08 standardized uptake value ratio, respectively (Landau et al. 2013), resulting in the ADNI dataset of $n = 160$. After quality assessment and preprocessing of the MRI data, $n = 9$ participants did not meet the predefined image quality criteria (for details section see MRI Preprocessing) and were excluded from the subsequent analyses, resulting in a final dataset of $n = 151$ participants (mean age = 75 years, 84 females), including $n = 121$ Aβ-positive and CDR ≥ 0.5 AD patients (mean age = 75 years, 63 females), and $n = 30$ Aβ-negative and CDR = 0 controls (mean age = 77 years, 21 females).

In total, 171 participants in the DELCODE dataset met the inclusion criteria. $N = 5$ participants did not meet the predefined image quality criteria and were excluded from all further analyses, resulting in a final cohort of $n = 166$ (mean age = 72 years, 93 females). Aβ-positive participants with CSF Aβ1–42 < 496 pg/ml (Jessen et al. 2018) and CDR ≥ 0.5 were defined as AD ($n = 103$, mean age = 74 years, 57 females), whereas Aβ-negative participants were defined as healthy controls (HC) with CSF Aβ1–42 > 496 pg/ml and CDR = 0 ($n = 63$, mean age = 69 years, 32 females).

MRI Acquisition

The subjects included in the present study were scanned at various sites with 3T MRI scanners manufactured by GE Healthcare, Philips Medical Systems, or Siemens Healthineers. The Alzheimer's Disease Neuroimaging Initiative (ADNI) MRI protocol is reported elsewhere (http://adni.loni.usc.edu/methods/mri-tool/mri-acquisition/). DELCODE MRI scanning was performed at nine different DZNE imaging sites on Siemens Healthineers 3T MRI scanners, using synchronized acquisition parameters. We included T1-weighted MPRAGE sequences (repetition time [TR], 2500 ms; echo time [TE], 4.37 ms; flip angle [FA], 7°; and isotropic voxel size, 1 mm) in our analyses. FMRI imaging was performed using the following parameters: DELCODE: 180 volumes; FoV, 224 × 224 × 165 mm; TR, 2580 ms; TE, 30 ms; FA, 80°; isotropic voxel size, 3.5 mm; 7 min 54 s and ADNI: 200 volumes; FoV, 220 × 220 × 160 mm; TR, 3000 ms; TE, 30; FA = 90°; and isotropic voxel size: 3.4 mm; 10 min.

MRI Preprocessing

Every scan was visually inspected by an experienced radiologist for completeness, cuts, subject motion, and other artifacts (e.g., "blurring," "echoes," "ghosting"). Following this step, the image was classified as "usable, questionable, and unusable." We included only images classified as usable in the analysis.

Brain atrophy was analyzed using FreeSurfer version 6 (http://surfer.nmr.mgh.harvard.edu/). All T1-weighted images were processed in the FreeSurfer segmentation recon-all pipeline (Fischl et al. 2002). Segmentations were visually checked for accuracy and corrected if necessary.

Functional connectivity analysis was performed using the CONN-fMRI Functional Connectivity Toolbox (V17, www.nitrc.org/projects/conn) and SPM 12 (www.fil.ion.ucl.ac.uk/spm/). The default preprocessing pipeline for volume-based analyses was used, comprising realignment, slice-time correction, segmentation and structural and functional normalization, ART-based outlier detection, and functional smoothing using a 6-mm kernel (https://web.conn-toolbox.org/fmri-methods/preprocessing-pipeline). Temporal filtering was performed to remove physiological noise. Assessment of motion in both cohorts revealed comparable results (DELCODE: 0.01 ± 0.12 [79.6% match with null hypothesis]; ADNI: 0.02 ± 0.12 [80.1% match with null hypothesis]). After preprocessing, region-of-interest (ROI)-based intrinsic connectivity was obtained with bivariate correlation matrices in cortical and subcortical ROIs, using the multimodal Brainnetome (BN) atlas (Fan et al. 2016), registered to the functional image. Correlation coefficients were Fisher-r-to-z-transformed consecutively.

AD Atrophy Subtype Identification

For subtype classification, individual cortical surfaces obtained from each participant's T1-weighted MRI using FreeSurfers recon-all were registered to the FreeSurfer standard subject template (fsaverage6) and resampled to 40 962 vertices for each hemisphere to account for intersubject variability of brain shapes and size (Park et al. 2017). Subsequent analyses were performed using in-house MATLAB (TheMathWorks, Inc.) scripts in both cohorts.

To obtain an atrophy z-score vector, representing the atrophy pattern of each AD subject, the mean cortical thickness value from every vertex in the AD subjects was subtracted from the cortical thickness values of every vertex in the controls divided by the standard deviation in both hemispheres. Atrophy z-score vectors were consecutively concatenated and a similarity matrix of correlation coefficients between the obtained atrophy z-score vectors of any two AD subjects was calculated.

To identify atrophy subtypes in the AD cohorts based on the correlation of atrophy pattern between any two subjects, an unsupervised cluster detection approach using the Louvain community analysis method implemented in the brain connectivity toolbox was applied (Rubinov and Sporns 2010). This subtyping approach uses the similarity correlation matrix and has previously shown high reproducibility and strong associations with cognitive performance (Park et al. 2017). This unsupervised clustering approach is suggested to be less vulnerable to sampling bias compared with hierarchical clustering approaches. The outcomes in hierarchical clustering tend to cluster based on the overall similarity of the cortical thickness rather than cortical atrophy patterns so that the chosen approach is suggested to be more sensitive to cortical atrophy (Park et al. 2017). In addition, the approach showed excellent reproducibility and the Louvain method was shown to be suitable for high-dimensional data (Blondel et al. 2008).

To determine the ideal cluster number, we tested three-cluster and four-cluster solutions where four-cluster solutions were generally more suitable to subtypes previously found in neuroimaging datasets (Ferreira et al. 2017; Ten Kate et al. 2018; Ferreira et al. 2019), with several studies report four subtypes in a recent review by Ferreira et al. (Ten Kate et al. 2018; Ferreira et al. 2020).

We modified the approach using a consensus community structure approach to obtain stable results through 1000 iterations with a correction of individual-level modular decomposition (Lancichinetti and Fortunato 2012). The level of subtyping can be controlled by the gamma value, a resolution parameter of the Louvain community structure analysis controlling the number of clusters, with a smaller value resulting in a smaller number of subtypes (Blondel et al. 2008). The gamma value was controlled, obtaining subtyping results equivalent to previous imaging and postmortem studies (Murray et al. 2011; Whitwell et al. 2012; Ten Kate et al. 2018).

Dice Overlap

To quantify the overlap of atrophic regions between the two datasets, we compared the regions after setting the threshold level of uncorrected log-$p > 1.31$ ($P < 0.05$) on vertex-wise overlay imaging data derived from the statistical comparison with controls. We calculated dice coefficients (DCEs) between atrophy subtypes from both datasets in MATLAB.

Functional Connectivity Analysis

We analyzed functional connectivity characteristics of the atrophy subtypes in seven cortical intrinsic functional connectivity networks (Yeo et al. 2011). Within each network, intra-network connectivity (INC) composite score was calculated by averaging the network ROIs (based on the cortical Brainnetome atlas parcellation) functional connectivity Fisher-r-to-z-transformed correlation values (Brier et al. 2012). The ROIs with the nodes used for the functional network analysis are presented in Supplementary Figure 1 and Supplementary Table 2. To investigate the global and local network properties and differences between the different subtypes in the resting-state brain networks, we performed a graph theory network analysis. An undirected network was constructed from the functional connectivity correlation values with subsequent analysis of graph metrics comparing each subtype using permutation-based analysis of covariance (ANCOVA) statistics with Benjamini and Hochberg false discover rate (FDR) correction to control for multiple comparisons in the GraphVar toolbox (Kruschwitz et al. 2015). The following graph metrics were calculated on a global level: 1) global transitivity (referred to as global clustering coefficient), 2) global efficiency, 3) modularity using the Louvain method, and 4) global strength. On a local level 1) local efficiency, 2) degree, 3) clustering coefficient, and 4) betweenness centrality were investigated (Rubinov and Sporns 2010). The visualization of the global and local network properties was obtained using ggplot2 in R (https://www.r-project.org/) and BrainNetViewer (Xia et al. 2013). We showed our findings on the median threshold.

Clinical Characteristics and CSF Biomarkers

The severity of dementia symptoms was quantified using the CDR sum of the boxes (CDR-SoB) score. The cognitive performance was assessed using established cognitive composite scores for memory (MEM) and executive functions (EXEC) in the DELCODE (Jessen et al. 2018) and ADNI (Crane et al. 2012; Gibbons et al. 2012) datasets. In addition, the Mini-Mental-State Examination (MMSE) score is reported given its high relevance in everyday clinical practice. CSF biomarkers were assessed in both cohorts using established commercially available analysis kits, following standardized procedures (Jessen et al. 2018). The CSF concentrations in the ADNI cohort for Aβ-42, p-tau181 was quantified in aliquoted samples, analyzed using the electrochemiluminescence immunoassay Elecsys on a fully automated Elecsys cobas e 601 instrument (Roche Diagnostics GmbH) using a single lot of each reagent for each of the 3 measured biomarkers. In the DELCODE cohort, V-PLEX Aβ Peptide Panel 1 (6E10) Kit (K15200E) and V-PLEX Human Total Tau Kit (K151LAE; Meso Scale Diagnostics LLC), and Innotest Phospho-Tau (181P; 81 581; Fujirebio Germany GmbH) were used.

Statistical Analysis

Statistical differences between AD atrophy subtype groups and HC in each dataset were tested on cortical z-score maps using two-tailed, two-sample unpaired $n = 1000$ permutation-based t-tests in FSL-Permutation Analysis of Linear Models (Winkler et al. 2014), applying threshold free cluster enhancement and controlling for family-wise error rate (FWE); additionally, uncorrected contrasts are reported (both $P < 0.05$).

SPSS (IBM, v25) and R (https://www.r-project.org/) were used for statistical analyses. Subtype group differences in relevant

confounding variables (age, gender, *APOE* genotype, and educational years) were compared with Kruskal–Wallis tests. We detected significant differences in relevant covariates between the subtype groups in the pooled dataset for educational years and gender but not for age or *APOE* genotype. All consequent subtype group comparisons were therefore adjusted for gender and educational years. All fcMRI analyses were adjusted to account for different imaging acquisition sites using several MRI vendors with harmonized protocols in different cohorts. Functional connectivity scores, neurocognitive scores, and CSF biomarker scores were compared in the entire cohort as well as between subtypes using ANCOVA. Post-hoc pairwise comparisons were Bonferroni corrected as appropriate. Results were considered significant at $P < 0.05$ (two-tailed). Deviation from normal distribution was assessed by visual inspection of the data distribution and Shapiro–Wilk test. Deviations from the normality distribution were detected for the functional connectivity and CSF biomarker scores. We transformed these variables into normal scores of ranks using the Rankit's method (Chambers 2018). Cognitive composite scores and CSF biomarkers were z-transformed within each cohort to compare the results independent of the measuring scale.

Comparisons of network properties between the subtypes were performed in the GraphVar Toolbox (Kruschwitz et al. 2015) using nonparametric permutation tests at a range of network thresholds (min = 0.1 to max = 0.4) with a 0.02 interval. Nonparametric analyses were conducted testing against shuffled data with $n = 1000$ permutations. A median threshold of 0.24 was used for comparisons of network measures. There is currently a no broader consensus on what threshold should be reported in graph-based analyses (Garrison et al. 2015). Our decision to report a median threshold was based on the idea to provide the reader with the most representative number as an overview. A random networks/groups FDR correction for multiple permutation comparisons was used at $P < 0.05$ (two-tailed) for global and nodal measures at various network densities.

Data Availability Statement

All ADNI data are deposited in a publicly accessible repository and can be accessed at adni.loni.usc.edu. For the DELCODE dataset, anonymized data analyzed in the current study will be made available upon reasonable request from qualified investigators.

Results

Characteristics of the Cohorts

The characteristics of the ADNI and DELCODE cohorts are presented in Table 1. The AD participants in both cohorts demonstrated comparable sociodemographic and neurocognitive measures, except for years of education, with more years in ADNI. In DELCODE, controls were younger and included a lower proportion of female participants compared with ADNI controls.

Atrophy Pattern in AD Subtypes

In both datasets (DELCODE and ADNI), similar four subtypes were identified, including 1) a medio-temporal predominant subtype (S-MT); 2) a limbic predominant subtype (S-L); 3) a diffuse subtype (S-D); and 4) a mild-atrophy subtype, with relative parahippocampal sparing (S-MA). The differences between the four subtypes within the AD group and compared with the HC are shown in Figure 1A for the ADNI dataset and Figure 1B for the DELCODE dataset. S-MT showed atrophy mainly in the (medial) temporal lobe, while S-L had an atrophy pattern, including the cingulate cortex and parahippocampal brain areas. In contrast, S-D was associated with a diffuse atrophy pattern, including large areas of the neocortex comprising the parietal lobe. The S-MA subtype was characterized by patchy cortical atrophy with a relatively low degree of parahippocampal atrophy. Importantly, cortical atrophy in each of the four subtypes followed a similar pattern in both datasets, with overall more severe atrophy across all subtypes in DELCODE. The spatial overlap of the atrophy subtypes between the two datasets was evaluated using the DCE, showing good overlap for S-MT (DCE = 0.44), S-L (DCE = 0.51), and S-D (DCE = 0.64) and less pronounced overlap for S-MA (DCE = 0.07), most likely explained by the patchy pattern with less atrophy overall.

Clinical, Cognitive and CSF Biomarker Differences between the Atrophy Subtypes

Similar differences in clinical and cognitive scores and CSF biomarkers between the four subtypes were observed in both datasets. Dementia severity measured by CDR was highest in the S-MT and S-D subgroups with lower scores in S-L and S-MA and HC. Concordantly, cognitive performance measured by the MMSE was lowest in S-MT and S-D with higher scores in S-L and S-MA and HC (Table 2). Since the atrophy subtypes showed good overlap and similar clinical characteristics across DELCODE and ADNI, we pooled the participants in each sub-group across the datasets for all subsequent analyses as shown before (Ten Kate et al. 2018).

ANCOVA test revealed significant differences between the subtypes and HC for MEM ($P < 0.001$), EXEC ($P < 0.001$), CSF t-tau ($P < 0.001$) and p-tau181 ($P < 0.001$), and Aβ1–42 ($P < 0.001$). For MEM, post-hoc pairwise comparisons showed lower z-scores in S-MT and S-D compared with S-L and S-MA and HC. A similar pattern was found for EXEC, with lower z-scores in S-MT and S-D compared with S-L and S-MA and HC. CSF t-tau was higher in S-MT and S-D compared with S-L and S-MA and HC; similar differences were also observed for p-tau181 with higher z-scores in S-MT and S-D compared with S-L and S-MA and HC (Fig. 2A). *APOE* genotype did not differ between the subtypes. In the comparison between subtypes, hippocampal atrophy was most prominent in S-MT and S-D. Differences in participant's characteristics, cognitive composite, hippocampal volume, and CSF biomarker z-scores between the subtypes are presented in Table 2. Independent analysis results for both cohorts are shown in Supplementary Table 1.

Intra-network Resting-State Functional Connectivity Differences

Following FDR correction for multiple comparisons assessing the INC in seven resting-state networks, differences between the subtypes and HC in the DMN ($P = 0.035$), LN ($P = 0.035$), dorsal attention network (DAN; $P = 0.035$) and visual network (VN; $P = 0.007$) but not in the frontoparietal network (CON; $P = 0.28$), salience network (SAL; $P = 0.18$)and somatosensory network (SMN; $P = 0.89$) and were detected using ANCOVA test. Subsequent post-hoc comparisons revealed a higher INC of the DMN in S-L versus S-MT ($P = 0.01$), S-L versus S-D ($P < 0.001$) and S-L versus S-MA ($P < 0.02$), higher INC in the DAN in HC versus S-MT ($P = 0.003$), HC versus S-D ($P = 0.001$) and HC versus

Table 1 Characteristics of the two study cohorts (ADNI and DELCODE)

	DELCODE		ADNI			
	AD (*N* = 103)	HC (*N* = 63)	AD (*N* = 121)	HC (*N* = 30)	*P* between AD groups	*P* between HC groups
Age, mean (SD)	74 (6)	69 (5)	75 (8)	77 (8)	0.33[a]	<0.001[a]
Sex, no. female %, (SD)	57 (55)	32 (49)	63 (52)	21 (70)	0.72[b]	<0.001[b]
Years of education, mean (SD)	14 (3)	14 (3)	16 (2)	16 (3)	<0.001[a]	0.07[a]
MMSE, mean (SD)	26 (3)	29 (1)	25 (4)	29 (1)[d]	0.36[a]	0.06[a]
CDR-SoB, mean (SD)	2.7 (2.2)	0	3.2 (2.6)	0	0.06[a]	1[a]
APOE, no. (%) ε4 allele carrier (SD)	66 (64)[d]	9 (14)	68 (56)[c]	6 (21)	0.39[b]	0.64[b]

Abbreviation: APOE, apolipoprotein ε4 genotype.
[a]Kruskal–Wallis test.
[b]Chi-squared-test.
[c]Missing data for *n* = 4 participants.
[d]Missing data for *n* = 1 participant.

S-MA (*P* = 0.04). In the LN, higher INC was revealed in S-MT versus S-MA (*P* = 0.03), S-L versus S-D (*P* = 0.03), S-L versus S-MA (*P* = 0.01) and HC versus S-MA (*P* = 0.01). In the VN INC was higher in HC versus S-MT (*P* < 0.001), HC versus S-D (*P* = 0.001), S-L versus S-MT (*P* = 0.01) and S-L versus S-D (*P* = 0.04). Z-score differences between the subtypes and HC in the pooled dataset are presented in Figure 2B and Table 3. INC differences between HC and subtypes for both cohorts independently are shown in Supplementary Table 3 and Supplementary Figure 2.

AD Subtype Characteristics in Global Network Analysis

In a graph theory analysis of global network properties on whole-brain level, significant differences between the subtypes in global efficiency (*P* < 0.001), strength (*P* < 0.001) and transitivity (*P* < 0.001), but not in modularity (*P* = 0.68) were revealed. On a network level, DMN but not LN showed significant differences between the subtypes for global efficiency (*P* < 0.001), strength (*P* < 0.001) and transitivity (*P* < 0.006), but not modularity (*P* = 0.61).

In post-hoc pairwise comparisons on a global level, S-L showed higher global efficiency and transitivity versus S-MT, S-D. Both were lower in S-MT than in S-MA. Moreover, S-L exhibit lower transitivity versus S-MA, and S-MT lower global efficiency than S-D. Global strength was lowest in S-MT and highest in S-L, with S-L significantly higher than S-MT and S-D and S-MA higher than S-MT, but lower than S-L.

Within the DMN, S-L showed the highest global efficiency versus S-MT, S-D and S-MA. Global efficiency was higher in S-MA than in S-MT. Additionally, S-L had higher transitivity in comparison with S-MT and higher transitivity versus S-D and S-MA. Again, global strength was lowest in S-MT and highest in S-L, with S-L significantly higher than S-MT and S-D and S-MA (Table 4 and Fig. 3).

AD Subtype Characteristics in Nodal Network Analysis

Addressing the main research question of this study (i.e., how local changes in network properties of subtypes are related to characteristics of atrophy patterns), we calculated the nodal measures of betweenness centrality, degree, clustering coefficient and local efficiency on whole-brain level (median threshold = 0.24). Differences in degree (a measure of integration and one of the most important measures of network structure) are shown in Figure 3. The S-L subtype showed a reduced degree in the cingulate gyrus versus S-MT, S-D and S-MA. S-MT exhibited a reduced degree in the caudal area of the right parietal and left temporal lobe versus S-L. Clustering coefficient (indicating resilience against random network damage) was reduced in S-MT versus S-L in multiple ROIs comprising the frontal, temporal, parietal, and occipital lobe. A similar pattern, with pronounced changes in lateral temporal and frontal regions, comprising fewer significant ROIs was observed comparing S-D and S-L. S-MA showed reduced clustering coefficient in frontal and temporal regions versus S-L. Significant differences between the subtypes in clustering coefficient are shown in Figure 3.

To compare the differences of nodal measures within RS networks between the subtypes, we selected the nodes belonging to the DMN, LN, and VN, as these networks show significant differences in functional connectivity between the subtypes. Within nodes of the DMN, differences between the subtypes were found for local efficiency, comprising multiple ROIs in the frontal, temporal and parietal lobe as well as cingulate gyrus and precuneus reduced in S-L and S-MA compared to S-MT with a similar pattern in S-L versus S-D. Local efficiency was reduced in the frontal, parietal, and temporal lobe, including the precuneus in S-MA versus S-L. Clustering coefficient was significantly lower in S-MT and S-D versus S-L in the frontal and temporal lobe, the gyrus cinguli and the precuneus. However, clustering coefficient in S-L differs with S-MA in the frontal and temporal lobes. Degree was lower in the posterior temporal lobe in S-MT versus S-L and S-MA. Betweenness centrality was reduced in the cingulate gyrus in S-L versus S-MT. Nodes belonging to the LN showed significant reductions in local efficiency in the frontal and temporal lobe and the fusiform and parahippocampal gyrus. Nodes belonging to the VN showed in S-MT versus S-MA reduced local efficiency but increased local efficiency in S-L versus S-D in several regions. Clustering coefficient was reduced in S-MT versus S-L, comprising mainly parietal and occipital lobes as well as fusiform, parahippocampal, and cingulate gyri; but increased in S-L versus S-D in parahippocampal and cingulate gyri. Results of nodal graph measures on a network level for the DMN, LN, and VN are summarized in Table 5.

Discussion

Substantial differences between individual AD patients can exist on clinical, cognitive, and biomarker levels. Only recently, the

Table 2 Differences in sociodemographic characteristics, *APOE* genotype, Alzheimer's disease severity, cognitive performance, and CSF biomarker levels between the atrophy subtypes and HC in the pooled dataset

	HC ($n=93$)	S-MT ($n=57$)	S-L ($n=41$)	S-D ($n=78$)	S-MA ($n=48$)	*P*-value (overall)	S-MT versus HC	S-L versus HC	S-D versus HC	S-MA versus HC	S-MT versus S-L	S-MT versus S-D	S-MT versus S-MA	S-L versus S-D	S-L versus S-MA	S-D versus S-MA
							Post-hoc comparison *P*-value									
Age, mean (SD)[a]	72 (7)	73 (8)	75 (6)	75 (6)	74 (7)	0.01	0.54	0.02*	0.01*	0.06	0.3	0.17	0.5	0.7	0.56	0.9
Sex, no. female (%)[b]	53 (57)	40 (70.2)	18 (43.9)	39 (50)	23 (47.9)	0.052	—	—	—	—	—	—	—	—	—	—
Years of education, mean (SD)[a]	15 (3)	14 (3)	15 (3)	15 (3)	16 (3)	<0.001	0.01*	0.45	0.47	0.01*	0.5	0.2	<0.001*	0.6	0.002*	0.002*
APOE, no. (%)[b] ε4 allele carrier[b]	15 (16)	32 (60)	21 (53)	50 (64)	31 (65)	<0.001	<0.001*	<0.001*	<0.001*	<0.001*	0.41	0.65	0.65	0.19	0.22	0.95
CDR-SoB, mean (SD)[c]	0 (0)	3.4 (3)	2.1 (1.8)	3.7 (2.5)	2.0 (1.5)	<0.001	<0.001*	<0.001*	<0.001*	<0.001*	0.11	0.01*	0.12	0.01*	0.93	0.01*
MMSE, mean (SD)[c]	29 (1)	24.8 (4.3)	27.0 (2.7)	24.4 (4.6)	27.5 (2.4)	<0.001	<0.001*	<0.001*	<0.001*	<0.001*	0.03*	0.71	0.002*	0.01*	0.4	<0.001*
CSF Aβ1–42, z-score[f] (SD)[c]	0 (1)	−2.2 (0.4)	−2.1 (0.5)	−2.1 (0.4)	−2.0 (0.5)	<0.001	<0.001*	<0.001*	<0.001*	<0.001*	0.51	0.4	0.18	0.93	0.5	0.49
CSF p-tau181, z-score[d] (SD)[c]	0 (1)	3.3 (3.0)	1.2 (2.2)	4.5 (4.0)	4.4 (5.0)	<0.001	<0.001*	0.02*	<0.001*	<0.001*	0.01*	0.06	0.37	<0.001*	<0.001*	0.4
CSF t-tau, z-score[d] (SD)[c]	0 (1)	2.8 (2.7)	1.6 (2.4)	4.5 (4.1)	4.2 (4.8)	<0.001*	0.001*	0.09	<0.001*	<0.001*	0.11	0.01*	0.21	<0.001*	0.01*	0.25
Mean Hippocampal volume, z-score (SD)[c]	0 (1)	−0.9 (2.0)	0.2 (2.1)	−0.5 (2.1)	−0.8 (1.3)	0.001*	0.03*	0.32	0.12	0.001*	0.01*	0.47	0.24	0.02*	<0.001*	0.047*
MEM, z-score (SD)[c]	0 (1)	−4.2 (2.3)	−2.8 (1.9)	−3.8 (2.2)	−1.6 (1.7)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.16	<0.001*	0.01*	0.3	<0.001*
EXEC, z-score (SD)[c]	0 (1)	−2.9 (1.8)	−2.2 (1.5)	−2.8 (1.7)	−1.1 (1.5)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.02*	0.94	<0.001*	0.01*	0.01*	<0.001

Notes: [a]Analysis of covariance with adjustments for age, sex, sites, *APOE* genotype and years of education. Post-hoc pairwise comparisons Bonferroni corrected; [b]Chi-squared test; [c]Analysis of covariance with adjustments for age, sex, *APOE* genotype, sites and years of education; [d]CSF biomarker data in $n=19$ participants were missing ($n=8$ in S-MT, $n=3$ in S-L, $n=6$ in S-D, and $n=2$ in S-MA). *Significant difference $P<0.05$ in post-hoc tests.
Abbreviations: Aβ, amyloid β; p-tau, phosphorylated-tau; t-tau, total-tau; *APOE*, apolipoprotein ε4 genotype.

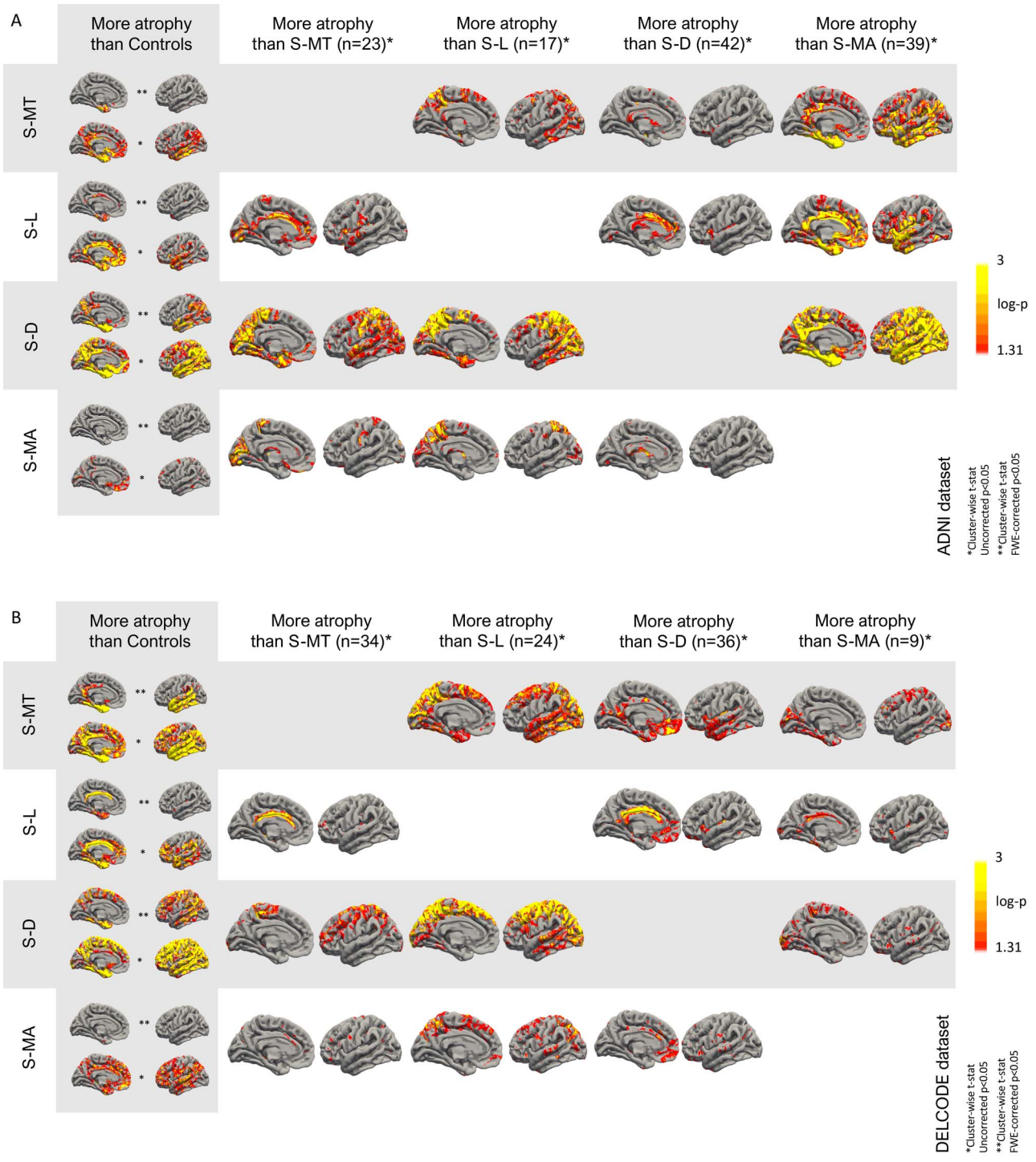

Figure 1. Atrophy regions in Alzheimer's disease subtypes versus healthy control subjects across atrophy subtypes in the ADNI (*A*) and DELCODE (*B*) dataset. *Uncorrected $P < 0.05$; **FWE-corrected $P < 0.05$.

unsupervised classification of atrophy patterns emerged as an approach allowing to distinguish separate AD subtypes with distinct cognitive and biomarker profiles (Ten Kate et al. 2018). However, until now, there was no evidence on brain functional network differences between the subtypes, limiting conclusions about their functional relevance. We addressed this key question by analyzing differences in resting-state functional connectivity networks and graph theory-based brain network measures on a global and nodal level. In addition, we explored biomarker and cognitive differences between atrophy subtypes in two independent datasets from the prospective DELCODE and ADNI cohorts.

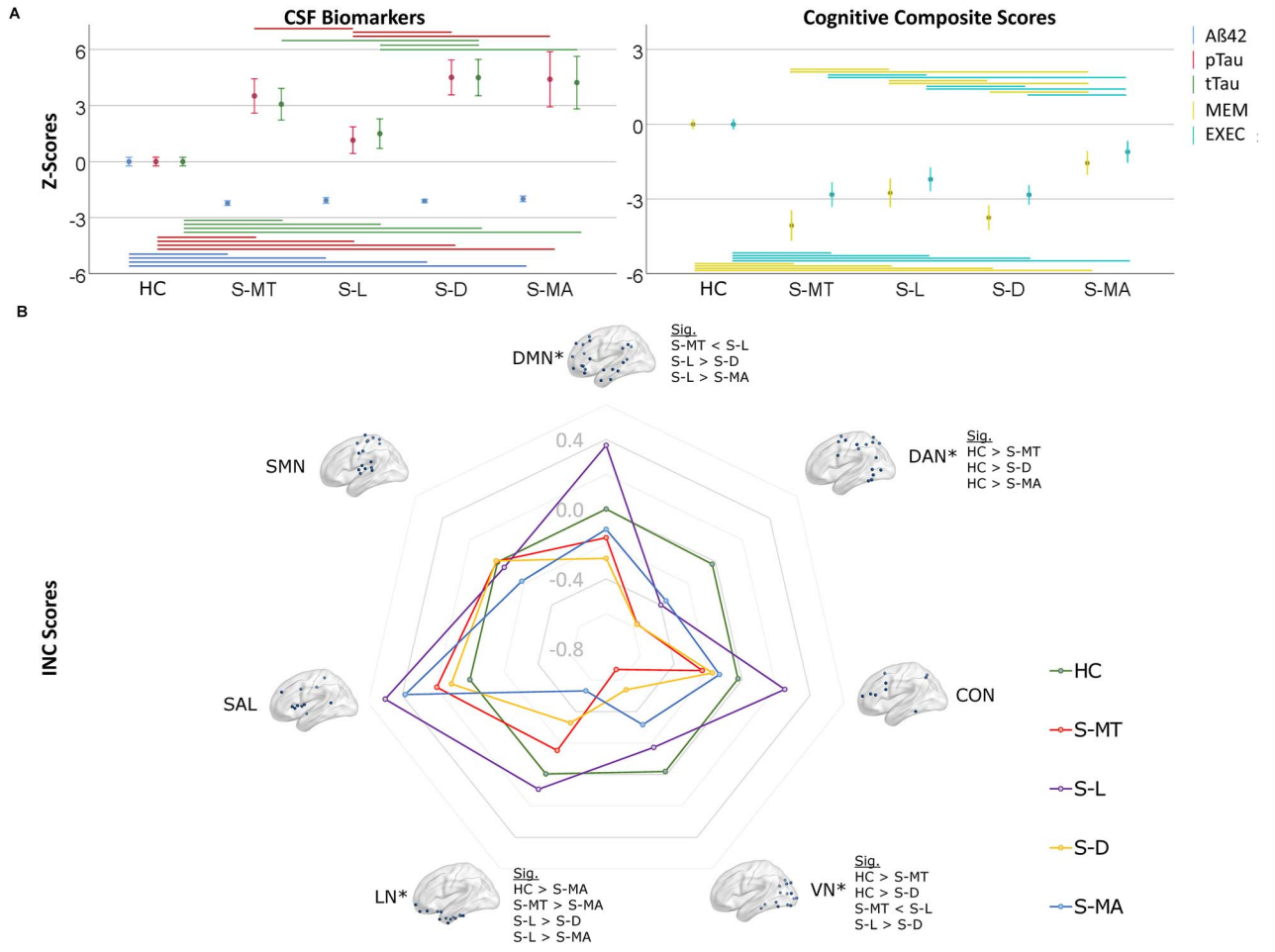

Figure 2. (*A*) Boxplots of the mean cognitive composite and cerebrospinal fluid biomarker normalized scores ±95% confidence interval (in *z*-scores). Significant post-hoc comparisons are shown with a line, top: sig. comparisons among the subtypes, bottom: sig. comparisons between HC and subtypes. (*B*) Spider plot of the estimated mean *z*-scores of INC in the resting-state networks. *Z*-scores of the HC are shown for comparison. *Abbreviations:* Aβ42, amyloid-β42; tTau, total tau; pTau, phosphorylated tau; INC, intrinsic network connectivity; SMN, sensorimotor network; $^{*}P$ (overall) < 0.05; Sig., significantly differing subgroups in post-hoc tests when FDR-corrected two-tailed P (overall) < 0.05.

The main findings of our study are: 1) in line with previous research, using an unsupervised similarity-based clustering algorithm, we identified four distinct subtypes in two independent datasets exhibiting similar brain atrophy patterns as well as clinical and cognitive characteristics; 2) INC exhibit a heterogeneous alteration pattern for the different subtypes compared among each other and to HC, with distinct INC reductions in S-MT and S-D and a divergent pattern of INC in S-L compared with the other subtypes for most RS networks; 3) the S-MT, S-D, and S-MA subtypes showed reduced global network efficiency compared with the S-L subtype; 4) on a nodal level, network analysis revealed reduced degree and clustering coefficient in regions highly overlapping with the atrophy pattern of the particular subtype; 5) CSF biomarkers were substantially more pathological in all subgroups compared with HC, among subgroups S-L exhibited the lowest tau elevations; and 6) Cognitive scores were reduced in all subgroups compared with HC, with S-MT and S-D revealing pronounced cognitive decline, less prominent in S-L and S-MA.

To the best of our knowledge, this is the first study to assess functional network connectivity changes between different atrophy subtypes in AD. We report differences between subtypes for INC in the DMN, VN, and the LN. Previous research described the DMN as one of the networks most vulnerable to degeneration in AD (Greicius et al. 2004; Buckner et al. 2005). A study comparing multiple imaging biomarkers and intrinsic functional connectivity networks in AD demonstrated substantial overlap between atrophic changes and INC in the anterior LN followed by the DMN (Grothe et al. 2016).

Considering the atrophy pattern, clinical and neurocognitive scores and CSF biomarkers using a two-dimensional framework including typicality and severity, S-MT and S-D can be characterized along the severity dimension, whereas S-L and S-MA appear to be different AD entities along the typicality dimension, exhibiting divergent network features with smaller cognitive differences (Ferreira et al. 2020). The pattern of INC changes between the subtypes accordingly suggests advanced network degeneration within the DMN in S-MT and S-D along the severity dimension. The S-L subtype, exhibits the greatest deviation of the INC pattern across several RSNs, including the DMN. Compared with HC, an increased INC was detected in the DMN. Interestingly, the S-MA subtype exhibits a decrease of INC

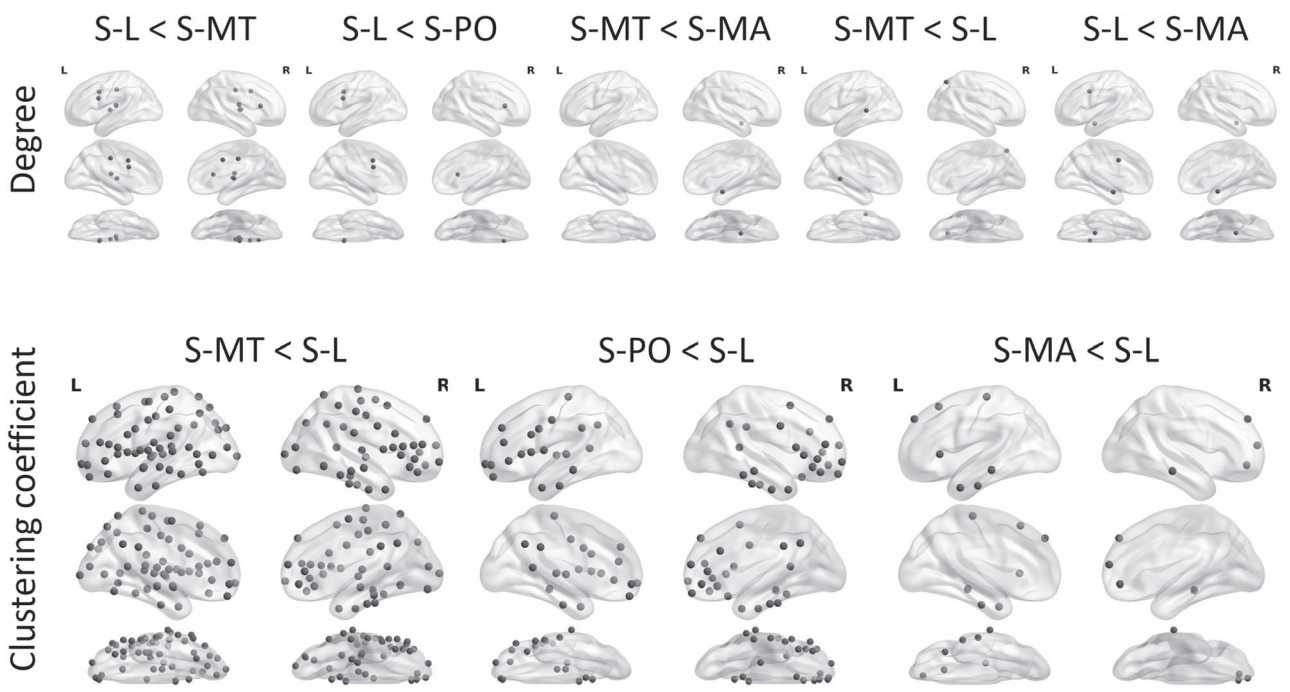

Figure 3. Differences between subtypes in degree and clustering coefficient in Brainnetome atlas derived regions of interest. Permutation based FDR-corrected two-tailed $P < 0.05$ are shown.

in the LN and DAN compared with HC, a distinct elevation of tau biomarkers and hippocampal atrophy despite very limited cortical atrophy and significant but modest cognitive changes. Atrophy patterns and functional connectivity changes are related, but as functional connectivity reflects the correlation of BOLD fluctuations between regions not necessarily directly connected by structural tracts, the resulting changes in functional connectivity are not identical to atrophy, emphasizing the need to study both variables to gain a better characterization of the derived subtypes.

All atrophy subtypes show some limbic involvement in the cortical atrophy pattern when compared with HC, but not when compared with each other. A similar atrophy pattern has been found in a recent publication in prodromal and early AD patients, where limbic involvement was also revealed for all subtypes versus HC but not when comparing the subtypes with each other (Ten Kate et al. 2018). Limbic structures are reported to be involved in tau pathology early in the disease (Trzepacz et al. 2013). In PET studies, severe hypometabolism was reported in AD and MCI patients in a network comprising structures of the limbic system, including hippocampus, thalamus and the posterior cingulate cortex (Nestor et al. 2003). These findings emphasize the importance of structures of the limbic systems and the associated limbic network (LN) system. Interestingly, the limbic atrophy subtype, despite pronounced atrophy in the limbic system, shows higher INC in the DMN and LN compared with HC, suggesting that atrophy is not directly correlated with functional connectivity on the network level. In synopsis with the CSF biomarker results, it appears that the moderate changes in cognition in S-L might be mainly associated with changes in INC and point to a significant impact of network disturbances over neurodegeneration traits in this subtype.

Differences between the four subtypes were consistently present on measures of global network properties. Our results suggest that measures of global network integration, most importantly global efficiency, are reduced in the S-MT and S-D subtypes along the severity dimension and strongly associated with cognitive performance, in line with the well-studied disconnection syndrome in AD (Stam et al. 2007). Differences in cognitive performance between the subtypes were previously shown (Liu et al. 2014). In comparison, the S-L, and to a lesser extent the S-MT, subtypes showed less severe disconnectivity on a global network level in conjunction with pronounced network changes on a nodal level (degree), suggesting a more localized underlying network pathology in these subtypes.

Nodal network changes in graph theory analysis showed a noticeable spatial overlap with the characteristic atrophy pattern of the corresponding subtype as measured by degree, expressing the number of links connected to a node as a reflection of the importance of a particular node in the network (Rubinov and Sporns 2010). In contrast, clustering coefficient, a measure of the extent of the local density or cliquishness of a network, was mainly reduced on a nodal level in the S-MT and S-D subtypes, following a typical distribution pattern of neurodegeneration in clinical and prodromal AD (Pereira et al. 2016).

Even though the S-MA subtype exhibits a pattern of sparse atrophy with better cognitive and clinical scores compared with the other subtypes, INC was reduced to a comparable degree as in S-MT and S-D. In addition, on a nodal level clustering coefficient was decreased in frontal and temporal regions, and local efficiency was reduced in areas belonging to the DMN. These changes on a local level might reflect ongoing pathological changes in the absence of clinical or neurocognitive symptoms. Compared with S-L, S-MA demonstrates no difference in Aβ but increased CSF t-tau and p-tau levels. Therefore, patients in the S-MA subgroup may have lower cognitive reserve (Persson et al. 2017) and be more likely to express AD pathology as network disruptions. Previously, the minimal atrophy pattern was shown to be associated with reduced metabolism in the parietal cortex

Table 3 Adjusted group means of INC scores of the pooled dataset

RSN	HC	S-MT	S-L	S-D	S-MA			S-MT versus HC	S-L versus HC	S-D versus HC	S-MA versus HC	S-MT versus S-L	S-MT versus S-D	S-MT versus S-MA	S-L versus S-D	S-L versus S-MA	S-D versus S-MA
	Mean (SE)					*P* (overall)	*P* FDR corrected	*P* post hoc comparisons									
DMN	−0.01 (0.11)	−0.18 (0.14)	0.38 (0.16)	−0.27 (0.12)	−0.12 (0.15)	0.02*	0.035*	0.36	0.054	0.11	0.57	0.01*	0.58	0.78	<0.001*	0.02*	0.40
DAN	0.01 (0.12)	−0.58 (0.15)	−0.37 (0.17)	−0.58 (0.12)†	−0.42 (0.16)	0.01*	0.035*	0.003*	0.07	0.001*	0.04*	0.36	1.00	0.48	0.32	0.83	0.43
CON	−0.06 (0.12)	−0.24 (0.15)	0.25 (0.17)	−0.16 (0.12)	−0.09 (0.16)	0.24	0.28	0.33	0.15	0.55	0.88	N.a.	N.a.	N.a.	N.a.	N.a.	N.a.
SAL	−0.02 (0.14)	0.12 (0.18)	0.53 (0.20)	0.13 (0.15)	0.47 (0.19)	0.13	0.18	0.57	0.03*	0.51	0.05	N.a.	N.a.	N.a.	N.a.	N.a.	N.a.
LN	−0.04 (0.10)	−0.10 (0.13)	0.07 (0.15)	−0.32 (0.11)	−0.52 (0.14)†	0.02*	0.035*	0.76	0.53	0.08	0.01*	0.4	0.18*	0.03*	0.03	0.01*	0.25
VN	0.02 (0.12)	−0.74 (0.14)	−0.14 (0.16)	−0.55 (0.12)	−0.32 (0.15)	<0.001*	0.007*	<0.001*	0.41	0.001*	0.08	0.01*	0.30	0.05	0.04*	0.42	0.24
SMN	−0.06 (0.10)	−0.02 (0.13)	−0.03 (0.15)	0.04 (0.11)	−0.13 (0.14)	0.89	0.89	0.78	0.84	0.49	0.72	N.a.	N.a.	N.a.	N.a.	N.a.	N.a.

Notes: *Two-tailed $P < 0.05$.
†$P < 0.05$ in analysis of covariance -with adjustments for age, sex, *APOE* genotype and years of education—between any atrophy subgroup DELCODE versus ADNI.

(Shima et al. 2012) and a higher rate of cerebral amyloid angiopathy (Ferreira et al. 2018), causing network disruptions. Consistent with this finding, we observed a locally reduced local efficiency in this area, accompanied by network disruption in the DAN and LN. High vulnerability within nodes of the DMN and other brain network regions in structural graph theory analysis in the S-MA subtype was previously demonstrated (Ferreira et al. 2019).

Compared with some previous studies, this study did not show differences between the atrophy subtypes and HC in the DMN. Numerically, S-L showed increased INC, and in contrast to the other subtypes, decreased INC compared with HC. It is possible that the results of the comparison in DMN functional connectivity between controls and AD patients might vary depending on the proportion of S-L subtype in a particular cohort. Furthermore, the individuals represent a spectrum of AD patients, including MCI and AD participants. A recent meta-analysis shows that depending on the clinical disease stage, hyper- or hypoconnectivity can occur in the DMN (Badhwar et al. 2017). The question of how differences in neuropathology among subtypes affect INC changes depending on the AD stage should be addressed in further research.

There are potential limitations of our study. First, pathological data to verify the clinical diagnoses were not available; however, we selectively included participants in the AD groups of both datasets following a biomarker-based diagnostic scheme including only Aβ-positive individuals with CDR ≥ 0.5, according to the ATN classification system following the recommendations of the NIA-AA Research Framework (Jack Jr et al. 2018), minimizing heterogeneity and potential misdiagnosis. Second, the dice overlap in the minimal atrophy subtype was comparatively low; this can be partly explained by the low number of vertices with reduced thickness in participants belonging to this group with a high probability of unequal distribution, although the clinical and neurocognitive scores showed high similarity. Third, the atrophy similarity clustering method could detect clinical AD stages rather than distinct subtypes. Indeed, this is likely the case for the S-MA and the S-D subtypes, however, the S-L and the S-MA subtypes exhibit aberrant network properties and CSF biomarker concentrations and are most likely entities along the typicality and not the severity dimension. Future investigations should consider tau PET as an additional imaging parameter to gain important information about spatial associations between tau distribution and network degeneration particularly in the S-MA subtype. Finally, the controls in the DELCODE dataset were younger compared with the AD patients, which may have resulted in more severe atrophy measures in this cohort; however, it is unlikely that this difference affected the resulting atrophy patterns and therefore the main results of the study.

In conclusion, we demonstrate a robust detection of different AD subtypes using a similarity-based clustering approach. These subtypes show distinct differences in functional connectivity networks and network properties on the local and global levels, accompanied by CSF biomarker and cognitive differences. Our study contributes toward a better understanding of heterogeneity in AD, with important ramifications for a more individualized approach to diagnosis and treatment. A better characterization of the heterogeneity of functional connectivity changes in AD subtypes lays the foundation for advanced neuromodulatory noninvasive brain stimulation, pharmacological treatment or tailored cognitive interventions aimed at modifying functional connectivity networks. Known differences in patterns of network degeneration may lead to a better-informed, individualized treatment strategy. Follow-up studies should

Table 4 Adjusted group means of graph theory derived global network properties on a whole brain level and within the DMN, the LN, and VN

Group means		S-MT	S-L	S-D	S-MA	*P* (overall)	S-MT versus S-L	S-MT versus S-D	S-MT versus S-MA	S-L versus S-D	S-L versus S-MA	S-D versus S-MA
Global network	Efficiency	0.23	0.26	0.24	0.25	<0.001*	<0.001*	0.02*	<0.001*	<0.001*	0.06	0.1
	Modularity	0.4	0.4	0.4	0.4	0.68	—	—	—	—	—	—
	Strength	5266	6130	5541	5745	<0.001*	<0.001*	0.05	0.002*	0.001*	0.03*	0.18
	Transitivity	0.21	0.25	0.22	0.23	<0.001*	<0.001*	0.11	0.04*	<0.001*	0.01*	0.46
Within DMN	Efficiency	0.3	0.34	0.31	0.32	<0.001*	<0.001*	0.17	0.02*	0.001*	0.03*	0.21
	Modularity	0.31	0.29	0.31	0.31	0.61	—	—	—	—	—	—
	Strength	199	225	203	207	<0.001*	<0.001*	0.41	0.24	<0.001*	0.006*	0.56
	Transitivity	0.46	0.52	0.47	0.47	0.006*	0.004*	0.84	0.74	0.001*	0.001*	0.86
Within LN	Efficiency	0.21	0.22	0.21	0.21	0.25	—	—	—	—	—	—
	Modularity	0.37	0.36	0.38	0.37	0.30	—	—	—	—	—	—
	Strength	68	73	68	65	0.12	—	—	—	—	—	—
	Transitivity	0.25	0.27	0.24	0.22	0.14	—	—	—	—	—	—
Within visual network	Efficiency	0.28	0.31	0.3	0.35	0.08	—	—	—	—	—	—
	Modularity	0.33	0.34	0.33	0.3	0.28	—	—	—	—	—	—
	Strength	160	175	172	167	0.16	—	—	—	—	—	—
	Transitivity	0.39	0.43	0.42	0.4	0.33	—	—	—	—	—	—

Notes: *Two-tailed permutation-based FDR-corrected $P < 0.05$.

Table 5 Summary of changes in nodal topography in regions of interest (ROIs) associated with the DMN (top) and LN (bottom) at a median threshold of 0.24

	Betweenness centrality	Degree	Clustering coefficient	Local efficiency
DMN				
S-MT versus S-L	CG ↑	pSTS ↓	SFG, MFG, IFG, OrG, STG, MTG, ITG, PCun, CG ↓	SFG, MFG, IFG, OrG, STG, MTG, ITG, pSTS,IPL, PCun, CG ↓
S-MT versus S-D	—	—	—	
S-MT versus S-MA	—	—	—	IFG, OrG, STG, MTG, pSTS, IPL, CG ↑
S-L versus S-D	—	—	SFG, IFG, OrG, MTG, ITG, PCun, CG ↑	SFG, MFG, IFG, OrG, STG, MTG, ITG, pSTS, IPL, PCun, CG ↑
S-L versus S-MA	—	—	SFG, OrG, MTG, ITG ↑	SFG, IFG, OrG, MTG, ITG, PCun ↑
S-D versus S-MA	—	—	—	—
LN				
S-MT versus S-L	—	—	MFG, OrG, ITG ↓	MFG, OrG, STG, ITG, FuG, PhG ↓
S-MT versus S-D	—	—	—	—
S-MT versus S-MA	—	—	—	STG, ITG, PhG ↓
S-L versus S-D	—	—	MFG, OrG, ITG ↑	MFG, OrG, STG, ITG, FuG, PhG ↑
S-L versus S-MA	—	—	—	—
S-D versus S-MA	—	—	—	—
VN				
S-MT versus S-L	—	—	FuG, PhG, IPL, CG, LOcC ↓	—
S-MT versus S-D	—	—	—	—
S-MT versus S-MA	—	—	—	FuG, PhG, IPL, CG, MVOcC, LOcC ↓
S-L versus S-D	—	—	PhG, CG ↑	FuG, PhG, IPL, PCun, CG, MVOcC, LOcC ↑
S-L versus S-MA	—	—	—	—
S-D versus S-MA	—	—	—	—

Note: Permutation FDR $P < 0.05$ (two-tailed). *Abbreviations:* S-MT-S-MA, subtype 1–4; SFG, superior frontal gyrus; MFG, medial frontal gyrus; IFG, inferior frontal gyrus; OrG, orbitofrontal gyrus; STG, superior temporal gyrus; MTG, medial temporal gyrus; ITG, inferior temporal gyrus; pSTS, posterior superior temporal sulcus; PCun, precuneus; CG, cingulate gyrus; FuG, fusiform gyrus; PhG, parahippocampal gyrus; IPL, inferior parietal lobule; MVOcC, medial ventral occipital cortex; and LOcC, lateral occipital cortex.

address the longitudinal consequences of the identified heterogeneity.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

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Ersin Ersözlü

Berlin, 04.01.2025

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Academic Career and Education

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