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Interindividuelle Variabilität im alternden Hirn: Von Generalisierbarkeit hin zur individuellen Phänotypisierung

Habilitationsschrift

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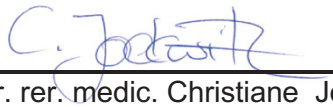

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1. **Jockwitz**, C., S. Merillat, F. Liem, J. Oschwald, K. Amunts, S. Caspers* and L. Jäncke* (2019). "Generalizing age effects on brain structure and cognition: A two-study comparison approach." Hum Brain Mapp 40(8): 2305-2319. *these authors contributed equally
2. **Jockwitz**, C., S. Merillat, F. Liem, J. Oschwald, K. Amunts, L. Jäncke* and S. Caspers* (2021). "Generalizing Longitudinal Age Effects on Brain Structure - A Two-Study Comparison Approach." Front Hum Neurosci 15: 635687. *these authors contributed equally
3. **Jockwitz**, C., L. Wiersch, J. Stumme and S. Caspers (2021). "Cognitive profiles in older males and females." Sci Rep 11(1): 6524.
4. **Jockwitz**, C., N. Bittner, S. Caspers* and K. Amunts* (2021). "Deep characterization of individual brain-phenotype relations using a multilevel atlas." Current Opinion in Behavioral Sciences 40: 153-160. *these authors contributed equally
5. **Jockwitz**, C., C. Kramer, J. Stumme, P. Dellani, S. Moebus, N. Bittner and S. Caspers (2022). "Characterization of the angular gyrus in an older adult population: a multimodal multilevel approach." Brain Struct Funct. In press.

Inhaltsverzeichnis

Einleitung

Der demografische Wandel stellt die Bevölkerung stetig vor neue Herausforderungen. Nach Angaben des Statistischen Bundesamtes (DeStatis; www.destatis.de) wird der Anteil der über 65-Jährigen in der deutschen Bevölkerung im Jahr 2050 bereits bei rund 30 % liegen, während die Zahl der 20- bis 64-Jährigen stetig abnimmt. Mit der zunehmenden Alterung der Bevölkerung geht ein starker Anstieg nicht übertragbarer Krankheiten einher, der eine enorme Herausforderung für das Gesundheitssystem darstellt. Neben Herz-Kreislauf- und Stoffwechselerkrankungen machen neurodegenerative Erkrankungen einen großen Teil der Fälle aus. Allein in Deutschland leiden derzeit 1,5 Millionen Menschen an der Alzheimer-Krankheit, welche die häufigste Form der Demenz darstellt. Die biologische Alterung des Menschen gilt dabei als größter Risikofaktor für das Auftreten dieser Krankheiten. Aktuelle Statistiken zeigen, dass die Prävalenz von Demenz im Alter von über 65 Jahren derzeit 8,46% beträgt, in der Altersgruppe über 90 Jahre liegt sie bereits bei 36,32% (World Health Organization 2020). Das Bundesministerium für Gesundheit prognostiziert, dass sich allein die Zahl der Demenzkranken bis zum Jahr 2050 verdoppeln wird. Aus diesem Grund wurde von der Weltgesundheitsorganisation (World Health Organisation; WHO) das „Jahrzehnt des gesunden Alterns“ (2021 bis 2030) ausgerufen. Dieses hat zum Ziel den kognitiven Verfall zu verstehen und die gesunde Alterung durch präventive Maßnahmen zu fördern, um die Unabhängigkeit der älteren Bevölkerung so lange wie möglich zu erhalten.

Altersabhängige Veränderungen kognitiver Leistungen

Der normale Alterungsprozess geht mit einer Abnahme der kognitiven Fähigkeiten einher ((Schaie 1993, Schaie 2009, Schaie and Willis 2010); für Übersichtsarbeiten siehe Harada, Natelson Love et al. (2013); Salthouse (2010), Kaup, Mirzakhanian et al. (2011)). Dazu gehören insbesondere die fluiden kognitiven Fähigkeiten in den Bereichen Aufmerksamkeit, exekutive Funktionen, episodisches und das Arbeitsgedächtnis (Hedden and Gabrieli 2004).

Kristalline Funktionen wie Sprachfunktionen (z. B. Wortschatz) und Allgemeinwissen scheinen dagegen während der gesunden Alterung relativ stabil zu bleiben (Hedden and Gabrieli 2004, Habib, Nyberg et al. 2007, Schaie and Willis 2010, Murman 2015). Hedden & Gabrieli (2004) fanden überdies heraus, dass die Verarbeitungsgeschwindigkeit ab dem frühen Erwachsenenalter linear abnimmt, während der Verfall der meisten fluiden kognitiven Funktionen einem nichtlinearen Trend folgt und erst ab Mitte 50 beginnt. Der stärkste Rückgang der fluiden kognitiven Fähigkeiten soll im Alter von 65 Jahren beginnen (Cornelis, Wang et al. 2019). Des Weiteren hat sich gezeigt, dass kognitive Funktionen nicht unabhängig voneinander altern. Der Abbau der allgemeinen Verarbeitungsgeschwindigkeit von Informationen sowie der exekutiven Funktionen scheinen sich zusätzlich auf die allgemeine kognitive Leistungsfähigkeit auszuwirken (Salthouse 1996, Miyake, Friedman et al. 2000, Salthouse 2010, Adrover-Roig, Sese et al. 2012, Albinet, Boucard et al. 2012). So kann beispielsweise eine verlangsamte Informationsverarbeitung zu einer schlechteren verbalen Wortflüssigkeit führen. Ebenso kann die unstrukturierte Organisation einer Aufgabe (bedingt durch mangelnde exekutive Funktionen) zu einer schlechten Leistung einer Gedächtnisaufgabe führen. All diese kognitiven Fähigkeiten sind hinsichtlich der Bewältigung alltäglicher Aufgaben wie zum Beispiel dem Kochen oder Einnahme von Medikamenten notwendig, um bis ins hohe Alter unabhängig zu bleiben.

Bei der Erschließung dieses Themas ist ferner zu bemerken, dass die ältere Bevölkerung durch eine extrem hohe interindividuelle Variabilität in ihren kognitiven Fähigkeiten gekennzeichnet ist (Hedden and Gabrieli 2004, Habib, Nyberg et al. 2007, Hartshorne and Germine 2015, Jockwitz, Merillat et al. 2019). Während zum Beispiel ein/e 80-Jährige/r noch die geistigen Fähigkeiten junger Erwachsener erreicht, kann ein andere/r 65-Jährige/r bereits eine deutliche Verschlechterung ihrer/seiner kognitiven Fähigkeiten erfahren. Obgleich es bereits einige eindeutige Belege für den Vergleich zwischen gesunden und pathologischen Zuständen hinsichtlich der kognitiven Fähigkeiten gibt, ist die Erklärung zur hohen

interindividuellen Variabilität innerhalb der gesunden Bevölkerung noch weitgehend unerklärt. Bezugnehmend auf den demographischen Wandel und der damit einhergehenden Verschiebung der Altersstruktur hin zu älteren Erwachsenen ist es allerdings unumgänglich die Varianz der kognitiven Leistungen innerhalb der älteren Population zu verstehen, um darauf aufbauend Strategien zu entwickeln, diesen möglichst gering zu halten.

Altersabhängige Veränderungen der Hirnstruktur als Korrelat der kognitiven Leistungseinbußen

Um die Grundlagen der kognitiven Leistungseinbußen innerhalb der älteren Population zu verstehen, ist es notwendig den Bezug zur Hirnorganisation aufzubauen. Die gängigste Art altersabhängige Veränderungen von Hirn und Verhalten zu untersuchen basiert auf querschnittlichen Studien, welche Differenzen zwischen Individuen unterschiedlichen Alters bewerten. Längsschnittliche Studien hingegen betrachten altersbedingte Veränderungen innerhalb eines Individuums über einen gewissen Zeitraum (Oschwald, Guye et al. 2019).
Beide Studiendesigns haben Veränderungen von Hirn und Verhalten mit zunehmendem Alter gefunden, wobei Querschnittsstudien im Vergleich zu Längsschnittstudien meist einen stärkeren Zusammenhang zwischen Alter und Hirnatrophie berichten (Hogstrom, Westlye et al. 2013, Fjell, Westlye et al. 2014, Storsve, Fjell et al. 2014). Weiterhin zeigen sowohl längsschnittliche als auch querschnittliche Studien, dass altersabhängige Abnahmen der Hirnstruktur nicht immer homogen stattfinden (Walhovd, Fjell et al. 2005, Fjell, Walhovd et al. 2006, Fjell, Westlye et al. 2009, Walhovd, Westlye et al. 2011, Hogstrom, Westlye et al. 2013, Fjell, McEvoy et al. 2014, Storsve, Fjell et al. 2014, Jancke, Merillat et al. 2015, Jockwitz, Caspers et al. 2017, Jancke, Sele et al. 2020). So zeigen Fjell, Westlye et al. (2009) stärkere Abnahmen der Hirnstruktur im Bereich des Frontal- (Gyrus frontalis superior und inferior) und oberen Temporallappens im Verlauf der Alterung von jungen hin zu älteren Erwachsenen. Längsschnittliche Studien, wie die von Storsve, Fjell et al. (2014), berichten die stärksten

jährlichen Abnahmen der grauen Substanz im Bereich des Temporal- und Okzipitallappens. Darüber hinaus scheint der Verlauf dieser altersabhängigen Abnahmen der grauen Substanz nicht in allen Regionen einem linearen Muster zu ähneln, sondern nimmt in einigen Regionen einen nichtlinearen Verlauf an (Sowell, Peterson et al. 2003, Ziegler, Dahnke et al. 2012, Fjell, Westlye et al. 2013).

Eine erhöhte Atrophie wurde wiederholt mit einem verstärkten Rückgang der kognitiven Leistung sowie der Entwicklung einer leichten kognitiven Beeinträchtigung oder Demenz in Verbindung gebracht (Korf, Wahlund et al. 2004, DeCarli, Frisoni et al. 2007, Karas, Sluimer et al. 2008, Sluimer, van der Flier et al. 2008, Yao, Hu et al. 2012, Poulakis, Pereira et al. 2018, van de Mortel, Thomas et al. 2021). In einer Meta-Analyse von Kaup, Mirzakhanian et al. (2011) wurde zum Beispiel eine Assoziation zwischen vermehrter Hirnatrophie und verminderten kognitiven Leistungen über mehrere Studien hinweg innerhalb der älteren Population gezeigt. Die Autoren betonen jedoch, dass diese Zusammenhänge nicht in allen betrachteten Studien, Hirnregionen und kognitiven Fähigkeiten gezeigt wurden. Der Zusammenhang zwischen Hirnstruktur und Verhalten scheint vielmehr komplexerer Natur zu sein (Park and Reuter-Lorenz 2009, Oschwald, Guye et al. 2019). Frühe Beobachtungen von Katzman (1993) zeigten die komplexen Zusammenhänge bereits bei einer Gruppe älterer Frauen, die zum Zeitpunkt ihres Todes keine Anzeichen für einen beschleunigten kognitiven Abbau zeigten, gleichzeitig jedoch hirnstrukturell eine Alzheimer-Pathologie in Form von Amyloid Plaques und Tau Proteinen aufwiesen. Diese Beobachtungen konnten kürzlich in einer Gruppe 100-jähriger Erwachsener repliziert werden, in der keine oder nur minimale Beeinträchtigungen der Gedächtnisleistung auftraten, obwohl post-mortem erhobene Befunde deutliche Anzeichen der Alzheimer-Krankheit zeigten (Amyloid Plaques und Tau Proteinen; (Beker, Ganz et al. 2021)). Demnach muss das Gehirn über eine Art Reservekapazität verfügen, die das Auftreten des kognitiven Verfalls trotz Schädigungen verhindern können. Traditionell wird hierbei zwischen der Hirnreserve ("Brain Reserve Capacity") und der

kognitiven Reserve („Cognitive Reserve Capacity“) unterschieden. Laut der Theorie der Hirnreserve, die bis heute als eine der zentralen Theorien der Hirnalterung gilt (Satz 1993, Stern 2002), können Menschen mit einer größeren Anzahl von Neuronen oder Synapsen mehr neurologische Schäden tolerieren, bevor es zu kognitiven Beeinträchtigungen kommt (Stern, Arenaza-Urquijo et al. 2020). Der derzeitige Stand der Forschung geht davon aus, dass die Hirnreserve, die eine passive Entität darstellt, in der pränatalen und frühesten postnatalen Phase des Lebens gebildet wird. So zeigte sich beispielsweise eine Assoziation zwischen einer pränatalen Unterernährung und einem geringeren Gehirnvolumen von Neugeborenen ((de Rooij, Wouters et al. 2010); für eine aktuelle Übersicht über die Literatur siehe de Rooij (2022)). Auch wenn die Hirnreserve-Theorie nach wie vor eine wichtige Theorie des Alterns darstellt, wurde jedoch durch spätere Studien ergänzt, dass die Hirnreserve durch genetische Faktoren oder Lebenserfahrung während des gesamten Alterungsprozesses beeinflusst werden kann (Nyberg, Lovden et al. 2012, Stern, Arenaza-Urquijo et al. 2020). So sind manche Menschen eher in der Lage, ihre Hirnstruktur zu erhalten als andere, indem sie die neurochemische, strukturelle und funktionelle Integrität aufrechterhalten, was auch als "Brain Maintenance" (Instandhaltung des Gehirns) bezeichnet wird.

Die kognitive Reserve hingegen, betrachtet das Gehirn eher als eine aktive Einheit (Stern 2002). Diese besagt, dass die Flexibilität und Plastizität der funktionellen Architektur (d. h. der funktionellen Netzwerke) des Gehirns den Auswirkungen alters- und krankheitsbedingter Veränderungen aktiv entgegenarbeiten. Menschen mit einer großen kognitiven Reserve sind dabei in der Lage, Hirnschäden zu kompensieren, indem sie alternative Strategien zur Aufrechterhaltung der kognitiven Funktion nutzen (Cabeza 2002, Cabeza, Anderson et al. 2002, Dolcos, Rice et al. 2002, Davis, Dennis et al. 2008, Reuter-Lorenz and Cappell 2008, Park and Reuter-Lorenz 2009, Reuter-Lorenz and Park 2014). Dies zeigt sich insbesondere in der Rekrutierung von alternativen oder zusätzlichen funktionellen Netzwerken. So zeigen beispielsweise Studien mit funktioneller Bildgebung, dass ältere Menschen, die ihre Leistung

bei einer Arbeitsgedächtnisaufgabe noch auf dem Niveau junger Probanden/-innen halten können, nicht nur die Hirnregionen rekrutieren, die bei jungen Menschen mit dieser Aufgabe in Verbindung stehen, sondern auch die homologen Bereiche der kontralateralen Hemisphäre (Cabeza 2002). Die älteren Menschen hingegen, die bereits einen Abbau der Leistung in dieser Aufgabe aufwiesen, zeigen diese zusätzliche Rekrutierung nicht (Cabeza et al., 2002). Die Theorie der kognitiven Reserve sieht das Gehirn als aktive Entität, dass sich im Laufe des Lebens anpassen kann. Inwieweit dies möglich ist, hängt von diversen genetischen und Umweltfaktoren ab.

Zusammenfassend lässt sich sagen, dass sich die Konzepte der Hirnreserve und der kognitiven Reserve nicht gegenseitig ausschließen, sondern vielmehr als komplementäre Modelle betrachtet werden können, die beide für ein gesundes Altern des Gehirns und somit für die Aufrechterhaltung der kognitiven Leistungsfähigkeit verantwortlich sind. Inwiefern das Gehirn in der Lage ist, die Hirnstruktur während des Lebens aufrecht zu erhalten, respektive, funktionelle Netzwerke kompensatorisch zu nutzen, hängt sowohl von genetischen als auch von umweltabhängigen Einflussfaktoren ab.

Einflussfaktoren auf die Hirnstruktur

Die zentrale Frage, die sich im Rahmen der Aufrechterhaltung der Hirnstruktur ergibt, ist, welche Faktoren, genetisch oder durch Lebenserfahrung geprägt, diese Reserve beeinflussen. Bisherige Studien zeigen, dass in der älteren Population der Faktor „Alter“ per se nicht mehr in der Lage ist, die Varianz zwischen älteren Menschen hinsichtlich ihrer Atrophie und den kognitiven Leistungen zu erklären (Jockwitz, Caspers et al. 2017, Jockwitz, Merillat et al. 2019, Krämer, Stumme et al. 2022). Im höheren Alter müssen somit weitere Faktoren hinzugezogen werden, um hier ein ganzheitliches Bild der normal alternden Population zu erhalten. Bezogen auf das Ziel der „Dekade für gesundes Altern“ ist dies eine grundlegende Aufgabe, um die große interindividuelle Variabilität innerhalb der älteren Population zu eruieren.

Mit Blick auf die Einflussfaktoren auf die Hirnstruktur gibt es mittlerweile eine Vielzahl von Studien, die sich diesem Thema annehmen und dabei auf die unterschiedlichen Aspekte eingehen (Maitland, Intrieri et al. 2010, Kohncke, Laukka et al. 2016, Miller, Alfaro-Almagro et al. 2016, Lovden, Karalija et al. 2018, Bittner, Jockwitz et al. 2019, Heim, Stumme et al. 2019, Caspers, Rockner et al. 2020, Cole 2020, Bittner, Jockwitz et al. 2021, Gronewold, Jokisch et al. 2021, Bittner, Korf et al. 2022, Brouwer, Klein et al. 2022). In einer Studie konnte beispielsweise ein Zusammenhang zwischen verschiedenen Lebensstilfaktoren (Bewegung, soziale Integration, Rauchen und Alkoholkonsum) und Hirnatrophie in einer aus älteren Menschen bestehenden populationsbasierten Kohorte gezeigt werden (Bittner, Jockwitz et al. 2019). Eine weitere Studie offenbarte Zusammenhänge zwischen einem erhöhten genetischen Risiko für die Entwicklung einer Demenz und regionaler Hirnatrophie im Bereich des unteren Frontallappens, des hinteren Temporallappens und des medialen Okzipitallappens (Caspers, Rockner et al. 2020). Darüber hinaus fanden sich vielversprechende Assoziationen zwischen Hirnstruktur und anderen Faktoren wie Schulbildung (Chen, Lv et al. 2019), Vitaminhaushalt , Body Mass Index (BMI) (Hamer and Batty 2019), Blutdruck (Bischof and Park 2015, Gronewold, Jokisch et al. 2021), Glukosespiegel (Enzinger, Fazekas et al. 2005), Mehrsprachigkeit (Heim, Stumme et al. 2019), Luftverschmutzung und Verkehrslärm (Nußbaum, Lucht et al. 2020, Lucht, Glaubitz et al. 2022) und sogar Persönlichkeit (Jackson, Balota et al. 2011) im höheren Alter. Allerdings ist hierbei zu betonen, dass all diese Studien nur einen kleinen Teil der Varianz innerhalb der älteren Population aufklären können. So zeigte sich etwa, dass Lebensstil lediglich 2% der Hirnatrophie (Bittner, Jockwitz et al. 2021), körperliche Bewegung nur 9,5% der Varianz im linken Hippocampusvolumen (Killgore, Olson et al. 2013) oder Rauchen nur ungefähr 4% der Varianz der kortikalen Dicke erklärt (Karama, Ducharme et al. 2015). Diese Ergebnisse zeigen die Notwendigkeit einer multifaktoriellen Varianzaufklärung der Hirnstruktur im höheren Alter, wobei die einflussnehmenden Risiko-

oder Schutzfaktoren jeweils einen kleinen Teil der großen interindividuellen Varianz einnehmen.

Methodologische Aspekte in der Identifizierung von Einflussfaktoren

Das Ziel der derzeitigen neurowissenschaftlichen Forschung, die sich mit dem alternden Gehirn befassen, ist die multifaktorielle Varianzaufklärung voranzubringen. Eines der großen Themen in diesem Rahmen ist, die vielen kleinen Effekte der möglichen Einflussfaktoren in statistischen Gruppenanalysen aufzudecken. Dazu benötigt es jedoch große Stichprobengrößen, um eine ausreichende statistische Aussagekraft zu gewährleisten (Button, Ioannidis et al. 2013, Brydges 2019). Ein vielversprechender Ansatz hierbei ist die gemeinsame Analyse verschiedener Stichproben. Dies kann entweder durch Datenpooling oder durch multizentrische Studien geschehen. Beim Datenpooling werden Daten aus verschiedenen Studien in einer übergeordneten Analyse zusammengefasst. In den letzten Jahren haben sich einige große Neurobildgebungskonsortien zusammengeschlossen, die auf diesem Verfahren beruhen wie beispielsweise das ENIGMA Konsortium (Thompson, Stein et al. 2014) oder Lifebrain (Walhovd, Fjell et al. 2018). Diese Konsortien bringen Daten aus verschiedenen unabhängigen Studien zusammen, um größere Stichproben zu erhalten. Dabei kann es sich sowohl um Rohdaten, als auch um bereits prozessierte Daten handeln. Eine weitere Möglichkeit bieten multizentrische Studien, die darauf abzielen, möglichst viele Daten in verschiedenen Studienzentren mit demselben Studienprotokoll zu generieren, wie es derzeit beispielsweise die Nationale Kohorte (NAKO; (Bamberg, Kauczor et al. 2015), ADNI (Alzheimer's Disease Neuroimaging Initiative; (Jack, Bernstein et al. 2008)), oder die UK Biobank (Sudlow, Gallacher et al. 2015, Miller, Alfaro-Almagro et al. 2016) tun. Während eine erhöhte Anzahl an Probanden/-innen die Möglichkeit bietet, auch Effekte mit kleinen Varianzaufklärungen zu ermitteln, entstehen hieraus zwei wichtige Aspekte, die in der neurowissenschaftlichen Forschung beachtet werden müssen.

Der erste Punkt betrifft die Zusammenführung von Daten aus verschiedenen Studienpopulationen, die zu einer Vermischung von stichprobenspezifischen biologischen und methodischen Aspekten führt. Diese künstlich generierte zusätzliche Variabilität der zusammengeführten Stichproben könnte die ‚wahren' Effekte hinsichtlich der Alterung von Hirnstruktur und kognitiven Leistungen verschleiern und zu *falsch negativen* Resultaten führen (Thirion, Pinel et al. 2007). Dabei handelt es sich häufig um Unterschiede in der Demografie von verschiedenen Stichproben; ein Aspekt, der thematisch dicht an den bereits beschriebenen Einflussfaktoren anzusiedeln ist. Erwachsene mit einer höheren Bildung, einem gesünderen Lebensstil oder einer gewissen genetischen Prädisposition weisen eine teils andere Hirnalterung auf als Erwachsene mit niedriger Bildung und einem ungesunden Lebensstil. Eine Zusammenführung der Daten könnte somit zu nicht signifikanten Alterseffekten der Hirnstruktur führen, getrieben durch eine der beiden Stichproben. Ein weiterer Aspekt zu diesem Punkt betrifft die methodischen Unterschiede von Studien (Han, Jovicich et al. 2006, Trachtenberg, Filippini et al. 2012, Hanggi, Langer et al. 2015, Jancke, Merillat et al. 2015, Liem, Merillat et al. 2015, Kohncke, Laukka et al. 2016, Afonso, Balardin et al. 2017, Lovden, Karalija et al. 2018). So zeigte sich zum Beispiel, dass unterschiedliche Magnetresonanztomographen (MRT; d. h. andere Modelle oder auch andere Magnetstärken), aber auch Abweichungen in den Standorten (bei gleichen MRT-Modellen) bereits zu kleinen Unterschieden in der kortikalen Dicke bei ein und derselben Person führen kann (Han, Jovicich et al. 2006, Schlett, Hendel et al. 2016). Zudem sind Differenzen in der Verarbeitung der MRT-Daten essentiell verantwortlich für Unterschiede in den Effekten. Insbesondere in der Hirnforschung haben sich in den letzten Jahren etliche methodologische Veränderungen in der Ermittlung der Hirnstruktur aufgetan, die eine Vergleichbarkeit von Studienresultaten erschweren. Zu den MRT-basierten Parametern, die üblicherweise zur Beschreibung der Hirnstruktur verwendet werden, gehören volumenbasierte Maße wie das Volumen oder die Dichte der grauen Substanz sowie oberflächenbasierte Maße wie die kortikale Dicke oder die

Hirnoberfläche. Hinzu kommen methodische Unterschiede innerhalb der spezifischen Analysen wie zum Beispiel die räumliche Glättung der Hirndaten, die ebenfalls dafür sorgen, dass Studienresultate häufig nicht vergleichbar sind (O'Sullivan, Jones et al. 2001, Westlye, Walhovd et al. 2010, Salat 2011, Walhovd, Westlye et al. 2011, Ziegler, Dahnke et al. 2012, Dickie, Job et al. 2013, Hogstrom, Westlye et al. 2013, Fjell, McEvoy et al. 2014, Fjell, Westlye et al. 2014, Liem, Merillat et al. 2015). Um die Vergleichbarkeit von Resultaten zu ermitteln, die methodologische Unterschiede in den Stichproben oder Analyseverfahren aufweisen, bedarf es Studien, die genau darauf abzielen, die Generalisierbarkeit der ermittelten Effekte zu überprüfen. Während diese im Bereich der genetischen Forschung durch sogenannte Replikationsstudien bereits gut etabliert sind, ist dies in der neurowissenschaftlichen Forschung noch nicht der Fall.

Der zweite Punkt, der prinzipiell alle Gruppenstudien betrifft, ist die verlorene Individualität der einzelnen Menschen und kann durch einen Perspektivwechsel verdeutlicht werden. Daten zusammenzufassen, führt zwangsweise zu einer Erhöhung der interindividuellen Varianz innerhalb der zu untersuchenden Daten. Diese interindividuelle Variabilität wird jedoch in Gruppenstudien als eine Art nicht-interessierendes, unerklärtes Rauschen betrachtet, das häufig durch eine Vielzahl von Kovariaten (z. B. Alter, Geschlecht, Bildung) zu eliminieren versucht wird und nur die Mittelung über alle Probanden/-innen im Fokus steht. Bezugnehmend auf die „Dekade des gesunden Alterns“ und der Zielsetzung, ein gesundes und unabhängiges Altern zu erreichen, ist es fraglich, inwiefern Gruppenstudien dem einzelnen Individuum helfen können. Dabei ist es insbesondere in Hinblick auf personalisierte Behandlungsmöglichkeiten, z. B. bei einer Demenz im höheren Alter, essentiell, individuelle, tiefgreifende Phänotypisierungen durchzuführen, um die Bedeutung verschiedener Faktoren für das einzelne Individuum aufzudecken und die beobachteten Unterschiede in der alternden Hirnstruktur und den kognitiven Leistungen zu erklären.

Zielsetzung und Aufbau der Arbeit

Die ältere Population ist durch eine große interindividuelle Variabilität von Verhalten und Hirnstruktur gekennzeichnet, die einen multifaktoriellen Ursprung zu haben scheint. Bisherige Studien zeigen jedoch, dass viele Einflussfaktoren nur kleine Teile der hohen Varianz in Hirn und Verhalten erklären können, wodurch große Stichprobengrößen erforderlich sind, um die nötige statistische Power zu erreichen. Während Datenpooling eine vielversprechende Methode darstellt, um Stichproben zu vergrößern, entstehen hierbei zwei methodische Probleme. Zunächst stellt sich die Frage, ob Stichproben ohne weiteres vereint werden können. Insbesondere die Heterogenität von Methoden und Stichprobencharakteristika führt dazu, dass Resultate nicht ohne weiteres auf andere Studienpopulationen generalisiert werden können, um so allgemeine Prinzipien zum alternden Gehirn aufstellen zu können – ein wichtiger Schritt in Hinblick auf das Bestreben, die gesunde Alterung zu verstehen. Dazu werden in der hier dargestellten Habilitationsschrift sowohl Vergleiche innerhalb einer populations-basierten Kohorte älterer Menschen, der sogenannten 1000BRAINS Studie, durchgeführt, als auch der Vergleich zwischen 1000BRAINS und einer unabhängigen Kohorte der Universität Zürich (Schweiz) im Quer- und Längsschnitt.

Darauf aufbauend stellt sich zudem die Frage, inwiefern die erzielten Resultate auf Gruppenebene den einzelnen Menschen widerspiegeln, was für den Schritt von der Grundlagenforschung in die Klinik von essentiellem Wert ist und den Zusammenhang „Einflussfaktoren – Generalisierbarkeit – Individualität“ komplementiert. Dazu wurden einerseits Probanden/-innen ausgewählt, die anhand einen Demenz-Screenings ein Risiko für eine Demenz haben. In einer weiteren Studie wurde anhand der Hirnstruktur Probanden/-innen ausgewählt, die im Vergleich zur Gesamtstichprobe hohe respektive niedrige Werte in der Hirnstruktur aufweisen. Mittels hirnstruktureller und kognitiver Profile wurden dann Vergleiche zur Gesamtstichprobe gezogen.

Ergebnisse und Diskussion

Generalisierbarkeit von Studienresultaten im höheren Alter

Die erste Studie behandelte den Aspekt der Generalisierbarkeit von Ergebnissen über verschiedene unabhängige Stichproben hinweg. Die Notwendigkeit einer Gegenprüfung der bisher ermittelten Ergebnisse zum alternden Gehirn, welche durch Unterschiede in den Stichprobenmerkmalen und einer Heterogenität der genutzten Methodik erschwert werden, wurden in einer ersten Studie aufgegriffen. Ziel der hier beschriebenen Studie war es, altersbedingte Unterschiede in sowohl kognitiven Fähigkeiten als auch der Hirnstruktur in zwei großen, unabhängigen Stichproben gesunder älterer Erwachsener zu validieren (1000BRAINS Studie am Forschungszentrum Jülich sowie Longitudinal Healthy Aging Brain (LHAB) Datenbank der Universität Zürich). Dabei ist zu betonen, dass die Stichproben hinsichtlich der demografischen Variablen Alter und Geschlecht angeglichen wurden, was zu 228 Datensätzen in jeder Stichprobe führte:

Tabelle 1: Demographische Variablen der beiden Stichproben, 1000BRAINS und LHAB (modifiziert nach Jockwitz, Merillat et al. (2019), mit freundlicher Genehmigung des Verlags, http://creativecommons.org/licenses/by/4.0/).

Stichprobe	Alter	Geschlechterverteilung	Bildung
1000BRAINS	70,7 +/- 5 Jahre (65 – 87 Jahre)	114 Frauen – 114 Männer	13,5 +/- 3,8 Jahre
LHAB	70,7 +/- 4,9 Jahre (65 – 87 Jahre)	114 Frauen – 114 Männer	14,7 +/- 3,4 Jahre

Zudem wurden in beiden Stichproben die gleichen kognitiven Testungen ausgewählt (in den Bereichen: Verarbeitungsgeschwindigkeit, Konzeptverschiebung, semantische Wortflüssigkeit, Vokabular und logisches Denken) und die strukturellen 3D MRT-Bilder mit der gleichen Software analysiert (FreeSurfer 6.0; Dale, Fischl et al. (1999), Fischl, Sereno et al. (1999)).

Es zeigte sich, dass die beiden Stichproben trotz einer Angleichung hinsichtlich der Alters- und Geschlechtsverteilungen Unterschiede in den ermittelten Stichprobencharakteristika

aufwiesen. Probanden/-innen der LHAB-Studie waren durch eine signifikant höhere Bildung und ein besseres körperliches Wohlbefinden gekennzeichnet. Sie zeigten zudem eine bessere Leistung in der Verarbeitungsgeschwindigkeit, dem logischen Denken und der semantischen Wortflüssigkeit. Probanden/-innen aus 1000BRAINS zeigten jedoch eine signifikant höhere globale wie auch regionale kortikale Dicke (als Maß der Hirnstruktur, global für beide Hemisphären sowie regional für die Regionen des Default Mode Networks [DMN], bestehend aus dem medialen präfrontalen Kortex, dem cingulären Kortex/ Precuneus und dem unteren Parietallappen (Jockwitz, Caspers et al. 2017)). Bezugnehmend auf die altersabhängigen Veränderungen der kognitiven Leistungen und der Hirnstruktur konnte trotz signifikanter Unterschiede in der Demografie und Hirnstruktur, folgendes gezeigt werden: Beide Stichproben zeigten vergleichbare Assoziationen und Regressionssteigungen zwischen Alter und den kognitiven Funktionen (für exemplarische Darstellungen der altersabhängigen Unterschiede in der kognitiven Leistung und kortikalen Dicke, siehe Abbildung 1).

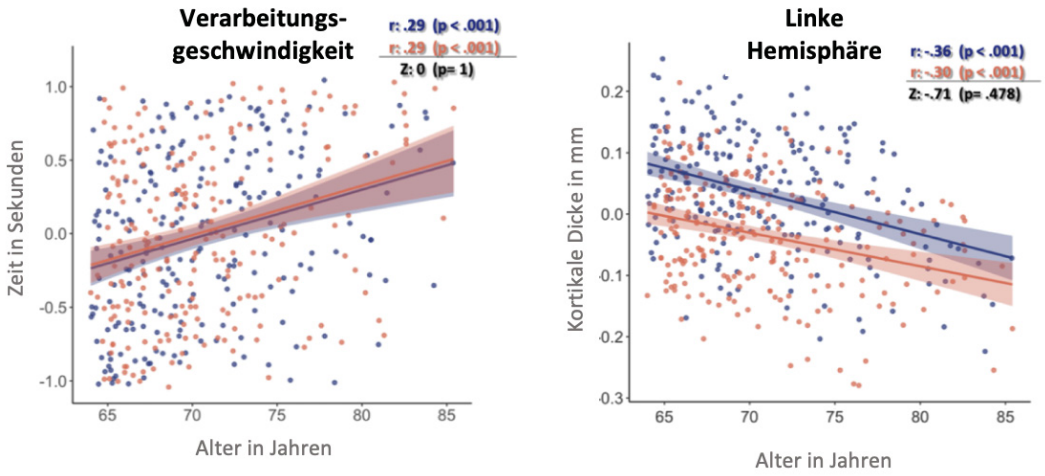

Abbildung 1: Altersabhängige Unterschiede der kognitiven Leistungen und der kortikalen Dicke. Links: Verarbeitungsgeschwindigkeit gemessen in Zeit (Sekunden). Rechts: gemittelte kortikale Dicke in mm für die linke Hemisphäre. Blau = 1000BRAINS; Orange = LHAB (modifiziert nach Jockwitz, Merillat et al. (2019), mit freundlicher Genehmigung des Verlags, http://creativecommons.org/licenses/by/4.0/).

Während der Wortschatz als kristalline kognitive Fähigkeit stabil blieb, wiesen alle anderen ausgewählten kognitiven Tests mit zunehmendem Alter Abnahmen der Leistungen in beiden Stichproben auf. Gleiches offenbarte sich für die globale sowie die regionale kortikale Dicke.

Beide Hemisphären sowie auch die posterioren Regionen des DMN waren von altersabhängigen Abnahmen der kortikalen Dicke betroffen. Die anterioren Anteile des DMN hingegen blieben über das Alter stabil. Der aktuelle Ansatz mit zwei Studien deutet somit darauf hin, dass altersbedingte Unterschiede in den kognitiven Fähigkeiten und der Hirnstruktur über verschiedene Stichproben hinweg verallgemeinert werden können, vorausgesetzt dieselbe Methodik wird angewandt. Diese robusten Effekte sprechen somit für die Zusammenführung von Daten, um den Stichprobenumfang und die statistische Aussagekraft zu erhöhen.

Wichtig zu erwähnen ist jedoch, dass die beiden Stichproben zunächst getrennt und dann erst zusammen analysiert wurden, um die Betrachtung von zusätzlichen Kovariaten hinsichtlich ihres Aufschlusses auf die Varianzaufklärung in den jeweiligen Stichproben zu überprüfen. Während 1000BRAINS zum Beispiel einen moderaten Effekt des psychischen Wohlbefindens auf die Verarbeitungsgeschwindigkeit zeigte, konnte dieser nicht innerhalb der LHAB reproduziert werden. Diese Beobachtungen weisen darauf hin, dass gewisse Merkmale studienspezifisch sind und eine gepoolte Analyse solche Einflüsse unterschätzen würde. Eine Kombination aus gepoolten und individuellen Analysen scheint somit eine optimale Lösung zu sein, um Einflussfaktoren auf das alternde Gehirn zu untersuchen **(Jockwitz, Merillat et al. (2019); Publikation 1).**

Die bisher beschriebenen Resultate basieren jedoch auf querschnittlichen Daten, welche per Definition interindividuelle Unterschiede ermitteln und somit nur eine Annäherung an die intra-individuellen altersabhängigen Veränderungen geben können (Raz and Lindenberger 2011). Bei bisherigen Vergleichen von Quer- und Längsschnittstudien wurden unterschiedliche Muster für sowohl kognitive als auch strukturelle Hirnalterung festgestellt (Hedden and Gabrieli 2004, Pfefferbaum and Sullivan 2015). Inwiefern sich nun längsschnittliche Beobachtungen zur Hirnalterung replizieren lassen, ist bisher ungeklärt. Ziel der zweiten Studie war es daher, altersbedingte Veränderungen der Hirnstruktur in zwei großen unabhängigen Stichproben

gesunder älterer Erwachsener zu vergleichen. Auch in dieser Studie wurden die beiden Stichproben (1000BRAINS und LHAB) zunächst hinsichtlich Alter (zum ersten Zeitpunkt) und Geschlecht mittels Propensity Score Matching in ihren Verteilungen angeglichen, was zu 161 Datensätzen pro Standort führte.

Tabelle 2: Demographische Variablen der beiden Stichproben, 1000BRAINS und LHAB (modifiziert nach Jockwitz, Merillat et al. (2021), mit freundlicher Genehmigung des Verlags, http://creativecommons.org/licenses/by/4.0/).

Stichprobe	Alter	Geschlechterverteilung	Messintervall
1000BRAINS	69,2 Jahre ± 4,6	76 Frauen – 85 Männer	3,7 Jahre ± 0,7
LHAB	69,9 Jahre ± 4,1	85 Frauen – 76 Männer	4,2 Jahre ± 0,1

In Bezug auf die kortikale Dicke zeigte die LHAB-Stichprobe im Vergleich zu 1000BRAINS etwas stärkere jährliche prozentuale Veränderungen (d. h. Abnahmen) der kortikalen Dicke. Diese wurde für beide Stichproben und beide Zeitpunkte sowohl auf globaler (beide Hemisphären) wie auch auf regionaler Ebene (alle Regionen des Desikan-Killiany-Atlas; Desikan, Segonne et al. (2006)) berechnet (longitudinale oberflächenbasierte Verarbeitungspipeline aus FreeSurfer 6.0, Reuter, Schmansky et al. (2012)). Abbildung 2 zeigt allerdings, dass die Muster der regionalen Unterschiede in den Abnahmen der kortikalen Dicke zwischen beiden Stichproben vergleichbar waren.

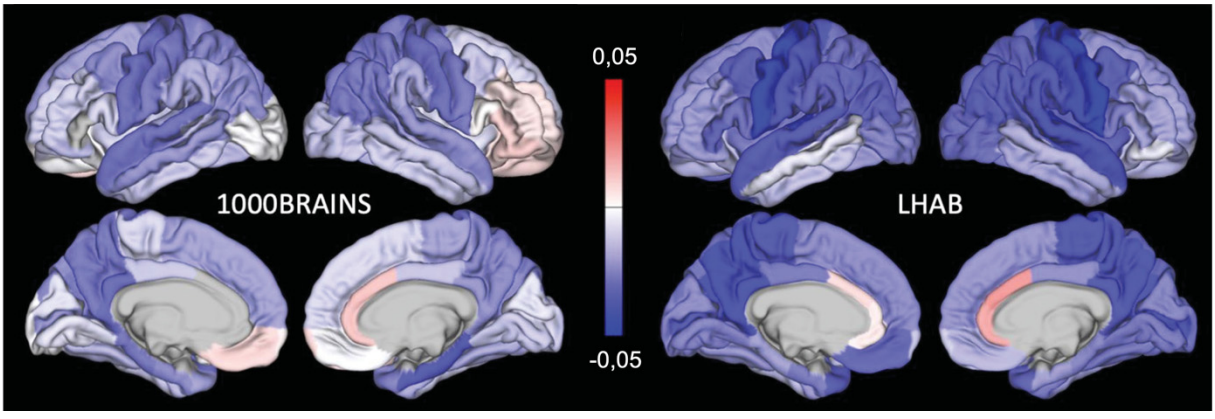

Abbildung 2: Jährliche prozentuale Veränderungen der kortikalen Dicke für 1000BRAINS (links) und LHAB (rechts). Rot = jährliche prozentuelle Zunahmen der kortikalen Dicke; Blau = jährliche prozentuelle Abnahmen der kortikalen Dicke (modifiziert nach Jockwitz, Merillat et al. (2021), mit freundlicher Genehmigung des Verlags, http://creativecommons.org/licenses/by/4.0/).

Aufbauend auf diese deskriptiven Vergleiche der beiden Stichprobenden wurden folglich die langzeitlichen Veränderungen der Hirnstruktur zunächst für beide Gruppen getrennt berechnet und dann statistisch miteinander verglichen (GLM mit Geschlecht, Ausgangsalter, Bildung und Euler-Zahl als Marker für die Bildqualität (Rosen, Roalf et al. 2018) als zusätzliche Kovariaten). Nach der Korrektur für die verschiedenen Kovariaten und für multiple Vergleiche fanden sich letztendlich nur sehr wenige Stichprobenunterschiede in Bezug auf die jährliche prozentuale Veränderung der 68 untersuchten Regionen (Gyrus frontalis inferior pars triangularis und pars opercularis sowie Gyrus temporalis transversus). Ebenfalls fanden sich nur sporadische Effekte der untersuchten Kovariaten auf die jährliche prozentuale Veränderung der kortikalen Dicke. Nach Korrektur dieser subtilen, meist nicht signifikanten Einflüsse wurden sogar die Achsenabschnitte (d. h. die Haupteffekte der jährlichen prozentualen Veränderung) nicht signifikant.

Insgesamt hat die Studie zur Generalisierbarkeit von längsschnittlichen Veränderungen der Hirnstruktur gezeigt, dass die jährlichen altersbedingten Veränderungen der kortikalen Dicke relativ gering sind, insbesondere wenn sie um die häufigsten Einflussfaktoren bereinigt werden. Dieser Effekt wurde in beiden Studien beobachtet, was darauf hindeutet, dass allgemeine Muster von Längsschnittveränderungen in der Gehirnstruktur generalisiert werden können. Jedoch zeigten sich ebenfalls Unterschiede in den interindividuellen Varianzen (1000BRAINS zeigte eine größere interindividuelle Varianz der jährlichen prozentualen Veränderung in den meisten untersuchten Regionen) sowie minimale Stichprobenunterschiede, was auf die Verschiedenheiten der beiden Stichproben in Bezug auf z. B. Demografie (z. B. Altersgruppen und Bildung) zurückzuführen sein könnte und im Datenpooling-Verfahren nicht außer Acht gelassen werden darf. Zusammenfassend lässt sich sagen, dass die Muster altersbedingter Veränderungen der Gehirnstruktur über die Zeit

hinweg in zwei unabhängigen Kohorten älterer Erwachsener bei Verwendung desselben methodischen Ansatzes sehr ähnlich sind **(Jockwitz, Merillat et al. (2021); Publikation 2)**.

In einer dritten Studie zum Thema Generalisierbarkeit wurde zudem auf die kognitiven Profile älterer Menschen fokussiert. Die Vergleichbarkeit von globalen Trends der Alterung zur Hirnstruktur konnte mit den vorherigen Studien bestätigt werden. Andererseits bleibt die Frage bestehen, inwieweit Effekte innerhalb einer Stichprobe generalisierbar sind. Ein wichtiges Thema diesbezüglich betrifft die kognitiven Profile älterer Menschen. Aus vorherigen Studien ist bekannt, dass sich Männer und Frauen hinsichtlich ihrer kognitiven Leistungen unterscheiden (Halpern, Benbow et al. 2007). So wurden häufig bessere Leistungen der Frauen in verbalen und der Männer in räumlichen Aufgaben berichtet. Aktuell wird dies anhand unterschiedlicher Verarbeitungsstrategien beim Lösen einzelner kognitiver Aufgaben erklärt (Pletzer, Scheuringer et al. 2017). Ziel der hier dargestellten Studie war daher der systematische Vergleich kognitiver Profile zwischen älteren Männern und Frauen (abgestimmt für Alter, Bildung und kognitiven Status mittels Propensity Score Matching):

Tabelle 3: Demographische Variablen der beiden Gruppen, Männer und Frauen (modifiziert nach Jockwitz, Wiersch et al. (2021), mit freundlicher Genehmigung des Verlags, http://creativecommons.org/licenses/by/4.0/).

Stichprobe	n	Alter	Kognitiver Status	Bildung
Frauen	338	66,0 Jahre ± 6,5	15,6 ± 2,2	6,1 ± 1,9
Männer	338	66,9 Jahre ± 6,7	14,2 ± 2,4	6,3 ± 1,7

Die Resultate zeigten Leistungsunterschiede zwischen Männern und Frauen bereits auf Einzeltestebene. So schnitten Männer bei Aufgaben, die visuelle und visuell-räumliche Fähigkeiten erfordern, z. B. beim visuell-räumlichen Gedächtnis, signifikant besser ab, während Frauen bei Aufgaben, die verbale Fähigkeiten erfordern, wie dem episodischen Gedächtnis und der phonematischen und semantischen Wortflüssigkeit, besser abschnitten. Auf systemischer Ebene wiesen Männer und Frauen unterschiedliche Zusammensetzungen ihrer kognitiven Profile auf.

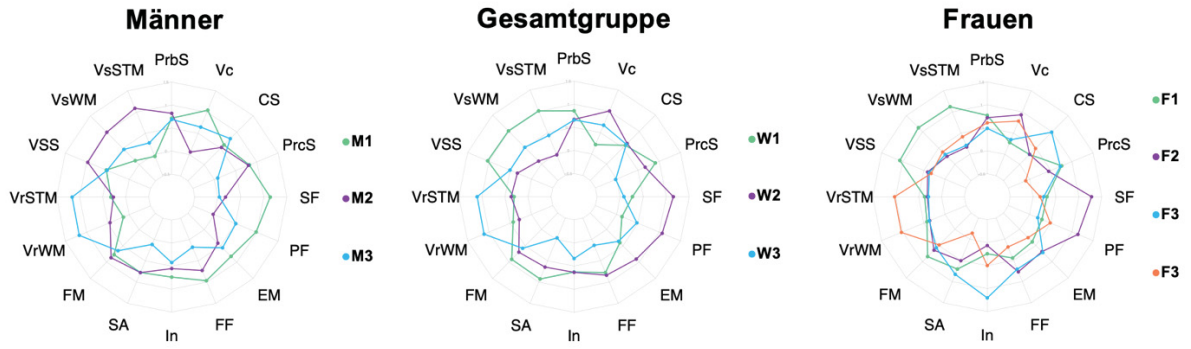

Abbildung 3: Komponentenlösungen der kognitiven Tests. Links = Männer (Komponenten M1-M3), Mitte = Gesamtgruppe (Komponenten W1-W3), rechts = Frauen (Komponenten F1-F4). PrbS = Problemlösen, VsSTM = visuelles räumliches Kurzzeitgedächtnis, VsWM = visuelles räumliches Arbeitsgedächtnis, VSS = visuelles Arbeitsgedächtnis, VrSTM = verbales Kurzzeitgedächtnis, VrWM = verbales Arbeitsgedächtnis, FM = figurales Gedächtnis, SA = selektive Aufmerksamkeit, In = Interferenz, FF = figurale Flüssigkeit, EM = episodisches Gedächtnis, PF = phonemische verbale Wortflüssigkeit, SF semantische verbale Wortflüssigkeit, PrcS = Verarbeitungsgeschwindigkeit, CS = Konzeptverschiebung, Vc = Wortschatz (modifiziert nach Jockwitz, Wiersch et al. (2021), mit freundlicher Genehmigung des Verlags, http://creativecommons.org/licenses/by/4.0/).

Während die kognitiven Testleistungen der Gesamtgruppe, wie auch die der Männer alleine, in drei Komponenten zerlegt werden konnte, so ergaben sich bei den Frauen vier Komponenten. Für die gesamte Gruppe wurden die extrahierten Komponenten von den folgenden Funktionen dominiert: Die erste Komponente umfasste eine Vielzahl von nonverbalen kognitiven Funktionen wie visuelles Arbeitsgedächtnis, Aufmerksamkeit, exekutive Funktionen und Gedächtnis. Die zweite Komponente umfasste die Flüssigkeit und das Gedächtnis. In der dritten Komponente dominierten verbale Funktionen wie das verbale Arbeitsgedächtnis und der Wortschatz. Das männliche Modell, ebenfalls ein Drei-Komponenten-Modell, bestand aus einer ersten Komponente, die Flüssigkeit, Gedächtnis, Aufmerksamkeit und exekutive Funktionen umfasste, einer zweiten Komponente, die von visuellem Arbeitsgedächtnis und exekutiven Funktionen dominiert wurde und einer dritten Komponente, die das verbale Arbeitsgedächtnis und die exekutiven Funktionen umfasste. Die Vier-Komponenten-Lösung für die weibliche Gruppe beinhaltete eine Komponente, die von visuellem Gedächtnis und Arbeitsgedächtnis dominiert wurde. Eine zweite Komponente umfasste die Wortflüssigkeit, den Wortschatz sowie exekutive Funktionen. Die dritte

Komponente bestand aus exekutiven Funktionen und Gedächtnis und die vierte Komponente aus dem verbalen Arbeitsgedächtnis und dem Wortschatz. Insgesamt deutet die Untersuchung der datengesteuerten kognitiven Komponenten auf unterschiedliche Zusammensetzungen der kognitiven Komponenten bei älteren Männern und Frauen hin. Vergleicht man diese mit der wiederum leicht abweichenden Komponentenlösung, die aus der Gesamtgruppe (Männern und Frauen) abgeleitet wurde, stellt sich die Frage, ob diese bisher nur deskriptiv verglichenen Unterschiede statistisch aussagekräftig sind, was anschließend durch die Testung der Messinvarianz bestätigt werden konnte.

Ältere Männer und Frauen unterscheiden sich also nicht nur bei bestimmten kognitiven Aufgaben, sondern generell in ihren kognitiven Profilen. Männer nutzen wahrscheinlich eine ganzheitlichere Art der Verarbeitung (Stumme, Jockwitz et al. 2020), indem sie verschiedene kognitive Funktionen integrieren, um bestimmte Aufgaben zu lösen. Dies könnte z. B. eine höhere exekutive Kontrolle und Gedächtnisfunktion bei einer Aufgabe zu Wortflüssigkeit sein. Frauen hingegen verarbeiten kognitive Aufgaben eher in aufgabenspezifischen Subsystemen. Folglich hätte z. B. eine Verschlechterung der exekutiven Funktionen nicht zwangsweise einen Einfluss auf die Gedächtnisleistung. Die vorliegende Untersuchung unterstreicht daher die Bedeutung geschlechtsspezifischer Analysen bei der Bewertung der kognitiven Leistung. Diese Unterschiede in den kognitiven Profilen könnten nicht nur für die Grundlagenforschung von Bedeutung sein, sondern auch Auswirkungen auf klinische Präventionsprogramme haben, z. B. auf ein kognitives Training im höheren Alter **(Jockwitz, Wiersch et al. (2021); Publikation 3)**.

Zusammenfassend lässt sich sagen, dass die hier beschriebenen Studien einen Beitrag zur derzeitigen Forschung im Bereich der Generalisierbarkeit von alters- und geschlechtsassoziierten Effekten in der kognitiven Leistung und Hirnstruktur leisten konnten. Wichtig ist dabei zu betonen, dass die Generalisierbarkeit von Alterseffekten nur dann gegeben ist, wenn die Stichproben hinsichtlich ihres Alters und Geschlechterverteilung

angepasst werden und die gleichen Methoden genutzt werden. Im Bereich der kognitiven Leistung ist eine getrennte Analyse der Geschlechter in Betracht zu ziehen, wenn kognitive Profile begutachtet werden.

Generalisierbarkeit von Gruppenebene zum Individuum

Im zweiten Teil wurde sich in zwei Studien mit der Frage befasst, inwieweit die erzielten Resultate auf Gruppenniveau eine Aussage zum einzelnen Individuum treffen können. Während in den vorherigen Studien der Fokus auf dem Vergleich von Gruppen lag (unabhängige Stichproben oder Männer und Frauen), liegt dieser im zweiten Teil in der Vergleichbarkeit zwischen Gruppen und dem Individuum. Die derzeitige Populations-Neurobildgebung ermöglicht die Etablierung allgemeiner Grundsätze zu den Beziehungen zwischen Gehirn und Phänotyp im höheren Alter. Wie im ersten Teil dieser Arbeit bereits diskutiert, wird hierbei versucht eine möglichst robuste und stabile Aussage zu treffen, umso eine Gültigkeit für die gesamte Population zu ermöglichen. Während Replikationsstudien dabei helfen können, diese zu ermitteln, bleibt die Erfassung von individuellen Gehirn-Verhaltens-Profilen in Gruppen mit ausgeprägter interindividueller Variabilität – wie bei älteren Erwachsenen – jedoch eine Herausforderung. Daher ist eine tiefgreifende Charakterisierung genau dieser Individuen mittels Daten aus verschiedenen Bereichen, wie Gehirn, Kognition oder Lebensstil dringend erforderlich.

In einer ersten dazu durchgeführten Studie wurde dies im Rahmen des demografischen Wandels und der damit steigenden Anzahl an Demenzkranken auf Risikoprobanden/-innen der Demenz in den Blick genommen. Dazu wurden fünf ältere Männer selektiert (1000BRAINS-Studie), die bei einem Demenz-Screening-Test im Risikobereich für eine mögliche Demenz lagen (ermittelt anhand des Demenz-Screening-Tests DemTect <=8; Kalbe, Kessler et al. (2004)). Diese Risikoprobanden wurden hinsichtlich ihrer kognitiven Leistungen, ihrem Lebensstil und ihrer Hirnstruktur mit einer gesunden Population älterer Männer

(ebenfalls aus der 1000BRAINS-Studie; n = 323, Durchschnittsalter: 67,6 Jahre +- 6,4; DemTect >12) verglichen.

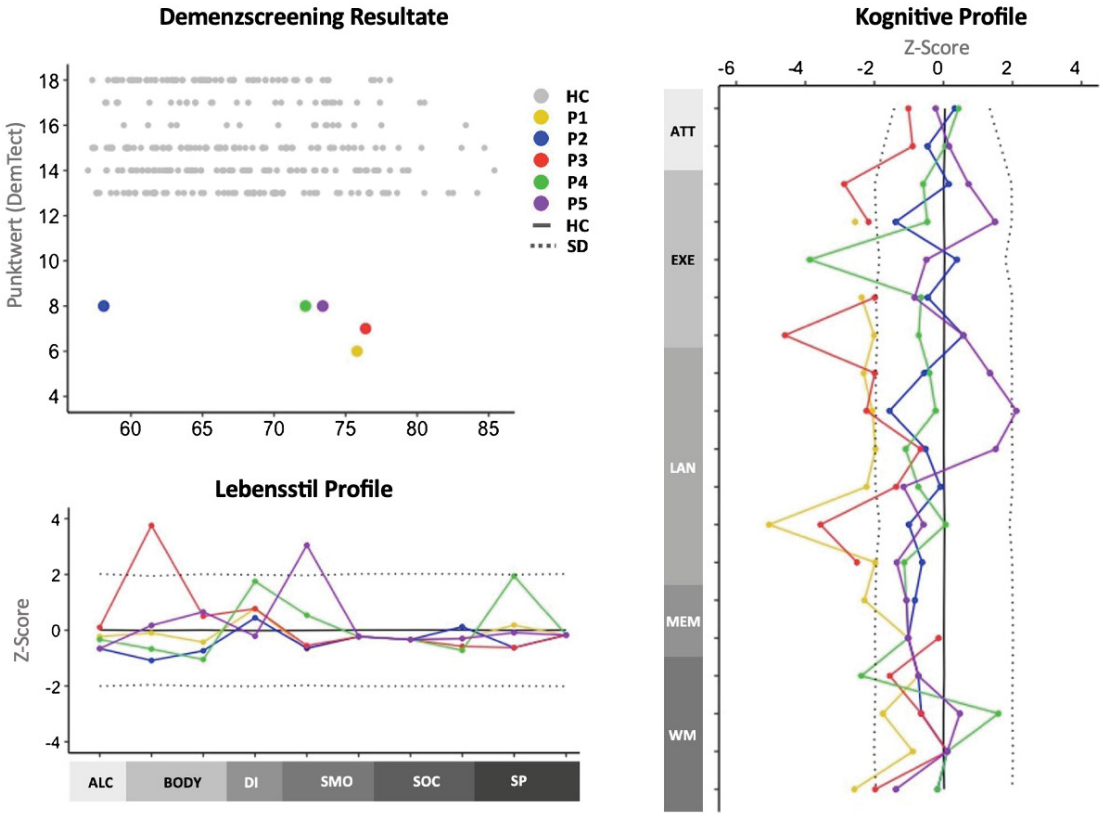

Abbildung 4: Vergleich von Teilnehmer/-innen mit Demenzrisiko (P1-5) mit gesunden Kontrollpersonen (HC). Oben links: DemTect-Score für HC (graue Punkte) im Vergleich zu P1-5; unten links: Lebensstilfaktoren (von links nach rechts: ALC = wöchentlicher Alkoholkonsum; BODY = Body Mass Index, Taillen-Hüft-Verhältnis; DI = Ernährungsindex; SMO = packyears, Zigaretten pro Tag; SOC = Familienstand, sozialer Integrationsindex; SP = metabolisches Äquivalent, Treppensteigen); rechts: Kognitive Leistung von oben nach unten: ATT = Aufmerksamkeit (Verarbeitungsgeschwindigkeit, selektive Aufmerksamkeit); EXE = Exekutivfunktionen (Konzeptverschiebung, figurale Flüssigkeit, Interferenz, Problemlösung); LAN = Sprache (Benennen, phonemische Wortflüssigkeit, phonemische Wortflüssigkeit [Wechselbedingung], semantische Wortflüssigkeit, semantische Wortflüssigkeit [Wechselbedingung], Wortschatz; MEM = Gedächtnis (episodisches Gedächtnis, figurales Gedächtnis); WM = Arbeitsgedächtnis (verbales Kurzzeitgedächtnis, verbales Arbeitsgedächtnis, visuell-räumliches Kurzzeitgedächtnis, visuell-räumliches Arbeitsgedächtnis, visuelles Arbeitsgedächtnis) (modifiziert nach Jockwitz, Bittner et al. (2021), mit freundlicher Genehmigung des Verlags).

Die selektierten Probanden zeigten heterogene individuelle Profile in Bezug auf die untersuchten Bereiche Kognition (in den Bereichen Aufmerksamkeit, Exekutivfunktionen, Sprache, Gedächtnis und Arbeitsgedächtnis), Lebensstil (in den Bereichen Alkoholkonsum, körperbezogene Aspekte, Ernährung, Rauchen, Sozialverhalten und Sport) und Volumina der

grauen Substanz (unter Verwendung der CAT-Toolbox, SPM12 (Gaser and Dahnke 2016); für alle zytoarchitektonisch definierten Bereiche des Julich-Brain-Atlas (Amunts, Mohlberg et al. 2020)). Diese Profile ließen, trotz der Tatsache, dass alle fünf Probanden als Risikoprobanden eingestuft wurden, keine Gemeinsamkeit erkennen (für eine Übersicht der kognitiven und Lebensstilprofile, siehe Abbildung 4). Hinzu kommt, dass auch die Abweichung der einzelnen Probanden von der Gesamtstichprobe keine systematischen Muster aufwiesen und ebenfalls nicht dem Atrophiemuster entsprachen, welches in Studien mit leichten kognitiven Beeinträchtigungen beobachtet wurden (medialer Temporallappen, einschließlich Hippocampus; Franke and Gaser (2012)). Einer der fünf Risikoprobanden zeigte beispielsweise generell niedrige kognitive Leistungen bei einem unauffälligen Lebensstil (gemessen am Mittelwert der gesunden Kontrollen). Ein anderer hingegen zeigte bei fast allen kognitiven Aufgaben Leistungen im Normalbereich, bei einem gleichzeitig erhöhten lebenslangen Zigarettenkonsum mit variablem Volumen der grauen Substanz über die einzelnen Regionen des Julich-Brain-Atlas hinweg.

Die einzelnen Profile weisen somit darauf hin, dass die allgemeinen Trends nur teilweise die Situation auf der Ebene des einzelnen Probanden widerspiegeln. Stattdessen ergibt sich ein eher heterogenes Bild, bei dem jedes Individuum eine Mischung aus verschiedenen schützenden und potenziell aversiven Lebensstilfaktoren aufweist, was auf eine multifaktorielle Genese kognitiver Beeinträchtigung im Alter hinweist. Damit betont die hier beschriebene Studie die Wichtigkeit der individuellen Untersuchung ältere Erwachsener, insbesondere im pathologischen Bereich und zeigt, dass die interindividuelle Variabilität nicht als Störfaktor, sondern als zu beobachtende Einheit gesehen werden muss **(Jockwitz, Bittner et al. (2021); Publikation 4)**.

Zur Verifizierung der soeben dargestellten Ergebnisse erfolgte daraufhin eine zweite Studie zur Vergleichbarkeit von Gruppenresultaten und individuellen Merkmalen der Kognition, dem Lebensstil und dem Gehirn. Im Gegensatz zur vorherigen Studie wurden diesmal Probanden/-

innen ausgewählt, die sich hinsichtlich der Hirnstruktur im Bereich des Gyrus angularis von der Population abgrenzen. Der Gyrus angularis (mit seinen zytoarchitektonisch definierten Arealen PGa und PGp) ist dahin gehend als interessante Region zu betrachten, da frühere Ergebnisse auf eine Schlüsselrolle dieser Region im Alterungsprozess hindeuten. So zeigten bereits jene Probanden/-innen, die unter subjektiven kognitiven Beeinträchtigungen litten (Kim, Lee et al. 2019) sowohl ein geringeres Volumen der grauen Substanz innerhalb des Gyrus angularis als auch eine geringere strukturelle Netzwerkkonnektivität zwischen dem Gyrus angularis und dem oberen Parietallappen sowie dem Gyrus prä- und postcentralis, welche wiederum mit ihrem kognitiven Abbau verbunden war. Zudem wiesen Patienten/-innen, die von einer leichten kognitiven Beeinträchtigung in die Alzheimer-Krankheit übergingen, eine Atrophie im linken Gyrus angularis auf (Karas, Sluimer et al. 2008).

In der hier dargestellten Studie wurden individuelle kognitive und Lebensstilprofile für fünf Probanden/-innen mit niedrigem Volumen der grauen Substanz und fünf Probanden/-innen mit hohem Volumen der grauen Substanz aus der bereits beschriebenen 1000BRAINS-Studie (Teilnehmer/-innen, welche in allen vier Teilen des Gyrus angularis zu den höchsten bzw. niedrigsten 25 % bezüglich des Volumens der grauen Substanz fielen) aufgestellt. Als zu vergleichende Einheiten wurden in dieser Studie Gruppeneffekte hinsichtlich der Veränderungen im Volumen der grauen Substanz des Gyrus angularis (Areale PGa und PGp) und dem Zusammenhang mit a) dem regionalen Volumen der grauen Substanz, der b) funktionellen und c) strukturellen Konnektivität (in Teilen des Julich-Brain-Atlas) berechnet. Darüber hinaus wurde das Volumen der grauen Substanz des Gyrus angularis (Areale PGa und PGp) mit d) Alter, e) kognitiver Leistung, und f) Lebensstil (korrigiert für Alter, Geschlecht, Bildung und Gesamthirnvolumen) assoziiert. Final wurden nun die individuellen extremen Profile mit den abgeleiteten Gruppentrends verglichen.

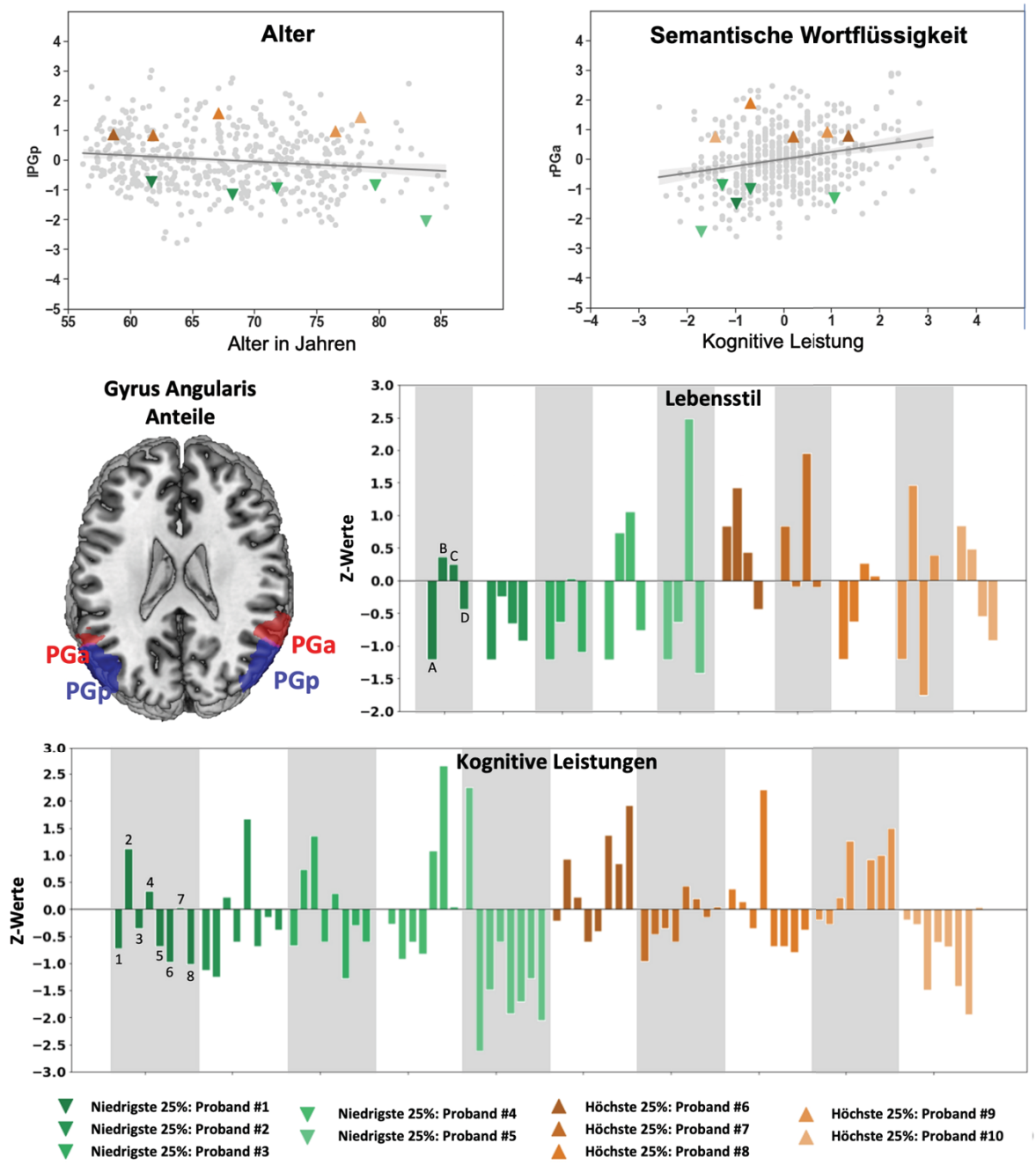

Abbildung 5: Oben links: Altersabhängige Unterschiede im Volumen der grauen Substanz für das Areal PGp der linken Hemisphäre; Oben rechts: Leistungsabhängige Unterschiede im Volumen der grauen Substanz für das Areal PGa der rechten Hemisphäre; Mitte links: Gyrus angularis Anteile PGa (rot) und PGp (blau). Mitte rechts: Lebensstilprofile der ausgewählten Probanden/-innen (A = Alkohol (ja/nein) - B = Sport - C = BMI - D = sozialer Integrationsindex) für diejenigen Variablen, die signifikante Einflüsse auf die GMV einer der Teile des Gyrus angularis aufweisen. Unten: Kognitive Profile der ausgewählten Probanden/-innen: 1 = Verarbeitungsgeschwindigkeit - 2 = logisches Denken - 3 = visuelles Arbeitsgedächtnis - 4 = verbales Arbeitsgedächtnis - 5 = figurale Flüssigkeit - 6 = semantische Wortflüssigkeit - 7 = phonematische Wortflüssigkeit (Wechselbedingung) - 8 = semantische Wortflüssigkeit (Wechselbedingung) (modifiziert nach Jockwitz, Kramer et al. (2022), mit freundlicher Genehmigung des Verlags, http://creativecommons.org/licenses/by/4.0/).

In den Gruppenanalysen zeigten sich heterogene Muster der Ganzhirn-Assoziationen mit dem regionalen Volumen der grauen Substanz, sowie der funktionellen und strukturellen Konnektivität. Hinsichtlich des Alters zeigten sich signifikante, aber geringe altersbedingte Abnahmen der grauen Substanz für alle Teile des Gyrus angularis. Darüber hinaus zeigte sich ein heterogener Zusammenhang zwischen dem Volumen der grauen Substanz der verschiedenen Teile des Gyrus angularis, den kognitiven Fähigkeiten und dem Lebensstil. Beispielsweise stand das Volumen der grauen Substanz des rPGa in einem positiven Zusammenhang mit der semantischen Wortflüssigkeit. Verglichen mit der Gesamtgruppe lässt sich aus den einzelnen Probanden/-innen folgendes ableiten: Alle zehn Probanden/-innen wichen deutlich von der Regressionslinie ab (Abbildung 5). Der Trend, der aus der Gruppenanalyse extrahiert werden konnte, dass zum Beispiel bessere kognitive Leistungen mit einem höheren Volumen der grauen Substanz einhergehen, lässt sich nicht auf die Ebene der einzelnen Probanden/-innen übertragen. Vielmehr zeigt jeder Proband ein individuelles Profil (siehe Abbildung 5 für Lebensstil und kognitive Profile). So liegt Proband #3 beim logischen Denken und beim visuellen Arbeitsgedächtnis über dem Durchschnitt und weist gleichzeitig eine unterdurchschnittliche semantische verbale Wortflüssigkeit und einen niedrigeren Index für die soziale Integration auf. Im Gegensatz dazu zeigt Proband #4, der ebenfalls kleine Volumina der grauen Substanz im Gyrus angularis aufweist, eine überdurchschnittliche Leistung in der semantischen und phonematischen Wortflüssigkeit und einen leicht überdurchschnittlichen BMI. Proband #10 weist ein hohes Volumen der grauen Substanz im Gyrus angularis auf, zeigt jedoch bei den meisten der vorgestellten kognitiven Aufgaben niedrige Leistungen. Diese individuellen Profile bestätigen somit, dass jede Person ihren eigenen kognitiven und Lebensstil-Fingerabdruck aufweist, mit unterschiedlichen Auswirkungen für verschiedene Faktoren, die sich nicht in den allgemeinen Gruppentrends widerspiegeln. Die zweite Studie komplementiert somit die erste Studie zur individuellen Phänotypisierung, da sowohl die Individuen, die in Bezug auf ihre kognitiven Leistungen einer

Extremgruppe angehören, als auch solche, die hinsichtlich ihrer Hirnstruktur einer Extremgruppe angehören, eigene Profile aufweisen. Daher kann zusammenfassend aus diesen beiden Studien der Schluss gezogen werden, dass globale Trends innerhalb der älteren Erwachsenenpopulation sorgfältig berücksichtigt werden müssen. Dies ist insbesondere von großer Notwendigkeit, wenn es um Präzisionsmedizin geht und persönliche Behandlungen neurodegenerativer Erkrankungen unerlässlich sind **(Jockwitz, Kramer et al. (2022); Publikation 5).**

Zusammenfassende Betrachtung der Resultate in Hinblick auf das alternde Gehirn

Die hier dargelegte kumulative Habilitation befasst sich mit der interindividuellen Variabilität des alternden Gehirns und greift zwei wichtige Aspekte der momentanen neurowissenschaftlichen Forschung auf: Das Thema der Generalisierbarkeit von Studienresultaten sowie die individuelle Phänotypisierung im höheren Lebensalter. Bisherige Studien zeigten auf Gruppenebene, dass die ältere Population vor allem durch eine erhöhte interindividuelle Variabilität charakterisiert werden kann, die nicht allein durch den Faktor ‚Alter' zu erklären ist (Mowinckel, Espeseth et al. 2012, Miller, Alfaro-Almagro et al. 2016, Bittner, Jockwitz et al. 2021, Jockwitz and Caspers 2021). Vielmehr scheinen andere Faktoren aus den Bereichen Genetik und Lebensstil in dieser Population an Relevanz zu gewinnen, die allesamt nur kleine Teile der Varianz erklären können (Jannusch, Jockwitz et al. 2017, Heim, Stumme et al. 2019, Caspers, Rockner et al. 2020, Nußbaum, Lucht et al. 2020, Bittner, Jockwitz et al. 2021, Glaubitz, Stumme et al. 2022, Gronewold, Jokisch et al. 2022, Lucht, Glaubitz et al. 2022). In Bezug auf die hohe Varianz zwischen älteren Erwachsenen scheint die Identifizierung von diesen eher kleinen Effekten schwierig und erfordert große Stichproben. Die Zusammenführung von unabhängigen Stichproben respektive die Durchführung von multizentrischen Studien, erreichen aus demselben Grund immer mehr Popularität in der neurowissenschaftlichen Forschungswelt, zum Beispiel im Rahmen von sogenannten genomweiten Assoziationsstudien (GWAS; aus dem englischen genome-wide association studies), die eine Identifizierung genetischer Polymorphismen im Zusammenhang mit bestimmten Erkrankungen ermöglichen (van Hoorn et al., 2004; Thompson et al., 2013). Der Frage, ob es auch in der Hirnforschung im Bereich der Alterung legitim ist, Studien zusammenzufassen, ohne damit Alterseffekte zu verschleiern oder gar in eine falsche Richtung zu bewegen, wurde im ersten Teil der Habilitationsschrift nachgegangen.

Die hier dargestellten Resultate zur Generalisierbarkeit des Faktors ‚Alter' zeigen, dass regional unterschiedliche Stichproben (Ruhrgebiet, Deutschland versus Zürich und Umgebung, Schweiz) hinsichtlich altersabhängiger Unterschiede und zeitlichen Veränderungen in der Hirnstruktur und kognitiven Leistungen generalisierbar sind, vorausgesetzt, die gleichen Methoden werden genutzt. Diese Beobachtung in der älteren Population deckt sich mit Studien, die sich mit der gesamten Population erwachsener Menschen beschäftigen (Fjell, Westlye et al. 2009, Walhovd, Westlye et al. 2011). Sie zeigt, dass es sich bei Studien, die für Alter und Geschlechtsverteilungen angepasst wurden, betreffend der Datenpooling Anwendungen um sehr repräsentative Stichproben handelt. Bezieht man diese Ergebnisse nun auf die bekannten, oben beschriebenen Alterungstheorien, wie die der Hirnreserve und der kognitiven Reserve, kristallisiert sich hier ein wichtiger Aspekt heraus. Probanden/-innen aus der LHAB Studie wiesen eine höhere Bildung und ein besseres körperliches Wohlbefinden auf, was in vorherigen Studien mit besserer kognitiver Leistung und einer besser erhaltenen Hirnstruktur im höheren Alter assoziiert wurde (Maitland, Intrieri et al. 2010, Kohncke, Laukka et al. 2016, Miller, Alfaro-Almagro et al. 2016, Lovden, Karalija et al. 2018, Bittner, Jockwitz et al. 2019, Heim, Stumme et al. 2019, Cole 2020, Bittner, Jockwitz et al. 2021, Gronewold, Jokisch et al. 2021, Bittner, Korf et al. 2022, Brouwer, Klein et al. 2022). Jedoch scheint es, dass trotz dieser Differenzen altersabhängige Unterschiede (im Querschnitt) und Veränderungen (im Längsschnitt) der Hirnstruktur und der kognitiven Leistungsfähigkeit zwischen unabhängigen Stichproben verglichen werden können. Der Verlauf von altersabhängigen Unterschieden beziehungsweise Veränderungen der Hirnstruktur als solcher scheint also trotz Unterschieden in den Stichprobencharakteristika ähnlich zu verlaufen. Damit konnten die bisherigen Studien bereits einen wichtigen Beitrag leisten, indem sie zeigten, dass dieser Aspekt nicht nur für Bildgebungskonsortien wie ENIGMA von Belang ist, in welchem bereits prozessierte Daten von unabhängigen Studien gesammelt werden. Hier zeigt sich auch eine wichtige Erkenntnis für multizentrische Studien

mit sowohl heterogenen Studienprotokollen und MRT-Geräten, wie zum Beispiel ADNI als auch mit homogenem Studienprotokoll und baugleichen MRT-Geräten wie beispielsweise NAKO, die Probanden/-innen aus unterschiedlichen geographischen Gebieten, z. B. innerhalb Deutschlands, rekrutieren.

Diese erste Schlussfolgerung ist jedoch zunächst auf den Faktor „Alter“ beschränkt. Die Resultate wiesen ebenfalls daraufhin, dass ein Zusammenschluss von unterschiedlichen Stichproben auch Effekte unterdrücken kann. Beispielsweise zeigte 1000BRAINS einen moderaten Effekt der Bildung auf das logische Denken. Bei LHAB hingegen zeigte sich dieser jedoch nicht. Das spricht dafür, dass die Generalisierbarkeit nicht notwendigerweise für alle Parameter gegeben ist. Protektive und Risikofaktoren, die die Reserve des Gehirns entweder positiv oder negativ beeinflussen können, scheinen somit unterschiedliche Auswirkungen auf Hirn und Verhalten in unabhängigen Stichproben zu haben. Die bisher allgemeingültigen Prinzipien zur Aufrechterhaltung der Hirnstruktur und den kognitiven Leistungen durch protektive Faktoren, wie zum Beispiel eine höhere Schulbildung, sind nach den hier dargestellten Resultaten nicht vollständig haltbar und damit im völligen Einklang mit der Heterogenität von Studienresultaten zur Reservekapazität. Während zum Beispiel einige Studien von einem protektivem Einfluss der Schulbildung auf die Hirnstruktur im höheren Alter berichten (Foubert-Samier, Catheline et al. 2012), zeigen andere Studie keinen (Bastin et al., 2012) oder sogar negative Einflüsse (Arenaza-Urquijo, Landeau et al. 2013) genau dieser Faktoren.

Unterschiedliche Resultate zwischen Studien werden häufig mit der hohen Variabilität in Methodik oder Stichprobencharakteristik erklärt (Oschwald, Guye et al. 2019). Um genau diese zu minimieren wurde in einer darauffolgenden Studie deshalb noch einmal ein weiterer Faktor in Betracht gezogen. Innerhalb der 1000BRAINS Studie wurden ältere Männer und Frauen hinsichtlich ihrer kognitiven Profile verglichen. Obwohl die Probanden somit keine stichprobenspezifischen Merkmale aufwiesen (beispielsweise durch unterschiedliche

Studiendesigns oder regionale Unterschiede) und Männer und Frauen zusätzlich hinsichtlich des Alters und der Bildung aufeinander angepasst wurden, zeigten sich signifikant unterschiedliche kognitive Profile für die beiden Geschlechter. Eine Zusammenfassung derer war hingegen nicht repräsentativ.

Insbesondere für die Alterungstheorien bedeutet dies, dass Gehirn-Verhaltens-Beziehungen erst auf eine Generalisierbarkeit geprüft werden sollten. Die Komplexität dieses Zusammenhangs zeigt beispielweise eine Studie von Mungas, Gavett et al. (2018). Während die Autoren keinen allgemeinen Zusammenhang zwischen Schulbildung und kognitiven Verfalls in einer Gruppe älterer Erwachsener fanden, änderte sich das Bild nachdem die Stichprobe nach dem Faktor Hirnatrophie geordnet wurde. Hier zeigte sich ein Zusammenhang zwischen einer hohen Schulbildung und einem langsameren kognitiven Verfall bei Personen mit geringer Atrophie, aber einem schnelleren kognitiven Verfall bei Personen mit größerer Atrophie. Die Ergebnisse dieser Studie verdeutlichen dadurch noch einmal, dass die Zusammenfassung von Daten falsch negative oder auch falsch positive Resultate produzieren könnte.

Auch im Bereich des Individuums zeigte sich, dass allgemeine Prinzipien von Gehirn-Verhaltens-Beziehungen nicht ohne weiteres auf jedes Individuum übertragen werden können. Abhängig von den zu ermittelnden Variablen passen einzelne Individuen nicht unbedingt auf die extrahierten Gruppenresultate. Dadurch kann es zu erheblichen Abweichungen kommen, was die Frage aufwirft, welche Bedeutung dies für die künftige Forschung im Bereich der kognitiven Neurowissenschaften hat. Insbesondere in der medizinischen Behandlung sind diese Resultate von extremer Notwendigkeit. Wendet man allgemeine Prinzipien von Gehirn-Verhaltens-Beziehungen auf klinische Fälle an, z. B. auf eine Gruppe von Alzheimer-Patienten, würde dies bedeuten, dass alle Patienten auf die gleiche Weise behandelt werden (Reitz 2016). Jedoch zeigt sich im Bereich der neurodegenerativen, wie auch in anderen psychiatrischen Erkrankungen (z. B. Depression), dass nicht jeder Patient auf die gleiche

Behandlung gleich reagiert (Reitz 2016). Vielmehr konnte in den dargestellten Studien gezeigt werden, dass nicht nur jede Stichprobe und Untergruppe (Publikation 1, 2, 3) sondern auch jedes Individuum (Publikation 4 und 5) seinen eigenen individuellen Fingerabdruck von Gehirn- und Verhaltensbesonderheiten aufweist. Obwohl die aus den Analysen auf Gruppenebene abgeleiteten Prinzipien natürlich einen Leitfaden für den/die durchschnittliche Probanden/-in oder Patienten/-in bilden, betonen die aktuellen individuellen Unterschiede, dass eine Charakterisierung auf individueller Ebene im Gegensatz zu den aus der Gruppe extrahierten Resultate ein unumgänglicher Schritt hin zu einer erfolgreichen Diagnostik und Behandlung sein muss (Reitz 2016, Zimmermann, Perry et al. 2018, Hahn and Lee 2019). Dazu ist es jedoch von besonderer Wichtigkeit, dass umfangreiche Datensätze zur Verfügung stehen, welche die verschiedenen Facetten der Gehirnorganisation, hinsichtlich Struktur, Funktion und Konnektivität, auf sowohl makroanatomischer als auch auf molekularer und genetischer Ebene, mit sich bringen. So können Gruppenresultate und individuelle Profile angereichert werden, um tiefgreifende und facettenreiche Charakterisierungen des Gehirns vorzunehmen (Amunts, Ebell et al. 2016, Jockwitz, Bittner et al. 2021, Jockwitz, Kramer et al. 2022).

Schlussfolgerung

Im Rahmen des demografischen Wandels und dem Ziel der WHO, den kognitiven Abbau zu verstehen und die gesunde Alterung durch präventive Maßnahmen zu fördern, um die Unabhängigkeit der älteren Bevölkerung so lange wie möglich zu erhalten, kann die hier dargestellte kumulative Habilitation einen Beitrag insbesondere auf methodisch-konzeptueller Ebene leisten. Die dargestellten Resultate weisen auf die Möglichkeiten der Zusammenschließung von Stichprobanden hin, zeigen aber auch die Gefahren der Übergeneralisierung von Effekten insbesondere im Hinblick auf die gängigen Alterstheorien. Basierend darauf geben die hier dargestellten Resultate einen Anreiz für eine zusätzliche

Betrachtung individueller Fälle mit multimodalen Datensätzen im höheren Alter. Nur so wird es in Zukunft möglich sein, die multifaktoriellen Einflussfaktoren der interindividuellen Varianz der Hirnalterung im späteren Lebensdekaden zu verstehen und den kognitiven Leistungseinbußen entgegenzuwirken.

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RESEARCH ARTICLE

Generalizing age effects on brain structure and cognition: A two-study comparison approach

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Abstract

Normal aging is accompanied by an interindividually variable decline in cognitive abilities and brain structure. This variability, in combination with methodical differences and differences in sample characteristics across studies, pose a major challenge for generalizability of results from different studies. Therefore, the current study aimed at cross-validating age-related differences in cognitive abilities and brain structure (measured using cortical thickness [CT]) in two large independent samples, each consisting of 228 healthy older adults aged between 65 and 85 years: the Longitudinal Healthy Aging Brain (LHAB) database (University of Zurich, Switzerland) and the 1000BRAINS (Research Centre Jülich, Germany). Participants from LHAB showed significantly higher education, physical well-being, and cognitive abilities (processing speed, concept shifting, reasoning, semantic verbal fluency, and vocabulary). In contrast, CT values were larger for participants of 1000BRAINS. Though, both samples showed highly similar age-related differences in both, cognitive abilities and CT. These effects were in accordance with functional aging theories, for example, posterior to anterior shift in aging as was shown for the default mode network. Thus, the current two-study approach provides evidence that independently on heterogeneous metrics of brain structure or cognition across studies, age-related effects on cognitive ability and brain structure can be generalized over different samples, assuming the same methodology is used.

KEYWORDS

aging, brain structure, cognition

1 | INTRODUCTION

As we get older, our brain undergoes substantial structural changes that seem to be related to changes in behavior (i.e., cognitive decline in older adults). However, previous research has shown that it is far from simple to bring the two domains—namely brain structure and behavior—together (Fjell et al., 2006; Jockwitz et al., 2017; Liu et al., 2011; Raz & Rodrigue, 2006; Ziegler, Dahnke, Gaser, & Alzheimer's Disease Neuroimaging, 2012). One important reason for this is that age-related changes in both domains are complex and insufficiently understood. For example, large between-study heterogeneity of designs and methods, differences in sample characteristics and the generally larger interindividual variability in samples of older adults hamper the extraction of consistent findings regarding age-related changes in brain structure in the existing literature.

Still, what we can conclude from previous work so far is that effects of age are not homogeneous across the brain, but depend on (a) the functional properties of the brain region of interest (e.g.,

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association cortices vs. primary sensory cortices), (b) the brain tissue (e.g., gray and white matter), (c) the brain structure metric looked at (e.g., brain volume-based vs. surface-based metrics or cortical thickness [CT] vs. surface area), and (d) methodological choices made during processing and analyses (e.g., differences in spatial smoothing) (Dickie et al., 2013; Fjell et al., 2014; Fjell, McEvoy, et al., 2014; Hogstrom, Westlye, Walhovd, & Fjell, 2013; Liem et al., 2015; O'Sullivan et al., 2001; Salat et al., 2005; Sowell et al., 2003; Walhovd et al., 2011; Ziegler, Dahnke, Jancke, et al., 2012).

Although there is a more solid database when it comes to cognitive aging (Schaie (1993); Schaie and Willis (2010); Schaie, Willis, and Caskie (2004); for reviews, see Harada, Love, and Triebel (2013); Kaup, Mirzakhanian, Jeste, and Eyler (2011); Salthouse (2010) it has also been established that—in analogy to brain aging—age-related changes in cognitive abilities are complex. First, different cognitive abilities are differentially sensitive to age effects. Abilities such as processing speed, executive functions, episodic, and working memory have shown to be more vulnerable to age-related decline as compared to verbal memory and world knowledge (Habib, Nyberg, & Nilsson, 2007; Hedden & Gabrieli, 2004; Park & Reuter-Lorenz, 2009; Schaie et al., 2004; Schaie & Willis, 2010). And second, several studies suggest that cognitive performance follows nonlinear trends from early to late adulthood with a higher interindividual variability in older adults (Habib et al., 2007; Hartshorne & Germine, 2015; Hedden & Gabrieli, 2004). Hence, it is difficult to generalize results from one sample to another and, therefore, to draw reliable conclusions. Considering, for example, that lifespan trajectories of structural atrophy vary between brain regions (Fjell et al., 2013; Hogstrom et al., 2013; Sowell et al., 2003; Walhovd et al., 2011; Ziegler, Dahnke, Jancke, et al., 2012), age-related differences in brain atrophy might not be replicable across samples when they do not match with respect to age distributions or other sample characteristics.

At this time, there is a clear progress toward brain imaging consortia and multicenter studies, such as ENIGMA (Thompson et al., 2014), the German National Cohort study (Nationale Kohorte; NAKO (Bamberg et al., 2015; German National Cohort, 2014), ADNI (Alzheimer's Disease Neuroimaging Initiative; Jack Jr. et al., 2008), U.K. Biobank (Miller et al., 2016; Sudlow et al., 2015), or Lifebrain (Walhovd et al., 2018). In the field of healthy aging, such projects use data pooling procedures (i.e., joint analysis of data from different independent samples) to fulfill the need for large sample sizes required to identify protective and risk factors that in combination might explain why some older adults develop neurodegenerative diseases, while others retain their cognitive integrity until very old. What comes along with this, however, is the necessity for a cross-validation of so far established results concerning the aging brain. Thus, the question that arises is whether independent samples of older adults that differ in demographics and lifestyle factors would still show similar association patterns between age, global and regional brain structure, and cognitive performance. While in the field of genetics, replication studies are already well established, it is not yet common practice in the field of neuroimaging. Therefore, the current study analyzed age-related differences in brain structure and cognitive ability in two large independent but closely matched cohorts of older adults—both situated in central Europe—to explore how similar results are when using the same state-of-the-art methodological protocols and what factors may explain potential between-study differences.

Regarding brain structure, we used mean CT for the two hemispheres as a rough outcome measure. In addition to that, we decided to focus on brain regions that constitute the default mode network (DMN), a network that recently received much attention in aging research—especially with regard to functional connectivity (e.g., Hafkemeijer, van der Grond, & Rombouts, 2012). Because recent evidence from our group suggests a structural correlate for age differences in functional connectivity (Jockwitz et al., 2017), we were particularly interested to validate such first findings and assessed regional within-network differences of the age-brain structure relationships.

2 | METHODS

Participants included in the current research project were recruited from two independent samples investigating brain–behavior relationships in older adults located in the larger Zurich area (Switzerland) and in the Ruhr district (Germany).

One sample comprised the ongoing Longitudinal Healthy Aging Brain (LHAB) database project at the University Research Priority Program "Dynamics of Healthy Aging" of the University of Zurich (Zollig et al., 2011). LHAB investigates age-related dynamics of brain–behavior relationships in healthy older adults. A particular focus is placed on assessing and explaining interindividual variability in the observed aging trajectories, thus a broad spectrum of factors that supposingly influence such trajectories (i.e., lifestyle, sleep, and nutrition) is collected. In LHAB, older adults from Zurich and surrounding areas aged 65 and older (at baseline) are observed longitudinally with between-measurement intervals of 1–2 years. Besides the eligibility requirements for the MR acquisition, further exclusion criteria were neurological and psychiatric diseases, a score on the Mini-Mental State Examination of 26 and below and left handedness. LHAB participants are German native speakers or at least as proficient in German as it would be their native language. The study protocol was approved by the local Ethics Committee (Kantonale Ethikkommission Zurich). The initial sample of LHAB comprised 231 participants ranging from 64 to 87 years of age. Data acquisition in the LHAB project started in 2011. Currently, the data set covers an observation period of 4 years.

The second sample comprised 1000BRAINS at the Institute of Neuroscience and Medicine, Research Centre Jülich, a longitudinal population-based study that assesses variability in brain structure and function during aging (Caspers et al., 2014). The 1000BRAINS sample is drawn from the 10-year follow-up cohort of the Heinz Nixdorf Recall Study, an epidemiological population-based study of risk factors for atherosclerosis, cardiovascular disease, cardiac infarction, and death (Schmermund et al., 2002) and the affiliated MultiGeneration study. In 1000BRAINS, older adults aged 55 and older (at baseline) from the Heinz Nixdorf Recall study and their relatives (spouses and offspring; sampled from MultiGeneration study) are recruited, measured two times over a period of about 3–4 years. Exclusion from the study was dependent on the eligibility requirements for the MR acquisition based on the MR safety guidelines only (e.g., stents and heart pacemaker led to exclusion from the study). The study protocol

was approved by the University of Duisburg-Essen. The initial sample of 1000BRAINS comprised 1,317 participants ranging from 18 to 87 years of age.

For the aim of the current study, we focused on the first time point in both samples. Participants with missing values for the whole neuropsychological and/or brain data were excluded. Furthermore, participants were matched with respect to the age ranges in the two samples. Therefore, we first excluded 666 participants from 1000BRAINS being younger than 64 years of age. Afterward, we matched the two samples for gender and group size by randomly selecting the same number of participants within each age and gender group (64–69 years, 70–74 years, 75–79 years, and 80–85 years). This resulted in 228 participants for each of the two final samples: (a) LHAB: mean age: 70.7 years ± 4.9, 114 males, and 114 females; (b) 1000BRAINS: mean age: 70.7 ± 5.0 years, 114 males, and 114 females. For an overview of demographic variables of the two samples, see Table 1. Both studies assessed years of formal education as part of a structured anamnestic interview. In addition, all participants filled in a questionnaire concerning their physical and mental well-being (LHAB: SF12; 1000BRAINS: SF36). In both samples, physical and mental health status scores (Ware, Keller, & Kosinski, 1995) were computed using only the SF12 items in order to assure comparability. Furthermore, global cognition was assessed in both samples. While participants from LHAB performed the Mini-Mental State Examination (Folstein, Robins, & Helzer, 1983), participants from 1000BRAINS performed the DemTect in order to estimate a global cognitive status for each participant (Kalbe et al., 2004).

2.1 | Cognitive performance

Participants from both LHAB and 1000BRAINS took part in a large neuropsychological assessment consisting of tests in the domains attention, executive functions, working memory, episodic memory, and language functions. For comparison between the two samples, the following tasks were chosen: Trail Making Test (TMT; processing speed and concept shifting; Morris et al. (1989)), Leistungsprüfungssystem 50+ (LPS50+) Subtest 3 (reasoning; Sturm, Willmes, and Horn (1993)), Regensburger Wortflüssigkeitstest (RWT, semantic condition (verbal fluency); Aschenbrenner, Tucha, and Lange (2000)) and vocabulary tests (LHAB: Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B; Lehrl (2005)), 1000BRAINS: Wortschatztest (WST); Schmidt and Metzler (1992)). To extract comparable scores from the two vocabulary tests, we calculated the ratio between the total amount of words (MWT_B: 37 words; WST: 40 words) and the amount of correctly identified words. Since the selected neuropsychological tests were not normally distributed, all cognitive tests were first rank-transformed and mean-centered afterward before entering the statistical analysis. For a detailed test description, administration differences between samples and mean values per sample, see Table 2.

2.2 | Data acquisition

For LHAB, data were acquired on a 3.0T Philips Ingenia scanner (Philips Medical Systems, Best, The Netherlands). T1-weighted structural brain images were measured per visits with: TR = 8.18 ms, TE = 3.8 ms, flip angle = 8°, field of view (FoV) = 240 × 240 mm, isotropic voxel size = 1 × 1 × 1 mm, 160 slices per volume. For 1000BRAINS, data were acquired on a 3.0T Tim-Trio MR scanner (Siemens Medical System, Erlangen, Germany). The T1-weighted structural brain images were scanned per visit with: TR = 2.25 s, TE = 3.03 ms, flip angle = 9°, FoV = 256 × 256 mm, voxel resolution = 1 × 1 × 1 mm, 176 slices per volume. In both studies, T1-imaging was part of a larger MR imaging protocol (see Caspers et al., 2014; Zollig et al., 2011).

2.3 | Preprocessing

Anatomical images from both samples were preprocessed using the same automated surface-based processing stream of the FreeSurfer Software package (version 6.0.0). For the LHAB sample, this was done via the FreeSurfer BIDS App (v6.0.0-2; Gorgolewski et al. (2017). A detailed description of this pipeline is provided by Dale, Fischl, and Sereno (1999) as well as on http://surfer.nmr.mgh.harvard.edu. In short, the surface reconstruction pipeline includes (a) the segmentation of the structural brain images into gray matter, white matter, and cerebrospinal fluid, (b) motion correction, (c) intensity normalization, (d) transformation into Talairach space, (e) tessellation of gray/white matter boundary, and (f) correction of topological defects. The gray/white matter interface was then (g) expanded to create the pial surface (boundary between gray matter and cerebrospinal fluid), which finally consists of about 150,000 vertices per hemisphere with an average surface area of 0.5 mm^2. Afterwards, (h) CT was calculated for each vertex as the shortest distance between the white matter surface and the corresponding

TABLE 1 Demographics of the two samples (1000BRAINS and LHAB). Mean values and *SD* of raw scores as well as group comparisons including *T* statistics, *p*-values, and effect sizes

	1000BRAINS	LHAB	Levene test of equal variances (*F*/*p*-value)	*T* test for equality of means (*T*/*p*-value)	Cohen's *d*
Age (years)	70.69 ± 4.95	70.69 ± 4.89	0.056/0.814	–0.005/0.996	<0.001
Gender	114 m/114 f	114 m/114 f	NA	<0.001/1.00	<0.001
Education (years)	13.51 (±3.76)	14.66 (±3.43)	0.398/0.529	–3.40/0.001	0.320
Physical WB	48.69 (±8.10)	51.06 (±7.21)	4.44/0.036	–3.31/0.001	0.309
Mental WB	54.39 (±6.83)	55.06 (±5.84)	8.38/0.004	–1.12/0.263	0.105
Dementia screening	14.55 (±3.76) (DemTect)	28.83 (±1.02) (MMSE)	NA/NA	NA/NA	NA

LHAB = Longitudinal Healthy Aging Brain; WB = well-being. *Note.* NA: not applicable since different tests were used that are not directly comparable.

TABLE 2 Overview of administered cognitive test. Test description and differences in test administration (if applicable), raw scores, and *SD* of performance in the two samples as well as group comparisons including *T* statistics, *p*-values, and effect sizes

	Test description	Differences in administration	1000BRAINS	LHAB	Levene test of equal variances (*F*/*p*-value)	*T* test for equality of means (*T*/*p*-value)	Cohen's *d*
Processing speed (TMT A)	Time (s) to connect randomly arranged digits in ascending order	–	43.48 (±15.71)	39.37 (±14.55)	1.85/0.175	−2.89/0.004	−0.271
Concept shifting (TMT B–A)	Time difference (s) between connecting alternately numbers and letters in ascending order (Part B) and randomly arranged digits in ascending order (Part A)	–	62.30 (±48.37)	53.79 (±28.13)	15.10/<0.001	−2.30/0.022	−0.215
Reasoning (LPS50+, Subtest 3)	Total number of correctly identified irregularities in rows of geometric figures within 5 min	–	19.37 (±5.14)	23.23 (±4.54)	3.30/0.070	−8.50/<0.001	0.796
Verbal fluency (RWT, semantic)	Total number of produced words belonging to a specific category in 2 min	1000BRAINS: category = jobs; overtly naming LHAB: category = animals; writing	22.26 (±6.71)	25.44 (±6.30)	1.49/0.224	−5.21/<0.001	0.489
Vocabulary (WST/MWT-B)	Total number of correctly identified real words within rows of five pseudowords divided by total amount of rows	1000BRAINS: WST, LHAB: MWT-B	0.76 (±0.14)	0.88 (±0.07)	51.18/<0.001	−12.10/<0.001	1.08

LHAB = Longitudinal Healthy Aging Brain; RWT = Regensburger Wortflüssigkeitstest; TMT = Trail Making Test; LPS50+ = Leistungsprüfungssystem 50+; WST = Wortschatztest; MWT = Mehrfachwahl-Wortschatz-Intelligenztest.

vertex on the pial surface. No manual correction of the reconstructed surfaces (white matter, pial surface) was performed in the two studies.

For the purpose of the current study, mean measurements of CT per hemisphere were extracted from FreeSurfer (Fischl and Dale, 2000). In addition, CT was determined for six regions of interest belonging to the DMN, a bilateral network composed of the medial prefrontal cortex (anterior DMN), the posterior cingulate cortex/precuneus (medial posterior DMN) as well as the inferior parietal lobule (lateral posterior DMN). Those regions have been defined for the purpose of a previous study and are described in detail by Jockwitz et al. (2017). In short, functional resting state scans from 691 subjects in 1000BRAINS were preprocessed using the preprocessing pipeline provided by the FSL software package 5.0 (including denoising strategies: FIX; Griffanti et al. (2014); Salimi-Khorshidi et al. (2014)). Afterwards, the DMN was extracted using an independent component analysis (ICA; MELODIC, implemented in FSL). To provide high reliability, this procedure was repeated 100 times (each sample consisted of 200 subjects). Finally, the resulting probability map was thresholded at 95% (using fslmaths, FSL) and binarized.

2.4 | Statistical analysis

The purpose of the current study was to compare age-related differences in cognitive abilities and CT in two large independent samples of older adults. Therefore, we first assessed general differences in sample characteristics (i.e., demographic variables), as well as cognitive abilities and CT (i.e., mean CT per hemisphere and regions of the DMN) using independent samples *T* tests. Thereafter, we assessed the following general linear models for each sample individually: (a) age-related differences in CT, (b) age-related differences in cognitive abilities, and (c) the relation between CT and cognitive abilities. To correct for possible factors that might influence the relation between age and cognitive abilities and CT, different models were set up including several covariates of no interest. The BASE model included the factors age and gender. The MAIN model was set up with age, gender, and education as factors, and the SENS (sensitivity) model included the factors age, gender, education as well as mental and physical well-being. Results were corrected for multiple comparisons using the Bonferroni approach. To test whether trajectories of age-related differences in the different dependent variables (cognitive abilities and CT) are comparable between the two samples, we calculated correlations between age and cognitive abilities and CT (while correcting for gender and education; MAIN) and compared them using Fisher's *Z* test (Eid, Gollwitzer, & Schmitt, 2011). Finally, in a supplementary analysis, we assessed age-related differences in terms of cognitive performance and CT in a joint analysis (pooled samples), with additionally including "sample" as covariate (for results, see Supporting Information). The reason for this was an additional validation whether the results obtained by the "individual analyses" versus the "joint analysis" would be comparable in the current study.

3 | RESULTS

When matching the two independent samples for age and gender, the two samples differed in both, demographic variables and cognitive performance. For raw scores and *T* statistics and Cohen's *d*, see Table 1 (Cohen's $d < 0.5$ = small; $d < 0.8$ = medium, and $d > 0.8$ = large). In more detail, participants from LHAB generally had a significantly higher formal education (years of education: $T = -3.4$; $p = 0.001$; $d = 0.32$) and higher physical well-being ($T = -3.31$; $p = 0.001$; $d = 0.31$) as compared to participants from 1000BRAINS. Mental well-being, however, did not differ between the two samples ($T = -1.12$; $p = 0.263$; $d = 0.11$).

With respect to cognitive abilities, we found that participants from LHAB showed better performance as compared to participants from 1000BRAINS in all psychometric tests assessed (processing speed: $T = -2.89$; $p = 0.004$; $d = 0.271$, concept shifting: $T = -2.30$; $p = 0.022$; $d = 0.215$, verbal fluency: $T = -5.21$; $p < 0.001$; $d = 0.489$, reasoning: $T = -8.50$; $p < 0.001$; $d = 0.796$ and vocabulary: $T = -12.10$; $p < 0.001$; $d = 1.08$; for detailed information, see Table 2).

When comparing structural brain metrics, we observed higher values for the participants from 1000BRAINS as compared to participants from LHAB, that is, total mean CT for right and left hemispheres, (right: $T = 6.13$; $p < 0.001$; $d = 0.714$; left: $T = 7.62$; $p < 0.001$; $d = 0.574$). The same was found for CT within the different parts of the DMN (left aDMN: $T = 7.11$; $p < 0.001$; $d = 0.665$; right aDMN: $T = 5.02$; $p < 0.001$; $d = 0.470$; left medial pDMN: $T = 2.52$; $p = 0.012$; $d = 0.236$; right medial pDMN: $T = 4.79$; $p < 0.001$; $d = 0.448$; left lateral pDMN: $T = 6.93$; $p < 0.001$; $d = 0.649$; right lateral pDMN: $T = 4.48$; $p < 0.001$, $d = 0.420$).

In the following analyses, the relation between age and cognitive performance and CT, respectively, was assessed using different models (BASE, MAIN, and SENS). With respect to BASE (covariate: gender), we found age-related differences for most of the cognitive tasks (i.e., lower cognitive performance in older adults). Effect sizes, measured using partial eta square were estimated as small to moderate (partial eta square is measured as the proportion of the total variance explained by the independent variable while correcting for the other independent variables, with partial eta square <0.01 is ranked as small; <0.06 as medium and >0.14 as large (Field, 2005; Richardson, 2011). Performance on the vocabulary tests remained stable across the ages in both samples. Almost all of these results remained significant in the MAIN model (covariates: age, gender, years of education; only exception: verbal fluency in 1000BRAINS did not survive correction for multiple comparisons) and in the SENS model (covariates: age, gender, years of education, mental well-being, and physical well-being; exceptions: verbal fluency and concept shifting did not survive correction for multiple comparisons). Importantly, age-related differences were highly similar in the two samples (see Figure 1; results based on MAIN model: Fisher's *Z*: processing speed <0.001 [$p = 0.251$]; concept shifting = −0.67 [$p = 0.503$]; reasoning = 1.28 [$p = 0.200$]; verbal fluency = 1.45 [$p = 0.147$]; vocabulary = −1.5 [$p = 0.134$]). For profile plots showing the effects of the different covariates (age, gender, years of education, mental well-being, and physical well-being), see Figure 2. Table S1 (see Supporting Information) contains the detailed statistics for the age differences in cognitive performance and for the effects of the covariates of no interest (gender, years of education, mental, and physical well-being).

In the second part of our analysis, we assessed age-related differences in mean CT within left and right hemisphere (Figure 3, for effects sizes, see Figure 4, for statistics, see Table S2, Supporting Information), as well as parts of the DMN (see Figure 5; left and right: anterior DMN, medial posterior DMN, and lateral posterior DMN, for effect sizes, see Figure 6, for statistics, see Figure S3, Supporting Information). In our two samples, we find mean CT differences with age for the two hemispheres (left hemisphere: $F = 33.24$ [$p < 0.001$], right hemisphere: $F = 40.15$ [$p < 0.001$]; Table S2, see Supporting Information). With respect to regional differences in the association between CT and age, we found more pronounced age differences in CT for the posterior as compared to the anterior parts of the DMN (Table S3, see Supporting Information). For both samples, we found that for the left and right medial and lateral posterior DMN CT was smaller with higher age with a moderate effect size (partial eta square ranged from 0.07 to 0.12 in 1000BRAINS and from 0.08 to 0.13 in LHAB). Again, these effects were highly similar in the two samples (Fisher's *Z*: left medial posterior DMN = 0 [$p = 1$]; left lateral posterior DMN = −0.34 [$p = 0.734$]; right medial posterior DMN = −0.95 [$p = 0.342$]; right lateral posterior DMN = −0.82 [$p = 0.412$]; left anterior DMN = 0.11 [$p = 0.913$]; right anterior DMN = 1.2 [$p = 0.230$]).

Moreover, we assessed the relation between age (and other demographics), CT (of the DMN ROI's), and cognitive performance, with age and CT of the six ROIs being independent variables and cognitive performance being the dependent variable. Only the relations between age and cognitive performance (partial eta square ranged from 0.02 to 0.073 in 1000BRAINS and from 0.039 to 0.102 in LHAB) and education and cognitive performance (partial eta square ranged from 0.047 to 0.243 in 1000BRAINS and from 0.051 to 0.116 in LHAB) remained significant even when including all covariates into one model with small to moderate effect sizes. For all other factors, none of the analyses revealed significant results (after correction for multiple comparisons) in any of the two samples (Table S4; see Supporting Information).

In subsequent analyses, we also assessed age-related differences of CT and cognitive abilities in a joint analysis for the two samples to additionally validate the results obtained by the individual analyses of the two samples. Here, again, the pooled sample showed age-related differences in both, cognitive abilities (exception: vocabulary) as well as for the posterior parts of the DMN. In addition, the relation between CT and cognitive performance remained nonsignificant even when the two samples were analyzed in one statistical model. For a detailed overview of statistics, see Tables S1–S4 (Supporting Information).

Furthermore, assessing nonlinear effects of age (age^2) on CT and cognitive performance (corrected for gender, education, physical, and mental well-being) revealed no significant results after correction for multiple comparisons (for statistics, see Tables S5 and S6, Supporting Information). Finally, to rule out confounding of differences in data or surface reconstruction quality, we performed a supplementary analysis of the relation between age and CT in the DMN while including

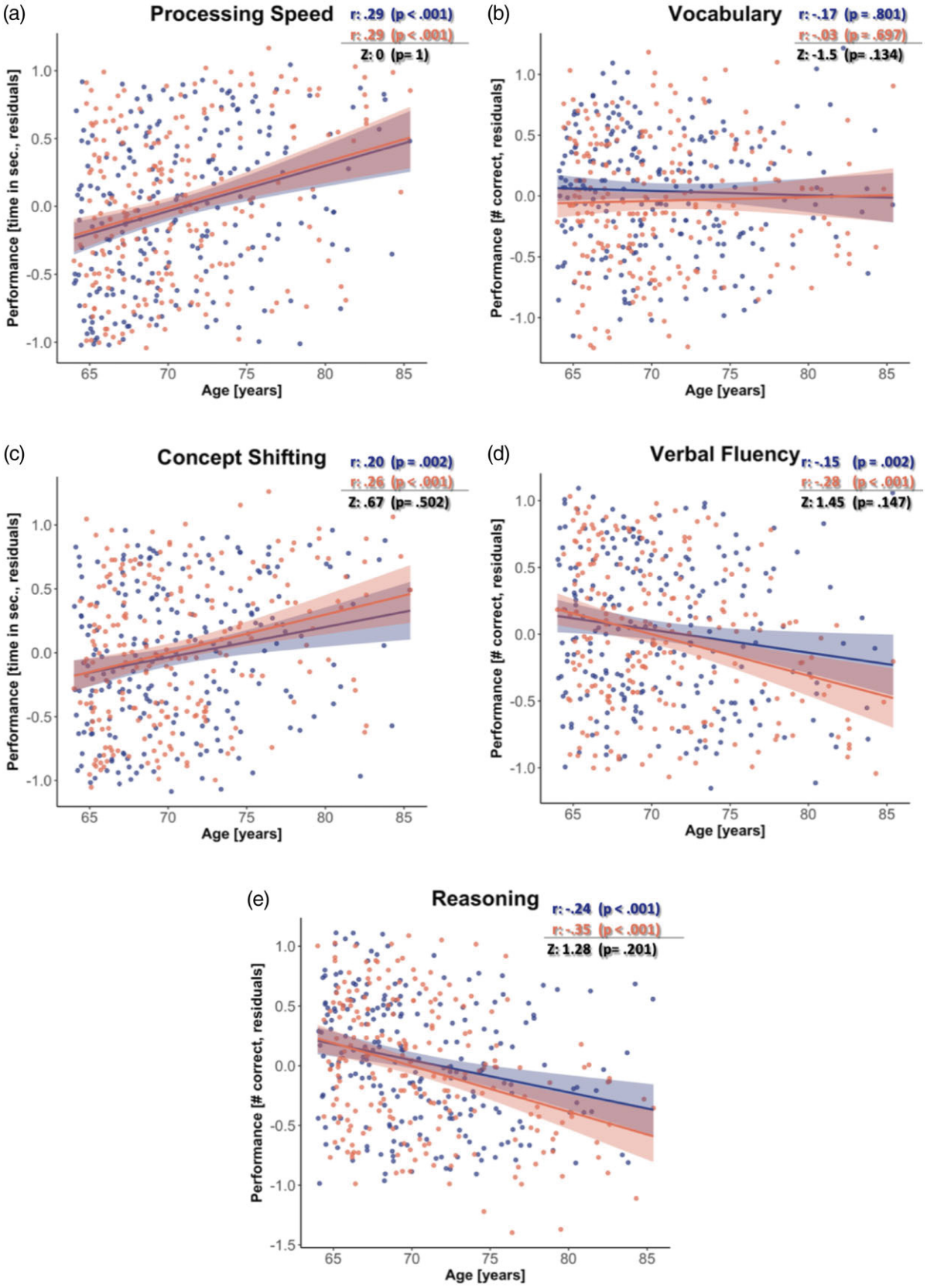

FIGURE 1 Relation between age and cognitive performance (residuals, corrected for gender and education) for the two samples, including regression lines, 95% confidence intervals, correlation coefficients, corresponding *p*-values as well as the Fisher's *Z* test statistic and corresponding *p*-value. 1000BRAINS is presented in blue and LHAB is presented in orange: (a) processing speed; (b) vocabulary; (c) concept shifting; (d) verbal fluency; and (e) problem solving. LHAB = Longitudinal Healthy Aging Brain [Color figure can be viewed at wileyonlinelibrary.com]

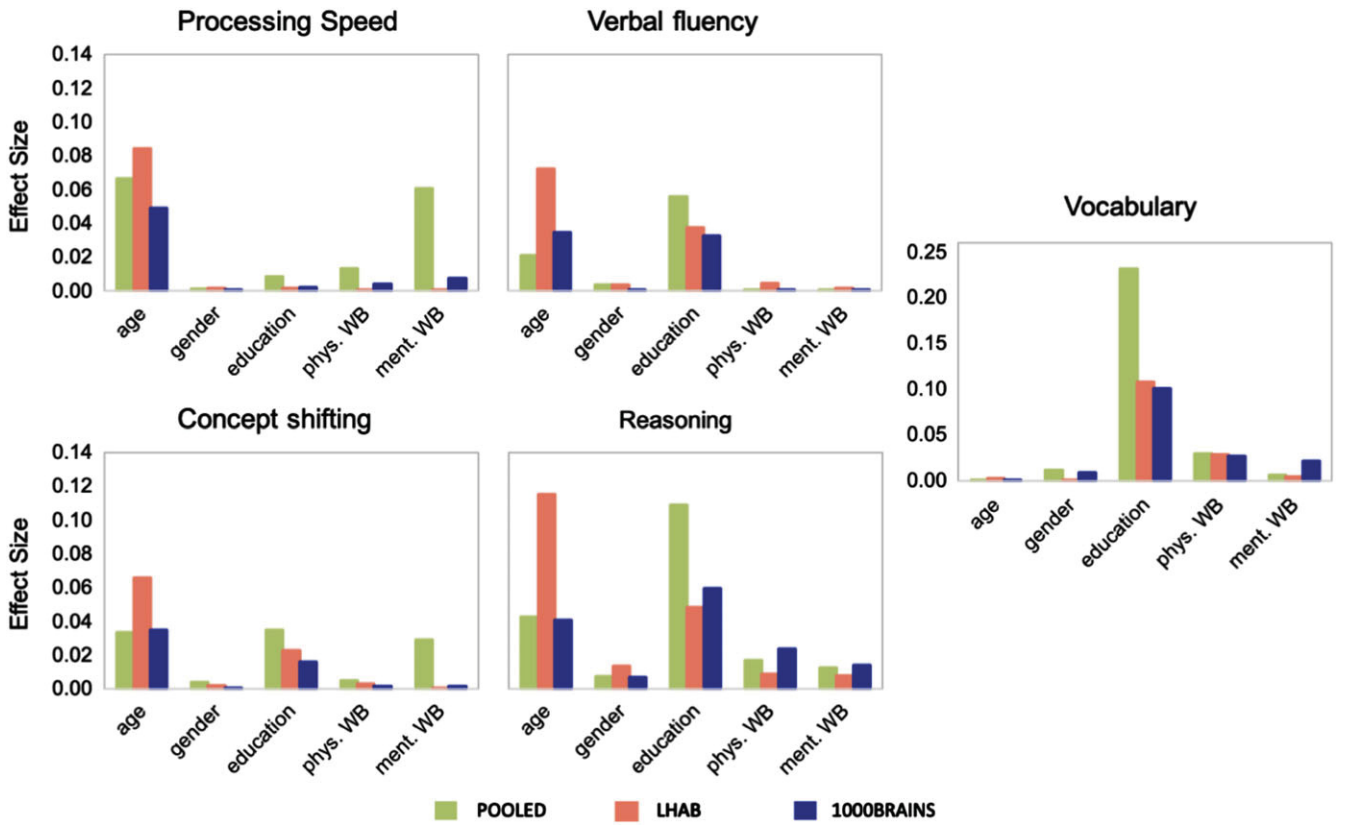

FIGURE 2 Profile plots of effect sizes (partial eta square) for cognitive performance with all covariates assessed: age, gender, education, physical WB, and mental WB 1000BRAINS are presented in blue, LHAB is presented in orange and the pooled data set is represented in green. LHAB = Longitudinal Healthy Aging Brain, WB = well-being [Color figure can be viewed at wileyonlinelibrary.com]

quality measurements (contrast to noise ratio for general data quality and Euler Numbers for quality of the surface reconstructions) as additional covariates to the SENS model. Age-related differences in CT remained stable even when including these quality control parameters to the general linear model, that is, age-related differences in CT for all posterior parts of the DMN but not the anterior DMN. For detailed statistics including group means and comparison, as well as general linear models, see Tables S7 and S8, Supporting Information.

Taken together, participants from LHAB seem to show a general superiority in cognitive performance as compared to participants from 1000BRAINS. However, the analysis of age-related differences in cognitive performance and global and regional metrics of CT revealed similar results in both samples.

4 | DISCUSSION

The present study assessed age-related differences in cognitive abilities (processing speed, concept shifting, reasoning, verbal fluency, and vocabulary) and brain structure (measured by global and regional CT) in two closely matched samples of older adults. Despite significant differences in demographics between the two independent samples, we observed highly similar patterns of age-related differences in both, cognitive abilities and brain structure, when using the same methodological approach.

4.1 | Comparability of independent samples of older adults

In times of population aging, there is an increasing interest in assessing risk and protective factors that promote brain and cognitive health until old age. Especially in older adults, however, there is an enormous amount of variability between individuals regarding brain structure and cognitive abilities and the "biological age" does not prove itself sufficient to explain this variability (Goh & Park, 2009; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Lustig, 2005; Reuter-Lorenz & Park, 2014). Previous research rather suggests that interindividual differences in variables such as education, lifestyle habits, or genetic markers should be taken into consideration to explain why some older adults exhibit decline (up to developing neurodegenerative diseases), while others are able to retain their level of functioning until old age (Barnard et al., 2014; Kohncke et al., 2016; Laukka et al., 2013; Lovden et al., 2017; Raz et al., 2005; van Hooren et al., 2007). The problem with identifying such factors is that single risk or protective factors only explain small parts of the interindividual variance regarding cognitive performance and brain structure in the older adult population, which necessitates large sample sizes to increase statistical power to uncover these small effects (Button et al., 2013). One promising approach here is the pooling of existing data, that is, the joint analysis of different samples. Data pooling with different samples covering the whole adult age range revealed

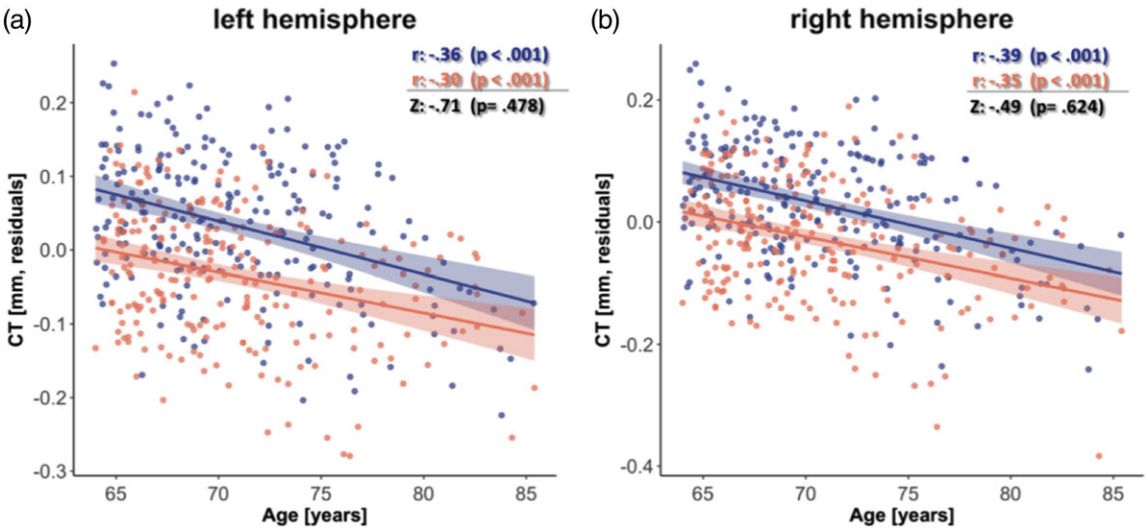

FIGURE 3 Relation between age and mean cortical thickness (residuals, corrected for gender and education) for the two samples, including regression lines, correlation coefficients, and corresponding *p*-values, as well as the Steiger's *Z* test statistic and corresponding *p*-value. 1000BRAINS is presented in blue and LHAB is presented in orange: (a) left hemisphere and (b) right hemisphere. LHAB = Longitudinal Healthy Aging Brain [Color figure can be viewed at wileyonlinelibrary.com]

age-related differences in terms of CT (Dickerson et al., 2008; Fjell et al., 2009; Jahanshad & Thompson, 2017; Jovicich et al., 2013). However, one has to keep in mind that data pooling across different study populations, might lead to an intermixture of sample-specific biological as well methodological variability which might result in an absence of effects, especially when assessing heterogeneous populations such as older adults. Differences in demographics, methods applied as well as scanner variability have been proposed to be main factors that lead to the heterogeneity of results in terms of brain structure and function in older adults in the field of neuroscience (Afonso et al., 2017; Han et al., 2006; Hanggi et al., 2015; Jancke, Merillat, Liem, & Hanggi, 2015; Kohncke et al., 2016; Liem et al., 2015; Lovden et al., 2017; Trachtenberg et al., 2012). The two samples used in the current study, LHAB and 1000BRAINS, represent such heterogeneous study populations consisting of older adults. Therefore, in the interest of the current study, we individually characterized and compared two different independent samples in terms of demographics, cognitive abilities, and their relationship with brain aging.

LHAB has its focus on healthy older adults excluding participants with a history of neurological diseases and cognitive impairment (Zollig et al. (2011). On the other hand, 1000BRAINS is conducted as a population-based epidemiological cohort study, excluding subjects only if they do not meet the eligibility requirements for the MR acquisition based on the MR safety guidelines (Caspers et al. (2014). Thus, although in the current study, we assured that the two samples would not differ in their age ranges and gender distribution, the two samples differed in several sample characteristics. Participants from LHAB on average had more years of education, as well as a higher physical well-being as compared to participants from 1000BRAINS. This result is completely in line with the observations made by the Organization for Economic Co-operation and Development, namely

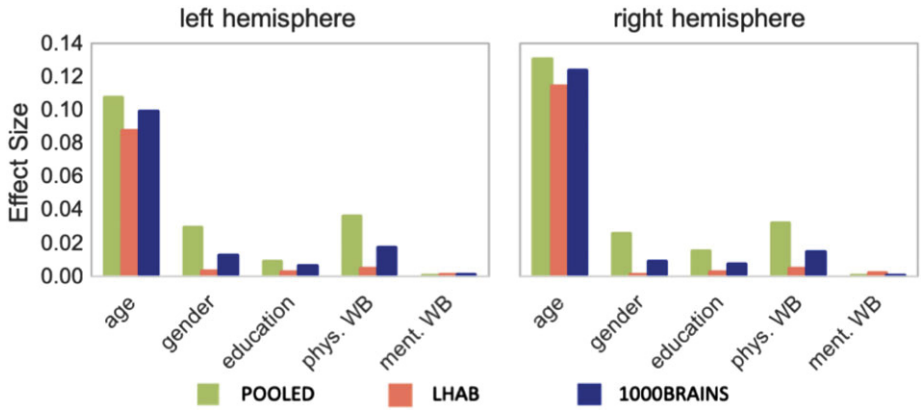

FIGURE 4 Profile plots of effect sizes (partial eta square) for mean cortical thickness with all covariates assessed: age, gender, education, physical WB, and mental WB 1000BRAINS are presented in blue, LHAB is presented in orange, and the pooled data set is represented in green. LHAB = Longitudinal Healthy Aging Brain, WB = well-being [Color figure can be viewed at wileyonlinelibrary.com]

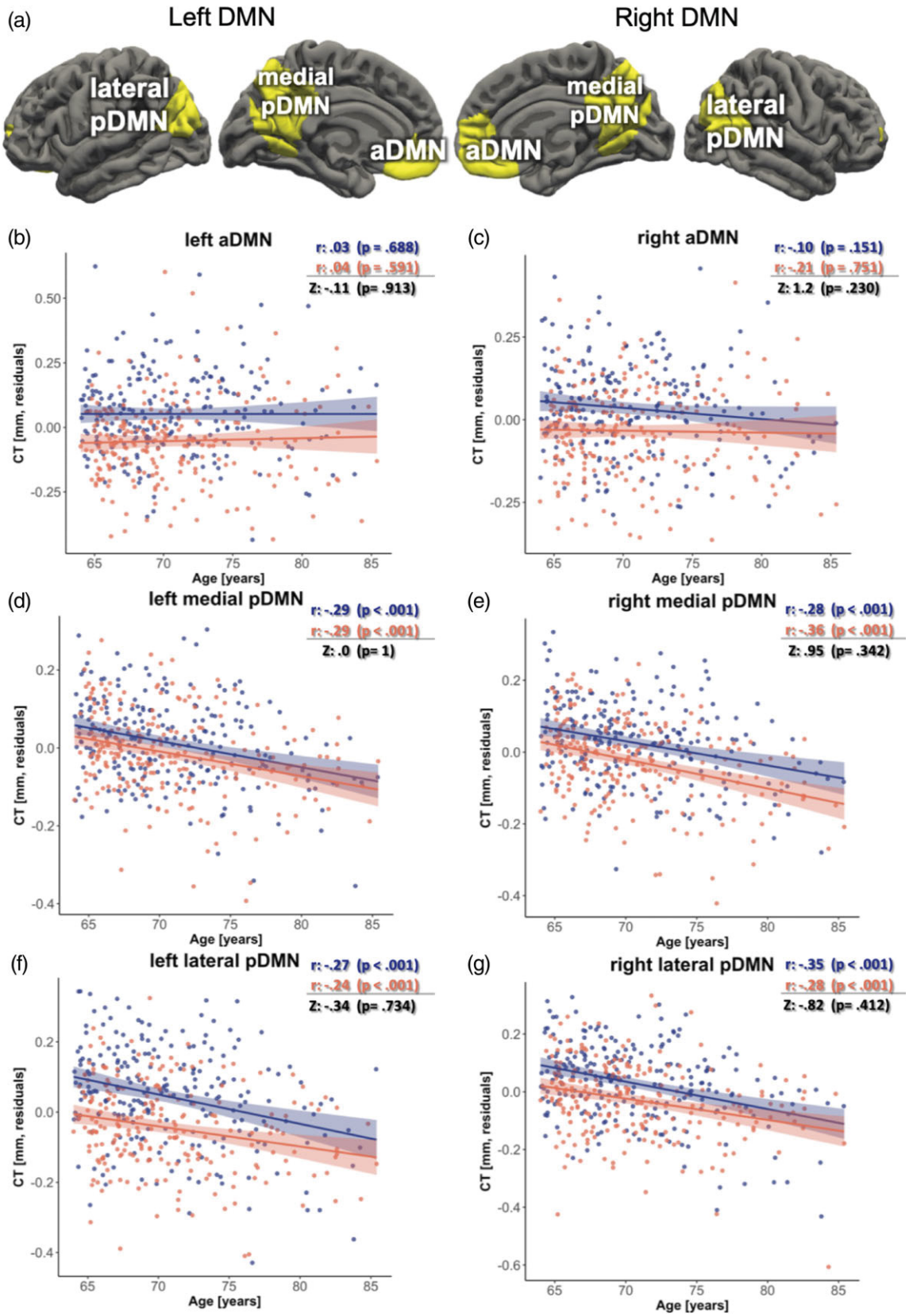

FIGURE 5 Relation between age and regional mean cortical thickness for parts of the DMN (residuals, corrected for gender and education) for the two samples, including regression lines, correlation coefficients and corresponding *p*-values, as well as the Steiger's Z test statistic and corresponding *p*-value. 1000BRAINS is presented in blue and LHAB is presented in orange: (a) DMN projected on a brain's surface consisting of the anterior (a)DMN (medial PFC), medial posterior (p)DMN (PCC and precuneus) and the lateral pDMN (caudal IPL); (b) left anterior (a)DMN; (c) right aDMN; (d) left medial posterior (p)DMN; (e) right medial pDMN; (f) left lateral pDMN; and (g) right lateral pDMN. LHAB = Longitudinal Healthy Aging Brain, PFC = prefrontal cortex, IPL = inferior parietal lobule, DMN = default mode network [Color figure can be viewed at wileyonlinelibrary.com]

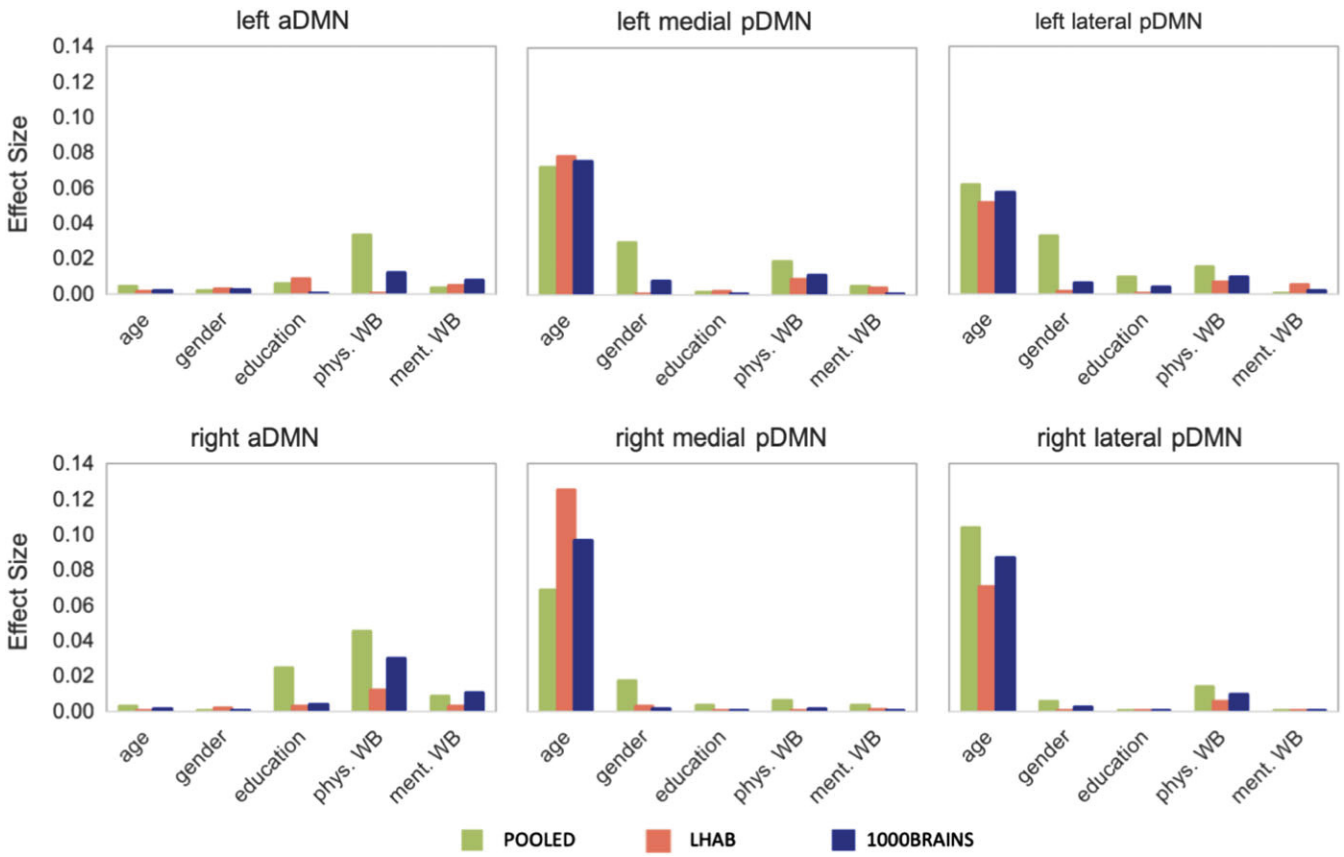

FIGURE 6 Profile plots of effect sizes (partial eta square) for regional mean cortical thickness (parts of the DMN) with all covariates assessed: age, gender, education, physical WB, and mental WB. 1000BRAINS are presented in blue, LHAB is presented in orange, and the pooled data set is represented in green. LHAB = Longitudinal Healthy Aging Brain, WB = well-being, DMN = default mode network [Color figure can be viewed at wileyonlinelibrary.com]

that Switzerland compared to Germany is constantly ranked as being superior in terms of job income and quality, health, life satisfaction, as well as environmental and community factors (http://www.oecdbetterlifeindex.org/countries/switzerland/).

In line with the predictions of the scaffolding theory of cognitive aging (Goh & Park, 2009; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014), higher education as well as engagement in physical activities (which seems to be related to higher physical well-being as tested in the current studies; Bize, Johnson, and Plotnikoff (2007)) have repeatedly been shown to protectively influence the neurocognitive aging process. Both have been related to higher cognitive functioning and less brain atrophy during normal as well as pathological aging, such as mild cognitive impairment and Alzheimer's disease (Afonso et al., 2017; Amieva et al., 2014; Miller, Taler, Davidson, & Messier, 2012; Ritchie, Bates, Der, Starr, & Deary, 2013; Schneeweis, Skirbekk, & Winter-Ebmer, 2014; Sofi et al., 2011; Tucker-Drob, Johnson, & Jones, 2009; Zahodne et al., 2011). It is therefore plausible that participants from LHAB showed superior performances in all cognitive tests assessed (processing speed, concept shifting, reasoning, verbal fluency, and vocabulary).

The comparison of CT between the two samples, however, revealed higher global as well as regional CT values for participants from 1000BRAINS. This result seems counterintuitive at first sight. Based on the sample differences in terms of demographics and cognitive abilities, one would have predicted participants from LHAB to show thicker cortices given that the pertinent literature tends to show positive associations between cognitive ability and the amount of gray matter as measured with CT and gray matter volume or density in the aging population (for an overview, see, e.g., Harada et al., 2013). From our view, the most likely explanation is that these sample differences in CT are due to the different MR scanners used. It has been shown before that even when assessing structural 3D brain images from one and the same person, CT values, but also other metrics, such as brain volume differ between the different scanners (Bauer, Jara, Killiany, & Alzheimer's Disease Neuroimaging, 2010; Dickerson et al., 2008; Fortin et al., 2017; Han et al., 2006; Kruggel, Turner, Muftuler, & Alzheimer's Disease Neuroimaging, 2010; Schlett et al., 2016; Stonnington et al., 2008; Westlye et al., 2009). Thus, direct comparisons of brain metrics between different samples should only be executed with caution.

4.2 | Generalizability of age-related differences in cognitive abilities and CT

Within the scope of the current study, we decided to separately analyze the associations between age and brain structure and cognitive abilities in the two samples and compared the resulting associations using Fisher's *Z*. Although the two samples differed regarding both, cognitive performance and CT, we revealed highly similar slopes for age-related differences in global as well as regional CT. In line with

preceding studies examining global CT, higher age was associated with lower mean CT in both hemispheres for the two samples (Lemaitre et al., 2012; Long et al., 2012; Salat et al., 2004). Similarly, the age-effect patterns found for cognitive ability did not differ across samples. Higher age was associated with lower cognitive functioning in all cognitive tasks assessed, except in the vocabulary test, where no significant relationship was revealed between age and ability scores.

The similarity of the cross-sectional age-effect patterns that we observe across LHAB and 1000BRAINS indicates that the lower level of education or physical well-being evident in 1000BRAINS does not considerably enhance age differences (i.e., steeper slope in 1000BRAINS sample). Put into the context of cognitive reserve, the between-sample differences in cognitive ability together with the similarity of age slopes, may suggest that participants from LHAB (with a higher education and higher physical well-being) reach the criterion for cognitive impairment later as compared to participants from 1000BRAINS, primarily because they started off at higher levels of cognitive ability. However, by means of the presently used cross-sectional data sets, this proposition cannot be tested on the level of individual trajectories. More empirical studies in the field of cognitive reserve and longitudinal changes of cognitive abilities are necessary to shed more light on the role of cognitive reserve—and education as one important proxy of it—in defining the rate of cognitive decline (for a recent review, see Christie et al. (2017)).

To explore in more detail whether the relationship between age and cognitive performance/CT would be differentially influenced by the different covariates (education, physical, and mental well-being) in the two samples, we set up different statistical models (BASE, MAIN, and SENS). Although the different covariates seemed to explain different amounts of variance in the cognitive abilities/CT in the two samples, age-related differences in cognition/CT remained highly similar across samples. For example, mental well-being had a significant influence on processing speed for the sample of 1000BRAINS, but not LHAB. Nevertheless, this difference obviously did not have a considerable impact on the age-related differences in processing speed. Thus, while education and physical well-being might influence the general level of cognitive performance, it seems that these age-related differences seem to be robust against the possible influences tested in the current samples.

4.3 | Regional differences in CT

Beyond assessing mean CT for the two hemispheres, we also analyzed age-related differences in regional CT (different parts of the DMN). The choice of regions of interest was based on an earlier study of Jockwitz et al. (2017). Herein, the authors aimed at assessing structural correlates for functionally established theories of the aging brain. In detail, it has been shown that during performance of a memory task (but also in the resting state), older in comparison to younger adults, show stronger activation/connectivity patterns in the more anterior parts of the DMN. At the same time, activation patterns in the more posterior parts of the DMN were reported to be stronger in younger compared to older participants. Thus, with increasing age, there seems to be a shift in brain activation patterns from more posterior to more anterior brain regions (posterior to anterior shift in aging [PASA]) that helps to maintain cognitive performance as stable as possible (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Jones et al., 2011).

In the current study, we exemplarily used the parts of the DMN to assess regional generalizability of age-related differences in brain structure and found age-related decreases in CT for all the posterior parts of the DMN in both samples. In contrast to that, the anterior parts of the DMN did not show age-related differences in any of the two samples. This finding supports a previous study by Jockwitz et al. (2017), in which the authors presented a structural correlate for the posterior to anterior shift in activation patterns, namely a more pronounced decrease in cortical folding for the posterior parts of the DMN as compared to the more anterior parts of the DMN in a sample of older adults (1000BRAINS). Moreover, the current results extend previous results by showing that structural correlates for PASA can also be generalized over different independent samples of older adults with different demographical characteristics and different brain metrics used (local gyrification index vs. CT).

4.4 | Brain–behavior associations

In the current study, the associations between cognitive abilities and CT were weak and did not survive correction for multiple comparisons. This result was stable over the different statistical models used (BASE, MAIN, SENS) as well as for the different samples (1000BRAINS, LHAB, pooled sample of the two). This result is in line with previous studies showing only weak associations between brain structure and cognitive performance, especially when examining older adults (e.g., Gunning-Dixon & Raz, 2000; de Mooij, Henson, Waldorp, & Kievit, 2017). This, in turn accords with the scaffolding theory of aging stating that intraindividual regulatory processes (e.g., changes in functional connectivity) within older adults might compensate for structural brain decline thereby keeping cognitive abilities relatively stable (Reuter-Lorenz & Park, 2014). Thus, in the current study, the relation between CT and cognitive abilities were expected to be rather weak. To explore this in more detail, further longitudinal studies are warranted that assess both, structural as well as functional changes in the course of aging in relation to intraindividual changes in cognitive abilities.

Another reason, especially when comparing the current results to the results reported in Jockwitz et al. (2017) for an absence of significant relationships between cognitive abilities and CT could be due differences in structural brain metrics used. The aforementioned study of Jockwitz et al. (2017) used the local gyrification index as measure for cortical atrophy in the regions of interest, measuring the complexity of the brain composed of gray matter and structural connectivity. The current study used CT as measure for cortical atrophy, since this is one of the most often used brain metrics to study the effects of age on brain structure. CT measures rather local gray matter differences only. Thus, different structural brain metrics might result in different results. Beyond that, it might still be possible that the chosen regions of interest (DMN) might not be directly related to performance in the neuropsychological tests assessed. Beyond that, it might still be possible that the chosen regions of interest (DMN) might not be directly related to performance in the neuropsychological tests assessed. Although parts of the DMN have previously been associated with attention and executive functions, other tests, which

were not available for the two samples, might be interesting to investigate in this context for example, episodic memory function. And finally, larger sample sizes might be necessary to obtain small but significant results, as it has been the case in the aforementioned study of Jockwitz et al. (2017); n = 749.

4.5 | Pooled versus individual analyses

In the current study, we decided not to pool data of the two samples but to analyze the samples individually with respect to age-related differences in cognitive performance and brain structure. While the results were highly similar for the cross-sectional age trajectories in terms of CT and cognitive performance, differences were found for the relation between the other covariates included in the models (i.e., SENS) and cognitive performance and CT, respectively. For example, when looking at 1000BRAINS, we found a moderate effect of mental well-being on processing speed. On the other hand, for LHAB and for the pooled sample, there was no effect of mental well-being on processing speed. These distinct outcomes might be the result of differences in sample characteristics. The sample of 1000BRAINS is a population-based sample. In contrast to that, the LHAB study only included participants without any neurological and psychiatric diseases and a score on the Mini-Mental State Examination of at least 26. These sample characteristics might be one explanation why mental well-being plays a significant role in terms of cognitive performance differences in 1000BRAINS but not in LHAB. Previous studies often assessed age as independent factor in pooled data analyses consisting of older adults (e.g., Fjell et al. (2009)). In the current study, we could show that age revealed the strongest effects on both cognitive performance and CT, and this seems to be highly similar even in independent samples of older adults. Thus, for such robust effects data pooling might be a good option to increase sample sizes and statistical power (Button et al., 2013). However, other risk and protective factors on the aging brain (such as mental well-being) might be study specific, depending on the sample characteristics. Following, when samples are highly heterogeneous, a pooled analysis might underestimate such influences. A combination of both, pooled and individual analyses seem to be an optimal solution to explore influencing factors on the aging brain.

4.6 | Limitations and future directions

The study has several advantages as well as limitations which should be addressed. First, the current study investigated CT as one metric of brain structure. CT is a popular and sensitive metric in the frame of age-related differences or changes in gray matter, for example, see Fjell et al. (2009, 2013, 2015); Hogstrom et al., 2013. Given the upcoming trend in data pooling procedures, we thought that CT would therefore be of interest in the current cross-validation study. Nevertheless, in future research, other estimated of gray and white matter as well as functional connectivity should be validated between independent studies, to further evaluate the generalizability of results and advantages and disadvantages of data pooling procedures. Second, with respect to the current study, we decided to match the two samples with respect to age and gender distributions and compare the correlations using Fisher's Z. For the future, we suggest to further evaluate different methodological approaches when cross-validating independent samples with regard to brain metrics and or cognitive functions. First, different matching procedures should be investigated and compared. For example, future studies could not only match samples with regard to age and gender, but also with respect to cognitive functioning using propensity score matching. Furthermore, it would be useful to evaluate other statistical methods to cross validate age-related differences in brain structure and cognitive performance, especially when examining more than two samples. Finally, future studies should explore the importance of covariates. Since the choice of covariates to include into statistical models is highly variable across studies (see Silberzahn et al., 2017), future research should investigate this topic more intensively. For example, the current study assessed education as one indicator for socioeconomic status. Since socioeconomic status includes more than education, for example, occupation and income, future research should also assess other indicators and investigate the influence of these factors on cognition and brain structure.

Moreover, we are aware of the fact that scanner differences might contribute to the differences in sample means in terms of CT in the current study. One way to systematically explore this would be a traveling phantom that can be used to assess scanner differences. The current analyses investigated two independent samples of already completed measurements. Therefore, a retrospective methodical validation was not feasible. However, we would suggest such quality control measurement for future studies with planned study comparisons.

Finally, we have to mention that PASA is just one explanation for the results found in the current study. However, differences in image quality between anterior and posterior parts of the brain might be also responsible for the findings on age-related differences in CT. Future studies should be designed to systematically investigate between-subject variability across the different regions of the brain, its sources (i.e., measurement quality) and implications for analysis of data resulting from regions with differing variability.

5 | CONCLUSIONS

Taken together, the current results show that when comparing age-related differences in cognitive abilities and CT in two different and independent samples within the same age range and composed of the same gender distribution, age-related differences in cognitive performance as well as global and regional CT can be generalized over different samples, assuming the same methodology is used. While data pooling has the advantage to increase statistical power to uncover small effects in the aging population, the current results show the usefulness of conducting separate analyses across samples consisting of distinct study populations, with comparison of the overall trends obtained in each analysis. Future multicenter studies and imaging consortia might at least use a combination of the two approaches to unravel the complexity of the aging brain in its entirety.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Generalizing Longitudinal Age Effects on Brain Structure – A Two-Study Comparison Approach

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Cross-sectional studies indicate that normal aging is accompanied by decreases in brain structure. Longitudinal studies, however, are relatively rare and inconsistent regarding their outcomes. Particularly the heterogeneity of methods, sample characteristics and the high inter-individual variability in older adults prevent the deduction of general trends. Therefore, the current study aimed to compare longitudinal age-related changes in brain structure (measured through cortical thickness) in two large independent samples of healthy older adults (n = 161 each); the Longitudinal Healthy Aging Brain (LHAB) database project at the University of Zurich, Switzerland, and 1000BRAINS at the Research Center Juelich, Germany. Annual percentage changes in the two samples revealed stable to slight decreases in cortical thickness over time. After correction for major covariates, i.e., baseline age, sex, education, and image quality, sample differences were only marginally present. Results suggest that general trends across time might be generalizable over independent samples, assuming the same methodology is used, and similar sample characteristics are present.

Keywords: brain structure, aging, cognition, longitudinal change, old age, cortical thickess

INTRODUCTION

Normal aging can be accompanied by a decline in cognitive abilities (Hedden and Gabrieli, 2004) and changes in brain structure (Sowell et al., 2003). Both phenomena show high inter-individual variability, especially during later decades of life (Habib et al., 2007; Dickie et al., 2013). Results derived from cross-sectional studies have revealed a negative relationship between age and brain structure across adulthood, with differential effect sizes for specific brain regions (Fjell et al., 2009; Jockwitz et al., 2019), depending on the functional properties of the brain region of interest as well as the brain structure metric investigated (e.g., brain volume-based versus surface-based metrics or cortical thickness versus surface area) (O'Sullivan et al., 2001; Sowell et al., 2003; Salat et al., 2005; Walhovd et al., 2011; Ziegler et al., 2012; Dickie et al., 2013; Hogstrom et al., 2013; Fjell et al., 2014a,b; Liem et al., 2015).

While the associations between brain structure and age are rather heterogenous across studies, we recently showed consistent cross-sectional age associations for two different cohorts when

applying the same analysis protocol [e.g., age range, processing of the neuroimaging data (Jockwitz et al., 2019)]. At the same time, cross-sectional studies inherit a potential problem concerning the validity of inferences: Cross-sectional studies assess age-related differences between individuals, which is not comparable to age-related changes within individuals. One important disadvantage of cross-sectional studies concerns interindividual differences that might obscure intraindividual changes of aging (Raz and Lindenberger, 2011).

Longitudinal studies are still relatively rare and inconsistent with respect to their outcomes, preventing the deduction of general trends of age-related changes in brain structure. When comparing cross-sectional and longitudinal research designs, different patterns were shown for structural brain aging (Hedden and Gabrieli, 2004; Pfefferbaum and Sullivan, 2015). Large between-study heterogeneity of designs and methods, differences in sample characteristics and the generally larger inter-individual variability in samples of older adults make it difficult to extract general trends. However, general decreases in brain structure have been reported, although to a lesser degree than those reported in cross-sectional research designs [for a recent review, see Oschwald et al. (2019)].

To extract general age trends for brain structure, comparability between independent study samples is necessary. A few studies have already performed comparability analyses of cross-sectional age-related differences in brain structure metrics (i.e., brain volume or cortical thickness) between different samples, e.g., Fjell et al. (2009); Jockwitz et al. (2019). These studies indicate that general associations between age and brain structure are similar across independent samples, assuming that the same methodology and analysis protocol was used. However, such between study comparisons are lacking for investigations of longitudinal aging trajectories, especially in the older adult population, where inter-individual variability is particularly high. With the growing trend of large imaging consortia, e.g., UK Biobank (Miller et al., 2016), ENIGMA (Thompson et al., 2014), German National Cohort Study [NaKo; Bamberg et al. (2015)], or ADNI [Alzheimer's Disease Neuroimaging Initiative; Jack et al. (2008)] which aim at pooling datasets from a variety of study centers to increase sample size and statistical power, it will be crucial to establish the validity of age-related changes in brain structure. Therefore, the current study aimed to compare longitudinal age-related changes in brain structure in two large independent samples of healthy older adults: The Longitudinal Healthy Aging Brain (LHAB) database project at the University of Zurich (Switzerland; Zollig et al. (2011)] and 1000BRAINS at the Research Centre Juelich (Germany; Caspers et al. (2014)].

MATERIALS AND METHODS

Participants included in the current research project were recruited from two longitudinal studies investigating brain-behavior relationships in older adults located in the larger Zurich area (Switzerland) and in the Ruhr district (Germany).

The first sample comprised the ongoing LHAB database project at the University Research Priority Program (URPP) "Dynamics of Healthy Aging" of the University of Zurich (Zollig et al., 2011). LHAB investigates age-related dynamics of brain-behavior relationships in healthy older adults. A particular focus is placed on assessing and explaining interindividual variability in the observed aging trajectories. For this purpose, a broad spectrum of factors assumed to influence such trajectories (e.g., lifestyle, sleep, and nutrition) is collected. In LHAB, older adults from Zurich and surrounding areas are observed longitudinally with between-measurement intervals of one to 2 years. Inclusion criteria for study participation at baseline were age $\geq$ 64, right-handedness, fluent German language proficiency, a score of $\geq$ 26 on the Mini Mental State Examination [MMSE; Folstein et al. (1975)], no self-reported neurological disease of the central nervous system and no contraindications to MRI. The study was approved by the ethical committee of the canton of Zurich. Participation was voluntary and all participants gave written informed consent in accordance with the declaration of Helsinki. The initial sample of LHAB was comprised of 232 participants ranging from 64 to 87 years of age. Data acquisition in the LHAB project started in 2011. Currently the dataset covers an observation period of 7 years.

The second sample comprised 1000BRAINS at the Institute of Neuroscience and Medicine, Research Centre Juelich. 1000BRAINS is a longitudinal population-based study that assesses variability in brain structure and function during aging with respect to various influencing factors (Caspers et al., 2014). The 1000BRAINS sample is drawn from the 10-year follow-up cohort of the Heinz Nixdorf Recall Study, an epidemiological population-based study of risk factors for atherosclerosis, cardiovascular disease, cardiac infarction, and death (Schmermund et al., 2002) and the affiliated MultiGeneration study. In 1000BRAINS, adults aged 55 and older (at baseline) from the Heinz Nixdorf Recall study and their relatives (spouses and offspring; sampled from MultiGeneration study) were recruited, and were examined two times over a period of about 3 to 4 years. In contrast to the LHAB study, inclusion in the study was only dependent on the eligibility requirements for the MR acquisition based on the MR safety guidelines (e.g., stents and heart pacemakers led to exclusion from the study). The study protocol was approved by the University of Duisburg-Essen. Participation was voluntary and all participants gave written informed consent in accordance with the declaration of Helsinki. The initial sample of 1000BRAINS was comprised of 1,315 participants ranging from 18 to 87 years of age.

For the current study, we focused on two time points in both samples (LHAB: baseline and 4-year follow-up; 1000BRAINS: baseline and 3 to 4-years follow-up). Participants with missing values for the brain data were excluded. In order to assure comparability between the two samples, we matched them with respect to baseline age and sex using propensity score matching implemented in R (Stuart et al., 2011).

This resulted in 161 participants for each of the two final samples with the following demographic characteristics: LHAB: mean age = 69.9 $\pm$ 4.1; 85 females, mean interval = 4.2 $\pm$ 0.1; 1000BRAINS: mean age = 69.2 $\pm$ 4.6, 76 females, mean interval = 3.7 $\pm$ 0.7. For an overview of demographic variables

of the two samples at both timepoints, see **Table 1**. Education was measured according to the international classification of education (ISCED) and afterward divided into three educational classes: 1. school and/or vocational training, 2. grammar school or vocational baccalaureate, specialized secondary school/diploma, or commercial school degree, and 3. Bachelor, Master, Doctorate or equivalent.

Data Acquisition

For LHAB, anatomical T1-weighted images of both timepoints were acquired on a 3.0 T Philips Ingenia scanner (Philips Medical Systems, Best, The Netherlands). T1-weighted structural brain images were measured per visits with: TR = 8.18 ms, TE = 3.8 ms, Flip Angle = 8°, FoV = 240 mm × 240 mm, isotropic voxel size = 1 mm × 1 mm × 1 mm, 160 slices per volume. For 1000BRAINS, anatomical T1-weighted images of both timepoints were acquired on a 3.0 Tesla TIM-Trio MR scanner (Siemens Medical System, Erlangen, Germany). The T1-weighted structural brain images were scanned per visit with: TR = 2.25 s, TE = 3.03 ms, flip angle = 9°, FoV = 256 mm × 256 mm, voxel resolution = 1 mm × 1 mm × 1 mm, 176 slices per volume. In both studies, T1-imaging was part of a larger MR imaging protocol [see Caspers et al. (2014); Zollig et al. (2011)].

Preprocessing

Anatomical images from both samples were preprocessed using the same automated surface-based processing stream for longitudinal analyses of the FreeSurfer Software package [1000BRAINS: version 6.0.0; LHAB: FreeSurfer BIDS App v6.0.0-2; Gorgolewski et al. (2017)]. A detailed description of this pipeline is provided by Reuter et al. (2012); Dale et al. (1999), Fischl et al. (1999) as well as on http://surfer.nmr.mgh.harvard.edu. In short, first the cross-sectional surface reconstruction pipeline was applied to every subject, which includes (a) the segmentation of the structural brain images into gray matter, white matter, and cerebrospinal fluid, (b) motion correction, (c) intensity normalization, (d) transformation into Talairach space, (e) tessellation of the gray/white matter boundary, and (f) correction of topological defects. The gray/white matter interface was then (g) expanded to create the pial surface (boundary between gray matter and cerebrospinal fluid), which finally consists of about 150,000 vertices per hemisphere with an average surface area of 0.5 mm^2. Afterwards, each subject was preprocessed using the longitudinal surface reconstruction pipeline (Reuter et al., 2012) in which, based on the results of the cross-sectional preprocessing pipeline, a within-subject anatomical template was built across the two timepoints. Subsequently, cortical thickness was calculated based on the cross-sectional as well as longitudinal information from each subject. This procedure has previously been shown to be more sensitive in calculating surface-based brain metrics, since, due to the common template for the two timepoints, within-subject variability is reduced (Reuter et al., 2012). No manual correction of the reconstructed surfaces (white matter and pial surface) was performed in the two studies.

TABLE 1 | Demographics of the two samples and group comparisons (Independent *T*-test for continuous and Wilxon-Cox test for categorical variables) with corresponding *T*/*W* and *p*-values.

	1000BRAINS	LHAB	*T*/*W* (*P*-Values)
Age (TP1)	69.2 ± 4.6	69.9 ± 4.1	−1.39 (0.166)
Sex	0.53 ± 0.5	0.47 ± 0.5	13685 (0.317)
ISCED 3	2.0 ± 1.0	2.3 ± 0.8	11000 (0.010)
Age (TP2)	72.9 ± 4.7	74 ± 4.1	−2.28 (0.024)
Intervall (TP1 – TP2)	3.7 ± 0.7	4.2 ± 0.1	−8.02 (<0.001)

Regions of Interest

For the current study, we used the widely used Desikan-Killiany atlas (Desikan et al., 2006) as implemented in FreeSurfer to extract cortical thickness from left and right cortices. Specifically, for each of the 68 regions of interest (ROIs), mean cortical thickness was calculated as the average shortest distance between the white matter surface and the corresponding vertex within the respective ROIs on the pial surface.

Cognitive Performance

Participants from both LHAB and 1000BRAINS took part in a large neuropsychological assessment consisting of tests in the domains attention, executive functions, working memory, episodic memory and language functions. For comparison between the two samples, the following tasks were chosen: Trail Making Test A: processing speed, B: concept shifting; Morris et al. (1989), LPS50 + subtest three [reasoning; Sturm et al. (1993)] and [Regensburger Wortflüssigkeitstest (RWT), semantic condition (verbal fluency); Aschenbrenner et al. (2000)]. For descriptives of cognitive tasks, see **Table 2**.

Statistical Analysis

The purpose of the current research project was to compare intra-individual changes in brain structure (cortical thickness) across the ROIs of two independent population-based cohort studies. We calculated annual percentage changes to estimate yearly changes in cortical thickness and cognitive performance. Annual percentage changes were calculated as the following: [(Value at last measurement occasion in the study/Value at baseline)$^{1/(totalyearsinstudy)}-1$] × 100. Positive values represent increases and negative values represent decreases. We next identified outliers for all annual percentage changes (mean annual percentage change ± 3 SD) and excluded those values that deviated more than 3 SD from the mean.

To examine whether the two samples showed similar changes in cortical thickness over time, we first used a one sample *t*-test to estimate general changes in cortical thickness for the two groups separately. To investigate whether the two samples differed concerning their variances, we conducted Levene's test for sample homogeneity. Finally, between sample differences in cortical thickness annual percentage changes were assessed using a General Linear Model (GLM) with cortical thickness as the dependent variable and sample and sex as fixed factors. Baseline age (TP1), education, and Euler number were included as covariates of non-interest. Euler number represents a marker of image quality that summarizes the topological complexity of the reconstructed cortical surface (Rosen et al., 2018).

TABLE 2 | Raw cognitive performance values for TP1 and 2, as well as the APC together with *T* and *p*-values for the APC (Sig. of APC; one sample *T*-test) and *F* and *p*-values for sample homogeneity (Levene's test).

	1000BRAINS				LHAB				
	Tp1	Tp2	APC	Sig. of APC	Tp1	Tp2	APC	Sig. of APC	Levene's test
Processing speed	40.22 ± 12.46	41.12 ± 14.12	0.34 ± 7.06	0.61 (0.54)	37.16 ± 12.90	39.37 ± 16.15	1.07 ± 6.88	1.93 (0.056)	0.25 (0.614)
Concept shifting	93.20 ± 41.55	96.87 ± 43.33	0.84 ± 7.98	1.32 (0.188)	86.69 ± 33.86	94.22 ± 39.77	2.04 ± 6.83	3.63 (<0.001)	2.40 (0.122)
Verbal fluency	23.96 ± 6.67	22.81 ± 6.73	−1.31 ± 5.76	−2.81 (0.006)	26.06 ± 6.46	25.98 ± 5.83	0.17 ± 4.41	0.47 (0.633)	9.59 (0.002)
Reasoning	20.99 ± 4.65	20.56 ± 5.42	−0.13 ± 5.14	−0.31 (0.757)	24.02 ± 4.45	26.48 ± 4.75	2.35 ± 3.70	7.99 (<0.001)	10.66 (0.001)

Subsequently, we assessed the cortical thickness annual percentage changes with the mentioned covariates (baseline age, sex, education, and Euler number) separately for the two samples to examine whether changes in cortical thickness would be driven by one sample. Finally, we additionally assessed the relation between annual percentage changes of cortical thickness and cognitive performance for the two samples separately.

RESULTS

When matching the two samples for baseline age and sex, the two samples did not differ in the respective variables (baseline age: $T = -1.39$, $p = 0.166$; and sex: $W = 13{,}685$, $p = 0.317$). However, we found significant differences in terms of education ($W = 11{,}000$, $p = 0.01$), with participants included in LHAB generally showing a higher formal education as compared to participants included in 1000BRAINS. Furthermore, the time intervals between the two measurements differed, with a longer interval between measurements in the LHAB project (1000BRAINS: 3.7 ± 0.7 years; LHAB: 4.2 ± 0.1 years; $T = -8.02$; $p < 0.001$; for group differences, see **Table 1**). To address this difference in time intervals we calculated annual percentage changes of cortical thickness. **Table 3** includes cortical thickness values for the two hemispheres at both timepoints as well as the annual percentage change in cortical thickness for the two samples separately (for all ROIs see **Supplementary Table 1**).

Cortical Thickness

With respect to cortical thickness, the LHAB sample showed slightly stronger annual percentage changes (i.e., decreases) in cortical thickness over time as compared to 1000BRAINS (see **Figures 1A,B**). On the other hand, we found 1000BRAINS to generally show more variance between participants regarding the annual percentage change in most of the ROIs (for Levene's test, **Supplementary Table 1**), although variances in mean CT did not differ significantly between the two samples (see **Table 3**). **Figure 1C** shows difference maps in terms of standard deviations of the annual percentage changes. For example, one of the most significant differences in standard deviations is observed in the right postcentral gyrus (see **Figure 1C** for a density plot; 1000BRAINS: SD = 0.7, LHAB: SD = 0.5; Levene's test: $F = 14.64$, $p < 0.001$).

Next, we again used GLMs to examine sample differences in annual percentage changes in cortical thickness with age, sex, education and Euler number as covariates (for all significant influences, see **Table 4** and **Supplementary Table 2**). Overall, after correcting for the different covariates and for multiple comparisons, only very few sample differences in terms of annual percentage change were present, i.e., inferior frontal gyrus pars triangularis (lh: $F = 13.67$, rh: $F = 16.54$) and inferior frontal gyrus pars opercularis (rh: $F = 21.43$) and transverse temporal gyrus (rh: $F = 20.47$).

In addition, after correcting for the above-mentioned variables, only a few regions showed significant intercepts (i.e., main effects of time), age effects or relations to sex, education or the Euler number (almost no effects did survive correction for multiple comparisons). **Figure 2** shows age-related annual percentage changes in cortical thickness for left and right hemispheres. As one can see in the two plots, the annual percentage change was not significantly related to baseline age for the left hemisphere ($F = 2.41$; $p = 0.121$) but was at trend level for the right hemisphere ($F = 4.95$; $p = 0.027$). The plots also show that the relationship between age and annual percentage change follows a linear, rather than a non-linear trend.

For a better understanding of the regional specificity of sample differences in the cortical thickness annual percentage changes, we projected the effect sizes (partial eta squared) of the sample differences onto the brains surface (**Figure 3**). Effect sizes ranged from 0 to 0.06, being interpreted as small to medium effects. Regarding the covariates, we only found sporadic effects on cortical thickness annual percentage change. After correcting for these subtle, mostly non-significant influences, and even the intercepts (i.e., main effects of annual percentage change) became non-significant. To verify that these influences were not driven by only one of the two samples, we further calculated the GLMs for the two samples separately (see **Supplementary Table 3**).

Finally, we assessed the relation between annual percentage changes of cortical thickness and cognitive performance for the two samples separately, which, after correcting for multiple comparisons, revealed non-significant results (see **Tables 2**, **5** and **Supplementary Table 4**).

DISCUSSION

Generalizability and replicability of age effects on brain and behavior are vital requirements to understand major aging mechanisms in our older adult population. The complexity of the aging process, in which the effect of single contributing factors, i.e., lifestyle or genetics, is assumed to be highly individual and rather small. To unravel even subtle brain-behavior relationships

TABLE 3 | Cortical thickness values for TP1 and 2, as well as the annual percentage change (APC) together with *T* and *p*-values for the APC (Sig. of APC; one sample *T*-test) and *F* and *p*-values for sample homogeneity (Levene's test).

	1000BRAINS				LHAB				
	Tp1	Tp2	APC	Sig. of APC	Tp1	Tp2	APC	Sig. of APC	Levene's test
Mean CT left	2.46 ± 0.09	2.45 ± 0.09	−0.15 ± 0.45	−4.17 (<0.001)	2.4 ± 0.08	2.37 ± 0.09	−0.29 ± 0.45	−8.21 (<0.001)	0.17 (0.677)
Mean CT right	2.46 ± 0.09	2.45 ± 0.10	−0.14 ± 0.40	−4.49 (<0.001)	2.41 ± 0.08	2.38 ± 0.09	−0.3 ± 0.42	−9.07 (<0.001)	0.19 (0.664)

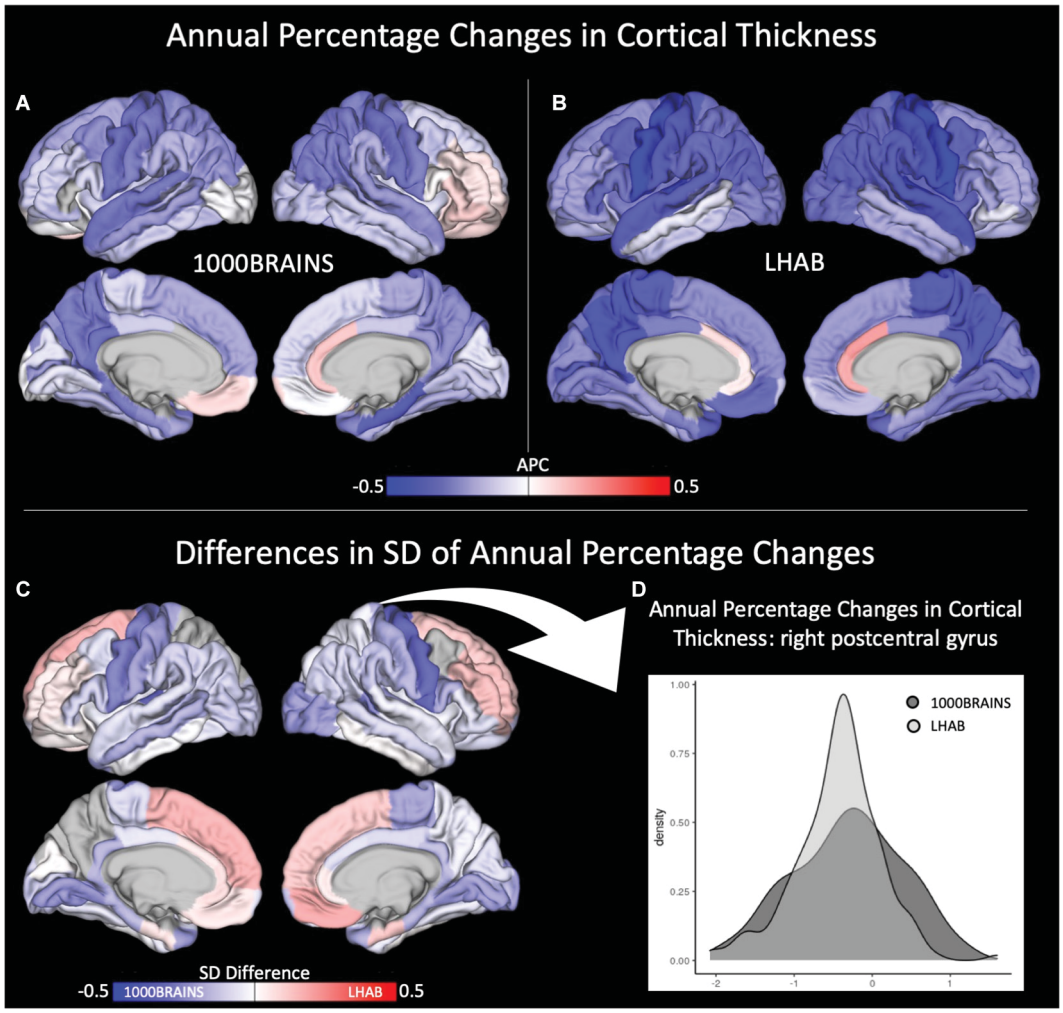

FIGURE 1 | Annual percentage changes (APC) in cortical thickness for **(A)** 1000BRAINS and **(B)** LHAB. Differences in SD between the two samples is shown in **(C)** together with a corresponding density plot **(D)** showing the variance in cortical thickness for 1000BRAINS and LHAB within the postcentral gyrus.

TABLE 4 | *F* and *p*-values derived from general linear models assessing annual percentage changes in cortical thickness in relation to sample, age, sex, education, and data quality (Euler number).

	Intercept	Age (TP1)	Sex	Education	Euler	Sample
Mean CT left	1.83 (0.177)	2.41 (0.121)	0.00 (0.966)	0.10 (0.756)	0.94 (0.334)	7.5 (0.007)
Mean CT right	4.35 (0.038)	4.95 (0.027)	0.44 (0.508)	0.95 (0.331)	0.32 (0.572)	8.85 (0.003)

during aging (Button et al., 2013; Wiseman et al., 2019) there is an upcoming trend of data pooling approaches to increase statistical power. However, data pooling procedures, particularly in imaging consortia, require proof of generalizability of observed age-related brain changes. The present study set out to meet this need and assessed age-related changes in brain structure

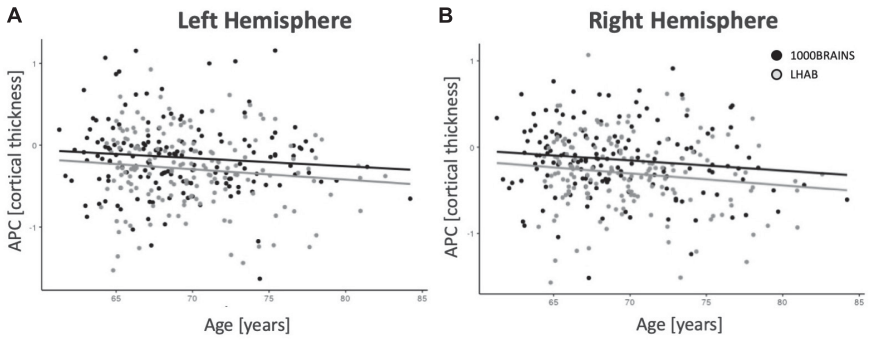

FIGURE 2 | Mean thickness annual percentage changes for the left **(A)** and right **(B)** hemispheres. With increasing age, there are slightly decreasing annual percentage changes for both samples.

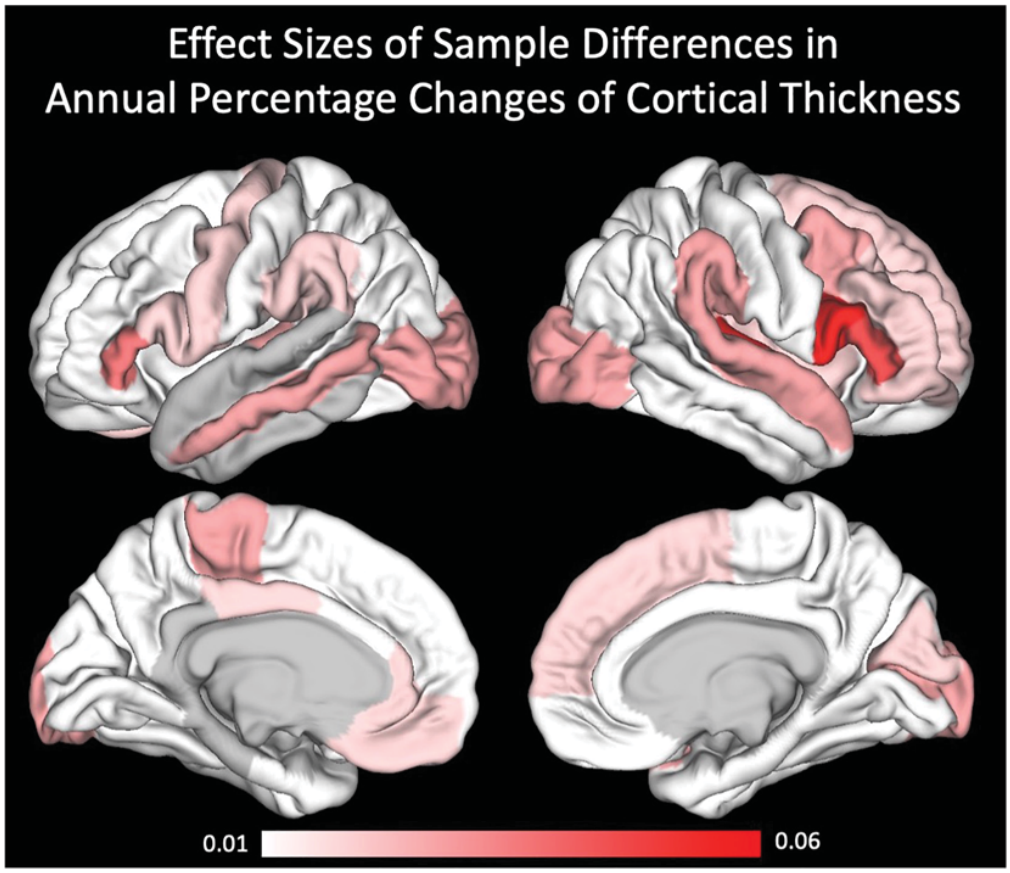

FIGURE 3 | Effect sizes of sample differences using partial eta square.

(measured by global and regional cortical thickness) in two closely matched samples of older adults over an average time period of three to four years. Despite significant differences in demographics between the two independent samples, we observed highly similar patterns of age-related changes in brain structure, when using the same methodology and analysis.

Cross-sectional age-related atrophy patterns have been reported by many previous studies (Walhovd et al., 2011; Storsve et al., 2014; Jancke et al., 2015). From those studies we would have expected to see a pattern of small but consistent cortical thickness decline in our two studies.

Overall, this decrease was found for both studies (cf. **Figure 1**) with participants included in the LHAB study showing a slightly more pronounced decline in cortical thickness. Highest annual percentage changes were found for pre- and postcentral gyri together with medial and lateral temporal and parietal

TABLE 5 | *F* and *p*-values derived from general linear models assessing the relation between annual percentage changes in cortical thickness with annual percentage changes in cognitive performance, calculated separately for the two samples, corrected for age, sex, education, and data quality (Euler number).

	Processing speed		Concept shifting		Verbal fluency		Reasoning	
	1000BRAINS	LHAB	1000BRAINS	LHAB	1000BRAINS	LHAB	1000BRAINS	LHAB
Mean CT left	0.21 (0.651)	5.45 (0.021)	1.27 (0.263)	0.31 (0.581)	0.26 (0.609)	0.00 (0.997)	2.40 (0.124)	1.03 (0.311)
Mean CT right	1.55 (0.215)	2.63 (0.107)	0.03 (0.864)	0.00 (0.971)	0.45 (0.505)	0.41 (0.522)	0.49 (0.484)	3.50 (0.063)

brain regions in both samples. In turn, the anterior cingulate cortex showed slight increases in cortical thickness over time. Importantly, the results are in line with previous longitudinal studies on cortical thickness investigating the whole adult lifespan (Storsve et al., 2014). Further, sample inhomogeneity testing revealed a higher between-subject variance for 1000BRAINS as compared to the LHAB study.

When adjusting the longitudinal effects of time for sex, education, baseline age and data quality (Euler number), only sporadic brain areas exhibited significant sample effects in annual percentage changes, i.e., left and right inferior frontal gyrus, pars triangularis, right inferior frontal gyrus pars opercularis and the right transverse temporal gyrus. Here, participants included in the LHAB study showed a more pronounced decrease over time. Based on sample characteristics, e.g., higher education in the LHAB sample, one would expect 1000BRAINS to show a more pronounced cortical thinning. However, especially for the inferior frontal gyrus (i.e., Broca's region involved in language functions), it has been shown that a higher brain reserve, in terms of higher gray matter volume, may diminish during the aging process, i.e., at older ages (Heim et al., 2019). If this holds true, then it might be the case that participants of the two samples assimilate during older ages in terms of brain structure. However, further research is necessary to unravel this complex relationship of age and brain structure.

Thus, the analysis of cortical thickness in two samples of healthy older adults revealed only marginal changes over time and only minimal sample differences. We are aware that our models include more covariate variables (age, sex, education, and data quality) than previous studies [e.g., Walhovd et al. (2011); Storsve et al. (2014); Thambisetty et al. (2010)]. We deliberately decided to include this set of variables since we know from previous research that cross-sectionally, the factors age, sex, education and data quality have an impact on brain structure (Sowell et al., 2003; Jancke et al., 2015; Jockwitz et al., 2019). Interestingly, when examining "raw annual percentage changes," these changes were partly in accordance with previous studies investigating changes in cortical thickness over time (Walhovd et al., 2011; Storsve et al., 2014). For example, Storsve found a mean annual percentage change of −0.35 in a sample ranging from 23 – 87 years and Fjell et al. (2014b) reported a mean annual percentage change of −0.59 in a sample of older adults. While we found a mean annual percentage change of −0.29 for the LHAB study, in 1000BRAINS this was slightly less pronounced, i.e., −0.15. In addition, we showed that the investigated covariates, i.e., baseline age, sex, education, and image quality, might be important in the investigation of longitudinal changes of brain structure. As an example, we found slightly negative relationships between baseline age and annual percentage changes in cortical thickness for the right hemisphere, which supports previous results (e.g., Fjell et al., 2009).

Finally, it has to be mentioned that neither of the two studies showed significant relations between annual percentage changes in cortical thickness and cognitive performance (i.e., processing speed, concept shifting, verbal fluency, and reasoning). First, these results complement previous results of our research group. In this cross-sectional study, no relation between cortical thickness and cognitive performance could be established in neither of the two study samples (Jockwitz et al., 2019). Likewise, other studies also revealed no associations between cognitive performance and particularly cortical thickness (in contrast to, e.g., brain volume [Cox et al., 2019], or white matter [Ziegler et al., 2012]). Furthermore, research regarding changes in both, brain structure and cognitive performance is quite heterogeneous. In the literature review of Oschwald et al. (2019) half of the studies revealed no association between changes in brain structure and cognitive performance, which fits to the current observation. In turn, those studies showing a significant association between changes in particularly cortical thickness and cognitive performance, differed from the current study. First, other cognitive functions were investigated, such as episodic memory or composite scores of executive functions (Fjell et al., 2014b; Möller et al., 2016; Sala-Llonch et al., 2017) and second, the above-mentioned studies included less or no covariates. Thus, when correcting for major confounding effects, cortical thickness changes were not related to cognitive performance changes over time. This is also well in line with the idea that in healthy older adults, correlations between changes in brain structure and simultaneous changes in cognitive performance are expectedly small and accompanied by high amounts of variability due to potential compensation mechanisms (Oschwald et al., 2019).

Methodological Considerations

The current study assessing longitudinal changes in brain structure has several advantages as well as limitations that we would like to address. With respect to the brain metric used in the current study, we chose cortical thickness, since it represents a prominent brain metric that seems to be sensitive to the aging process. However, it should also be mentioned that other metrics might be useful when comparing effects of aging, i.e., brain volume or gray matter density (Jäncke et al., 2019). Also, future studies may adopt Deformation-Field Morphometry

methods, such as Tensor-based morphometry (TBM), in order to compute longitudinal change in structural MRI data (Hua et al., 2008). Furthermore, with regard to the atlas used in the current study, i.e., Desikan-Killiany atlas, it needs to be stressed that other atlases might be more sensitive to functionally dependent changes in brain structure, such as the cytoarchitectonic Juelich Brain Atlas (Amunts et al., 2020) or functionally derived brain parcellations (Schaefer et al., 2018). In addition, future studies should also investigate longitudinal changes in brain structure and function with samples that are matched not only for age and gender, but also education or cognitive abilities. In the current study, we showed that covariates, such as age and education might explain small parts of the changes seen over time. Future studies should elaborate on these influencing factors to explore intra-individual aging processes.

CONCLUSION

Taken together, the current study showed that age-related changes in cortical thickness are relatively small, when adjusting for the most common influencing factors. This effect was seen in both independent studies, suggesting that general patterns of longitudinal changes in brain structure may be generalizable if the same methods are used and similar study populations with similar age and sex distributions are selected. However, fine-grained change patterns differ and the question whether results can be generalized over different samples cannot easily be answered because of the between-study differences regarding demographics (e.g., age ranges and education) or methodology (e.g., time intervals, different brain metrics, and such as brain volume versus cortical thickness). Furthermore, differences in covariates often hamper the extraction of generalizable age trends in different samples. With our study, we contribute to the field by showing that patterns of age-related changes in brain structure in two independent cohorts of older adults are highly similar when using the same methodological approach.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the used consent does not allow for the public sharing of the data. Requests to access the datasets should be directed to LJ, lutz.jaencke@uzh.ch (LHAB) and SC, s.caspers@fz-juelich.de (1000BRAINS).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the Canton of Zurich, Switzerland (LHAB) and the University of Duisburg-Essen, Germany (1000BRAINS). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SM and LJ contributed to the design, set-up, maintenance, and support of the LHAB project. SC and KA contributed to the design, set-up, maintenance, and support of the 1000BRAINS study. FL and CJ performed processing of the longitudinal neuroimaging data and wrote the first draft of the manuscript. CJ and JO performed the statistical analysis. LJ and SC supervised the project. All authors discussed the results, contributed to manuscript revision, and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2021.635687/full#supplementary-material

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Cognitive profiles in older males and females

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Males and females are subject to differences in cognitive processing strategies, i.e. the way males and females solve cognitive tasks. So far primarily reported for younger adults, this seems to be especially important in older adults, who also show sex differences in cognitive impairments. Therefore, the aim of the current study was to examine the older adult population with respect to cognitive profiles derived from a large variety of cognitive functions. Using an exploratory component analysis with consecutive confirmatory factor analysis in a sample of 676 older adults, neuropsychological performance data in a variety of cognitive domains was decomposed into cognitive components. A general cognitive profile based on the whole group fits unequally well on the two sexes. Importantly, cognitive profiles based on either males or females differ in terms of their composition of cognitive components, i.e. three components in males versus four components in females, with a generally better model fit in females. Thus, related to the established differences in processing styles between males and females the current study found a rather decomposed (or local) cognitive profile in females while males seem to show a holistic (or global) cognitive profile, with more interrelations between different cognitive functions.

There has been a longstanding debate about whether males and females differ in terms of cognitive abilities. Males are often supposed to outperform females in visual spatial tasks, while females outperform males in terms of verbal and episodic memory tasks[1–6]. While these sex stereotypes are well accepted in our society[7], there is a non-negligible amount of studies showing exactly the opposite, namely that men and women do not differ in most of the cognitive tasks, also referred to as the "Gender Similarity Hypothesis"[8,9]. That is, cognitive performance differences on average show an effect size of $d = 0.22$ (range: 0.05–0.57) which is interpreted as rather small differences. Using a meta-synthesis approach, Zell et al.[10], however, concluded that sex differences in terms of psychological and cognitive variables is rather small but stable across ages, generations and cultures.

Besides investigating sex differences in absolute cognitive performance outcome measures (i.e. females remember more words from a word list as compared to males), recent studies rather focussed on sex differences in cognitive processing styles, i.e. the way males and females solve a given cognitive task[11,12]. For example, in spatial navigation tests, females were found to use local landmarks to find a specific route, while males rather construct cognitive maps of the environment[11,13,14]. Interestingly, when males and females are instructed to actively choose a landmark-based style, females outperform males in this task[13]. Similarly, in a verbal fluency task, Weiss et al.[15] as well as Lanting et al.[16] showed that the males' processing strategy is typically characterized by a systematic and extensive scan of the word space of a given category before moving to the next one (e.g. listing jobs, males would first list all jobs within a hospital, then within an office etc.). In contrast, females switch more often between different categories. Changing the instructions, i.e. inducing more switches between categories, led to superior performance of females[12]. Thus, based on previous research investigating specific cognitive tasks, it has been established that males and females use different cognitive processing strategies: Males seem to use a rather holistic processing style with a focus on global aspects of the task (i.e. having in mind the whole map of a city when performing a spatial navigation task). Females instead use a decomposed processing style with a focus on more local aspects of the task (i.e. remember more details of a given word list). Similar sex differences in terms of a global versus local focus have been found for other tasks such as mental rotation tasks[17], number-comparison-task[18] and Navon paradigms[19].

Although sex-related differences in cognitive processing styles do not necessarily result in differences in performance in everyday life, i.e. males and females perform equally good in an everyday multitasking paradigm[20], they give rise to the question of whether males and females do not only differ in single cognitive abilities. Rather, the two sexes might generally differ in the overall composition of their cognitive abilities. So far, studies mostly

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focus on cognitive profiles that are predefined based on specific cognitive theories or derived from data-driven approaches (e.g. principal component analyses)[21–25]. For example, single cognitive abilities are often categorized into cognitive domains, such as attention, memory and executive functions, based on correlations between performance in the tasks administered[21]. Performance within the cognitive domains, then, together represent cognitive profiles. Typically, such approaches are based on an entire group including both, males and females. However, whether these cognitive components and profiles reflect the cognitive architecture equally well across the two sexes remains unclear. The relation between performance in distinct cognitive tasks might be differentially related to each other in males and females and therefore might form different sex-specific cognitive profiles.

Particularly interesting in this aspect is the older adult population, since sex differences in cognitive performance were found to persist until late adulthood and might even lead to differences in cognitive impairments during older age and disease[2,22,23]. So far, the majority of studies investigate cognitive performance during aging while correcting for sex differences. Averaged over the two sexes, cognitive performance decline is well established during the aging process[24–27] with a significant decline starting in the mid 50's[24], especially in the domains of executive functions, working memory and episodic memory. However, previous studies not only showed that sex-differences in cognitive performance persist until late adulthood[2,22,23], they also reported unbalanced prevalence in neurodegenerative diseases that are accompanied by different cognitive impairments, i.e. males rather suffer from MCI and Parkinson's disease, while females are more often affected by Alzheimer's disease[28,29]. Potentially, different interrelations between cognitive functions might explain parts of these different age-related trajectories and therefore depict a promising research topic. To examine this, the current study took advantage of a large older adult population of males and females between 55 and 85 years from the 1000BRAINS cohort, matched for age and education, and examined the sex-specificity of cognitive profiles based on a large variety of neuropsychological functions. Using a data-driven approach, neuropsychological test performance was first decomposed into cognitive components. Afterwards the different component solutions were statistically compared between the two sexes. Based on the sex-specific strategies found when investigating specific cognitive tasks (i.e. global versus local processing strategies), we would expect these differences to be also reflected in sex-specific cognitive profiles.

Methods

Subjects. Subjects included in the current study were drawn from 1000BRAINS[31], a population-based epidemiological cohort study, recruited from the Heinz-Nixdorf recall study that has been conducted in the Ruhr area in Germany[32]. Along the line of being population-based, exclusion from the study was based on eligibility for MR measurements for scientific purposes. From the initial cohort of 1314 subjects, 968 subjects being 55 years and older were selected to assess the older adult population. 20 subjects had to be excluded due to missing variables of interest for the current study (DemTect[33]: n = 18; or information on education: n = 2). Furthermore, subjects missing more than three values of the neuropsychological assessment (n = 2; for all other subjects missing values (ranging from 0 to 2.1% depending on the test) were replaced by the median of the respective age- (< 60; 60–64; 65–69; 70–74; 75–79; < 79) and sex-group. Subjects representing outliers (n = 83; outliermax > mean + 3*SD; outliermin < mean − 3*SD) in at least one of the cognitive variables were removed from the dataset. To establish similar demographic conditions in the two sex groups, propensity score matching (method = "nearest", caliper = 0.25; implemented in R: matchit, version 3.0.3) was used to match males and females for age and education (measured by ISCED[30]) which resulted in a final sample size of 676 subjects between 55 and 87 years of age: 338 males with a mean age of 66.9 years (SD = 6.7) and a mean ISCED score of 6.3 (SD = 1.74) and 338 females with a mean age of 66 years (SD = 6.5) and a mean ISCED score of 6.1 (SD = 1.86). All participants gave written informed consent before participating in 1000BRAINS. All experiments were performed in accordance with relevant named guidelines and regulations. The study protocol was approved by the local Ethics Committee of the University of Essen.

Neuropsychological assessment. All subjects underwent intensive neuropsychological testing during their participation in 1000BRAINS[31]. In total, 16 different cognitive functions, namely selective attention, processing speed, problem solving, concept shifting, susceptibility to interference, figural fluency, phonematic and semantic verbal fluency, vocabulary, verbal episodic memory, figural memory, visual-, visual-spatial- and verbal short-term/working memory were assessed. For cognitive functions and tests used, as well as raw mean scores for males and females, see Table 1.

Statistical analyses. First, sex differences in cognitive performance were examined for the different cognitive functions assessed in 16 different neuropsychological tests using Independent Sample T-Tests. Effect sizes were calculated using Cohen's d. Afterwards, we calculated z-scores for each variable followed by Pearson correlations between all neuropsychological variables included in the current analysis for the whole group, as well as for males and females separately.

The major research question in this study concerned whether males and females would show different cognitive profiles, i.e. different compositions of cognitive components. To investigate this, we divided our analyses in two parts (for an overview of analyses, see Fig. 1, part A and part B). In the first part (part A), we extracted cognitive components for both, the whole group (n = 676) including males and females, as it is commonly done in research investigating cognitive performance (e.g. see[46–51], as well as for males (n = 338) and females (n = 338) separately to identify commonalities as well as differences in cognitive profiles between the two sexes. For all the groups (whole, males and females) a two-step approach was applied:

Cognitive Function	Test description	Females: mean ± SD (Min; Max)	Males: mean ± SD (Min; Max)	T-value	*p*- value	Cohen's d
Age		65.99 ± 6.5 (55.2;85.4)	66.87 ± 6.65 (55.1;85.4)	− 1.735	0.083	0.132
DemTect	*DemTect*[33]*: Global cognitive score*	15.55 ± 2.22 (8;18)	14.17 ± 2.36 (8;18)	**7.860**	**0.000**	**− 0.587**
ISCED97	*International Classification*[30]*: Education classification*	6.1 ± 1.86 (3;10)	6.29 ± 1.74 (3;10)	− 1.370	0.171	0.109
Problem solving	*Leistungsprüfungssystem 50 + (Subtest 3)*[34]*: Number of correctly identified non-matching figures among geometrical figures*	20.39 ± 4.71 (8;35)	20.82 ± 5.13 (8;34)	− 1.132	0.258	0.084
Visual STM	*Block-Tapping-Test*[35]*: Number of correctly repeated blocks, forwards*	6.32 ± 1.76 (2;10)	6.57 ± 1.65 (2;10)	− 1.937	0.053	0.154
Visual WM	*Block-Tapping-Test*[35]*: Number of correctly repeated blocks, backwards*	4.69 ± 1.65 (1;10)	5.04 ± 1.7 (0;10)	**− 2.738**	**0.006**	**0.208**
VisualSpatial STM	*Visual pattern (Jülich version; similar to* [36]*): Number of memorized patterns presented in a grid of black and white squares*	7.32 ± 1.7 (4;12)	8.06 ± 1.68 (4;12)	**− 5.711**	**0.000**	**0.443**
Verbal STM	*Zahlennachsprechen (from Nürnberger Alters-Inventar*[37]*): Number of correctly repeated digits, forwards*	7.63 ± 1.84 (4;13)	7.66 ± 2.02 (4;13)	− 0.179	0.858	0.013
Verbal WM	*Zahlennachsprechen (from Nürnberger Alters-Inventar*[37]*): Number of correctly repeated digits, backwards*	6.79 ± 1.65 (2;12)	6.87 ± 1.77 (2;12)	− 0.653	0.514	0.049
Figural memory	*Benton-Test*[38]*: Number of errors during free recall of 20 remembered figures*	− 16.33 ± 7.57 (− 40; − 2)	− 16.17 ± 7.56 (− 36; − 1)	− 0.275	0.784	− 0.021
Selective attention	*Alters-Konzentrations-Test*[39]*: Time(s) to recognize target figures among distractors*	− 33.54 ± 8.74 (− 64.78; − 17)	− 33.66 ± 8.38 (− 65.87; − 18.22)	0.183	0.855	0.014
Interference	*Farb-Wort-Interferenztest (Jülich version; similar to: Bäumler*[40]*; Stroop*[41]*): Time(s) to name ink color of words with color meaning but printed in a different color (subtracted by the time(s) to read color words)*	− 39.63 ± 16.64 (− 110.6; − 9.47)	− 43.36 ± 17.58 (− 109.97; − 3.66)	**2.833**	**0.005**	**0.212**
Figural fluency	*Fünf-Punkte-Test (Jülich version; similar to: Regard* et al.[42]*): Number of unique drawn patterns by connecting five points in 3 min*	26.15 ± 6.89 (4;44)	26.38 ± 7.22 (11;49)	− 0.425	0.671	0.032
Episodic memory	*Verbaler Gedächtnistest*[43]*: Number of free recalled words in five trials from a list containing 15 words*	45.76 ± 10.05 (2;66)	38.61 ± 10.01 (6;65)	**9.262**	**0.000**	**− 0.714**
Phonematic fluency	*Regensburger Wortflüssigkeitstest*[44]*: Number of produced words beginning with the letter "B"*	19.32 ± 6.04 (4;37)	17.49 ± 5.93 (5;37)	**3.992**	**0.000**	**− 0.310**
Semantic fluency	*Regensburger Wortflüssigkeitstest*[44]*: Number of produced words belonging to the category "jobs"*	24.47 ± 6.19 (11;44)	23.39 ± 6.76 (6;43)	**2.153**	**0.032**	**− 0.159**
Processing speed	*Trail Making Test (taken from CERAD-Plus*[45]*): Time(sec.) to connect randomly arranged digits in ascending order*	− 38.62 ± 11.71 (− 79.41; − 16.06)	− 40.22 ± 13 (− 84.18; − 16.13)	1.677	0.094	0.123
Concept shifting	*Trail Making Test (taken from CERAD-Plus*[45]*): Time(sec.) to alternately connect letters and numbers in ascending order (TMT B), then calculating: TMT B-TMT A*	− 48.71 ± 28.33 (− 183.44; − 1.78)	− 54.28 ± 32.46 (− 166.6;0.67)	**2.375**	**0.018**	**0.171**
Vocabulary	*Wortschatztest*[46]*: Number of correctly identified real words among five pseudo-words*	30.96 ± 4.34 (16;40)	30.8 ± 4.17 (16;40)	0.493	0.622	− 0.039

Table 1. Descriptives of neuropsychological variables including cognitive functions, tasks used, mean and standard deviation (SD) and Min; Max values, T value of group comparison with corresponding *p* value and effect size measured with Cohen's d. Values written in bold indicate significant differences between groups ($p < .05$). STM = short-term memory, WM = working memory.

(1) *Data reduction* We reduced the cognitive performance data into independent cognitive components by using exploratory principal component analysis (ePCA) with Varimax rotation (implemented in the "psych" package, R Studio), as one of the most commonly used technique for data reduction[52]. The number of extracted components was based on the eigenvalue criterion (eigenvalue > 1). This resulted in three independent data-driven component solutions: whole ePCA based on the whole group, male ePCA within males only, females ePCA within females.

(2) *Component solution validation within respective groups* To validate the obtained component solutions in their respective group (whole ePCA, male ePCA, females ePCA), a confirmatory factor analysis (CFA, implemented in the "lavaan" package, R Studio) was set up with Maximum Likelihood estimator with robust standard errors and a Satorra-Bentler scaled test statistic. In detail, each component solution represents a measurement model that is composed of a specific number of cognitive components, with each including a specific number of cognitive performance tests. In the current study, we based the measurement models on the component solutions obtained by ePCA and included all cognitive performance tests with a component loading of at least 0.4[53].

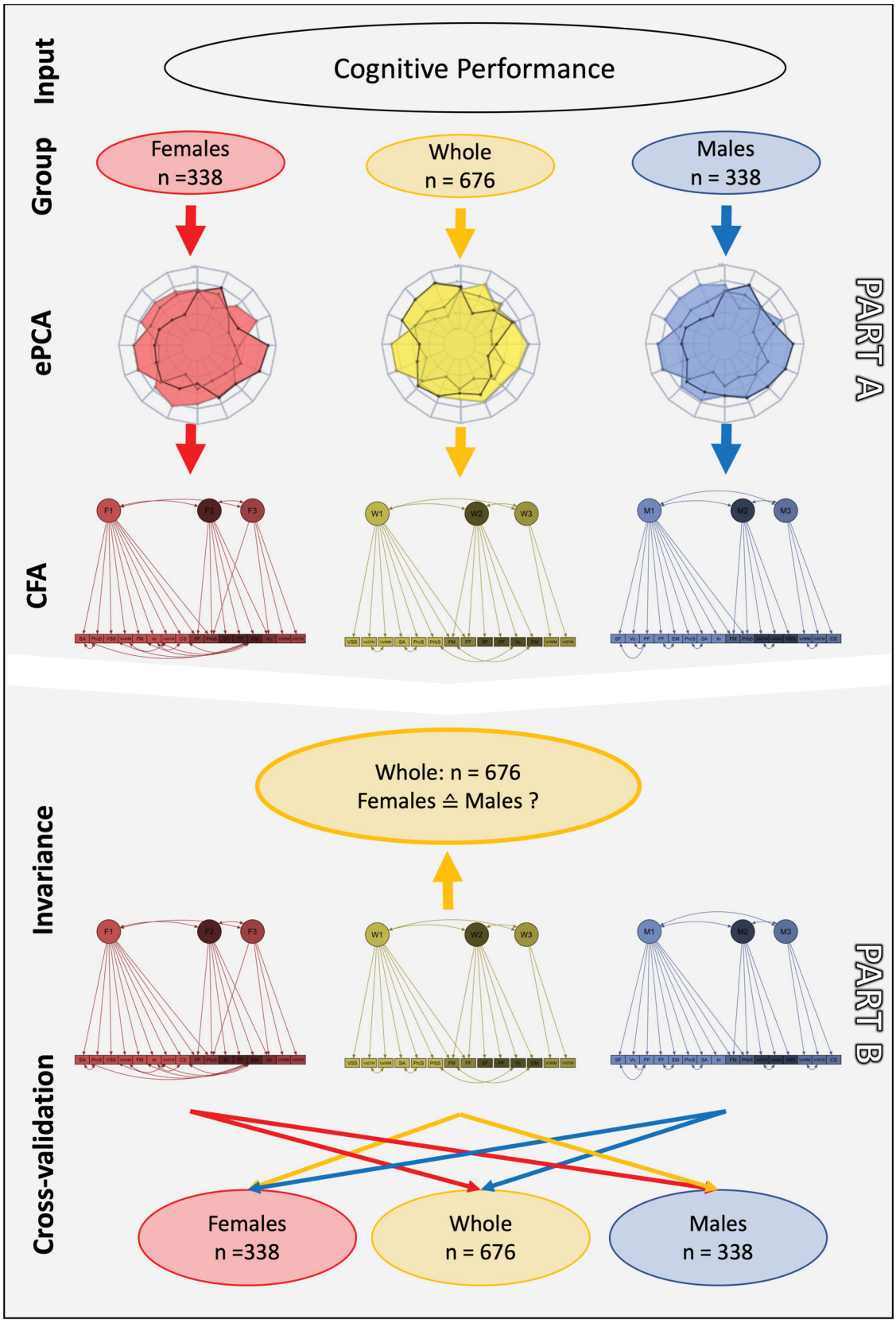

Figure 1. Flowchart presenting the study design.

To examine model fit of the respective ePCA's, we used comparative fit index (CFI), tucker lewis index (TLI), root mean square error of approximation (RMSEA) and standardized root mean square residual (SRMR). Quality of model fit was assessed based on frequently reported fit indices indicating excellent model fit at CFI > 0.95, TLI > 0.95, RMSEA =< 0.06, SRMR < 0.09[54,55]. All initial models were subsequently refined to increase model fit: From the initial model, we first modelled residual covariances (included when residual covariances were > 0.1) between variables and components, and afterwards, removed non-significant variables from the model, if present.

After this measurement model configuration, we attempted to validate the established models across the two sexes (Fig. 1, part B). To do so, we first examined measurement invariance for all three models (whole CFA, male CFA, female CFA). Measurement invariance addresses the question whether a scale measures the same attribute in different groups of subjects. Hence, in the current study, measurement invariance would test whether the different cognitive component solutions, i.e. cognitive profiles would be the same across males and females. Measurement invariance was tested with the following aspects: (1) configural invariance: the measurement models derived from the CFA would fit equally well in males and females (same data structure across variables); (2) loading invariance: loadings of variables onto a cognitive component would be the same for males and females (groups have the same factor loadings); (3) intercept invariance: males and females would show the same intercept on the measured variables (groups have same intercepts of the observed variables); (4) mean invariance: males and females would show the same means on the measured variables (groups have the same means across the observed variables). In a second step, we applied a strict cross-validation by applying the sex-specific models to the other sex group only to test whether the male component solution would also obtain a good fit in females and vice versa. Model fit changes across the models were considered as significant with a change in CFI > 0.01[56] and a significant likelihood chi square difference test ($p < 0.05$).

Results

The current study assessed sex differences in cognitive profiles between older males and females based on a large battery of cognitive tests assessing attention, memory, executive and language functions. Differences in performance between males and females were already observed at single test level in several of the 16 neuropsychological tests used in the current study. For example, males performed significantly better in tasks requiring visual and visual-spatial abilities, e.g. visual-spatial memory, whereas females performed better in tasks requiring verbal abilities, such as episodic learning, phonematic and semantic fluency (see Table 1).

Investigating intercorrelations between cognitive performance scores of the different cognitive functions revealed a second interesting and important observation: While we overall found high intercorrelations between the assessed cognitive performances, these intercorrelations do not seem to be identical in males and females, already hinting at differences in cognitive profiles for the two sexes (for chord diagrams for the whole group, males and females separately as well differences between males and females, see Fig. 2, for Pearson correlation values between cognitive task, see Supplement, Tables S1–S3). Sex differences in cognitive performance correlations are shown in Fig. 2d. Noticeably, females show higher correlations between verbal and non-verbal test performance while males show higher correlations between verbal, non-verbal and executive functions (e.g. interference, concept shifting and problem solving).

Principal component analyses and confirmatory factor analyses for the whole group and males and females separately. Based on the correlations between cognitive performance tests, ePCA was applied to individual cognitive performance measurements of the whole group as well as males and females separately. Extraction of components was based on the eigenvalue criterion (eigenvalue > 1, see Supplement, Table S4). Three components were extracted for the whole group (eigenvalues: 4.94, 1.48, 1.19) as well as when assessing males only (eigenvalues: 5.08, 1.58, 1.25). Regarding females only, the optimal component solution consisted of four cognitive components (eigenvalues: 4.97, 1.36, 1.09, 1.02). For all eigenvalues, see Supplement, Table S4.

For the whole group, the extracted components were dominated by the following functions: The first component covered a variety of non-verbal cognitive functions such as visual working memory, attention, executive functions and memory. The second component included fluency as well as memory. The third component was dominated by verbal functions, such as verbal working memory and vocabulary (Fig. 3a, for component loadings of all groups, see Supplement, Table S5). Afterwards, we extracted fit values for the PCA-derived three-component model using CFA. All variables were found to significantly contribute to the components (> 0.4), However, fit values of the initial model were not to be considered as of sufficient quality (CFI = 0.894; TLI = 0.866; RMSEA = 0.07, SRMR = 0.053). After model refinement via inclusion of residual covariances and exclusion of non-significant variables, the model improved significantly, but did not reach the threshold for being an excellent model in all fit indices (CFI = 0.941; TLI = 0.921; RMSEA = 0.054, SRMR = 0.045). The resulting model is shown in Fig. 3b (for results of the CFA for all groups, see Supplement, Table S6 and S7).

The male model (Fig. 3c,d), also a three-component model, consisted of a first component that included fluency, memory, attention and executive function, a second component that was dominated by visual working memory and executive functions and a third component including verbal working memory and executive functions. The initial male model revealed fit values not to be considered as of sufficient quality (CFI = 0.883, TLI = 0.854, RMSEA = 0.071, SRMR = 0.06). After additional refinement, the male model fitted on males revealed fit indices of: CFI = 0.94, TLI = 0.923, RMSEA = 0.051, SRMR = 0.049. This is a significant increase in model fit although it still does not reach the threshold for being an excellent model.

The female component solution (Fig. 3e,f) revealed one component dominated by visual memory and working memory, a second component including fluency and vocabulary and executive functions, a third component that consisted of executive functions and memory and a fourth component including verbal working memory

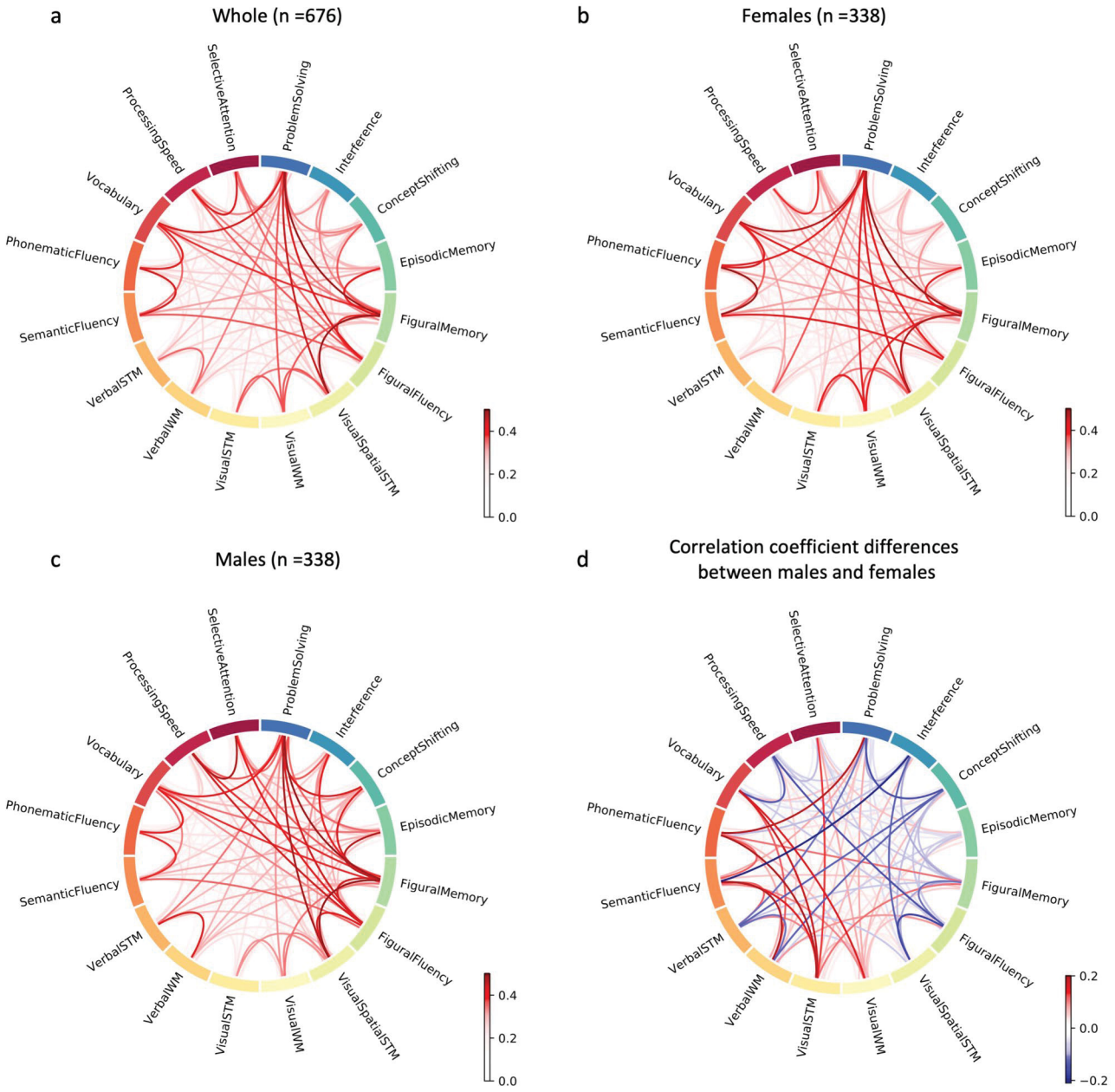

Figure 2. Chord diagrams of correlations between cognitive performance tests: (**a**) whole group, (**b**) females and (**c**) males, (**d**) differences in correlation coefficients between males and females: blue = males > females, red = females > males.

and vocabulary (for variable loading on the different components, see Supplement, Table S5). The initial female model fitted on females revealed fit indices of: CFI = 0.964, TLI = 0.953, RMSEA = 0.037, SRMR = 0.039. Although this model fulfilled the requirements for being an excellent model, we additionally refined the model by the same conditions we did before. This resulted in an additional significant increase in model fit (CFI = 0.984, TLI = 0.979, RMSEA = 0.025, SRMR = 0.034).

Taken together, the investigation of data-driven cognitive components in the three groups (whole group, males and females) hint at different compositions of cognitive components in older males and females (i.e. three versus four components, for an additional overview of three versus four component solutions for the whole group, males and females, see Supplement, Figure S1). Comparing these to the again slightly different component solution derived from the whole group (including both males and females) raises the question of whether these so far descriptively compared differences would be statistically meaningful, which was tested afterwards.

Measurement invariance and cross-validation. In the second part of the study (Fig. 1, part B), we addressed the distinctiveness of cognitive components between males and females by using measurement invariance and cross-validation. In detail, we started with the component solution that was derived from the whole group (including males and females) and tested whether this whole group cognitive component solution would

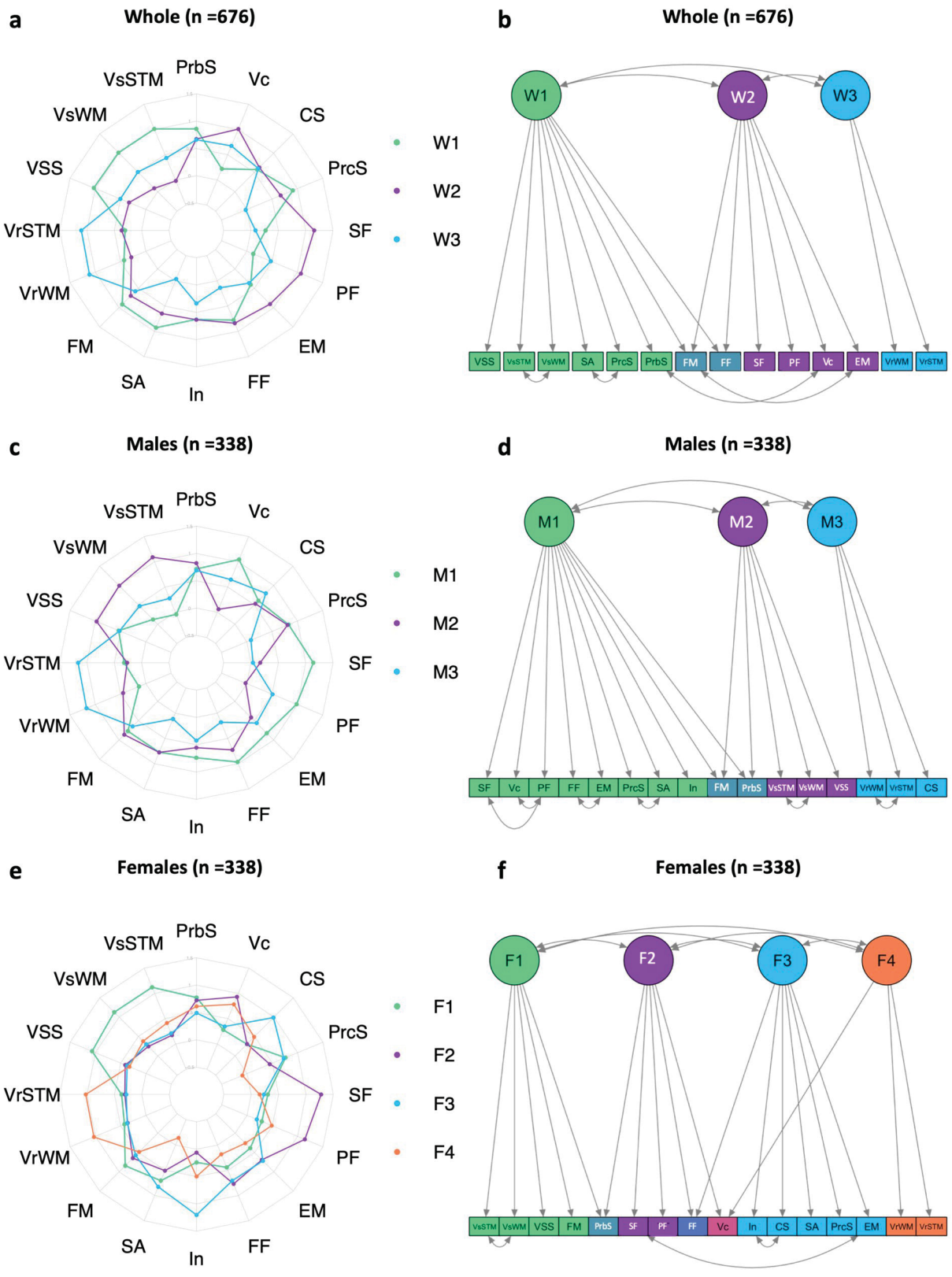

Figure 3. Exploratory Principal Component Analysis (ePCA) and Confirmatory Factor Analysis (CFA): (**a**,**c**,**e**): ePCA for the whole group, males and females. (**b**,**d**,**f**): CFA for the whole group, males and females. *PrbS* problem solving, *VsSTM* visual spatial short-term memory, *VsWM* visual spatial working memory, *VSS* visual working memory, *VrSTM* verbal short-term memory, *VrWM* verbal working memory, *FM* figural memory, *SA* selective attention, *In* interference, *FF* figural fluency, *EM* episodic memory, *PF* phonemic fluency, *ST* semantic fluency, *PrcS* processing speed, *CS* concept shifting, *Vc* vocabulary.

Model	Group	X2	CFI	TLI	RMSEA	SRMR
WHOLE	WHOLE	**201.647**	0.941	0.921	**0.054**	**0.045**
WHOLE	MALES	**165.421**	0.919	0.892	0.065	**0.058**
WHOLE	FEMALES	**109.756**	**0.962**	0.949	**0.043**	**0.043**
MALE	WHOLE	**221.151**	**0.95**	0.935	**0.045**	**0.04**
MALE	MALES	**175.919**	0.94	0.923	**0.051**	**0.049**
MALE	FEMALES	**142.817**	**0.959**	0.947	**0.04**	**0.043**
FEMALE	WHOLE	**247.081**	0.939	0.921	**0.05**	**0.04**
FEMALE	MALES	**207.401**	0.917	0.891	0.061	**0.051**
FEMALE	FEMALES	**117.601**	**0.979**	**0.972**	**0.029**	**0.036**

Table 2. Model fit indices for male and female refined models applied to the different groups. Values in bold reach the threshold for being an excellent model.

be statistically the same across males and females, i.e. invariant (for CFA model estimates, see Supplement, Table S8). Model fit indices did not reach the threshold for measurement invariance in terms of configural model (i.e. same data structure: CFI = 0.939, RMSEA = 0.055) and loading invariance (i.e. same factor loadings: CFI = 0.938, RMSEA = 0.053), it did even less so in the intercept (i.e. same intercept: CFI = 0.893, RSMEA = 0.067) and means invariance (i.e. same means: CFI = 0.871, RSMEA = 0.073). Thus, the cognitive component solution derived from the whole group, as it is often done in research investigating cognitive performance, does not seem to be completely generalizable over males and females. This, in turn, leads to the question which group (males or females) would fit better to the whole group component solution. While the model fit increased when the whole group model was applied to females only (whole group: CFI = 0.941; TLI = 0.921; RMSEA = 0.054, SRMR = 0.045; females: CFI = 0.962, TLI = 0.949, RSMEA = 0.043, SRMR = 0.043), it significantly decreased when investigating males only (CFI = 0.919, TLI = 0.892, RSMEA = 0.065, SRMR = 0.058). Thus, the current results indicate that the overall composition of cognitive components derived from the whole group is better suited for the female group as compared to the male group.

In a final cross validation, we applied the different cognitive component models obtained by either the whole group, males or females to the other groups, e.g. male component solution fitted onto the female group and vice versa (for fit indices, see Table 2). Applying the whole group model to males and females separately revealed an excellent model fit for the female group and a worse model fit for the male group. Applying the female cognitive component model to the male group reveals an overall insufficient model fit, which underpins the results obtained by the examination of measurement invariance. In turn, applying the male component model to the female group revealed a reasonable fit, with excellent fit indices. Thus, while males' cognitive performance does not seem to be sufficiently explained by the female model, female's cognitive performance can be sufficiently composed into both, male and female component solutions, with a slightly better fit of the female cognitive component model. Nevertheless, applying the male component solution to the female group revealed high covariances between the components (> 1), which indicates collinearity between the components. Thus, the validation of the component solutions indicate that separate cognitive component solutions might better describe a cognitive profile as compared to a common component solution.

Discussion

Using a data-driven approach, the current study examined sex-specific cognitive profiles based on a large variety of cognitive functions in older males and females. Our results show that a general model consisting of cognitive components that combine numerous cognitive tasks calculated based on the whole group (including both, males and females) fit unequally well on the two sexes. Males and females differ in terms of their composition of cognitive components, i.e. three components in males versus four components in females, with a generally better model fit in females. Thus, the current study found a rather decomposed (or local) cognitive profile in females while males seem to show a holistic (or global) cognitive profile, with more interrelations between different cognitive functions.

In a first step, we systematically examined sex differences in 16 different cognitive functions, namely selective attention, processing speed, problem solving, concept shifting, susceptibility to interference, figural fluency, phonematic and semantic verbal fluency, vocabulary, verbal episodic memory, figural memory, visual-, visual-spatial- and verbal short-term/working memory. We showed that older women perform better in verbal fluency, verbal episodic memory, processing speed and interference while older men significantly performed better on visual and visual-spatial working memory tasks. Importantly, these differences were rather small with only visual short-term memory and episodic memory showing medium effect sizes. Hence, the results are in line with a large amount of previous studies showing that males and females differ in some but not all cognitive functions and that these differences tend to be small[5,9,10]. Thus, in normal older adults, we were able to show that those tasks requiring high verbal versus visuospatial processing show the largest sex differences.

Further, de Frias et al.[2] presented long-term sex differences in cognitive performance in a sample of adults with an age range from 35 to 80 years (at baseline). Over a period of ten years, women remained better in tasks assessing verbal episodic memory and verbal fluency, while men outperformed women in tasks assessing visuospatial functions. Additionally, and in line with Maitland et al.[57] and Pauls et al.[58] we showed that sex

differences, especially in the verbal versus spatial domains remain stable even in older ages. Thus, the current study adds to the notion that, even in later decades of life, sex differences in verbal versus visuospatial cognitive functions persist.

The observed sex differences in cognitive performance might be due to different processing styles to solve cognitive problems. Men usually inspect new scenes in a more 'global' way (e.g. having in mind the whole map in a spatial navigation task), while women usually prefer to inspect tasks more locally (i.e. remember more details of a given word list)[18,19,59]. This might explain why men outperform women with respect to visual-spatial tasks and why women perform better in verbal episodic memory. Based on these task specific differences between the two sexes, the main goal was to investigate whether we could extend this global versus local phenomenon, to cognitive profiles in males and females, i.e. the relations between cognitive abilities. Using a data-driven ePCA we revealed a three-component solution for the whole including: (1) a non-verbal component composed of tasks including attention, executive functions and (working-) memory, (2) a mixed component including verbal and non-verbal fluency and memory functions and (3) a verbal short-term/working memory. This data-driven cognitive component solution shows the high complexity between cognitive functions, i.e. verbal fluency tasks require a large memory span and vice versa, an observation that has been found to be impaired in amnestic mild cognitive performance[60]. It furthermore shows that cognitive components do not necessarily comply with the classical theory-driven cognitive domains of attention, executive functions, working and episodic memory and language functions, an observation that has already been described by Harvey[21].

Noticeably, CFA was used to examine the model fit indices of this component analysis and whether this component solution fit equally well to males and females. The overall model shows an acceptable, although not excellent fit (CFI > 0.95)[54,55] for the whole group (even after refinement of the model by including residual covariances between cognitive variables and exclusion of non-significant variables). When examining measurement invariance between the two sexes, thus whether a cognitive profile would fit equally well to males and females, we again found an acceptable but not excellent model fit already in the configural model (composition of the components), with further significant decreases when it comes to mean and intercept invariances. While some fit values do not differ from previous results obtained by Siedlecki et al.[22], who interpreted a CFI value of 0.941 as being acceptable, they are low as compared to other studies investigating measurement invariance in cognitive or psychological profiles between, e.g. healthy adults and Alzheimer patients or using longitudinal models of sex differences over the whole adulthood[61,62]. These differences in model fit to the aforementioned studies might be due to differences in neuropsychological tests used or differences in group characteristics. In the current sample, normal older adults were examined that were matched for age and sex, since both factors are well known to correlate with cognitive performance[24,63]. Thus, the sex-specific effects found in the current study regarding cognitive profiles line up with previous studies showing that sex differences exist, and might be of special importance for our society, but are of rather small effect size[10].

After stratifying the current sample for sex, we again performed an ePCA and obtained different component solutions for each group. While in the male group, three components were preferred (according to the Eigenvalue criterion), females' cognitive performance was best described by a four-component solution. More importantly, the extracted components differed in their composition, i.e. cognitive tasks involved in the different components. While for the whole group, the first component was composed of heterogeneous but consistently non-verbal functions, verbal as well as non-verbal functions belong to the same component in males, additionally including fluency, memory, attention and executive functions. The second male component contained visual working memory and executive functions and the third component consisted of verbal working memory and executive functions. Relating these results to the observations made regarding task specific differences in processing styles, i.e. global–local hypothesis of sex-differences[11], one could argue that males' holistic/global processing style to solve cognitive task, is in line with the current cognitive profile. Males show a quite holistic first component, including attention, executive functions, episodic memory and fluency tasks, hinting at higher interrelations between different cognitive abilities. Furthermore, since executive functions and/or attention depict essential parts in all three components it could be assumed that these functions serve as a higher order executive-attention system that monitors cognitive performance[63–66]. Thus, this would mean that males rely strongly on their attentional and executive functions, e.g. goal-directed planning, monitoring, mental flexibility, to process cognitive tasks belonging to different cognitive domains. In terms of a global way of cognitive processing, males potentially manage cognitive processing using one superordinate system that links different cognitive abilities. Likewise, if these functions decline, a decline of all other cognitive domains follow, as has been stated by theories, such as the frontal executive theory of aging[67]. Investigating females only revealed a different picture compared to both the whole group or males only. Females' cognitive performance within the functions examined is best decomposed into four cognitive components. In contrast to the males' first component which was quite heterogeneous including fluency, executive functions and attention, in the females' cognitive profile visual-verbal fluency and executive functions—attention—built separate components; together with a component composed of visual (working) memory and executive functions and another component dominated by verbal functions including working memory and vocabulary. Thus, females' cognitive profiles consist of more subsystems as compared to males, with systems including different cognitive functions (i.e. [1] visual (working) memory/[2] fluency/[3] executive functions/[4] verbal (working) memory). Although these functions share covariances, they themselves represent distinct cognitive systems or modules. On the other hand, males might have a superordinate system, i.e. the attentional-executive-fluency-memory component, which includes several cognitive domains, thereby representing a stronger interplay of cognitive functions with a probably superordinate system (i.e. executive functions). Hence, this could be potentially related to a more global processing strategy during cognitive performance, meaning that irrespective of the task (e.g. memory or fluency), males might activate similar cognitive processing strategies. In contrast to that, females would rather choose different processing strategies, depending on the cognitive task, e.g. visual versus verbal working memory. Together, similarly to the global versus local

processing at single task level[11,12,15,18,68], cognitive profiles derived from either males or females seem to be differentially composed along the global vs. local processing dichotomy in the current study.

Furthermore, focussing on the cross-validation model fit values, an additional support for the existence of sex-related cognitive profiles in line with these processing strategies became evident. While applying the female component solution to the female group reveals excellent fit values, the male component solution only reveals acceptable fit values when applied to the male group. These lower fit values might arise from the stronger interconnectedness of different cognitive functions in the male group, which has been shown when comparing correlation strength between males and females (cf Fig. 2). For example, interference is correlated to both, verbal fluency as well as visual spatial short-term memory, which in turn is correlated with figural fluency. As a consequence, a clear division of cognitive functions into different (independent) cognitive domains, might not be possible in the male group. Thus, males' cognitive abilities seem to be not fully suitable for a modular cognitive structure as compared to females. This again, would be in accordance with global versus local processing styles.

Importantly, the current study investigated an older adult population to examine sex-specific cognitive profiles. This population is of special interest when examining sex differences in cognitive performance and cognitive profiles since previous research has shown that first, sex-differences in cognitive functions remain stable until older ages, and second, pathological conditions with cognitive impairments differ in prevalence between males and females[28,57]. However, research so far, most often includes sex as a covariate of non-interest when assessing cognitive impairment.

Previous studies often showed steeper decline in general cognitive functions in males[1,69]. Similarly, in pathological conditions, such as Parkinson's disease, males were reported to show a faster decline in cognitive functions[28]. However, when it comes to Alzheimer's disease, females show a faster decline in memory scores as compared to males[29]. This observation might be related to distinct cognitive profiles in older males and females. If, within the 'global' cognitive profile of males, the executive-attentional monitoring system breaks down this would lead to a global decline in cognitive functions. Especially for the aging process, theories such as the prefrontal-executive theory[67] as well as the processing speed theory[70] of aging, stating that decreasing executive functions and attention, respectively, predict cognitive decline in a diversity of cognitive functions belonging to different domains[64]. Thus, in males these two theories that try to explain cognitive performance decline during the aging process, would be in line with the current results. On the other hand, if females' cognitive profiles are rather composed of different cognitive subsystems or modules (thus 'local' cognitive profile), impairments within the executive-attentional component would not necessarily lead to an impairment in other cognitive components. Hence, this would rather result in function-specific cognitive decline, e.g. executive impairment. These differences in cognitive profiles might thus serve as a possible explanation for why males show generally steeper decreases in overall cognitive abilities during aging[69].

Methodological considerations. The current study has several advantages and disadvantages. While we were able to show that cognitive profiles differ, when investigating males and females independent of each other, it is important to mention that the effects of sex differences are rather of smaller sizes, which becomes obvious when focussing on the differences in terms of intercorrelations between different cognitive tasks. Nevertheless, as stated by Zell et al.[10], although effect sizes might be small, when investigating sex differences in cognitive performance, these differences might be important to understand cognitive performance differences.

In addition, it has to be mentioned that the current study investigated these cognitive profiles in a sample ranging from 55 to 85 years of age. It might be the case that with increasing age, cognitive profiles change, especially when cognitive impairments arise, e.g. due to pathological conditions. Future studies should investigate this topic, especially using longitudinal data, to show whether cognitive profiles change in the course of the aging process, potentially also with respect to pathological conditions.

Further, it has to be mentioned that the set-up of cognitive profiles is not straightforward. We used a Principal Component Analysis with Varimax rotation method for extracting cognitive components in the two groups and extracted four factors for females and three factors for males, based on the Eigenvalue criterion (cut-off for selection of components being an Eigenvalue > 1). Nevertheless, the fourth Eigenvalue is only slightly above one for females (1.02) and the fourth Eigenvalue is only slightly below 1 (0.97) for males, which both are very close to the cut-off value. Further, the model refinement highly depends on the input data (in this case the cognitive tasks used). Until now, there is no gold standard in this respect. More research is needed to address this important topic.

Finally, the question that arises when observing these differences is which factors might be responsible for the development of sex differences. From previous studies it is known that males and females differ in terms of brain structure and function, which might relate to differences in cognitive processing strategies[71,72]. Furthermore, it has been shown that hormonal differences, but also genetic variations might be related to differences in cognitive and social behavior between the two sexes[73]. Social factors, such as gender role models, significantly influence differences in cognitive performance, which is less pronounced in countries that promote gender equality[74]. Further studies are warranted to examine this question.

Conclusion

Conclusively, males and females show not only differences in specific cognitive tasks but generally in cognitive profiles across cognitive domains. Males are likely to use a more holistic way of processing, by integrating different cognitive functions to solve specific tasks. This could be, for example, a higher executive control and memory function in a verbal fluency task, which in turn, would result in larger clusters of the same category. Females, on the other hand are likely to process cognitive tasks in smaller, rather domain-specific subsystems. The results showed that older males and females exhibit different cognitive profiles, that are likely to be related to

differences in cognitive decline across the aging process. Therefore, the current research stresses the importance to use sex-stratified analyses when assessing cognitive performance. Future research is warranted to extend the current results to pathological conditions, such as Alzheimer's disease. Furthermore, differences in cognitive profiles might not only be important in basic research but, might also impact clinical prevention programs, i.e. cognitive training.

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Current Opinion in Behavioral Sciences

Deep characterization of individual brain-phenotype relations using a multilevel atlas

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Population neuroimaging allows for extracting general principles of brain-phenotype relationships. Capturing individual brain-behavior profiles in groups with pronounced inter-individual variability, like the older adult population, however, remains challenging. Therefore, deep characterization is required to link multilevel brain, cognitive and lifestyle data. We here proposed a use case of five older males scoring low on a dementia screening test. We showed quite heterogeneous individual cognitive, lifestyle and grey matter atrophy profiles. Integrating additional regional genetic, molecular and connectional data using a multilevel atlas framework revealed (dis-) similarities between the atrophied brain areas, thereby helping to explain the individual phenomena and emphasizing the need for integrating multifactorial and multilevel information on the way toward individualized predictions.

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Introduction

One of the major goals in modern population neuroimaging is the extraction of robust trends of brain-phenotype relationships to understand general principles of human brain organization under healthy conditions, and capture transitions to disease. The challenge of extracting such trends, however, lies in the high inter-individual variability including variations at the level of behavior, brain structure and function, and age-dependent changes [1,2]. During the last decade multicenter studies and imaging consortia, such as ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis [3]), UK Biobank [4], Human Connectome Project [5], Rotterdam study [6], ADNI (Alzheimer Disease Neuroimaging Initiative [7]) and NAKO (German National Cohort [8]) have been established that capitalize on large sample sizes to increase statistical power which in turn allows for a more robust identification of various sources for inter-individual variability along the different levels.

The older adult population represents a prime example for a particularly high inter-individual variability. Studies have indicated signs of cognitive decline [9,10] and brain atrophy [11] from early to late adulthood, but also adaptions of the brain's functional network architecture [12,13]. Focusing on older age, though, reveals high inter-individual differences in these features going beyond what can be explained by the factor 'age' alone [1,14,15]. Rather, changes in brain structure and/or functional connectivity have been associated with inter-individual differences in cognitive performance [16], lifestyle [17••,18], sex [3], genetic predispositions [19], and/or environmental influences [20]. It has to be mentioned, though, that the influence of such factors is typically rather small. Smoking habits, for example, only explain 4% of the variability of cortical thinning in older adults [21]. Furthermore, effects of different influencing factors might interact and lead to (non-)additive effects. Along a similar line of reasoning, the risk for developing neurodegenerative diseases, that is, Alzheimer's disease (AD), increases with age. Nevertheless, at the age of 70, 10% of the population develop AD, while the remaining 90% do not [22]. Previous studies additionally showed that prodromal stages of AD, that is, subjective or mild cognitive impairments do not necessarily convert into AD over time [23,24], indicating that other factors than 'age' contribute to the risk for developing such a neurodegenerative disease. Thus, to finally understand normal and pathological aging there is an urgent need to decode the factors that drive this older adult population's variability.

While population-based studies are essential and important, for example, to build hypotheses and inform brain modeling approaches, analyses on the group level lack an important aspect: Inter-individual variability is often regarded as some kind of unexplainable noise, that cannot be explained by focusing on main effects. Instead, we

emphasize to approach variability as a target of research, to study the different factors contributing to variability in more detail, and to quantify factors characterizing brain-behavior relationships [25].

This requires deep, multifaceted analyses to consider various influencing factors on the individual aging process. Potentially important aspects that explain why some subjects age at a faster rate as compared to others hence require large, phenotypically deep and rich datasets — both in terms of group size, and on the individual level. This allows to derive 'individual fingerprints' of phenotypical characteristics and neuronal correlates. Secondly, towards a holistic understanding of brain aging it is necessary to link multilevel brain data, from the molecular and cellular to the systems network level. As many molecular and cellular data are accessible only from post-mortem tissue and not directly available for subjects of large cohorts with systems level neuroimaging and phenotypic data, linkage through a common reference framework can help to fill this gap. We here propose a use case of how to integrate individual deep phenotypic characterization and multilevel brain imaging using data of five older males of a large population-based cohort study, 1000BRAINS [26], as an example. The here selected subjects represent a group of interest. They were defined a priori, based on a standardized dementia screening test in contrast to a large group of age- and sex-matched controls.

Inter-individual variability, deep phenotyping and multilevel brain data: a use case

A use case will illustrate the relevance of individual deep phenotypic characterization, based on cognitive, lifestyle and grey matter atrophy profiles to obtain a deeper understanding of normal and pathological aging, and to develop indicators in the future to distinguish both from each other. We a priori selected five male participants from 1000BRAINS scoring low on a dementia screening test and created individual profiles of cognitive performance, lifestyle measurements and modulated grey matter volume (P1-5). Subsequently, regional genetic, molecular and connectional data were drawn from a multilevel atlas framework based on the Julich Brain atlas [38••] as provided in EBRAINS (https://ebrains.eu/services/atlases/brain-atlases/) to identify atrophied brain regions (for a description, see Box 1).

Participants being at risk for dementia (DemTect Score [27] $\leq$8, see Figure 1a) came from 1000BRAINS, a large population-based cohort study assessing the inter-individual variability during aging [26]. Healthy controls (HC) were males from the same cohort, within the same age-range ($n = 323$, mean age: 67.6 years $\pm$ 6.4), but performed adequate on the dementia screening test (>12; mean DemTect score: 15.2 $\pm$ 1.8). To examine the variability of the 'at risk' participants (P1-5), we created cognitive and lifestyle profiles, that is, individual fingerprints using 19 cognitive [26,28,29] and 10 lifestyle features [17••,30] (Figure 1b and c). Higher cognitive scores indicate higher performance. Regarding lifestyle, higher scores indicate protective behavior for the dietary index (DI), social behavior (SOC) and physical activity (SP) and risky behavior for alcohol consumption (ALC), body related factors (BODY) and smoking habits (SMO). In order to better assess the individual values (with regard to interpretation and rating in, e.g., good or bad), we also calculated the mean value and standard deviations (dashed grey line in the figures) within the HC group.

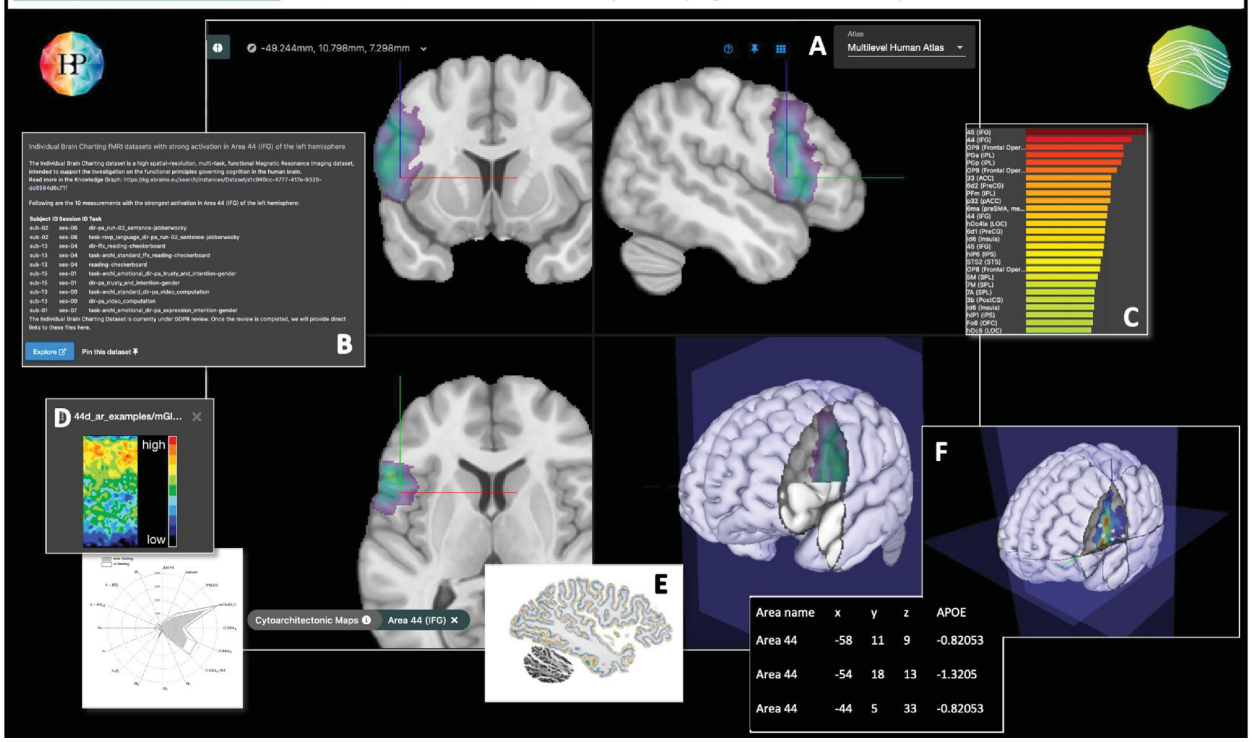
Participants P1-5 performed at a 'at risk' level regarding the dementia screening test and clearly scored below HC (Figure 1a). At the same time, the cognitive and lifestyle profiles were highly variable, and no common trends were seen for participants P1-5. Differences, however, were seen at an individual level. P1 and P3 generally performed at a lower cognitive level (P1 especially in the domains of attention and language and P3 in the domains of executive functions and language). In turn, P2 and P5 remained within the normal range in almost all cognitive tasks (P5 even performed at a higher level in the language domain) and P4 showed single cognitive abilities to be impaired, that is, executive functions and working memory (Figure 1b).

With respect to lifestyle, a similarly heterogenous picture has been found (Figure 1c). P1 and P2 seem to be centered around the mean of the HC, with a slightly lower body mass index (BMI) and a slightly healthier diet. P3 had the highest BMI, while P5 had a high amount of packyears (referring to smoking amount during the lifespan) and P4 followed healthier diet, together with a low BMI and higher physical activity. The development of dementia or mild cognitive impairment is assumed to be related to impairments in at least one cognitive domain (e.g. learning and memory), a high BMI, low physical activity, unhealthier diet or high smoking (for recent reviews, see Refs. [31,32]). The individual profiles, however, show that these general trends only partially reflect the situation at the level of the individual subject. Instead, a rather heterogenous picture emerges with each individual showing a mixture of different protective and potentially aversive lifestyle factors [33]. Hence, it rather seems that each individual has its own cognitive/lifestyle fingerprint hinting at multifactorial genesis of cognitive impairment during older ages.

Beyond cognitive alterations and behavioral differences, previous studies reported specific atrophy patterns in healthy subjects during aging as compared to patients suffering from (or being at risk for) dementia [11,34,35]. With respect to Alzheimer's disease (AD), the medial temporal lobe would be one of the first regions affected [36], depending on the subtype [35]. In the current

Box 1

EBRAINS Research Infrastructure of the HBP provides the interactive atlas viewer (A) that allows for exploring different brain atlases (including the Julich-Brain) integrated on multiple reference spaces. These information are complemented by region-specific information based on a growing set of multimodal datasets including information from neuroimaging studies, e.g. functional imaging (B) or structural connectivity (C), distributions of receptors (D) and cells (E) as well as genetic representation (F) in cytoarchitectonically defined brain regions. For more information, see https://atlases.ebrains.eu/viewer. Besides the interactive viewer, EBRAINS provides programmatic access via Python and HTTP.



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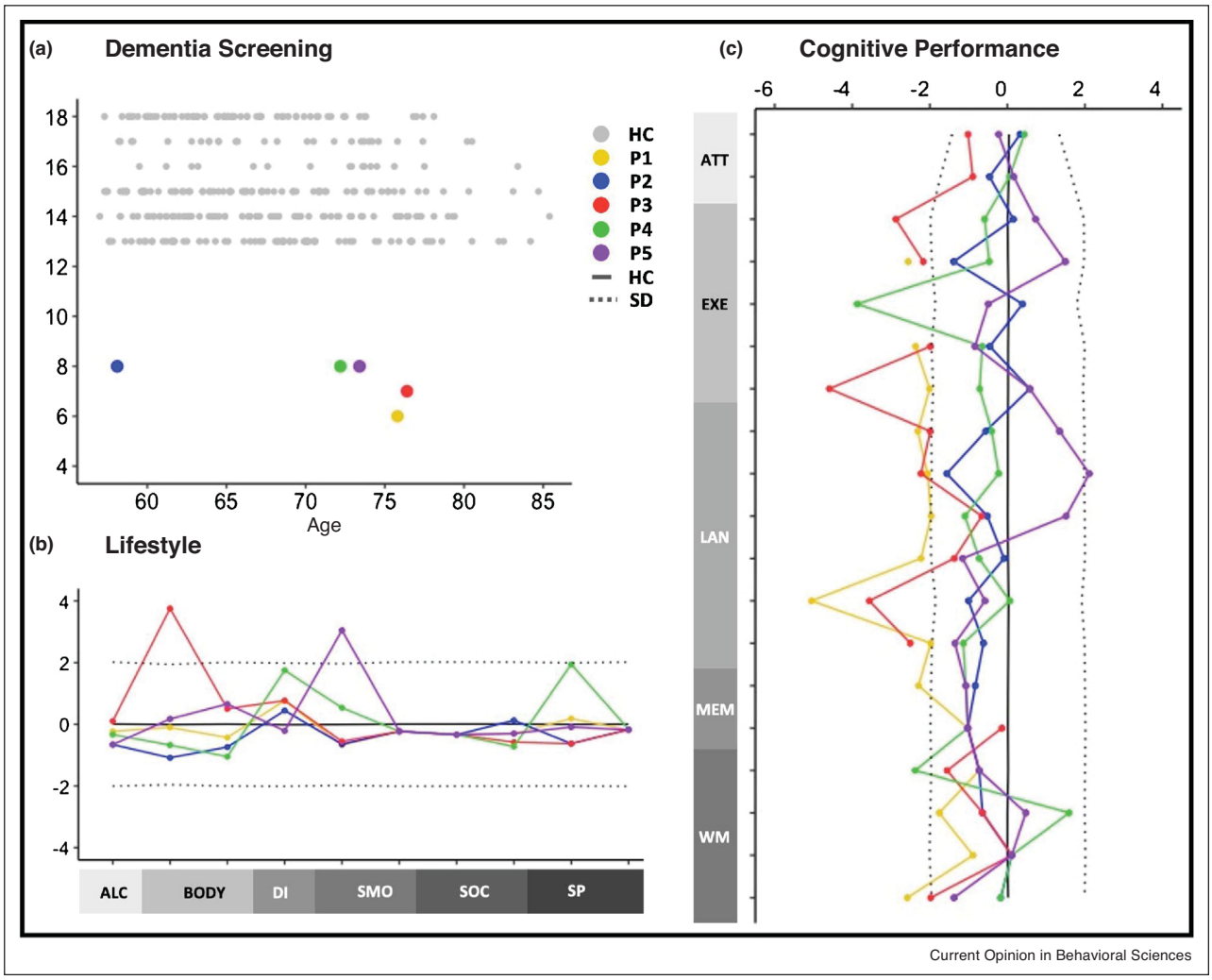
EBRAINS Interactive Viewer.

participants P1-5, we extracted therefore modulated grey matter volumes values (using the CAT toolbox, SPM12, [37]) for the cytoarchitectonically defined areas of the Julich-Brain atlas [38••].

The analysis of the grey matter volume profiles (Figure 2a and b) of P1 showed a variety of deviations from the distribution of HC, across all brain regions. These observations fit to the behavioral profiles, since P1 also showed the most pronounced cognitive impairments. This was different from the lifestyle profile, which was centered around the mean of the HC. In turn, P4 is characterized by high physical activity, a healthy diet together with a lower BMI and social integration in combination with worse performance in some cognitive tasks. In turn, grey matter volume values were centered around the mean of HC. Although cognitively stable across all domains, this was also true for P2, showing lower BMI and a rather healthier diet. P3, with high BMI and selective cognitive impairments, contrarily tended to have grey matter volume values within the lower end of the normal range of HC. P5, who showed a high amount of packyears together with normal to high cognitive abilities, had regionally variable grey matter volume, with some regions showing volume comparable to the upper and some comparable to the lower end of the HC distribution.

The comparison of the participants P1-5 showed, that each of them showed individual rather than common atrophy patterns. These individual profiles do not seem to fit to the atrophy pattern observed in subjects with mild cognitive impairments as shown in a group study (i.e. medial temporal lobe, including the hippocampus [35]; *cf.* Figure 2a and b). Thus, regardless of the information that has been considered (i.e. cognitive, lifestyle and grey matter atrophy), all of the five 'at risk' subjects seem to have their own brain-phenotype profile. Putting these results into the context of group analyses it needs to be stressed that analyzing the older adult population on an individual level should be an inevitable next step in the

Figure 1

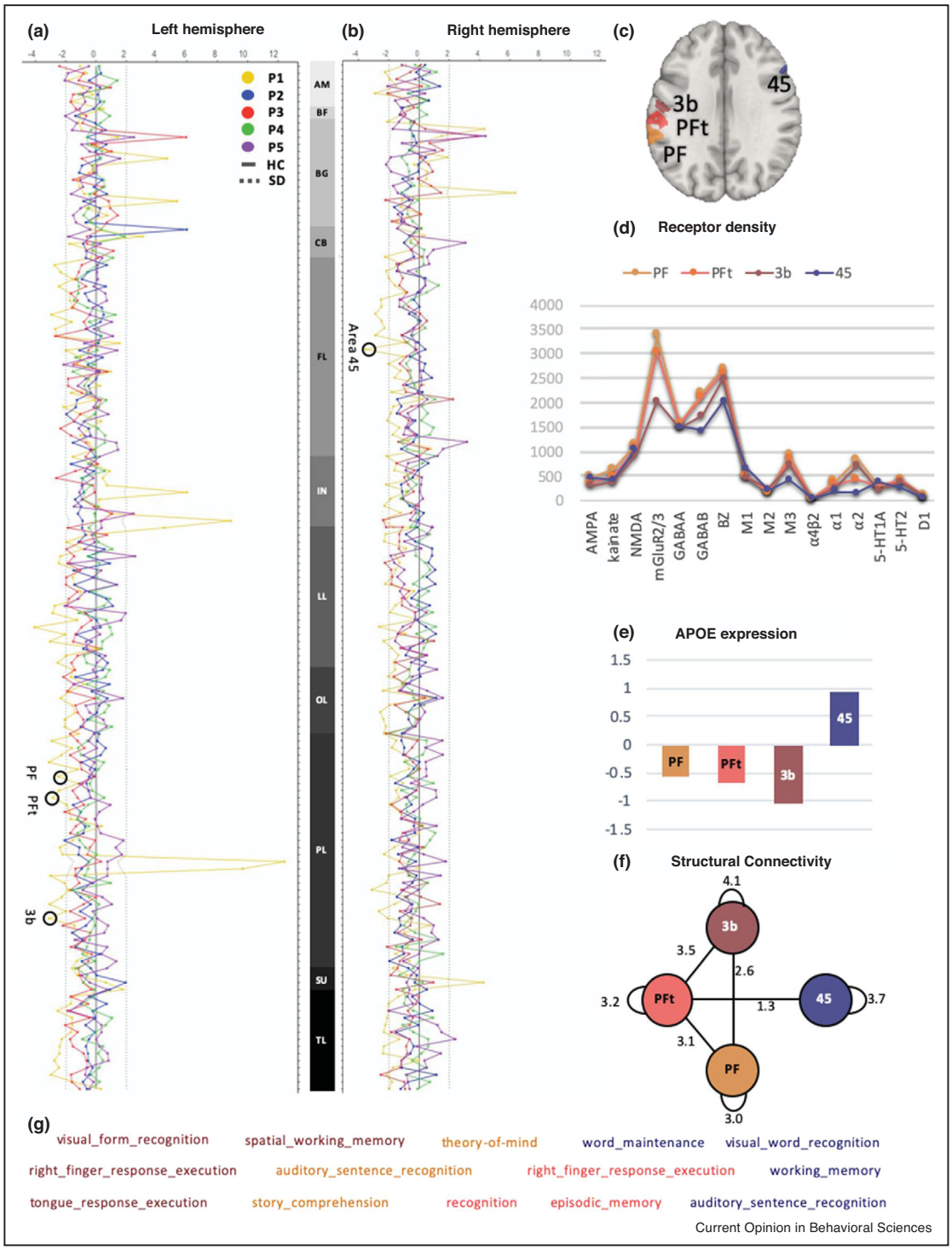


Comparison of participants at risk for dementia (P1-5) with healthy controls (HC) scoring normal in dementia testing where the black line represents the mean of HC and dashed grey lines represent two standard deviations from the mean of HC; **(a)** DemTect score for HC (grey dots) compared to P1-5; **(b)** Lifestyle factors (from left to right: ALC = weekly alcohol consumption; BODY = body mass index, waist hip ratio; DI = dietary index; SMO = packyears, cigarettes per day; SOC = family status, social integration index; SP = metabolic equivalent, walking stairs); **(c)** Cognitive performance from top to down: ATT = attention (processing speed, selective attention); EXE = executive functions (concept shifting, figural fluency, interference, problem solving); LAN = language (naming, phonemic verbal fluency, phonemic verbal fluency [switching condition], semantic verbal fluency, semantic verbal fluency [switching condition], vocabulary; MEM = memory (episodic memory, figural memory); WM = working memory (verbal short-term memory, verbal working memory, visuospatial short-term memory, visuospatial working memory, visual working memory). All cognitive and lifestyle variables were standardized to facilitate comparability across variables. Discontinued lines between tasks indicate that one task was not performed by the specific subject.

neuroscientific community, particularly when it comes to individual treatment or prevention strategies [48].

Deep characterizations of the individual, however, are challenging due to limited availability of individual data, difficulties in integrating heterogenous multilevel information of distinct levels of granularity in one reference space as well as the choice of well suited methodological and statistical approaches. While the current use case described the individual profiles at various levels, that is, cognition, lifestyle and grey matter volume, to decode the aging brain and its underlying mechanisms, additional information might be needed at molecular, cell and system levels that is ranging from macro- to microscopic scales. For example, cellular, molecular and genetic characterizations of the affected brain regions would help to gain insights at the most fundamental level. From a network point of view, the question would be whether the affected brain areas of P1 (e.g. left areas 3b, PF, PFt and right area 45; *cf.* Figure 2c) would be structurally or

Figure 2



(a) and **(b)** Grey matter volume [scaled] values of healthy subjects (HC) and participants at risk for dementia (P1-5) for the cytoarchitectonically defined Julich-Brain areas ([38••]; www.julich-brain.org) for the left (a) and right (b) hemispheres: AM = Amygdala, BF = Basal Forebrain, BG = Basal Ganglia, CB = Cerebellum, FL = Frontal Lobe, IN = Insula, LL = Limbic Lobe, OL = Occipital Lobe, PL = Parietal Lobe, SU = Subcortical, TL = Temporal Lobe; dashed grey lines represent 2 standard deviations from the mean of the control group; circled data points represent examples of brain regions that deviate more than 2 standard deviations below the mean of the HC (left areas PF, PFt, 3b and area 45 of the right-hemispheric homologue of Broca's region). **(c)** four selected brain regions showing low grey matter volume values in P1 (>2 standard deviations

functionally connected. Receptor and genetic characterizations of affected brain regions might additionally be of special interest here, since both have been associated with successful treatment response [49]. Such information can be considered using the EBRAINS multilevel brain atlas, provided by the Human Brain Project (HBP) [50••]. This atlas provides a multitude of such data on multiple levels of brain organization in a common reference space with a large number of macroscopic and microscopic data from different sources (see Box 1).

We here show exemplarily data provided in EBRAINS for a more in-depth analysis of the individual aging process of participant P1. We assessed four different regions that showed significant brain atrophy (left areas 3b, PF, PFt and right area 45) using EBRAINS to gather multimodal information about these areas.

First, receptor densities of neurotransmitter systems (Figure 2d) show a regionally specific distribution in the brain, are highly relevant for signal transduction in the healthy brain, but also in the pathologically altered brain, and serve as targets for drug therapy [51,52]. The analysis of receptor data from the atlas indicates that $GABA_B$ receptors seem to be highest in parietal areas PF and PFt, followed by area 3b, and lowest in right area 45 of Broca's region. In turn, the density of the cholinergic receptor M1 for acetylcholine seem to be highest in right area 45 compared to left hemispheric brain regions.

Secondly, regional differences in terms of the apolipoprotein E (APOE) expression levels, a genetic component that has frequently been associated with AD [53•], were found. Specifically, right area 45 showed a higher APOE expression as compared to the left hemispheric brain regions (Figure 2e).

Third, EBRAINS provides deep information on structural connectivity patterns: Areas 3b, PF and PFt seem to be highly inter-connected whereas right area 45 is only connected to area PFt. Thus, these observations raise the possibility of different networks to be affected in P1, which, in turn, might be related to the general decline in different cognitive domains (Figure 2f).

Fourth, this is further supported by information collected from task-based functional imaging studies investigating a variety of brain functions (Individual Brain Charting (IBC) fMRI datasets [47]). Figure 2g shows exemplary brain–behavior relationships for the selected brain regions: While each brain region seems to be activated during different cognitive tasks, there is also overlap in terms of functions involved, that is, all four areas seem to be involved in the mental process of recognition. Taken together, the additional multilevel information combining microstructural as well as macrostructural information allows for an in-depth characterization of brain–behavior relationships.

Personalized versus group analyses

The current use case demonstrated the feasibility of multilevel brain organizational information for enhancing deep characterization of brain-phenotype relations on the individual level. Characterizing the individual subject, in contrast to group averages, might be the inevitable step towards successful diagnostics and treatments, as previously described for, for example, epilepsy surgery [54–56] or AD [57,58]. Group analyses follow the principle of 'one size fits all' meaning that a group of patients suffering from the same disease or symptom would be treated the same way. Based on the current use case, we urgently need to realize that the here presented individuals show more differences than similarities regarding their individual cognitive, lifestyle and brain atrophy fingerprints. Following, these analyses emphasize the benefit of different treatment strategies on individual subjects, for example, physical versus cognitive interventions or a combination of both. The impact of personalized medicine is very promising since it allows for individual therapeutic approaches that could be preventive in nature, rather than reactive. It can be expected that individual diagnostics based on factors such as examined in the present study, and /or other factors such as genetics, could finally lead to less side effects after pharmacological treatments [59]. Certainly, two aspects must be considered here. First, while it is desirable to characterize an individual with as much data as possible, the question arises as to which aspects are the most important, for example, in order to tailor individual therapies. The analysis of brain-phenotype relationships on the group level, for example, relying on statistical comparisons, has different constraints than examining such relations on the individual level, for which tools are needed to estimate the weighted influences and potential relevance of all factors included in an individual fingerprint. Second, since individualized science and personalized medicine focus on individual trajectories, for example, during aging or disease progress, longitudinal data would be highly beneficial to better understand such processes.

Currently, methods and research infrastructure are being built for handling and processing huge amounts of

below the mean of the control group) projected on a standard brain (MNI152): areas PF, PFt of the posterior parietal cortex: [39,40]; area 45: [41]; somatosensory area 3b: [42,43]. **(d)** Receptor fingerprints for the selected brain regions: [44,45]; **(e)** APOE gene expressions within the four selected brain regions derived from the Allen brain atlas (https://alleninstitute.org/what-we-do/brain-science) analyzed with respect to the Julich Brain areas using JuGEx tool [46••]; **(f)** Structural connectivity values (log transformed) between the selected brain regions; **(g)** Individual Brain Charting (IBC) fMRI datasets with exemplary strong activations in the four selected brain regions (left areas PF, PFt, 3b and right 45) derived from Ref. [47].

individual data to enable predictions and simulations of effects of factors such as age, sex or disease status on the brain. Machine learning approaches, for example, have the potential to successfully predict such factors on an individual level based on respective training data [60]. Simulation tools, such as 'The Virtual Brain' (https://www.thevirtualbrain.org), build neurobiologically informed computational models based on potential disease or other relevant mechanisms (e.g. aging), requiring multilevel data (for first applications, see Refs. [61•,62]).

Such ongoing efforts require bridging the gap between cellular-molecular and systems level neuroscience. The European Human Brain Project (HBP) aims at integrating information of the brain at multiple scales from different research disciplines via EBRAINS (Box 1), an interactive tool combining multilevel data from various sources to enable enriching subject-specific analyses. The importance of such a platform can be derived from the current use case example: the five 'dementia at risk' subjects in the 1000BRAINS study showed individual profiles for various phenotypes, which is accompanied by individual brain atrophy patterns, for which multilevel atlas information revealed commonalities and differences at the connectional, genetic and molecular level potentially explaining parts of the peculiarities.

Conflict of interest statement

Nothing declared.

CRediT authorship contribution statement

Christiane Jockwitz: Investigation, Methodology, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Nora Bittner:** Methodology, Formal analysis, Writing - review & editing. **Svenja Caspers:** Conceptualization, Supervision, Resources, Funding acquisition, Writing - review & editing. **Katrin Amunts:** Conceptualization, Supervision, Resources, Funding acquisition, Writing - review & editing.

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ORIGINAL ARTICLE

Characterization of the angular gyrus in an older adult population: a multimodal multilevel approach

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Abstract
The angular gyrus (AG) has been associated with multiple cognitive functions, such as language, spatial and memory functions. Since the AG is thought to be a cross-modal hub region suffering from significant age-related structural atrophy, it may also play a key role in age-related cognitive decline. However, the exact relation between structural atrophy of the AG and cognitive decline in older adults is not fully understood, which may be related to two aspects: First, the AG is cytoarchitectonically divided into two areas, PGa and PGp, potentially sub-serving different cognitive functions. Second, the older adult population is characterized by high between-subjects variability which requires targeting individual phenomena during the aging process. We therefore performed a multimodal (gray matter volume [GMV], resting-state functional connectivity [RSFC] and structural connectivity [SC]) characterization of AG subdivisions PGa and PGp in a large older adult population, together with relations to age, cognition and lifestyle on the group level. Afterwards, we switched the perspective to the individual, which is especially important when it comes to the assessment of individual patients. The AG can be considered a heterogeneous structure in of the older brain: we found the different AG parts to be associated with different patterns of whole-brain GMV associations as well as their associations with RSFC, and SC patterns. Similarly, differential effects of age, cognition and lifestyle on the GMV of AG subdivisions were observed. This suggests each region to be structurally and functionally differentially involved in the older adult's brain network architecture, which was supported by differential molecular and genetic patterns, derived from the EBRAINS multilevel atlas framework. Importantly, individual profiles deviated considerably from the global conclusion drawn from the group study. Hence, general observations within the older adult population need to be carefully considered, when addressing individual conditions in clinical practice.

Keywords Angular gyrus · Aging · Brain structure · Resting-state functional connectivity · Structural connectivity · Cognition · Lifestyle

Introduction

The angular gyrus (AG) is a heterogeneous brain structure that has been associated with a variety of cognitive functions, including language functions (i.e., semantic information processing), spatial and memory functions, number and attentional processing, social cognition as well as multisensory perception (Binder et al. 2009; Seghier 2013; Humphreys et al. 2021). During the aging process, the AG has been shown to undergo substantial structural atrophy starting during midlife and continuing until older ages (Walhovd et al. 2005; Fjell et al. 2009, 2013; Jockwitz et al. 2017a). Furthermore, associations between gray matter volume (GMV) of the AG and subjective and mild cognitive impairment (MCI) as well as dementia have been reported (Yao et al. 2012; Quiroz et al. 2013; Oh et al. 2014; van de Mortel et al. 2021; Zhang et al. 2021). For example, Karas et al. (2008) showed that subjects who converted from MCI to Alzheimer's disease showed higher atrophy in the left AG as compared to those who remained mild cognitively

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impaired. Likewise, subjects suffering from subjective cognitive impairment (Kim et al. 2019) were depicted by lower GMV within the AG, as well as lower structural network connectivity between the AG and superior parietal and pre- and postcentral gyri, which, in turn, was associated with their cognitive decline. Hirst et al. (2021) even highlighted the AG as possible cross-modal hub region associated with age-related changes in multisensory perception. Hence, previous results hint at a key role of the AG during the aging process with a potential relation to neurodegenerative diseases and cognitive decline.

By exploring the key role of the AG during the aging process, previous research often focused on the AG as a macro-anatomical entity. Commonly, it is anatomically summarized together with the rostrally lying supramarginal gyrus as the inferior parietal lobule (Seghier 2013), or integrated into functional units such as the temporoparietal junction including posterior parts of the temporal lobe (Schurz et al. 2017). Yet, these approaches disregard multimodal evidence that the AG is a composition of two micro-anatomically distinct structures. For instance, post-mortem cyto-architectonic analyses revealed the AG to be subdivided into a rostrally lying area PGa and a caudally lying area PGp, which were shown to be involved in distinct functional brain networks and hence related to different cognitive functions (Caspers et al. 2006, 2008). Based on this multimodal evidence, the examination of these AGs subdivisions may be highly promising to further unravel the potential key role of the AG in terms of age-related differences and its association to behavior.

To this aim, when focusing on the older adult population, we are confronted with a particularly high inter-individual variability at the level of behavior, brain structure as well as brain function (Habib et al. 2007; Dickie et al. 2013). Precisely, from early to late adulthood, the factor 'age' is able to explain large parts of the variance in terms of both, cognitive abilities and brain structural parameters (Hedden and Gabrieli 2004; Schaie 2009). Focusing on samples of only older adults, however, reveals a quite different picture. Here, the factor 'age' alone is not able to explain large parts of the variance. Despite the consideration of other factors, such as lifestyle (Bittner et al. 2019; Hamer and Batty 2019), sex (Jahanshad and Thompson 2017; Jockwitz et al. 2021a, b), genetic predispositions (Honea et al. 2009; Caspers et al. 2020), or environmental influences (de Prado Bert et al. 2018; Nussbaum et al. 2020; Lucht et al. 2022), the high inter-individual heterogeneity remains only partly explained. In fact, to identify general brain–phenotype relations in the older adult population on the group level, where each factor might show small effect sizes, very large sample sizes are required (Button et al. 2013). On the other hand, averaging behavior across large groups may suppress and underestimate differences on the individual level (Jockwitz et al. 2021a, b). Identifying global trends in these large samples with high inter-individual variability comes at the cost of losing perspective on and neglecting the specific pattern of influencing factors of individual subjects, as is particularly important in case of personalized treatment considerations. As these individual profiles might deviate considerably from the global conclusion drawn from the group study, individual deep phenotyping approaches are required to uncover the relevance of different factors for each individual to explain observed differences in the aging AG.

Consequently, the investigation of a possible key role of AG in the aging brain requires the consideration of two essential aspects: first, a functionally meaningful definition of AG sub-regions, as available through the Julich-Brain atlas (Amunts et al. 2020), (i.e., areas PGa and PGp) and second, a specific focus on the diverse multimodal profiles of factors influencing the aging process of the AG sub-regions in individuals. The current study first employed a multimodal, multilevel (i.e., brain structure, functional and structural connectivity) characterization of the AG subdivisions PGa and PGp in a large population-based study of older adults. Such multimodal investigations have been proven to be useful since different brain modalities were found to be distinctively related to differences in brain structure. For example, previous studies revealed that during the aging process, global as well as regional GMV decreases would be associated with both, positive and negative changes in brain connectivity of functional networks sub-serving cognitive functions in the older adult population (Jockwitz et al. 2017; Stumme et al. 2020; Spreng et al. 2016; Reuter-Lorenz et al. 2011). We here built upon this principle and examined the association between GMV of the AG subparts and either GMV, resting-state functional connectivity [RSFC] or structural connectivity [SC] of all ROIs included in the Julich-Brain Atlas to explore brain–brain relationships in a systemic approach. Furthermore, we additionally consulted the EBRAINS (https://ebrains.eu), a multilevel atlas framework, to characterize the ROIs on the molecular and gene expressions level. Second, group analyses were conducted to assess the relation between AG structure and age, cognition and lifestyle. Finally, we switched to the "individual view". For this purpose, we selected individuals who exhibited either a particularly high or low GMV within the AG to subsequently highlight their respective individual cognitive and lifestyle profiles compared to the overall study sample.

Methods

Subjects

All subjects included in the current study were drawn from 1000BRAINS (Caspers et al. 2014), a population-based

Table 1 Variables included in the current study with mean of raw values and corresponding standard deviations (SD) respectively the proportion *n* (%)

	Variable	Mean (SD)		Variable	Mean (SD)
Demographics	Age (years)	67.4 (6.6)	Cognition	Selective attention (time in sec.)	34.76 (11)
	Sex	1.46 (0.5)		Processing Speed (time in sec.)	40.52 (14.37)
	Education	6.41 (1.97)		Reasoning (correct answers)	20.37 (5.09)
	TBV	1473.55 (132.81)		Interference (time in sec.)	43.34 (22.68)
GMV of AG				Concept shifting (time in sec.)	55.41 (37.87)
	lPGa	1.84 (0.26)		Visual spatial STM (correct answers)	5.44 (0.88)
	rPGa	2.95 (0.38)		Visual spatial WM (correct answers)	4.66 (1.06)
	lPGp	4.31 (0.53)		Visual WM (correct answers)	7.65 (1.77)
	rPGp	3.81 (0.47)		Verbal STM (correct answers)	6.06 (1.07)
Lifestyle				Verbal WM (correct answers)	4.65 (1.07)
	Packyears	13.35 (21.78)		Figural fluency (correct answers)	26.02 (7.26)
	Dietary index	11.39 (18.34)		Phonematic fluency (correct answers)	18.71 (6.58)
	BMI	0.92 (0.1)		Semantic fluency (correct answers)	23.76 (6.83)
	Sports (metabolic equivalent)	37.69 (107.51)		Phonematic fluency switch (correct answers)	18.86 (6.09)
	Social integration index	11.97 (3.3)		Semantic fluency switch (correct answers)	19.87 (4.79)
	Alcohol consumption	Yes (n =202; 40.5%); No (n = 297; 59.5%)		Vocabulary (correct answers)	30.86 (4.9)
	Smoking	Never (n = 219; 43.9%); ever (n = 233; 46.7%); current (n = 41; 8.2%)		Figural memory (correct answers)	8.59 (4.12)
				Verbal memory (correct answers)	41.68 (10.29)

Total brain volume; *BMI* body mass index; *STM* short-term memory; *WM* working memory

cohort study, recruited from the Heinz Nixdorf recall study that has been conducted in the Ruhr area in Germany (Schmermund et al. 2002). Exclusion from the study was based on eligibility for MR measurements for scientific purposes. From the initial cohort of 1314 subjects, we selected subjects being 55 years and older (n = 969).

Furthermore, subjects being at risk for dementia [as measured using the DemTect; (Kalbe et al. 2004)] were excluded (n = 31). From these 938 subjects with available data sets for cognitive performance, brain structure (available for n = 878 subjects), RSFC (available for n = 829), SC (available for n = 685) and lifestyle (available for n = 499) have been selected. All participants gave written informed consent before participating in 1000BRAINS. All experiments were performed in accordance with relevant guidelines and regulations. The study protocol was approved by the local Ethics Committee of the University of Essen.

Cognitive performance and lifestyle

All subjects underwent intensive neuropsychological testing during their participation in 1000BRAINS. In total, 16 different cognitive functions, namely selective attention, processing speed, reasoning, concept shifting, susceptibility to interference, figural fluency, phonematic and semantic verbal fluency (with and without switching between different letters/semantic categories), vocabulary, verbal episodic memory, figural memory, visual, visual–spatial and verbal short-term (STM)/working memory (WM) were assessed. For detailed information, see (Caspers et al. 2014; Jockwitz

et al. 2017). In terms of lifestyle behavior (Ainsworth et al. 2011, Bittner et al. 2019), we assessed information regarding alcohol consumption (yes-no), body mass index (BMI), dietary index (Frolich et al. 2017), smoking behavior (never-ever-current), social integration (social integration index) and sports (metabolic equivalent, Ainsworth et al. (2011)). For an overview of parameters used, mean values and standard deviations, see Table 1.

Image acquisition

All brain images were acquired in the frame of the imaging protocol of 1000BRAINS (Caspers et al. 2014) using a 3T Siemens Tim-TRIO MR scanner with a 32-channel head coil. For the purpose of the current study, the following sequences were of interest: (1) 3D high-resolution T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) (176 slices, slice thickness = 1, TR = 2250 ms, TE = 3.03 ms, FoV = 256 × 256 mm^2, flip angle = 9°, voxel resolution = 1 mm^3); (2) 300 gradient-echo planar (EPI) images (slices = 36, slice thickness = 3.1 mm, TR = 2200 ms, TE = 30 ms, FoV = 200 × 200 mm^2, voxel resolution = 3.1 mm^3; participants were instructed to keep their eyes closed, to relax and let their mind wander, but not to fall asleep, which was checked during a post-scan debriefing) and (3) diffusion-weighted images (DWI) with two different *b*-values: *b* = 1000 s/mm^2 (HARDI subset, EPI, TR = 6.3 s, TE = 81 ms, 7 b0-images (interleaved) and 60 diffusion-weighted volumes, voxel resolution = 2.4 mm^3) and *b* = 2700 s/mm^2 (HARDI subset, EPI, TR = 8 s, TE = 112 ms, 13 b0-images (interleaved) and 120 diffusion-weighted volumes, voxel resolution = 2.4 mm^3).

Brain image analyses

Brain regions of interest

For the purpose of the current study, the regions of interest included left and right PGa and PGp within the AG as defined by Caspers et al. 2006, 2008, 2013. Both areas, PGa and PGp are part of the cyto-architectonically defined Julich-Brain atlas (version 2.6; https://search.kg.ebrains.eu/instances/Dataset/2eaa3dc6-a21b-41c1-b703-bf06f82adf25 ; (Amunts et al. 2020). All other areas included in the Julich-Brain atlas served as regions for network analyses of AG alterations (for areas PGa and PGp, see Fig. 1A; for the Julich-Brain atlas as represented in EBRAINS, see Fig. 1B).

Brain structure

From the T1-weighted structural brain images, we extracted GMV (in ml) using the standalone version of the CAT12v8 SPM12 toolbox, release 1853 (Franke and Gaser 2019)) for all cyto-architectonically defined areas of the Julich-Brain atlas as well as the total brain volume (TBV). This included (a) initial registration and bias field correction, (b) segmentation into tissue probability maps (TPM) of gray matter, white matter, and cerebrospinal fluid, (c) a spatial normalization to the standard template derived from 555 healthy subjects between 20 and 80 years of the IXI-database (http://www.brain-development.org) computed using the geodesic shooting and Gauss–Newton optimisation-based diffeomorphic registration (Ashburner and Friston 2011).

Resting-state functional connectivity

For each participant, the first four echo planar imaging (EPI) volumes were discarded. Using a two-pass procedure, all functional images were corrected for head movement by fist aligning all volumes to the first image and second to the mean image using affine registration. By the use of the "unified segmentation" approach (Ashburner and Friston 2005), all functional images were spatially normalized to the MNI152 template (Holmes et al. 1998; Calhoun et al. 2017; Dohmatob et al. 2018). Additionally, ICA-based Automatic Removal Of Motion Artifacts [ICA-AROMA (Pruim et al. 2015)] was applied to identify and remove motion-related independent components from functional MRI data. Afterward, global signal regression was applied to minimize the relationship between motion and RSFC (Burgess et al. 2016; Ciric et al. 2017; Parkes et al. 2018). Lastly, all RS-fMRI images were bandpass-filtered (0.01–0.1 Hz). For RSFC, a mean time series were extracted for each region of interest using fslmeants (Smith et al. 2004) and correlated with the mean time series of the AG parts (left and right PGa and PGp) using Pearson's correlations.

Structural connectivity

First, DWI data were corrected for eddy current and motion artifacts including interpolation of slices with signal dropouts (Andersson and Sotiropoulos 2015; Andersson et al. 2016). Suboptimal volumes or datasets (ghosting, remaining signal dropouts or very noisy data) were removed from further analysis. Afterwards, brain masks were created, all DWI data were rigidly aligned to the T1-weighted data set using mutual information as cost function (Wells et al. 1996) and resampled to 1.25mm. B-vectors were rotated according to the transformations.

Regarding distortion correction Anisotropic Power Maps (APM; Dell'Acqua et al. 2014) were computed from the b2700 DWI data in 1.25 mm space, which were used to compute the non-linear transformation from diffusion to anatomical T1 space taking EPI induced distortions into account. These non-linear transformations were used to transform the TPMs to diffusion space for computing an

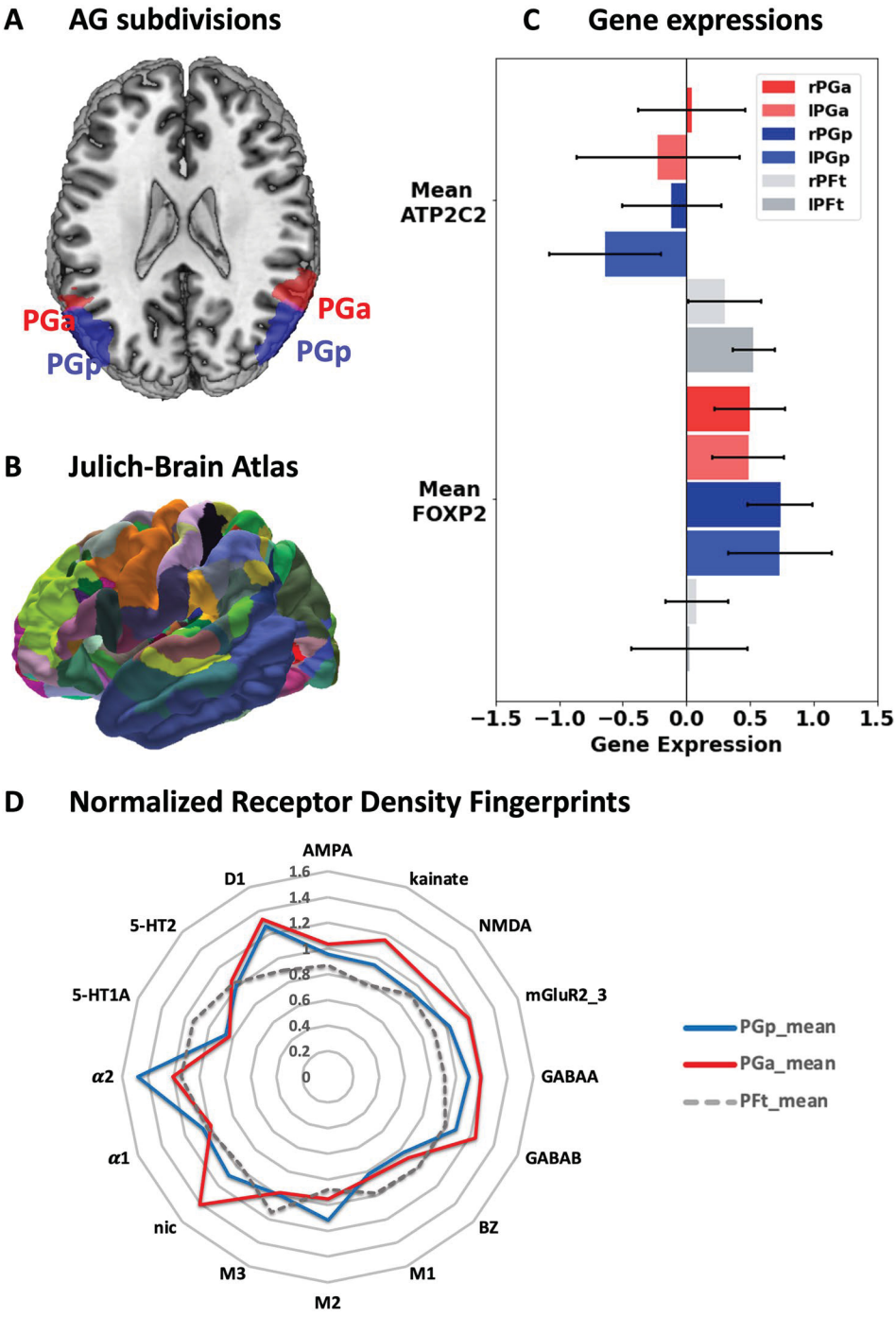

Fig. 1 **A** AG subdivisions PGa and PGp; **B** 3D Visualization of the Julich-Brain Atlas; **C** normalized gene expressions of the two genes of interest: ATP2C2 and FOXP2. Areas PGa is colored in red (light red = left PGa), areas PGp are colored in blue (lighter blue =left PGp), areas PFt (part of supramarginal gyrus, colored in grey, light grey = right PFt) serves as control region; **D** normalized receptor densities fingerprints for 15 receptors as reported by Caspers et al. (2013). Area PGa is colored in red, area PGp is colored in blue, area PFt is colored in grey and serves as control region

optimally fitting brain mask for the DWI data in the absence of field maps and b0 volumes with opposite EPI readout directions. All transformation steps were computed using the Advanced Normalization Tools (ANTs) version 2.1.1 (Avants et al. 2014).

The two datasets with b1000 and b2700 were merged into one single file and corrected for different echo times. This correction was computed by voxel-wise multiplying the b2700 data with the ratio of the non-diffusion-weighted data of the two datasets.

Calculation of CSD and streamlines Local modeling and probabilistic streamline tractography were performed using the MRtrix software package (Tournier et al. 2012), version 0.3.15 (https://www.mrtrix.org/). The constrained spherical deconvolution (CSD) local model was computed using multi-tissue CSD of multi-shell data (Jeurissen et al. 2014) using all shells and a maximal spherical harmonic order of 8. Ten million streamlines were computed with dynamic seeding in the gray-white matter interface for every subject using the probabilistic iFOD2 algorithm and the anatomically constrained tractography framework (Smith et al. 2012) with a maximal length of 250 mm and a cut-off value at 0.06. Afterwards, optimized Spherical-deconvolution Informed Filtering of Tractograms (SIFT2) was applied to match the whole-brain tractograms to the fixel-wise fiber densities (Smith et al. 2015).

Connectivity matrices Next, both maps were merged into one single file, dilated using fslmaths and transformed into diffusion native space using the SyN algorithm (ANTs 2.1.1). The whole-brain atlas in diffusion native space, the whole-brain tractogram and the SIFT2 weights per streamline were then fed into tck2connectome (MRtrix 0.3.15). This resulted in a symmetric 248 × 248 matrix which contained the sum of streamline weights per ROI combination per subject.

Statistical analyses based on the total sample

In the first part, we aimed at characterizing the AG subparts in terms of brain structure, functional and structural connectivity. Therefore, GMV of the AG subdivisions were related to either region-wise whole-brain GMV, RSFC or SC (in parts of the Julich-Brain atlas). All three analyses were carried out using multiple regression analyses (forward-selection approach with sex, education and TBV as additional predictors) with GMV of the respective AG subdivision as independent variable and (a) GMV, (b) RSFC between AG subdivision and all other parts for the Julich-Brain atlas and (c) SC between AG subdivision and all other parts for the Julich-Brain atlas as dependent variables.

Second, to assess brain–phenotype relations for the two subdivisions of the left and right AG (areas PGa and PGp), we calculated several multiple regression analyses: First, we assessed the influence of age on GMV of the AG subparts using the inclusion approach (with sex, education and TBV as additional predictors). For behavioral variables, we included either cognitive performance test scores or lifestyle variables as explanatory variables using forward-selection approaches (with age, sex, education and TBV as additional predictors).

To target individual subject assessments, we selected five subjects with low GMV and five subjects with high GMV (participants being within the highest or lowest 25% regarding GMV for all four parts of the AG). For these ten subjects, we created individual profiles regarding cognitive performance and lifestyle (visualized as bar plots). To do so, we calculated standard Z-scores to create comparable scores for all variables.

Consultation of multilevel atlas framework EBRAINS

In the frame of characterizing the AG subdivisions, we consulted regional genetic and molecular data using EBRAINS (https://ebrains.eu), a multilevel atlas framework, to explain the involvement of the AG subdivisions with respect to general as well as individual phenomena of the aging process. In terms of genetic data, we explored the JuGex tool (Bludau et al. 2018; https://ebrains.eu/service/jugex/). Since previous research claimed the involvement of the AG in language processing, we focused on genetic expression of language-related genes, i.e., FOXP2 and ATP2C2 (Lai et al. 2003; Newbury and Monaco 2010; Lambert et al. 2011; Unger et al. 2021a, b). While FOXP2 is supposed to be involved in the development of speech and language, ATP2C2 has been associated with dyslexia and other communication disorders (Lai et al. 2003; Newbury and Monaco 2010; Lambert et al. 2011; Unger et al. 2021a, b).

Functional differences in the individual regions were additionally investigated with respect to their receptor density fingerprints, since the function of a cortical area requires a well-matched receptor balance. We thus focused on the receptor density profiles of the AG subdivisions, as examined by Caspers et al. (2013) with densities of 15 different receptors (glutamatergic (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], kainate, *N*-methyl-D-aspartate [NMDA]), γ-aminobutyric acid (GABA)ergic (GABAA-, GABAB-, GABAA-associated benzodiazepine-binding sites), cholinergic (nicotinic, muscarinic M1, M2, M3), adrenergic (α1, α2), serotoninergic (5-HT1A, 5-HT2), and dopaminergic (D1)) which were measured in areas PGa and PGp in postmortem brains. We normalized the receptor densities (measured in fmol/mg) across all brain regions within the inferior parietal lobule (areas supramarginal gyrus: PF, PFt, PFop, PFm, PFcm; AG: PGa and PGp) by calculating the mean density values for each receptor and dividing the region-specific density value by the mean value. Finally, we compared the normalized receptor densities between areas PGa and PGp and additionally used area PFt as a control region.

Results

We performed a multimodal characterization of the AG subdivisions including data regarding GMV, RSFC and SC together with genetic and molecular information. Using

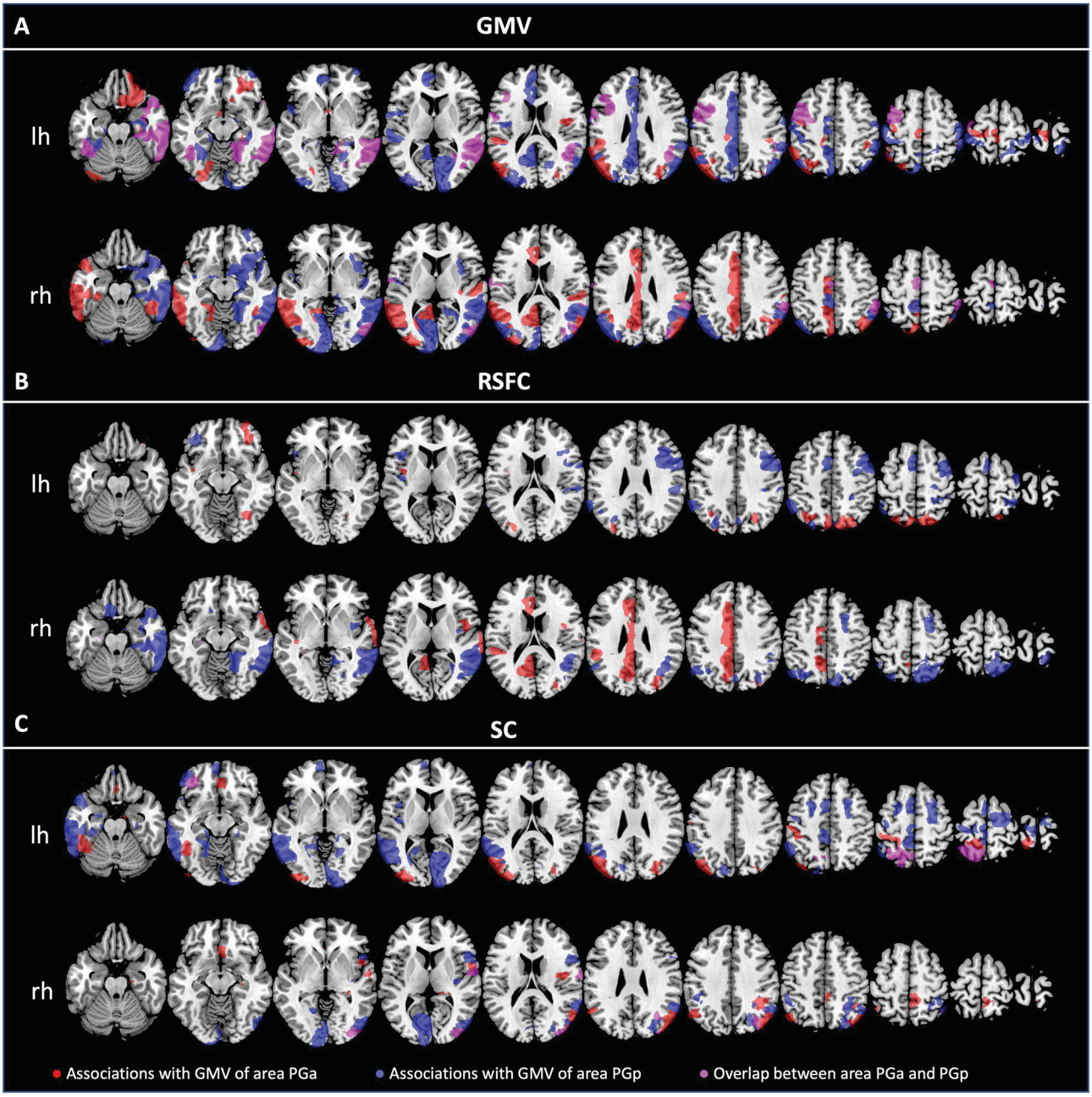

Fig. 2 Brain regions being significantly associated with GMV of the AG subdivisions (areas PGa and PGp) in terms of **A** GMV; **B** RSFC and **C** SC (irrespective of the direction of the effects). All associations with GMV of area PGa are colored in red, while associations with GMV of area PGp are colored in blue. Associations with both areas PGa and PGp are colored in pink. Results are shown for the left and right hemispheric AG subdivisions separately. *lh* left hemisphere, *rh* right hemisphere

demographics, cognition and lifestyle, we then identified brain–behavior relationships at the group level. Finally, we identified individual profiles for subjects showing low and high GMV in areas PGa and PGp (see Fig. 1A for brain regions of interest).

Group-derived relationships between GMV of the AG and its brain integration

For associations between GMV and brain metrics, again, several different forward-selection multiple regression analyses were performed. We first addressed the relationship between GMV of the AG subdivision as dependent variables and GMV of all regions included in the Julich-Brain atlas.

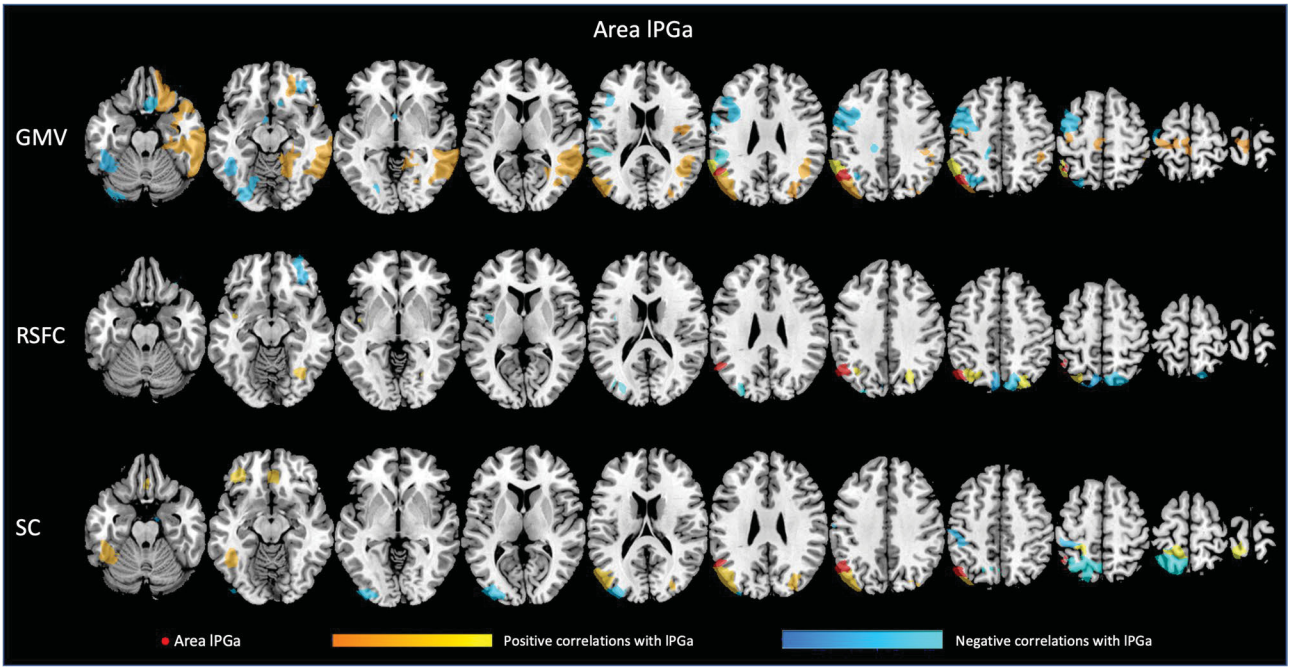

Fig. 3 Significant associations between GMV of left area (l) PGa and GMV, RSFC and SC of those areas included in the Julich-Brain atlas

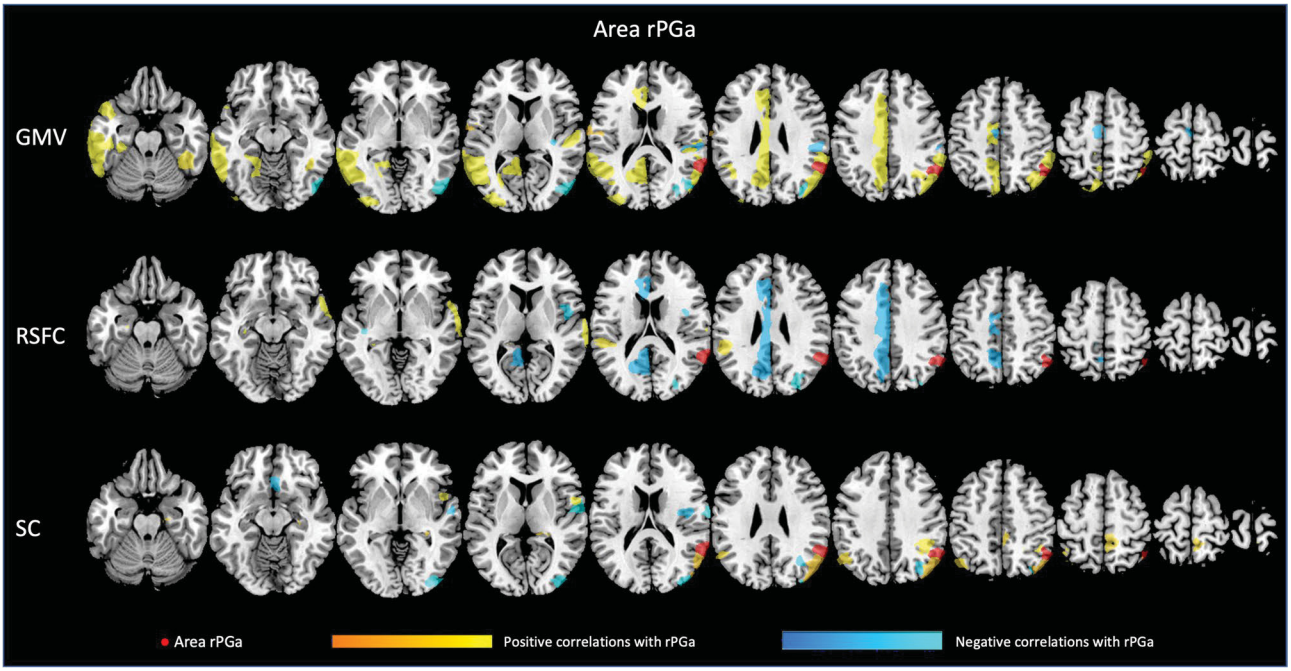

Fig. 4 Significant associations between GMV of right area (r) PGa and GMV, RSFC and SC of those areas included in the Julich-Brain atlas

Figure 2A shows those brain regions significantly related to GMV of the AG subdivisions.

Each of the four regions investigated seems to be related to GMV of different brain regions, with both, positive and negative associations. For all associations between GMV of the AG subdivisions and other parts of the Julich-Brain atlas, please refer to Figs. 3, 4, 5, 6 as well as Suppl. Table S1 (for exemplary scatterplots, see Figure S5), and for the comparison of associations between left and right areas PGa and PGp refer to Fig. 2A–C. Exemplarily, GMV of left PGa was

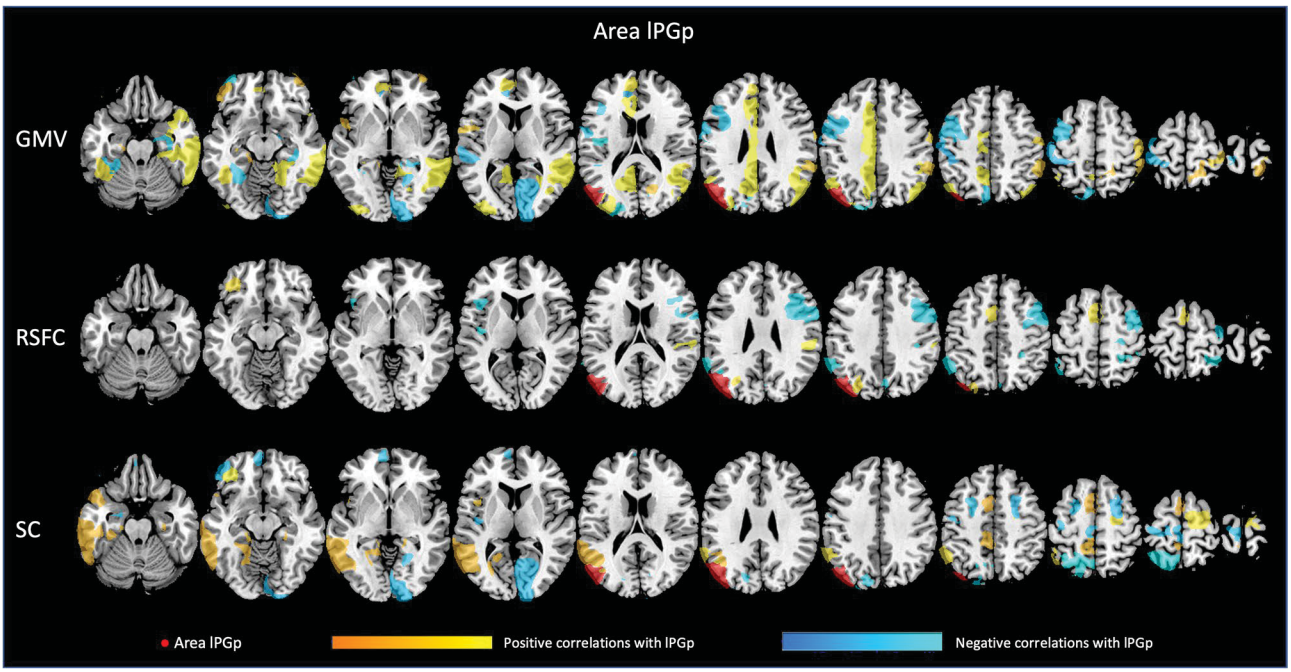

Fig. 5 Significant associations between GMV of left area (l) PGp and GMV, RSFC and SC of those areas included in the Julich-Brain atlas

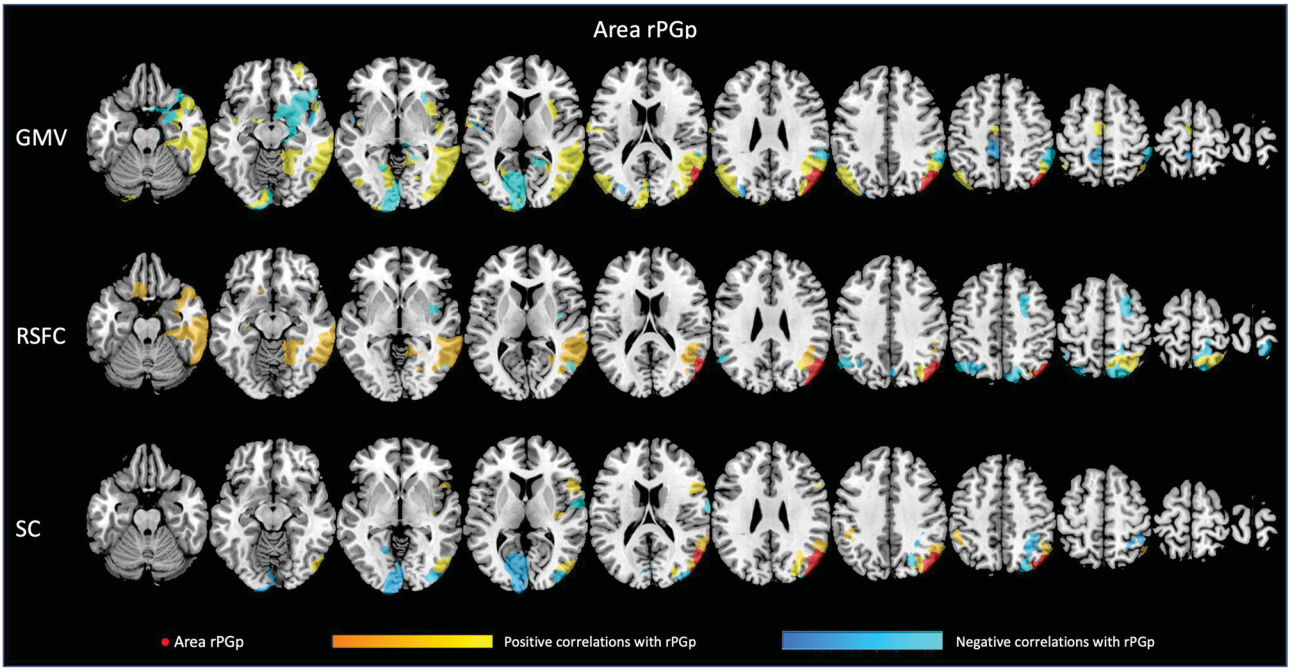

Fig. 6 Significant associations between GMV of right area (r) PGp and GMV, RSFC and SC of those areas included in the Julich-Brain atlas

associated with GMV of other sub-regions of the left inferior parietal lobule, as well as with the left dorsolateral prefrontal and orbitofrontal cortex, while GMV of right PGa was associated with GMV of other sub-regions of the right inferior parietal lobule. Moreover, GMV of left and right area PGp was additionally negatively associated with areas of the respective contralateral primary visual cortex.

In a next step, we addressed the association between GMV of AG regions and RSFC between AG and all other parts of the Julich-Brain Atlas (Fig. 2B; for positive and

negative associations, see Figs. 3, 4, 5, 6 and Table S2, for exemplary scatterplots, see Figure S5). In general, GMV of the left PGa was associated with RSFC between left PGa and left inferior parietal lobule and the intraparietal sulcus. GMV of the left PGp was associated with RSFC between left PGp and left inferior parietal lobule as well as the right dorsolateral prefrontal cortex. GMV of the right PGa was associated with RSFC between right PGa and left cingulate cortex, while GMV of right PGp showed widespread RSFC associations with parts of the left and right inferior parietal lobule, as well as parts of the temporal lobe.

Likewise, we addressed the association between GMV of AG regions and SC between AG and all other parts of the Julich-Brain Atlas (Fig. 2C; for positive and negative associations, see Figs. 3, 4, 5, 6 and Table S3, for exemplary scatterplots, see Figure S5). Here, again, each AG subdivision revealed a distinct composition of SC patterns related to the GMV of the AG subdivisions. GMV of left PGa was associated with SC between left PGa and left inferior and superior parietal lobule and intraparietal sulcus. GMV of left PGp was associated with SC between PGp and left parietal lobule, and with the primary visual cortex. GMV of right PGa was associated with SC between right PGa and right inferior and superior parietal lobule and intraparietal sulcus, with additional connections to right dorsal premotor cortex. In turn, GMV of right PGp was associated with SC between right PGp and, right inferior parietal lobule and intraparietal sulcus, and with the primary visual cortex and lateral occipital cortex.

Finally, we were interested whether the distinct involvement of the AG subdivisions in brain metrics (i.e., GMV, RSFC, SC) would be reflected in its regional genetic and molecular architecture. This was assessed by integrating information from the EBRAINS multilevel atlas framework. Regarding the molecular composition of the inferior parietal lobule, areas PGa and PGp show regional differences in receptor density fingerprints. Figure 1D represents the normalized receptor density fingerprints of areas PGa and PGp as well as area PFt, as one exemplary control region within the supramarginal gyrus. In general, the normalized receptor fingerprints of the two AG regions have a similar shape, whereas area PFt within the supramarginal gyrus is clearly differentiated from these two. For instance, area PFt showed a substantially lower receptor density of the D1 receptor, but also of the $GABA_A$ receptor. Comparing the two AG regions, area PGp is characterized by high concentrations of the αlpha2 receptor as compared to area PGa, whereas area PGa shows exceptionally high concentrations of the nicotinic receptor compared to area PGp.

Since the AG is involved in language functions, we were additionally interested in whether this also manifests in distinct gene expressions. To do so, we additionally examined several gene expressions of language-related genes, using the JuGex tool in EBRAINS (Bludau et al. 2018). Figure 1C represents the normalized gene expressions for the AG parts as well as supra-marginal area PFt. Regarding ATP2C2, we found lower gene expressions within the two AG parts as compared to area PFt, while for FOXP2, we found opposite patterns, i.e., higher gene expressions for areas PGa and PGp as compared to area PFt. Comparing the two AG sub-regions, we found lower gene expressions for FOXP2 in area PGp compared to area PGa bilaterally and higher gene expressions of ATP2C2 in area PGp compared to PGa.

Group analyses of AG subdivisions in light of age, cognitive performance and lifestyle

Using multiple regression analyses, we examined the associations between GMV of the left and right PGa and PGp and age (while adjusting for sex, education and TBV). We found age-related decreases in GMV for all four parts of the AG, with the highest age-related decrease for right PGa and the lowest decrease for the left PGa (Fig. 7A, Table 2).

For associations between GMV and behavioral factors, several different forward-selection multiple regression analyses were performed. Regarding cognitive performance, we found relations between GMV of left PGa and figural and semantic verbal fluency, as well as verbal WM. In turn, GMV of left PGp correlated with semantic verbal fluency and visual WM. GMV of right PGa correlated with semantic and phonematic verbal fluency as well as with reasoning, while GMV of right PGp correlated with processing speed. Thus, in both hemispheres, the AG subdivisions correlated with partially distinct cognitive functions in the older adult population. While GMV of all regions of interest but the right PGp were related to semantic verbal fluency, we additionally found the two posterior regions (left and right PGp) to be related to visual WM and (visual) processing speed (for exemplary scatterplots, see Fig. 7B; for all scatterplots, see supplementary Figures S1–4, for regression coefficients, see Table 3).

In terms of the association between GMV and lifestyle, multiple regressions revealed left hemispheric parts of the AG (PGa and PGp) to be related to BMI, i.e., higher BMI being related to lower GMV. Additionally, GMV of right area PGa correlated positively with sports. Further, GMV of right area PGp was negatively related to BMI and alcohol consumption and positively to social integration. Thus, there seems to be an overall relation between GMV of the AG and BMI (except for right area PGa), while sports, alcohol consumption and social integration were rather specifically related to GMV of distinct AG sub-regions (for exemplary scatterplots, see Fig. 7B; for all scatterplots, see supplementary Figures S1–4, for regression coefficients, see Table 3).

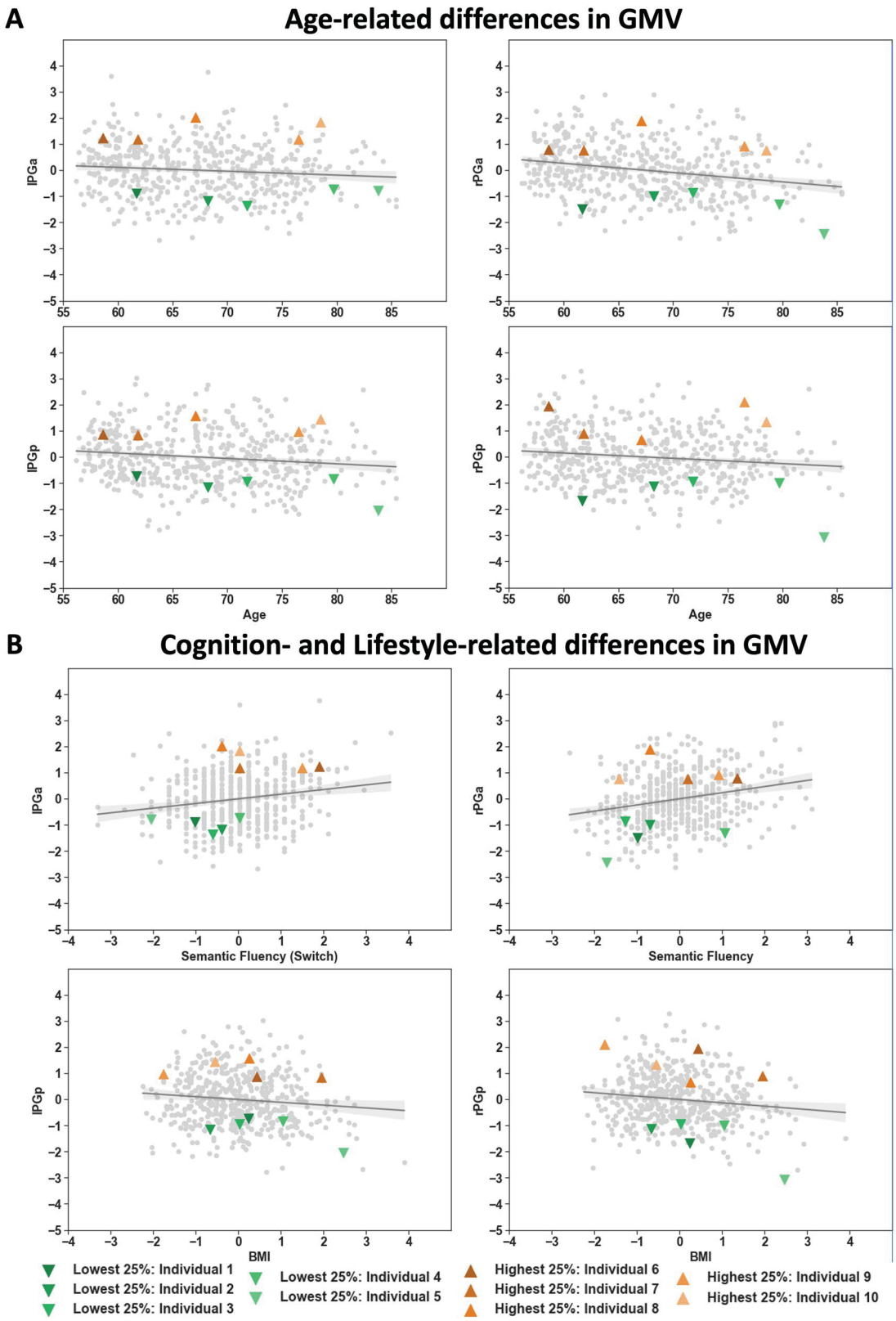

Fig. 7 **A** Age-related differences in GMV (*z*-scores) for areas lPGa, rPGa, lPGp and rPGp. **B** Cognitive performance (*z*-scores) and lifestyle-related differences in GMV (*z*-scores). The whole group is represented by gray dots including regression line and confidence interval. Selected individuals within the highest and lowest 25% are marked in orange and green triangles, respectively

Table 2 Multiple regression models (inclusion) with GMV of the regions of interest as dependent variables (left and right PGa and PGp) and age, sex, education and TBV as predictors

	lPGa	rPGa	lPGp	rPGp
Age	−0.092 (0.023)	−0.226 (<0.001)	−0.121 (0.001)	−0.131 (<0.001)
Sex	−0.066 (0.167)	−0.036 (0.441)	−0.026 (0.562)	−0.116 (0.007)
Education	0.019 (0.107)	0.034 (0.402)	0.038 (0.335)	0.009 (0.811)
TBV	0.422 (<0.001)	0.447 (<0.001)	0.525 (<0.001)	0.524 (<0.001)

The models include all predictors with standardized regression coefficients and *p*-values in brackets. *TBV* total brain volume

Table 3 Multiple regression models (forward-selection) with GMV of the regions of interest as dependent variables (left and right PGa and PGp) and A) cognitive performance test scores and B) lifestyle variables as predictors

A	lPGa		rPGa		lPGp		rPGp	
Cognition	TBV	0.445 (<.001)	TBV	0.436 (<.001)	TBV	0.533 (<.001)	TBV	0.521 (<.001)
	Figural fluency	0.111 (0.013)	Age	−0.158 (<.001)	Semantic Fluency	0.088 (0.024)	Age	−0.103 (0.009)
	Semantic fluency switch	0.118 (0.01)	Semantic fluency	0.192 (<.001)	Visual WM	0.085 (0.034)	Sex	−0.134 (0.002)
	Verbal WM	−0.093 (0.031)	Phonematic fluency switch	−0.135 (0.005)			Processing speed	−0.08 (0.043)
			Reasoning	0.114 (0.01)				
B	lPGa		rPGa		lPGp		rPGp	
Lifestyle	TBV	0.457 (<.001)	TBV	0.475 (<.001)	TBV	0.550 (<.001)	TBV	0.524 (<.001)
	BMI	−0.131 (0.001)	Age	−0.215 (<.001)	Age	−0.111 (0.003)	Age	−0.136 (<.001)
			Sports	0.093 (0.017)	BMI	−0.078 (0.039)	Sex	−0.143 (0.001)
							BMI	−0.104 (0.004)
							Alcohol	−.099 (0.009)
							Social integration	0.080 (0.025)

All models additionally include covariates of non-interest (age, sex, education, TBV). The models include all significant predictors with standardized regression coefficients and *p*-values in brackets. *TBV* total brain volume; *WM* working memory; *BMI* body mass index

Group trends versus individual subjects

To go beyond group level insights, we addressed the "individual view" bearing in mind the variability between GMV and cognitive abilities and lifestyle habits. We therefore targeted exemplary individual subjects regarding their specific 'multilevel AG profile' among those with either highest or lowest GMV (25% percentile groups). Scatterplots shown in Fig. 7A (age-related differences in GMV) and B (exemplary relations between AG GMV and cognitive performance or lifestyle habits, for all other scatterplots, see supplementary Figures S1–4) illustrate the selected subjects in the frame of the here examined sample. While subjects with, e.g., similarly low GMV already cover the whole age range, we additionally looked at their individual cognitive performance and lifestyle profiles (Figure 8A, B). Comparing two individuals with a low GMV in all AG subdivisions, revealed additional differences: In terms of cognitive functioning, individual #3 performs above average in reasoning and visual WM and below average in terms of semantic fluency. At the same time, individual #3 shows a slightly lower social integration index. In contrast, individual #4 shows an above average performance in semantic and phonematic fluency together with a slightly above average BMI. When selecting two subjects with high GMV in the AG, we see a similar heterogeneous picture: Individual #5 shows a high performance in the semantic fluency task, and an above average engagement in sports. In turn, individual #7 shows a high performance in verbal WM together with all lifestyle variables being within the normal range (*z*-scores within 1 SD). Finally, comparing individual #5 with individual #10, both subjects perform low

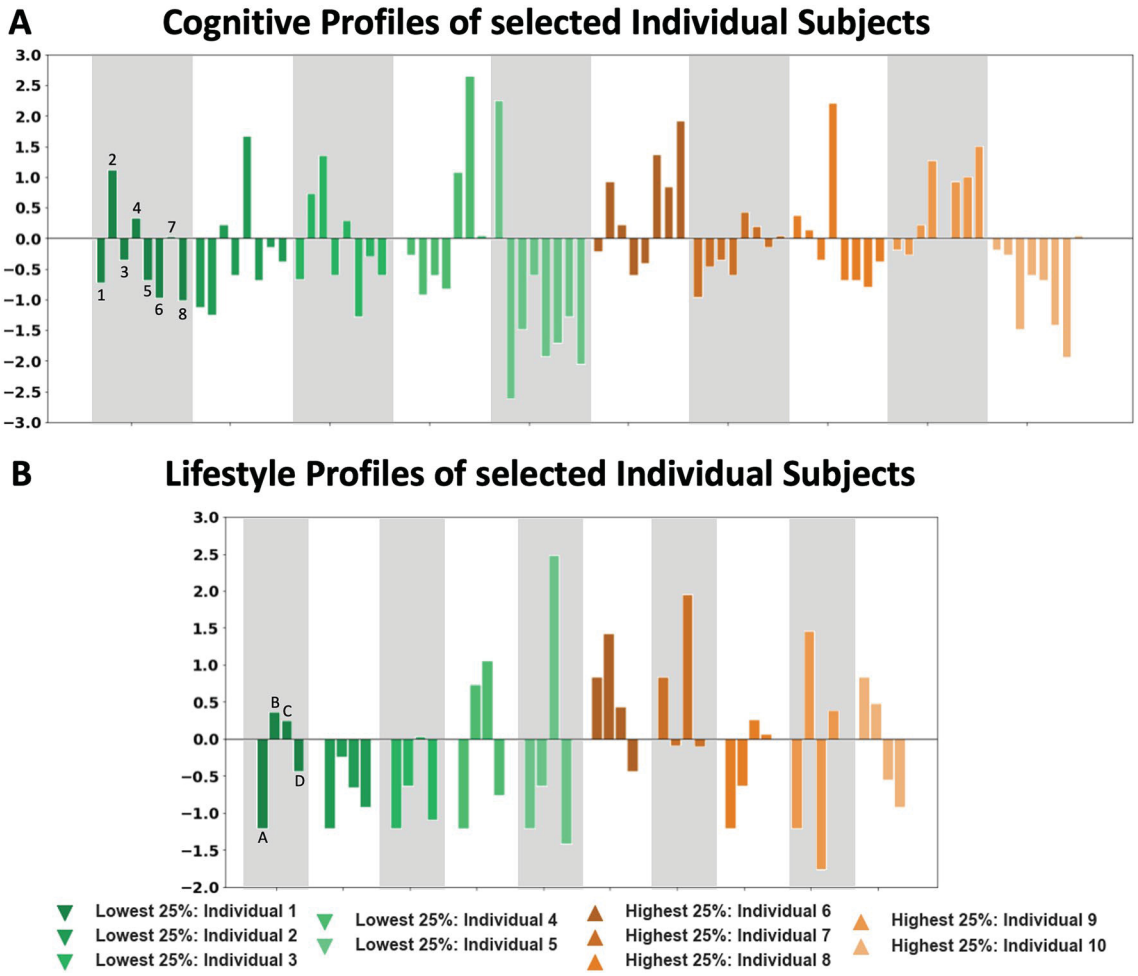

Fig. 8 Comparison of selected individuals regarding their **A** cognitive performance (1 = Processing Speed – 2 = Reasoning – 3 = Visual WM – 4 = Verbal WM – 5 = Figural Fluency – 6 = Semantic Fluency – 7 = Phonematic Verbal Fluency Switch – 8 = Semantic Verbal Fluency Switch) and **B** lifestyle habits (A = Alcohol (yes-no) – B = Sports – C = BMI – D = Social Integration Index) for those variables showing significant influences on GMV of any of the AG subdivisions. All cognitive and lifestyle variables were standardized to facilitate comparability across variables

in most of the cognitive tasks presented. However, individual #5 is one of the subjects with a low GMV, while individual #10 exhibited a high GMV. Thus, these individual profiles demonstrate that each individual shows its own cognitive and lifestyle fingerprint, with differential effects for different factors, not reflected by the general group trends.

Discussion

Aim of the current study was to characterize multimodal brain–phenotype relationships of the AG sub-regions in the older brain. Thereby, we first examined the GMV of the AG sub-regions and the relation to multilevel information about GMV, RSFC and SC of the rest of the brain. We additionally made use of the multilevel atlas framework EBRAINS to enrich the here established results by molecular, genetic and cellular information of these brain areas, to finally obtain a holistic understanding of the cyto-architectonically defined sub-regions, PGa and PGp. In a second step, we conducted group analyses of AG subdivisions in light of age, cognitive performance and lifestyle in older subjects using multimodal sources of information. We finally switched the perspective toward the "individual" to carve out the peculiarities that individual profiles of this multimodal picture of the AG might reveal in contrast to the insight based on group-level inference, an essential aspect when it comes to medical conditions and treatment considerations.

Multimodal characterization AG sub-regions

With respect to brain–brain relationships, in the current study, we performed regression analyses to examine the associations between GMV of the AG subdivisions and a) GMV of, and b) RSFC, and c) SC with all parcels of the Julich-Brain Atlas. The resulting patterns of these brain–brain relationships were found to be different for PGa and PGp as well as across modalities. With this, the current results support the notion of previous studies, reporting the AG to consist of different subdivisions (Caspers et al. 2006, 2008) and emphasize the need to explore these individually. We here extended these observations by showing that the AG subdivisions exhibit individual spatial patterns of covariance for all three modalities investigated (GMV, RSFC and SC). Thus, with the current results based on an older adult population, we show multimodal evidence for a clear distinction of areas PGa and PGp in the AG.

Importantly, it has to be mentioned that spatial association patterns were not only heterogeneous across the regions of interest, but also across the three modalities (GMV, RSFC, SC) within one ROI. In accordance with the notion of brain plasticity in even healthy older adults (for a review, see Reuter-Lorenz and Park 2014), differences in GMV of the AG subdivisions seem to, at least in part, affect GMV, RSFC and SC in a distinct way. For instance, we found GMV of left areas PGa and PGp to be associated with GMV of the left hemispheric parietal and dorsolateral prefrontal brain areas, possibly reflecting a frontoparietal network, involved in executive functions and working memory (Yeo et al. 2011; Smith et al. 2009). Interestingly, focusing on left area PGp, we also found a frontoparietal association in terms of RSFC. Here, a lower GMV was related to higher RSFC between this area and the dorsolateral prefrontal cortex of the contralateral hemisphere. Aging studies, so far, have shown that a decrease in GMV in posterior brain regions might be related to a higher functional connections to frontal brain regions, the so-called posterior to anterior shift in aging (Dolcos et al. 2002). These effects shown here are in line with this and might represent a compensatory mechanism of the brain, to maintain cognitive performance as stable as possible in our older adult population. Furthermore, while the frontoparietal network is supposed to be a mainly lateralized brain network, we here found a GMV dependent difference in RSFC with the dorsolateral prefrontal cortex of the contralateral hemisphere. With regard to the aging population and plasticity of the older adult brain, an increase in communication between the two hemispheres might reflect similar compensatory attempts for structural brain atrophy as discussed above to maintain cognitive performance as stable as possible [HAROLD, Cabeza et al. (2002); Jockwitz et al. (2017); Reuter-Lorenz and Lustig (2005); Holler-Wallscheid et al. (2017))]. Thus, the current results might, at least in part, represent multimodal evidence for the functionally derived aging theories in the older population.

In addition, both (left and right) areas PGp showed an association to GMV of the visual cortex. This fits to the results in terms of GMV patterns as well as in terms of SC, i.e., connectivity between areas PGp and the visual cortex in both analyses. Furthermore, Caspers et al. (2013) reported similar receptor distributions between area PGp and the visual cortex, which is in line with the current observations in terms of GMV and SC. The interaction of AG and the visual cortex, also known as dorsal visual stream, is essential for an intact visuomotor system and has already been reported to be age-sensitive (Yamasaki et al. 2012; Sciberras-Lim and Lambert 2017; Wu et al. 2020); i.e., substantially higher gray matter reduction for the dorsal visual stream as compared to, e.g., the ventral visual stream (Ziegler et al. 2012). This multimodal perspective supports previous notions that area PGp might be closely linked to higher-order visual processing, also during older ages.

Group analyses of AG subdivisions in light of age, cognitive performance and lifestyle

Based on the multimodal group results, the AG subdivisions can be characterized by different properties in terms of gray matter, functional and structural connectivity. In terms of brain–phenotype relationships on the group level, we additionally found differential associations for the AG subdivisions. We found the most pronounced age-related GMV decreases in right PGa, followed by right PGp, left PGp and finally left PGa. Asymmetric differences concerning age-related decreases in brain structure have been previously reported, also for the inferior parietal lobule and the AG itself (e.g., (Plessen et al. 2014; Jockwitz et al. 2017; Roe et al. 2021). This is in line with the so-called right hemi aging theory (Grady et al. 1994) stating that the right hemisphere, mainly responsible for visuospatial functions, declines earlier as compared to the left hemisphere. In a previous analysis, we could already establish that this rather global statement also holds true for the right versus left AG, at least in terms of cortical folding indices (Jockwitz et al. 2017). We now could verify this effect also regarding GMV.

In terms of cognitive performance, previous studies reported the right AG to be associated with visual spatial attention, calculations, or self-processing (Corbetta and Shulman 2002; Arsalidou and Taylor 2011; Seghier 2013), while the left AG is rather involved in language functions, especially semantic processing and memory (Seghier 2013; Heim et al. 2019). In the current study, however, we revealed associations between semantic verbal fluency and GMV of both, left PGa/PGp and right PGa. This is only partially in line with and rather extends results obtained by a large meta-analysis investigating the semantic system in the brain

(Binder et al. 2009). While Binder et al. (2009) showed a lateralization of semantic language processing to the left hemisphere, we here showed a bilateral relation between GMV and verbal fluency in the older adult population. In terms of semantic language processing, this performance-dependent GMV might serve as a structural correlate for the so-called HAROLD model (Cabeza et al. 2002), stating that older in comparison to younger adults recruit bilateral brain networks to maintain cognitive functions as stable as possible.

Interestingly, additionally focusing on the genetic information extracted from EBRAINS, we found differential language-related gene expressions in areas PGa versus PGp. Generally, area PGa shows a higher expression of ATP2C2 (with higher right as compared to left hemispheric expression) and a lower expression of FOXP2 as compared to area PGp. Since both genes are supposed to support successful language processing during the lifespan [i.e., FOXP2 is supposed to be involved in the development of speech and language, ATP2C2 has been associated with dyslexia and other communication disorders (Lai et al. 2003; Newbury and Monaco 2010; Lambert et al. 2011; Unger et al. 2021a, b)], the difference in gene expression may suggest a functional diversity to exist between areas PGa and PGp. These results, indeed, align with the functional diversity found between these areas, especially in the right hemispheric AG, i.e., area PGa is related to semantic fluency, whereas area PGp shows no correlation with semantic fluency. Emphasizing that the current study focused on the older adult brain, it needs to be highlighted that the right hemisphere is supposed to be more age-sensitive as compared to the left hemisphere. Thus, we here might unravel gene-dependent differences in the two areas, which might become particularly functionally relevant during older ages, when aging effects on brain structure already start to unveil.

Differences with respect to the brain–behavior relationships, however, were not only present within the right AG. Rather, we found verbal WM to be related to GMV of left PGa and visual WM to be related to GMV in left PGp. Generally, the current results are in accordance with functional connectivity-based results showing an involvement of the (left) AG during WM performance (Smith et al. 2009; Rottschy et al. 2012; Vatansever et al. 2016; Marek and Dosenbach 2018; Yao et al. 2020). As already shown for verbal fluency, at least in the older adult population, there might be a regional difference in the involvement of left AG in WM, with left area PGa being related to verbal WM and left area PGp being related to visual WM. Here, it is particularly useful to additionally incorporate information from the EBRAINS multilevel platform that supports the results found in the current sample of older adults. For instance, receptor fingerprints of the AG subdivisions show that especially the more posterior lying brain regions PGp bilaterally have receptor fingerprints similar to extra-striate cortices, which is in line with the current results.

These insights were supplemented by differences in lifestyle habits in association with age-related AG subregion volume differences. We found a higher BMI to be associated with lower GMV in all areas except right area PGa. A negative association between widespread brain structure and BMI has been established in several studies (e.g., Taki et al. 2008; Kharabian Masouleh et al. 2020). Some studies showed a particular association with the inferior parietal lobule. For instance, Kurth et al. (2013) showed a negative association between BMI and GMV of the inferior parietal lobule and Cheke et al. (2016) reported reduced functional activity during an episodic memory task in the AG, which could be explained by reductions in brains structure, as found in the current study.

Furthermore, we found GMV of the two right hemispheric AG parts to be associated with several other lifestyle variables. GMV of right area PGa was positively associated to sports and GMV of the right area PGp was negatively correlated with alcohol consumption and positively correlated to social integration. Sports and social integration have been shown to be beneficial in terms of gray matter structure during the aging process (Erickson et al. 2015; Bittner et al. 2019, 2021; Domingos et al. 2021). Particularly interesting, we found a relation between structural atrophy of area PGp and the social integration index. With the right AG being associated with social cognition (Bitsch et al. 2018) and social integration (Park et al. 2021), the current results might hint at a special role of right area PGp in social behavior during older ages.

Taken together, results derived from a large population-based sample of older adults reveal quite heterogenous patterns for left and right areas PGa and PGp. We found a mixed picture of age differences in terms of GMV, together with differential relations to cognitive performance and lifestyle. Together with the integration of information derived from EBRAINS, we highlight the need to investigate the AG subdivisions as different entities, rather than one macroanatomical structure, which might obscure specific relations between brain regional architecture and behavior and cognition.

Individual profiles

An important aim of the current study was to not only characterize global alterations of areas PGa and PGp in the older adult population, but to also investigate individual profiles of subjects showing particularly high or low GMV of the AG subdivisions as an example of relevant deviations from global trends typically reported in group-level analyses. The question of the transition from the group level to the individual subject tackles one of the most important topics when

it comes to modern neuroscience including precision medicine. By amending the group results with individual subject profiles in the present study, we aimed at gaining further awareness of this topic in the neuroscientific community.

For instance, the group results suggested that lower GMV would be related to lower performance in the verbal fluency tasks, together with a higher BMI. Looking at one of the individuals who showed low GMV in all AG subdivisions, we see that this individual #4 shows an above average performance in semantic and phonematic fluency together with a slightly above average BMI. Similarly, comparing two subjects, one showing low GMV of the AG (individual #5) and the other one showing high GMV (individual #10), both subjects perform low in most of the cognitive tasks presented. Thus, bearing in mind the variability between GMV and cognitive abilities and lifestyle habits (cf. Fig. 7A and B) when examining this individual, e.g., in case of a medical examination, group trends could not easily be applied to this specific individual as some might fit more or less, while for other factors, there is considerable and differential deviation. Rather, these individual profiles demonstrate that each individual shows its own cognitive and lifestyle fingerprint, that is not necessarily reflected by the group effects. In fact, results from the current data suggest that individuals and their cognitive/lifestyle profiles may largely deviate from estimated group trends leading to the question what this would mean for future research in the field of cognitive neuroscience.

Group analyses aim at extracting general principles of brain–behavior relationships, e.g., the "average" association between GMV decrease and cognitive performance decline in older adults. Applying this "one size fits all" approach to clinical cases, e.g., a group of Alzheimer patients, and relying on this principle would mean that all patients would be treated the same way (Reitz 2016). However, from previous work, it is well known that neurodegenerative diseases might show individual peculiarities, where not every patient exhibits the same symptoms. Likewise, not every patient responds to the same treatment (Reitz 2016). The here presented results between the poles of group results and individual cognitive/lifestyle profiles tap into this conflict, by showing that even in a normal older adult population, each subject has his/her own individual fingerprint of brain and behavioral particularities. Although principles derived from group-level analyses, of course, build a guideline for the average subject or patient, the current individual dissimilarities stress that a characterization at the individual level, in contrast to group averages, will be an inevitable step toward successful diagnostics and treatments (Reitz 2016; Zimmermann et al. 2016). Importantly, individual characterizations require rich datasets, including information on brain and behavior at different levels, such as molecular and genetics. Since this kind of information might not be accessible to every research group, the EBRAINS (Amunts et al. 2016) interactive tool combining multilevel data from various sources enables deep multifaceted characterizations of the brain at multiple level in one common framework. In the current study, we used EBRAINS to support the brain–behavior relationships presented here with both genetic and molecular findings to obtain a holistic characterization of the AG subdivisions.

Conclusion

Based on the multimodal group results, the AG can be considered as a structure heterogeneously affected in the aged brain: First, GMV, RSFC, and SC patterns provide multimodal evidence that the AG subdivisions seem to be involved in different brain networks sub-serving distinct cognitive functions, which could further be supported by integrating molecular and genetic information from EBRAINS. Second, age differentially affected GMV of the AG subdivisions, with the highest GMV decrease in rPGa. Third, the different AG parts showed distinct associations with cognitive abilities or lifestyle habits hinting at a functional specificity of each region. However, the individual profiles show that the relations identified at the group level are not necessarily transferable to the individual level. Hence, general observations within the older adult population need to be carefully considered, especially when it comes to the assessment and treatment of individual patients.

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Declarations

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