Title: The older adult brain is less modular, more integrated and less efficient at rest: A systematic review of large-scale resting-state functional brain networks across the adult lifespan.

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ABSTRACT

The literature on large-scale resting-state functional brain networks across the adult lifespan was systematically reviewed. Studies published between 1986 and July 2021 were retrieved from PubMed. After reviewing 2,938 records, 144 studies were included. Results on 11 network measures were summarised and assessed for certainty of the evidence using a modified GRADE method. The evidence provides high certainty that older adults display reduced within-network and increased between-network functional connectivity. Older adults also show lower segregation, modularity, efficiency and hub function. Higher-order networks reliably showed age differences, whereas basic processing and control networks showed more variable results. The inflection point for network changes is often the third or fourth decade of life. Age effects were found with moderate certainty for increased hemispheric lateralisation at rest, reduced BOLD signal variability within-subjects and altered patterns and speed of dynamic connectivity. Research on connectivity using glucose uptake provides low certainty of age differences but warrants further study. Taken together, these age-related changes may contribute to the cognitive decline often seen in older adults.

Key words: Large-scale networks, resting-state networks, functional connectivity, lifespan, ageing, systematic review, PRISMA, fMRI, PET.

1. Introduction

The number and proportion of older adults in the community is projected to increase significantly over the coming decades. It is estimated that the global population of adults aged over 65 years will increase from 703 million in 2019 to 1.5 billion by 2050 (United Nations, 2019). The rise in the number and proportion of older people stems from declining birth and fertility rates and an increase in the average lifespan across the world (United Nations, 2019).

An ageing population is expected to drive an increased societal burden from cognitive decline. Ageing is a major risk factor for cognitive decline, as well as many chronic and neurodegenerative diseases. Hence, an ageing population is likely to be associated with a growth in age-related diseases that will exact a significant health, social and financial toll on individuals and society (United Nations, 2019). These costs raise important questions about what can be done to ensure that the expected increase in the ageing population is accompanied by optimal cognitive ageing, and how age-related illnesses and their associated healthcare and social impacts can be minimised.

It is well established that extensive brain changes occur with age, from the molecular to the functional level. Age-related brain changes include alterations in the structure, function and metabolic processes of the brain, often with an associated decline in cognitive function (Salthouse, 2019; Smith et al., 2020; Wu et al., 2011). Older adults typically show a decline in a number of cognitive domains compared with younger adults (for reviews see Brown & Park, 2003; Glisky, 2007). Sometimes referred to as *fluid intelligence*, these cognitive domains have been shown to peak in the third decade of life and then gradually decline (Harada et al., 2013). They include executive function and attention, such as the ability to think abstractly, reason and problem-solve. In contrast, tasks relying on predominantly automatic or well-practiced processes, sometimes referred to as *crystalised intelligence*, are less impacted by age or may even increase slightly across the lifespan, such as vocabulary and general knowledge (Harada et al. 2013). Speech and language processing tend to be relatively stable with age (Salthouse, 2019), although processing time may be slower in older adults due to more generalised reductions in processing speed. Together, cognitive changes seen in the ageing process can have a widespread impact on an older individual's daily function and quality of life.

1.1 The Brain as a Network

Understanding the complex, multi-layered structure and function of the brain has been an area of scientific enquiry for many decades, and has led to a variety of schema for describing the organisation of the cortex. Early approaches provided insight into the functional *specialisation* of brain areas and how age-related and degenerative changes occur with local neuronal alterations. However, it soon became apparent that the function of brain regions also relate to their *connectivity* with other regions (Genon et al., 2018).

In the last two decades or so, there has been a rapid increase in the number of studies in which the brain is modelled as a complex network that consist of units (e.g., brain systems, regions, sub-regions, neurons) linked by structural connectivity, functional connectivity, or both (Liao et al., 2017).

In this research, “functional connectivity” is typically defined as the temporal dependency between spatially remote neurophysiological events (Shen, 2015). A large body of research has led to the understanding that communication in the brain is organised according to a topology that combines local information processing with global information integration across networks of functionally interacting regions. This combination of functional properties enables intricate, synchronised dynamics across multiple spatiotemporal scales (Fornito et al., 2015a; Sala & Perani, 2019).

In the neuroimaging field, the term “network” is often used to refer to a group of voxels or brain regions that have a consistent pattern of correlated activity in a resting-state or during a task. The construction of networks and their analyses draws on the concept of “small world” networks and graph theory (Rubinov & Sporns, 2010; Sporns, 2018; Sun et al., 2012). The key concepts and measures used in functional network and graph theory analyses and which form the basis for this review are defined in Table 1 and depicted in Figure 1. In graph theory analyses, the brain can be modelled as a group of *networks*, consisting of a set of *nodes* that represent the units of the system, and *edges* that denote the interactions between nodes (Liao et al., 2017). The nodes can be neurons, neuronal populations or brain regions, depending on the spatial scales of interest, and the edges represent the structural or functional connectivity that links the nodes (Liao et al., 2017). In this review we focus on large-scale networks of brain regions, involving tens to hundreds of nodes (across centimetres), as well as studies that use whole-brain, voxel-wise networks comprised of thousands of nodes (i.e., voxels of 1-2 millimetres).

Table 1. Network and graph theory properties, definitions and measures

Property	Definition	Example Graph Measure
Functional connectivity	Temporal correlation between time-series of neurophysiological events	The average of the weight of node edges, e.g., BOLD correlation or PET tracer uptake.
Path length	Distance between nodes in terms of edges traversed.	Average minimum path length is the shortest mean distance from a particular node to all other nodes in the network (in terms of edges traversed), and is a measure of integration.
Local efficiency	Efficiency of information transfer between nodes within a network.	Inverse of the average shortest path length of each node to its neighbours.
Global efficiency	Efficiency of information transfer across the entire network system.	Inverse of the average shortest path length between networks in the system.
Modularity	Degree to which the network is divided into distinct communities. Dense within relative to sparse between network connections. A modular network exhibits a 'clustering' of its nodes into multiple distinct subnetworks.	Fraction of connections (edges) within the communities of a network compared to if the connections were distributed at random across the network, e.g., ICA or thresholded correlations aim to reflect modularity.
Segregation	The amount of partitioning between distinct regions of a network. Reflects the ability for specialised processing to occur within densely interconnected groups of brain regions. Similar to modularity, except that it directly quantifies within versus between network connections.	Dense or strong connectivity among nodes in the same network (high within-network connectivity) coupled with sparse or weak connections between nodes belonging to different networks (low between-network connectivity), e.g., clustering coefficient.
Clustering	Nodes in the same network are more similar to each other than to those in other networks.	Clustering coefficient is a measure of the proportion of a node's neighbours that are themselves neighbours, and is a measure of segregation.
Integration	Reflects the degree of integration among multiple brain regions. The ability to rapidly combine specialised information from distributed brain regions.	The average number of edges of the shortest paths that connect nodes over the whole network. A smaller path length represents greater integration. Measures include shortest path length and node degree. Also related to global efficiency. i.e., as the inverse of the average shortest path length.
Hubs	Nodes that have highly centralised connections and strong relationships with each other via long-distance connection. A hub can be defined as a node that has many important connections running through it (is a member of the shortest path between many nodes), or a node that associates with (correlates to) many other networks.	Measures of centrality, including how many (degree) and weight (strength) of the connections, together with the shortest paths within the network pass through a given node (betweenness). For example, Participation Coefficient measure the connections that are <i>not</i> within a node's own network or that are across networks. When the between node connections are denser than expected by chance, they are form "rich clubs", serving as "way stations" for high volume transfer.
"Small World" network	High level of local and global efficiency in information processing, with economical "sparse" wiring costs. High segregation and integration.	In graph theoretical terms, a graph is "small world" if the path length is similar to that of a random graph, and the clustering coefficient is much greater than a random graph.

Figure 1. Illustration of functional networks and small-world metrics. A. Larger grey circles are *networks* of the graph (*networks 1, 2 and 3*). The dots within each of the *networks* are *nodes* and the lines are the *edges* (significant correlation between nodes in resting-state networks); solid lines are *within-network* edges and dashed lines *between-network* edges. Yellow nodes and edges depict a network displaying *within-network connectivity*. Connectivity *strength* of node *a* is the average weight of the *edges* linking with it; and *local efficiency* is the inverse of the average shortest path length of each node to its neighbours. Red edges depict the *shortest path* between the red node *b* and red node *c*. The shorter the average path length across all pairs of nodes, the higher the *global efficiency*. The blue node *d* depicts a *provincial hub* (strongly connects nodes within the same network); the green node *e* depicts a *connector hub* (connects nodes between different networks). B. *Modules* reflect the division of larger networks into smaller “building blocks” or communities, typically reflecting anatomically connected or functionally related regions. The human brain displays “small world” properties that balances an economical trade-off between efficiency, physical connection cost and maximising topological value. In *Module 4*, the networks are wired for *global efficiency* and integrative processing, with each node likely to connect to multiple other nodes within- and between-networks, minimising path length and optimising global efficiency. However, this topology comes at a high wiring cost owing to the large number of connections across the system, particularly long-range connections. In comparison, in *Module 5*, the networks are wired to *minimise cost* and support functional specialisation, with each node having within-network near neighbours topologically and spatially. However, insufficient topologically direct connections or edges between networks limits global integration and efficiency. Efficiency is reduced through information needing to transverse a high number of long-range paths or edges between nodes in different networks. Relative to *Module 4*, *Module 5* is also higher in *segregation* (stronger or denser links within-networks but weaker or sparser links between-networks) and *modularity* (higher proportion of within-network connections, or higher average path length, across the system). C. *Rich club* network are indicated by functional connections between dense networks (Adapted from Cohen & D’Esposito, 2016; Wig, 2017).

1.2 Functional Networks in Ageing as an Early Marker of Cognitive Decline

Although cognitive decline is generally considered a normal consequence of ageing, it is not in fact an inevitable consequence of the ageing process. There is significant heterogeneity in the onset and severity of age-related cognitive decline among older adults (Salat, 2011). While some older adults show clear signs of cognitive decline by age 60, others retain excellent cognitive function well into their 80s and beyond, performing as well or better than younger adults (Glisky, 2007). Improved understanding of the heterogeneity of the cognitive ageing process is an important empirical and clinical matter. From a neural systems perspective, crucial questions to answer include: how age impacts the segregation and integration of the building blocks of the brain's functional systems; how they connect in a context-dependent, system-wide manner; and how they impact cognition and behaviour. These questions are especially pertinent to the study of cognitive ageing and neurodegeneration, as neural changes can begin to occur several decades before the onset of overt cognitive decline and/or disease symptoms (Chen, 2019; Coupe et al., 2019). Better characterisation of the timeframe and profile of normal ageing and cognitive decline may provide an opportunity to delay, slow or even reverse or prevent cognitive decline and disease trajectories.

Conceptualising the brain as a multifaceted network has provided a useful framework to examine how neural information processing relates to cognition and behaviour, and how it may be altered in ageing and diseases (van den Heuvel & Hulshof Pol, 2010). Graph theory posits that the interplay between integration, segregation and "small world" properties of networks will have implications for cognitive ageing. In this framework, the heterogeneity between individuals and across networks in cognitive ageing is an emergent property of network interactions involving multiple brain regions and information processing capacities. Connections within- and between-networks may change over time in number, strength, configuration and efficiency and as a function of learning, age or disease states (Genon et al., 2018; Medaglia et al., 2015). Indeed, it is now understood that dysfunction can arise from alterations to connected regions, leading to cascades seen in degenerative disease, or more gradual changes seen in "normal" ageing (Fornito et al., 2015a). A complex interaction of both maladaptive and compensatory mechanisms can follow, resulting in a heterogeneous expression of cognition and behaviour depending on the time, location, and scale of the underlying changes (Fornito et al., 2015b). The complexity of this dynamic interplay is also reflected in the fact that individual brain regions are involved in multiple neural functions, depending on the context and degree of the specific connections (Naik et al., 2017).

The typology of the connections of a functional network will also dictate how age-related changes or damage impact the networks and their associated functions. Alterations to a “rich club” network hub, such as the executive control or the default mode networks, will have diffuse impacts across the system. In contrast, alterations to a more local or provincial hub will result in more specific deficits (Fornito et al., 2015b). For example, in a meta-analysis of a large magnetic resonance imaging (MRI) database of 20,000 subjects with 26 brain disorders, Crossley et al. (2014) found that perturbances to white matter “rich club” network hubs, or their longer distance edges, are especially likely to degrade system-wide global efficiency and are critical to communication across the network.

1.3 Resting-State Functional Networks Are Valuable for Understanding Cognitive Ageing

It has been suggested that humans spend as much as half of their waking lives in cognitive states that are not directed towards a specific task (Lurie et al., 2020). In 1995, Biswal et al. published a landmark neuroimaging study of the brain at rest. It was predicted that the recorded neural activity would be largely random, as it was not directed towards a specific task. However, Biswal et al. found synchrony between brain regions that were known to share functional properties (also see Biswal et al., 2010). Over the next two decades, investigation of the connectivity of brain activity in a resting, task-free state has been one of the primary methods for understanding the brain’s network structure and function (Mill et al., 2020). A large body of research has shown that resting-state fluctuations across brain regions and at multiple scales originate, at least in part, from spontaneous neural activity. It is also now well established that brain activity at rest is organised into functional resting-state networks, defined by their spatiotemporal configuration and functional roles (Beckmann et al., 2005; Calhoun et al., 2008).

An important advantage of resting-state analyses over task analyses is that it avoids the need to understand the response and source of differences between groups in behaviour, cognitive strategy or performance, especially where performance can be supported by more than one cognitive mechanism (Rugg, 2017). Nonetheless, resting-state functional connectivity has been questioned for its ecological and cognitive relevance. For this reason, the field has also extensively examined age differences in functional connectivity when undertaking cognitive tasks (Campbell & Schachter, 2017). A detailed review of task-related functional connectivity is beyond the scope of this review (see Lurie et al., 2020). It is worth mentioning that research has shown that resting-state functional connectivity patterns are often similar to cognitive task activation patterns, with as much as 80% shared variance (Cole et al., 2014, 2016; also see Chan et al., 2017) and that patterns of functional connectivity are

relatively stable across tasks, with similarity estimates ranging between $r = 0.5$ and $r = 0.9$ (Lurie et al., 2020). These patterns have been found in primary sensory and motor regions, memory, learning and emotion, language and attention and cognitive control (see Medaglia et al., 2015, for review). This suggests functional network architecture in the resting state likely reflects at least some of the underlying “map” or “circuitry” by which activity flows during cognitive task performance. This shared circuitry supports the importance of studying resting-state functional connectivity as a means to better understand cognitive ageing (Cieri & Esposito, 2018; Ferreira & Busatto, 2013).

1.4 Resting-State Functional Networks and Theories of Cognitive Ageing

In systematically reviewing the literature, we also relate the findings to theories that have been proposed to explain functional network differences in ageing. These include the *dedifferentiation hypothesis* and the *compensation hypothesis* (Grady, 2012). These hypotheses were originally developed to explain differences in task performance and task-related brain activity between younger and older adults. However, the compensation and dedifferentiation hypotheses are likely applicable to resting state functional connectivity because, as noted above, the same functional architecture implicated in task-related processing also applies in the resting state.

Dedifferentiation describes the loss of functional specialisation in networks that are engaged during the performance of a task (Cabeza & Dennis, 2012; Park et al., 2004; Rajah and D’Esposito, 2005). Dedifferentiation is underpinned by more diffuse, nonspecific recruitment of brain regions (Fornito et al., 2015b). It can reflect the capacity of structurally distinct components of the network system to provide the same contributions to a given output, providing functional “plasticity” as well as potentially compensation to perturbation or damage (Fornito et al., 2015b).

The *compensation hypothesis* in ageing postulates that older adults are able to recruit higher levels of activity in comparison to young subjects in some brain areas to compensate for functional deficits located in other regions. The Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH; Reuter-Lorenz and Cappell, 2008; Schneider-Garces et al., 2010; but see Jamadar, 2010) proposes that, older adults recruit higher levels of neural resources than young adults even at the same level of cognitive demand. As will be outlined below, this increased neural activity among older adults is often seen in the frontal areas of the brain both at rest and during task performance.

The theory of *coordination dynamics* (Tognoli and Kelso, 2014) proposes that brain networks transiently connect when people attend to a stimulus or undertake cognitive and behavioural tasks.

“Metastability” is central concept in the coordination dynamics theory. *Metastability* refers to the

human brain's ability to integrate several functional parts and to produce neural fluctuations in a coordinated manner, providing the basis for cognitive function and behaviour. Coordination dynamics theory proposes that the tendency for brain regions to express their individual specialised functions (segregation, modularity) coexist with tendencies to couple and coordinate globally for multiple functions (integration). Hence, *metastability* reflects a balance between integration and segregation, with signal variability within the network enabling the dynamic shift between integration and segregation (Naik et al., 2017; Nomi et al., 2017).

Another theoretical focus in cognitive ageing has centred on the overall *efficiency* in the recruitment and deployment of neuronal resources, sometimes referred to as “neural reuse” theories (see Anderson & Finlay, 2013). One such theory, the *scaffolding* theory of ageing and cognition (STAC; Reuter-Lorenz and Park, 2014), suggests that the recruitment of additional neural resources via network reorganisation provides the foundation to preserve cognitive function in the face of structural and functional decrements with age. According to scaffolding theory, dedifferentiation and compensation are two sides of the same coin (Naik et al., 2017), and metastable network dynamics are the outcome of functional brain interactions constrained by modular structural connectivity. In other words, network dedifferentiation in older age can be considered compensation for a change in the underlying “scaffolding” of the brain in terms of structural and functional alterations (Naik et al., 2017).

The *cognitive reserve* theory (Stern, 2002) posits that functional brain architecture may support cognitive performance in the face of other age-related brain changes, including structural brain changes. Factors such as life experiences, education and physical activity have been identified to increase reserve, although the biological processes underpinning these effects remain largely unknown and debated (Pernecky et al., 2019; Verangis et al., 2019). Evidence suggests that older people with substantial *cognitive reserve* can compensate for brain changes to maintain their overall cognitive performance, even in the presence of significant alterations.

1.5 Scope of the Current Review

The objective of this paper is to systematically review the imaging literature on large-scale resting-state network function across the adult lifespan. We aim to address whether age differences exist at rest in the static and dynamic functional connectivity within- and between-networks; the local and global efficiency of functional networks; the network segregation, integration, modularity and hub structure; the topological connectivity pattern of lateralisation across the hemispheres and between

the anterior and posterior regions of the brain; and “metabolic connectivity” based on positron emission tomography (PET) imaging.

An overview of likely mechanisms driving age differences in network function is also included. These mechanisms include brain structural changes in ageing, as well as shared central and peripheral pathways in ageing and certain disease states. Methodological considerations and possible future research directions are also discussed.

Oxygen and glucose in the brain are central players in brain physiology and function. They also underly two widely-used neuroimaging methods, MRI and FDG-PET imaging, respectively. For detailed reviews of the physiological bases of these methods, refer to (e.g., Chen, 2019; Cipolla, 2009; Grayson et al., 2013; Mergathaler et al., 2013). Suffice to say that many of the advances in our understanding of brain connectivity in health and disease have come from research using MRI and PET imaging. MRI has been widely used to study resting-state functional connectivity, as it provides exquisite spatial resolution with moderate temporal resolution (sub-second resolution is now obtainable with fast imaging techniques like multiband acquisition; Feinberg et al., 2010, 2013; see Risk et al., 2021 for resting-state multiband fMRI). FDG-PET has also been used to identifying specific patterns of glucose metabolism and the “metabolic connectivity” of regions of the brain. Both of these imaging methods also have limitations that can present challenges for research in ageing populations, which are discussed further below.

2. Method

2.1 Type of Studies and Participants

Studies of large-scale brain network function across the adult lifespan were retrieved from PubMed published between 1986 and July, 2021, following the PRISMA 2020 statement (Page et al., 2021). The identification, screening and selection process is summarised in Figure 2. We included studies in which participants were adults aged between 18 and at least 70 years of age. In some studies, the age of participants extended into the 80s. Studies of older adults only were also included if they covered at least three decades of life from the 40s or 50s to at least the 70s or 80s.

2.2 Search Strategy

Search criteria were based on combinations of the following keywords and terms: functional connectivity, resting-state, resting-state connectivity, large-scale networks, brain networks, intrinsic networks, functional network, functional brain, brain systems, functional architecture, functional organisation, fMRI, MRI, resting-state fMRI, metabolic connectivity, simultaneous PET, multimodal

PET, functional PET, fPET; together with age, aging, ageing, lifespan, age-related, and older adults. Additional papers were identified by manually searching the citations from the retrieved references. Studies were included if they were published in a peer-reviewed journal in English, and used human subjects.

Figure 2. The identification, screening and selection process of studies included in the systematic review.

2.3 Exclusion Criteria

Papers were excluded if the sole focus was on a single brain region or associated cognitive domain (e.g., executive, attention, visual, frontal, motor regions). Studies examining connectivity while performing a task in scanner or subjects with dementia were excluded, unless they also included a resting-state condition and a healthy cohort for which age differences were reported separately. Grey and white matter structural connectivity papers were excluded, unless they also reported resting-state functional connectivity separately. Disease states (mental disorders including developmental disorders, dementias, epilepsy), training, and intervention studies were excluded in the search criteria.

2.4 Selection Process and Included Studies

The literature search retrieved 2,938 unique records. Titles and abstracts were independently screened and reviewed by two raters (HD & RDP) for inclusion, reducing the articles for retrieval and

review against the inclusion criteria to 339. Where differences between raters were found, the articles for inclusion were discussed and reconciled. As a result, 144 references were included in the systematic review.

2.5 Network Measures

The studies included in the review reported one or a combination of the following functional network measures: static or dynamic functional connectivity within-networks or between-networks; local or global efficiency; segregation, integration, modularity or hub function; within-subject measures of BOLD signal variability; metabolic covariance using PET; homotopic measures of hemisphere laterality or shifts in the posterior-anterior functional connectivity.

Studies were entered into tables and the direction and nature of age differences classified across all reported measures. For each measure, counts were made of the total number of studies assessing age differences and the number of studies showing a consistent direction and pattern of statistically significant age effects. Counts were undertaken for the overall pattern of age differences across all resting-state networks in the studies and for specific networks where patterns of results varied by network and aided explanation of the heterogeneity of findings. Counts were also independently undertaken by two raters (HD & RDP) and any differences discussed and reconciled.

2.6 Certainty of the Evidence

We classified the overall level of certainty or strength of evidence for each network measure as high, moderate or low using a modified version of the GRADE method (Guyatt et al., 2008; Murad et al., 2017). GRADE was originally developed to provide a framework for presenting summaries of clinical trial evidence and an assessment of certainty when making clinical recommendations. We considered the following four criteria when assessing the strength of the evidence across the available literature: (1) The number and cumulative sample sizes of the studies; (2) the risk of bias from the study samples and recruitment procedures; (3) consistency of findings across the studies; and (4) directness of age comparisons across the adult lifespan. Risk of bias assessment was based primarily on geographical and public database diversity. For directness of age comparisons, we counted the number and calculated the percentage of studies that included participants across the full adult lifespan.

For each network measure, the four GRADE criteria were scored as either 5 (high), 3 (moderate) or 1 (low), except risk of bias, for which scoring was reversed so higher score corresponds to low risk of bias. The total GRADE score was calculated by weighting the four criteria scores as follows: Number

and size of studies (0.25), consistency of findings (0.35), risk of bias (0.2) and full adult lifespan represented (0.2). The final overall GRADE score for each measure could potentially range from 1 to 5. The final GRADE score for certainty of the evidence for each measure was based on the thresholds of: 1.0 – 2.3 (low certainty), 2.3 – 3.6 (moderate certainty), and 3.6 – 5.0 (high certainty).

3. Results

3.1 Summary Tables and Figures

Table 2 provides a summary of the findings from the systematic review and Figure 3 a visual representation of the findings. The data in Table 2 presents a global summary of the detailed study data in Supplementary Tables S1-S7 for each of the network measures and Table S8 for the GRADE assessment. As some studies reported multiple network measures, the studies listed in Tables S1-S8 are not mutually exclusive. It is also worth noting that the participant populations in the studies is also not always mutually exclusive, as several authors obtained samples from the same open source databases, such as the Nathan Kline Institute (NKI), Cambridge Centre for Ageing and Neuroscience (Cam-CAN), and 1000BRAINS databases. The origin of the data is reported in the Supplementary Tables for those studies using publicly available data sets.

Across the network measures, approximately 50% of studies do not include middle-aged individuals (see Table S8), which limits the age differences that can be characterised across the adult lifespan. As will be shown below, quadratic trajectories of age differences likely have an inflection point somewhere in the third to fifth decade of life. However, the lack of middle aged adults studies precludes the rigorous identification and quantification of ageing trajectories for adults from younger to older ages. This issue is most evident for the network measures where we assessed the strength of the evidence to be *moderate* to *low* (e.g., within-subject BOLD signal variability and lateralisation), as a smaller number of studies using these measures across the adult lifespan were available for review. The relative scarcity of studies examining middle age especially limits the ability to identify any quadratic relationships that exist between the network measures and age (see Figure 3B). In contrast, the measures for which we rated the certainty of evidence to be *high* (e.g., within- and between-network connectivity, segregation and integration), were used in a sufficiently large number of studies that covered the full adult lifespan to draw more certain conclusions.

Table 2. Summary Table of Systematic Review Findings for Functional Connectivity and Graph Theory Measures. Age Effects are counts (%) of studies.

Measure	Number of Studies	Total N-Size	Negative effect of age for all or some networks, together with absence of any positive age effects	No age differences in any networks	Positive effect of age for all or some networks, together with absence of any negative age effects	Varied direction of age effect by network	Level of certainty
Within-network connectivity (static)	49	20,407	36 (73%)	0 (0%)	1 (2%)	12 (24%)	High ¹
Between-network connectivity (static)	36	15,815	5 (14%)	1 (3%)	20 (56%)	10 (28%)	High ¹
Segregation, modularity, integration	31	9,046	29 (94%)	0 (0%)	1 (3%)	1 (3%)	High
Local efficiency	9	1,145	7 (78%)	0 (0%)	0 (0%)	2 (22%)	High
Global efficiency	13	1,768	7 (54%)	3 (23%)	3 (23%)	0 (0%)	High ²
Within-network connectivity (dynamic)	7	993	7 (100%) ²	0 (0%)	0 (0%)	0 (0%)	Moderate
Between-network connectivity (dynamic)	8	1,709	0 (0%)	0 (0%)	8 (100%) ³	0 (0%)	High
Lateralisation of functional connectivity at rest	8	2,819	5 (63%)	0 (0%)	1 (13%)	2 (25%) ⁴	Moderate
Posterior-anterior shift in functional connectivity at rest	8	2,124	0 (0%)	0 (0%)	7 (88%)	1 (12%) ⁴	High
Within-subject BOLD variability	6	1,321	3 (50%)	0 (0%)	1 (17%)	2 (33%)	Low
Metabolic connectivity	9	827	1 (11%)	0	4 (44%)	4 (44%)	Low

¹ Consistency of findings was considered *high*, with distinct and consistent age effects seen in higher-order and primary processing networks, see Sections 3.2.1 and 3.2.2.

² When nodal scale is held constant. This categorisation is based primarily on subset of six studies using a nodal scale of 90-114, see section 3.4.2.

³ For dynamic within- and between-network connectivity, the measures vary across studies although the direction of age effect was consistent, see section 3.6.

⁴ For lateralisation and posterior-anterior shift, “varied” age direction indicates partial support for the HAROLD and PASA models, respectively, see section 3.5.

Figure 3. Visual representation of systematic review findings on network measures reported in Table 2. The figures represent conceptual rather than quantified summaries of each measure to illustrate the relative pattern across the lifespan (refer to Table 1 for definitions of metrics and their units of measurement). For Panels A and B, a solid line with circular ends indicates *high certainty* of evidence; dashed line with circular ends indicates *moderate certainty*; and dashed lines with arrow ends indicate *low certainty*. For Panel B, the blank area from ages approximately 45-65 years indicates a smaller number of studies explicitly including these ages (see Table S8) and an absence of testing for non-linear relationships across the adult lifespan.

3.2 Older Adults Show Reduced Within-Network Functional Connectivity and Increased Between-Network Functional Connectivity Compared to Younger Adults

The economic “small world” organisation of brain regions, characterised by local clustering with efficient local and global information transfer, emerges in the first decades of life. A detailed review of early age research can be found in (e.g., Edde et al., 2021; Keunen et al., 2017; Liao et al., 2017). Briefly, the “small world” organisation is present as early as 30 weeks of gestation, and is strengthened across the first two decades of life. Networks also progressively shift from isolated local regions to a more distributed network organisation in infancy, before displaying additional and more subtle integration changes during early adulthood. The networks of the brain become a more interconnected system that extends over longer distances. The networks tend to follow a development sequence that is believed to reflect an adaptation to environmental demands (Fornito et al., 2015b) from an initial consolidation of primary processing networks by late childhood and higher-order networks in late adolescence. The networks reach their most stable period in the third or fourth decade of life (Edde et al., 2021).

Compared to younger adults, older adults show differences in the functional connectivity of large-scale resting-state networks. A consistent finding from the systematic review is a pattern of *decreased within-network connectivity* in older compared to younger adults. Thirty six of the 49 studies (73%) that assessed adult age differences in within-network connectivity reported lower connectivity in all or some of the networks analysed among older subjects, with an absence of any increased connectivity in older age (see Table S1 for details). Twelve studies (24%) reported age-related patterns of varying increases and decreases for specific networks.

Of the 36 studies that investigated between-network connectivity changes with age, 20 (57%) reported *increases in connectivity* with an absence of any decreased connectivity among older adults compared to young adults. Five studies (11%) reported a negative age effect, and nine studies (26%) reported age-related patterns of varying increases and decreases for specific networks.

We assessed the strength of the evidence as *high* for *decreased within-network connectivity* and *increased between-network connectivity* among older adults. This assessment reflects the relatively large number of studies, cumulative sample sizes, direct testing of age differences across the adult lifespan, and relative consistency of the findings. As will be discussed in the next section, consistency of the findings is increased when age effects are assessed separately for higher-order and primary processing networks

3.2.1 Higher-Order and Lower-Order Networks Show Varied Within-Network Functional Connectivity Trajectories

The varied within-network and between-network connectivity results across some studies may reflect differences in the trajectories of specific functional network differences with age. These different trajectories are illustrated in Figure 4. The lower-order perceptual processing and control systems (e.g., the sensorimotor, visual and auditory networks), as well as the sub-cortical and attention networks, appear to be more variably impacted by age than higher-order functional networks (e.g., default mode, front-parietal, executive control and cingulo-opercular networks). Across the 49 studies assessing within-network connectivity, none reported increases within the default mode network with age. Moreover, among the 21 studies reporting results for the default mode network separately, 20 (95%) reported lower within-connectivity among older adults; the remaining study reported no age difference (Jockwitz et al., 2017). Twenty of the 22 (91%) studies reporting other associative networks separately, such as the cingulo-opercular and fronto-parietal networks, reported lower within-network connectivity among older adults.

Large Scale Resting State Network Connectivity Matrix Differences Across the Adult Lifespan

Figure 4. Network connectivity matrix differences across the adult lifespan. The figure represents conceptual rather than a quantified connectivity measure (correlation) to illustrate the relative pattern across the lifespan. Diagonal cells show *within-network connectivity* differences with age; off-diagonal shows *between-network connectivity* (primary processing includes sensorimotor, visual and auditory networks). Cells on the diagonal of the matrix with graded shading reflects where study findings are variable in the effect of age, either showing no age difference (white) or increased connectivity among older compared to younger adults (yellow). Off-diagonal cells for the primary processing networks reflects mixed patterns of increased connectivity to higher order networks (yellow) and decreased (blue) connectivity to attention and control networks for older compared to younger adults.

There is more variability in results for the primary processing and control networks where they were reported separately. Eight of 23 (35%) studies reported no age differences or higher within-network connectivity among older adults in the sensorimotor network (Cao et al., 2014; Chan, 2014; Onada et al., 2013; Simon-Tov et al., 2017; Song et al., 2014; Tomasi & Volkow, 2012; Viviano et al., 2017; Wen et al., 2020a), three of 14 (21%) in the visual system (Farras-Permanyer et al., 2019; Petrican et al., 2017; Zonneveld et al., 2019) and two of two (100%) in the emotional network (Nashiro et al., 2017; Wang et al., 2012). Age-related reductions in integration within the sensorimotor network have also been reported (He et al., 2020; Roski et al., 2013).

3.2.2 Higher-Order and Lower-Order Networks Also Show Different Age Trajectories of Between-Network Connectivity

Decreases in *between-network* connectivity of associative networks was also relatively uncommon, reported in two of the 36 (6%) studies reviewed (Lou et al., 2020; Wen et al. 2020a). Sixteen studies reported on the default mode network separately, with 14 (88%) reporting increased connectivity to other large-scale networks. In contrast, 11 studies reported networks with decreased connectivity to primary processing and attention networks, such as between the motor regions and other resting-state networks (Allen et al., 2011; Geerligs et al., 2015; Hou et al., 2019; Luo et al., 2020; Wang et al., 2012), between the salience network and the visual, auditory and sensorimotor networks (Hou et al., 2019; Monteiro et al., 2019; Onada et al., 2012; Vij et al., 2012), and between sub-regions of the default mode, visual, auditory and dorsal attention networks (Huang et al., 2015; Spreng et al., 2016; Viviano et al., 2017; Zonneveld et al., 2019). Lower connectivity between the supplementary motor area and left anterior insular cortex has also been reported with increasing age (Li et al., 2015).

3.2.3 The Trajectory of Age Differences in Functional Connectivity are Non-Linear

There is evidence that the trajectory of age-related differences in resting-state functional network connectivity are non-linear, typically showing a quadratic pattern with age. Investigation of these non-linear relationships was reported in seven studies (see Table S1) at varying spatial scales, showing an inflection point in the third decade of life for within-network connectivity, and in the fourth decade for between-network connectivity. For example, Wei et al. (2018) found within-network connectivity followed a negative quadratic (inverted U-shape) relationship from 20-80 years of age across the whole brain, starting to decline around the age of 30 years, and accelerating from around 40 years of age.

In large sample of 5,967 subjects aged 13 to 72 years, Luo et al. (2020) found varied patterns of network correlations with age. Within-network connectivity decreased linearly, particularly in the visual and default mode networks. Increases in within-network connectivity at older ages was observed in the dorsal and ventral attention networks and separately in the sub-cortical regions. Connectivity between the default mode network and fronto-parietal network exhibited a positive quadratic (U-shape) relationship from the second to eight decades of life, with the lowest level of connectivity occurring in the fourth decade. Luo et al. noted that this pattern is consistent with a “last-in-first-out” configuration during maturation, in which the later-maturing higher-order brain regions are more sensitive to earlier age-related decline. Of note, Luo et al. (2020) also found coherence between the

timing and pattern of corresponding structural network changes with age, suggesting that structural changes may mediate or moderate at least some of the functional changes in ageing, consistent with the STAC theory of cognitive ageing.

3.2.4 Age Differences in Within- and Between-Network Functional Connectivity Are Also Found in Studies of Individual Resting-State Networks and Are Similar to Task Activation Patterns

Whole-brain analyses provide valuable insight into network organisation across the adult lifespan. However, they may not always be the most sensitive measure of subtle changes that occur with age and disease, particularly when changes may start or be driven by specific networks (Damoiseaux, 2017). Moreover, it is acknowledged that large-scale networks are composed of a set of distinct sub-regions that support the network function. In this framework, smaller, functionally specialised units connect in the context of large-scale networks, and subunits follow topographic organisational principles with representations at multiple scales within a full functional hierarchy. Hence, a complementary approach to whole brain studies is to investigate specific regions or networks across the adult lifespan. Although a systematic review of the literature that focuses on specific networks or regions is beyond the scope of this review, it is worth noting that the large-scale network differences noted above with ageing have also been shown to occur within-networks of higher-order cognitive functions, namely, the default mode, cingulo-opercular, executive control salience and attention networks (Andrews-Hanna et al., 2007; Bagarinao et al., 2019; Bo et al., 2014; Chan et al., 2014; La Corte et al., 2016; Onada et al., 2013; Goldstone et al., 2016; Grady et al., 2016; Geerligs et al., 2015; Hausman et al., 2020; He et al., 2014; Mowinckel et al., 2012; Nashiro et al., 2017; Tsvetanov et al., 2016; Vij et al., 2018; Wen et al., 2020b; Zhai & Li, 2019).

3.3 Networks Are Less Segregated, Less Modular and More Integrated Across the Adult Lifespan

Brain network modules divide larger brain systems into basic “building blocks” of internally densely connected clusters that are relatively weakly interconnected amongst each other (Sporns, 2017). Modularity is also closely related to two fundamental principles of functional organisation: *segregation* and *integration* (Sun et al., 2012). Segregation describes the fact the cerebral cortex is heterogeneous and can be divided into regionally distinct cortical areas, based on functional and structural properties (Genon et al. 2018). Integration relates to the notion that cognitive abilities rely on a dynamic interplay and exchange of information between different regions (Genon et al, 2018). The dense within-module connections increase the local clustering and thus facilitate functional specialisation within the

module, whereas the sparse (but not necessarily absent) between-module connections optimise the path length of the network and provide the basis for global information integration (Chan et al., 2014). Excess integration or segregation can be deleterious (see Figure 1B). Too much integration can lead to inefficiencies in information transfer and even rapid spreading of disease, whereas too much segregation can result in diminished network interaction (Wig, 2017). From a graph network perspective, although segregation is similar to modularity, it is different in that it directly quantifies the proportions of both within- and between-network connections that are present in the network (Wig, 2017).

It was noted earlier that the “small world” properties of brain networks emerge and strengthen over the first two decades of life. The coherence between structural and functional connectivity also strengthens during this period (Hagmann et al., 2010). In other words, there is a strengthening of the correlation between structural and functional connectivity with age suggesting that white matter connectivity plays an increasingly important role in creating brain-wide organisation. The developmental period of “plasticity” provides the foundation for functional specialisation and connectivity that supports the development of higher-order executive functions and other cognitive abilities. It is built on a foundation or “anatomical backbone” of myelinated white-matter pathways (Baum et al., 2020). Functional networks undergo a parallel change in the first two decades of life to those seen in the structural networks in terms of local segregation and global integration. The refinement of structural and functional connectivity during development results in a more modular system that balances low-cost neuronal resources with highly efficient information transmission (Figures 1B and 5). A more modular system supports the dynamic and efficient control of attention and behaviour, aligned with functional specialisation (Edde et al., 2020; Baum et al., 2020; Keulers et al. 2019).

3.3.1 Networks Are Less Segregated Among Older Adults

A reduction of within-network and an increase in between-network connectivity across the adult lifespan means that networks evolve to become less segregated, modular and more integrated in older age. We assessed the certainty of the evidence to be *high* for age-related changes in network segregation, integration and modularity (see Table 2). Of the 31 studies assessing segregation, integration or modularity, 29 (94%) showed increased integration, or a loss of segregation, modularity, or both (see Table S2 for details). One study reported varied results by network (Petrican et al., 2017), with decreased segregation of three higher-order networks (i.e., fronto-parietal, salience,

cingulo-opercular) and increased segregation of networks for external processing (e.g., language, subcortical). The other study reported an increase in segregation only, possibly because of the more limited age range of adults studied (mean, 65; standard deviation, 12 years) and a high dimension brain parcellation of 90 regions (Sala-Llonch et al., 2014).

Chan et al. (2014) found the sensorimotor and association networks exhibit distinct patterns of age differences in segregation. The sensorimotor networks comprised hand, visual, mouth and auditory networks; whereas the association network comprised the default mode, fronto-parietal, ventral and dorsal attention, and salience and cingulo-opercular networks. A linear association was found between decreasing sensorimotor system segregation and increasing age. The sensorimotor systems also exhibited linear age-related reductions in segregation with other systems, such as the visual system. In contrast, a negative quadratic relationship was found with the association system and age, with the inflection point of accelerated reductions in segregation at approximately 50 years. Han et al. (2018) found largely similar non-linear patterns between age and network segregation. The segregation of the primary processing system peaked around age 40, after which it declined in a linear pattern. Age-related reductions in the associative networks' segregation and between the associate and primary processing networks appeared as early as the third decade of life, stabilised, and then declined again at an increased rate from approximately age 60.

The decreased segregation in older adults compared to younger adults during rest has also been found to carry over into task states. For example, the composition of modules identified during rest changed more during an n-back task in older adults than young adults, particularly under higher task demands (Gallen et al., 2016). Older adults recruited additional between-module connections at all levels of task demand, whereas young adults only did so when task demands were highest. This is compatible with the CRUNCH model of cognitive compensation, whereby older adults recruit additional regions compared to younger adults at all levels of cognitive demands (Reuter-Lorenz and Cappell, 2008; Schneider-Garces et al., 2010). Similar age-related differences have been found using tasks requiring working memory (Crowell et al., 2020), the identification of target and novel stimuli (Geerligs et al., 2014), as well as tests of inhibitory control, including reaction time to stop signal and go/no-go tasks and visual search (Chou et al., 2013; Geerligs, et al., 2012; Tsvetanov et al., 2018). These studies have shown widespread decrease in functional specificity of regions in older compared with younger participants. That is, increased connectivity between areas belonging to different functional networks and decreased connectivity of areas belonging to the same functional network,

with older adults recruiting a more distributed network when shifting from rest to task and as task demands increased.

3.3.2 Network Hubs Are Less Modular Among Older Adults

Hubs are a particular type of node that have many important connections running through them and strong relationships with each other. They are also a key player in communication between different brain regions due to the number and positioning of their connections in a network. Hubs are often connected via long-distance neural pathways so that they can maintain information integration and coordination across spatially distributed regions, optimising the balance between the cost of neuronal resources and the efficiency of information transmission (Liao et al., 2017; Sporns, 2018). The spatial distance of the edges connecting hubs to the rest of the network is also considered to reflect their “wiring cost”. Hubs have high rates of cerebral blood flow, aerobic glycolysis and oxidative glucose metabolism, suggesting that they are “biologically costly”, although with associated high value for the integration of information processing (Crossely et al., 2014).

An established functional hub architecture is evident in late childhood, and strengthens by early adulthood, as connections between hubs and other regions increase (Hwang et al., 2013). In parallel with the maturation of the functional hub architecture is the alteration in the influence of white matter hubs and structural brain networks, providing the “scaffolding” for information transfer (Puxeddu et al., 2020). In normal ageing this is revealed by topological restructuring between- and within-hubs, with cognitively normal older adults displaying reduced connections running through the frontal and parietal hubs compared with younger adults (Ash & Rapp, 2014; Wu et al., 2012; Zimmerman et al., 2016; Zhu et al., 2012). Reduced “hubness” also predicts whether communication efficiency is compromised between networks in ageing (Betz et al., 2014).

Thirteen studies reported measures of modularity of the resting-state networks. All (100%) studies reported a decrease among older adults; namely, a reduction in the degree of centralised connections or the strength of their long-range connections (see Table S2 for details). For example, Meunier et al. (2009) derived 90 cortical and subcortical regions from fMRI data in a young (mean 24 years) and older (mean 67 years) group of participants. They found that some modules that were single, coherent regions in the young group were fractured into two modules in the older group. Based on its high inter-module connections, a frontal-striatal module appeared to be critical for coordinating information transfer in the younger group. However, the same pattern was not found in the older group, with the same functional role appearing to be taken-up by the posterior module.

Some hub regions play a key role in the overall network organisation and participate in multiple communities across the network. These hubs and their connections have been termed “rich club” because they are more densely connected than are nodes of a lower degree of connections (see Figure 1C). They tend to interconnect strongly with each other, forming the “rich clubs”. Because “rich club” connections link spatially distributed and remote hub nodes, their overall network cost is high, but this high cost is offset by their disproportionately large contribution to efficient communication (van den Heuvel et al, 2012). Compared to younger adults, older adults show a reduced hub structure, including “rich club” connectivity (Cao et al. 2014). These networks show a negative quadratic “rich club” connectivity pattern and a linear decrease in modular organisation with age, mainly localised to hubs in the frontal, parietal and occipital lobes. Because these networks are central in flexibly allocating resources to produce goal-directed behaviour, they are likely to have a relatively global impact on the cognitive ageing process. Indeed, these hubs support higher order executive functions that require high levels of information integration across the brain and have been shown to discriminate individuals’ executive function, IQ and behaviour (Finn et al., 2015; Miranda-Dominguez et al., 2018).

3.3.3 Age Differences in Functional Connectivity, Modularity, Segregation, Integration and Hubs Function: Summary and Implications for Cognitive Performance and Theories of Cognitive Ageing

Taken together, studies of (a) within- and between-network connectivity; (b) segregation, modularity and integration; and (c) hub differences across the lifespan support the notion that functionally related regions emerge during development, optimise during early adulthood and deteriorate in older age. This pattern of functional differences is illustrated in Figure 5 (comparing Panel C with Panel B and D). Differences between younger and older adults in terms of within- and between-network functional connectivity at rest may drive differences in functional network communication and possibly contribute to the decreased cognitive performance often seen in older adults, particularly in higher-order processes, such as executive function. Owing to its widespread role in human cognition and behaviour, executive function is central in theories of brain ageing, such as the frontal lobe hypothesis of ageing (Morrison & Baxter, 2013). Older adults tend to show less flexible thinking, such as forming new concepts and abstract thinking, response inhibition, as well as verbal and numeric reasoning (Salthouse, 2019; Harada et al., 2013; Darawski et al., 2008; Wecker et al., 2000). These executive function changes can be seen first in adults in their fifth decade of life (Sing-Manoux et al., 2012),

consistent with the findings of the systematic review that functional network connectivity changes reach their inflexion point in the fourth and fifth decade.

The finding that older adults show increased between-network connectivity (Section 3.2) and integration (Section 3.3) compared to younger adults is compatible with the “dedifferentiating” hypothesis (Cabeza & Dennis, 2012), in which more neural systems are activated in parallel in older adults during rest reflecting a more diffuse, nonspecific recruitment of brain regions. The literature reviewed in Section 3.3 also support the STAC theory by indicating that a loss of segregation with age impacts how brain regions integrate during rest (and task). These findings are also consistent with a decline in executive functions but maintenance of primary information processing in “normal” ageing, that implies an underlying compensation mechanism in aging to support higher-level cognitive functioning (Romero-Garcia et al., 2013). Age-related dedifferentiation is also seen in perceptual processing regions and may drive the need to recruit more neural resources further down the processing stream (Goh, 2011). In contrast, primary processing functions, such as visual information processing, benefit from clustered connections between adjacent areas. As these nodes are well connected, information exchange is more segregated, and the networks are more resilient to disruptions in connectivity with age (Geerligs et al. 2015; Song et al, 2014).

The results in Section 3.3 may also help explain the heterogeneity between individuals in cognitive ageing trajectories. Cognition and behaviour depend on the information flow sent and received between brain areas (Genon et al., 2018) and the interplay between network integration and segregation mediates this flow. As noted earlier, connections within- and between-modules may change in strength, configuration, and number, and may change over time as a function of learning, age or disease states. Some modules may remain relatively stable (e.g., primary processing) and others may vary substantially (e.g., associative regions), connecting and disconnecting (Medaglia et al., 2015). At the same time, hubs are biologically expensive and deteriorate with reduced metabolic activity in ageing (Arneman et al., 2018; Dai et al., 2015; Liang et al., 2013; Tomasi et al., 2013). Alteration to “rich club” network hubs in particular, such as the default mode network or executive control network, including their long range connections, reduce the communication between brain regions, a prerequisite for the fast and effective higher order cognitive functions. This complex interplay will dictate, at least in part, the differential cognitive expression of underlying functional changes with age. This is consistent with results that show that tasks relying on predominantly

automatic or well-practiced processes are less impacted by age than higher-order functions, or may even improve slightly across the life span (Grady, 2017; Harada et al., 2013).

Figure 5. Proposed brain network differences across the adult lifespan. Panel A shows network measures from Figure 3A across the adult lifespan. Panel C illustrates how the human brain sits between the extremes of *Module 4* and *Module 5* in Figure 1B, and displays “small world” properties, peaking in the fourth or fifth decade with local efficiency complemented by global efficiency. Local, short-distance connections reflect the capacity for information transfer between nodes across a short path length and are complemented by sparse long-distance connections that incur a higher wiring cost. Topologically direct connections between spatially remote brain regions are expected to yield benefits in terms of flexible function and behaviour. The system balances modularity, integration and segregation by balancing strength or density of within- and between-network connections and relatively short average path lengths. As shown in Panel B, brain networks in approximately the third decade of life show somewhat lower local and global efficiency and integration compared to the fourth and fifth decade (Panel C). Panel D, compared with younger adults (panel B and C), older adults display reduced local efficiency (increased path length to neighbouring nodes) and global efficiency (loss of long-range paths or longer average path lengths) between nodes across networks. For example, in Panel C, local efficiency is seen in the direct path from node a to node b traversing one edge only; whereas in Panel D the path from node a to node b traverses three edges (node a to c to d to b). In terms of global efficiency, in Panel C, the path length from node a to node h is via three edges: node a to b to f to h; whereas in Panel D, it is via six edges: node a to c to d to e to f to g to h. Within-network connectivity strength is also reduced in older adults in Panel D compared to younger adults in Panel B and C (indicated by thinner black lines in Panel D within networks) and between-network connectivity increased (indicated by thicker black lines across networks in Panel D compared to Panel B and C), leading to a less segregated and more modular, integrated system. (Adapted from Bullmore & Sporns, 2012).

3.4 Local and Global Efficiency Are Lower in Older Adults

3.4.1 The Brain is “Wired” for “Small World” Local and Global Efficiency

Brain networks with “small world” properties balance a high level of local and global efficiency in information processing, with economical “sparse” wiring costs (Bullmore & Sporns, 2012; see Figure 1B). Minimisation of cost is achieved by dividing the brain into localised modules that are close in space, with the nodes within each module having a short average path length of connection, increasing signal transmission speed and promoting local efficiency (Barbey, 2018). Local efficiency is complemented by global efficiency, which reflects the capacity for information transfer between any two nodes across the shortest possible path length. The complementary need for both local and global efficiency creates a need for long distance connections that incur a higher “wiring cost”. Thus, an efficient system is achieved by balancing competing constraints on brain organisation, demanding a decrease in the wiring cost for local specialisation and an opposing need to increase the connection distance to facilitate global, system-wide function (Barbey, 2018).

Higher order executive functions that require high levels of information integration across the brain benefit from global efficiency of long-range connections. Graph theory analyses indicate that older age is associated with reduced functional connectivity of long-range connections and higher connectivity of short-range connections (Sala-Llonch et al., 2014). Global efficiency of long-range connections is particularly important in the frontoparietal network and has been shown to discriminate individuals’ executive function, working memory, task switching and general intelligence (Miranda-Dominguez et al., 2018; Finn et al., 2015; Hakun et al., 2015; Rypma et al., 2005; Santarnecchi, et al., 2013; Stanley et al., 2015). Processing speed is also usually reduced in older adults, at least in part due to the need to traverse more nodes, leading to greater neural activity (between network connectivity) but less efficient, slower processing.

3.4.2 Older Adults Show Reduced Local and Global Efficiency of Large-Scale Networks

In line with the reduced within-network connectivity among older adults noted in Section 3.2, a corresponding loss of *local efficiency* (Table 2) is also reported consistently when compared to younger adults. Seven of nine studies (78%) that included a local efficiency metric reported lower efficiency among older adults compared to young adults in all or the majority of networks studied (see Table S3 for details). Two studies (22%) reported results that varied by network, both reporting higher local efficiency among older adults compared to younger adults in the sensorimotor network, and one in the visual system (Geerligs et al., 2015; Song et al., 2014). We consider the strength of the

evidence of loss of local efficiency in the associative networks with age to be *high*. There is also some evidence that there is an inverted-U shaped relation between age and local efficiency (Cao et al., 2014; Xie et al., 2020), with efficiency peaking around the third or fourth decade of life (Figure 3A). Seven of 13 studies (54%) reported lower *global efficiency* among older adults than younger adults; three reported no age differences (23%); and three (23%) reported higher efficiency among older adults. There are several possible reasons for the less consistent findings in global efficiency compared to local efficiency. Aging-related effects on global efficiency have been found to be of smaller effect size than local efficiency (e.g., Chong et al., 2019; Varangis et al., 2019), and so are likely to be more difficult to detect. This conclusion is aligned with our finding that the effects of ageing on local efficiency are more robust than on global efficiency.

Variation in image pre-processing, nodal scale (i.e., number of nodes within networks) and parcellation approaches may also have impacted the consistency of the global efficiency results. For example, a variety of parcellation approaches have been used, including independent component analysis to define networks (Bagarinao et al., 2019; Hou et al., 2019), atlas-based parcellation varying in dimensionality (Archard & Bullmore, 2007; Cao et al., 2014; Onada et al., 2012), community detection methods (Chong et al., 2019), algorithms optimising modularity (Geerligs et al., 2015), density and a novel subnetwork voting methods (Li et al., 2016).

Research has shown that global efficiency is one of the most sensitive graph theoretic metrics to nodal scale, as it can alter the number and length of edges between nodes (Zalesky et al., 2010; Stanley et al., 2013). The studies reviewed here used nodal scales ranging from 90 (e.g., Onada et al., 2013) to 1,204 (Cao et al., 2014) nodes. The variance in nodal scale will impact the path length of edges between nodes. Indeed, when nodal scale is largely constant, the results are consistent. Specifically, at a scale of 90 to 114 nodes, five out of six studies (83%) found decreased global efficiency among older compared to younger adults (Archard & Bullmore, 2007; Chong et al., 2019; Hou et al., 2019; Li et al., 2016; Onada et al., 2013; Sala-Llonch et al. 2014). Hence, the certainty of the evidence of loss of global efficiency with age is *high* among the subset of studies using a scale of 90 to 114 nodes. However, more research is required to explore the stability of global efficiency and age differences across other nodal scales.

3.4.3 Network Efficiency Among Older Adults: Summary and Implications for Cognitive Performance and Theories of Cognitive Ageing

Taken together, the results of the systematic review suggest that the balance of local and global efficiency indicative of “small world” brain networks is present across the lifespan, although it likely peaks in the fourth or fifth decade of life and then declines. As depicted in Figure 5, older adults display reduced local efficiency (increased path length to neighbouring nodes) and global efficiency (loss of long-range paths or longer average path lengths) between nodes across networks. Age differences in efficiency are likely contributing to the decline often seen in executive function, working memory and processing speed in ageing.

At least some of the differences in functional network efficiency with age may be driven by changes in anatomical connectivity and energy demands (Salat, 2011). Changes in structural efficiency based on graph theoretical measures of grey matter volume have been reported among older adults both longitudinally and cross sectionally (e.g., Wu et al., 2012, 2013) and reported to explain 83% of the age-related reductions in executive function (Fjell et al., 2017). These changes in structural efficiency are also in line with the “neuronal resource” and “scaffolding” theories of ageing outlined earlier. According to these theories, the efficiency of the transmission of neuronal communication is reliant on the integrity of white matter. Age-related functional changes are paralleled white matter changes that create a reduced capacity for global network integration and decreasing global efficiency. Reduced efficiency is mediated by alterations to the path length over which information needs to flow between nodes in different networks, as well as reductions in white matter global and local efficiency that provides a “scaffolding” for efficiency in the human brain (Burzynska et al., 2013; Niu et al., 2019; Zhu et al., 2015). Metabolic efficiency and cellular change that occur with age may also impact on network efficiency (Ramchandran et al., 2019).

3.5 Older Adults Show Posterior-Anterior and Inter-Hemisphere Functional Connectivity

Alterations at Rest

It is well established that brain regions show functional lateralisation, with the left hemisphere predominantly involved with language, analytical and logical functions, and the right hemisphere with non-verbal visuospatial, intuitive and sensory tasks (Agcaoglu et al., 2015). Moreover, the sensorimotor cortex exhibits stronger between hemisphere resting-state functional connectivity than the prefrontal and temporoparietal regions (Zuo et al., 2010), which is believed to be an evolutionarily conserved mechanism that supports fast and efficient information processing (Chen et al., 2019). The degree of lateralisation has been found to differ with age (e.g., Agcaoglu et al. 2015). Greater recruitment of prefrontal cortical regions involved in executive functions is also frequently reported in

older adulthood compared to younger adults. These lateralisation and frontal recruitment patterns have been described as hemispheric asymmetry reductions in old age (HAROLD) and a posterior-to-anterior shift in aging (PASA) (see Cabeza, 2002; Davis et al., 2008, 2012; Spreng & Turner, 2018, for review of these theories).

Although HAROLD and PASA were developed to explain task-related changes in ageing, studies have also shown their relevance in resting-state imaging. The available literature is summarised in Table 2, and indicates a *moderate* and *high* degree of certainty for age effects in line with HAROLD and PASA, respectively. Eight studies addressed age differences in the degree of lateralisation across the hemispheres (see Table S4 for details). Five of the eight studies (63%) provide support for decreased lateralisation with age (Agcaoglu et al. 2015; Chen et al., 2017; Jiang et al. 2020; Li et al. 2009; Yao et al., 2013) and two studies (37%) provided partial support (Sala-Loch et al., 2014; Zuo et al., 2010). For example, Yao et al. (2013) used a novel measure of brain entropy (i.e., the degree of underlying randomness) of the BOLD signal during rest. Variables with small entropy have a high level of predictability and low level of randomness. They pooled 26 fMRI resting-state datasets, with a total of 1,248 participants aged 6 to 76 years. Functional entropy of the BOLD activity increased with age: correlations in BOLD activity became more widely distributed among older adults, which was attributed to a reduction in the number of excitatory neurons and their connectivity. The increase in entropy was found in the connections between the hemispheres, suggesting that the hemispheres become more symmetric in functional connectivity with age, which is compatible with the HAROLD pattern. Functional entropy was also more evident in the frontal than in the occipital regions, supporting the PASA theory.

The studies testing the HAROLD pattern showed some variation by region with the sensorimotor network, visual network, attentional and frontal networks showing the greatest decrease in lateralisation (Agcaoglu et al., 2015). Chen et al. (2019) also noted that the increased inter-hemispheric segregation reported in their study may reflect a decrease in the integration ability of the dominant hemisphere, rather than a compensatory effect of the contralateral hemisphere, a phenomenon not studied in the other research reported above. In other words, the increased integration of whole-brain networks across hemispheres seen in other studies may reflect a combination of the decreased integration of inter-hemispheric networks and increased integration of the intra-hemispheric networks.

Eight studies (see Table S4) reported results related to PASA, with seven (88%) studies showing strong support (Chen et al., 2016, 2017, 2018a; McCarthy et al., 2014; Lee et al., 2015; Yao et al. 2013; Zhang et al., 2017); and one (12%) showing partial support (Sala-Lonch et al., 2014). For example, lower clustering and local efficiency have been found in posterior regions, together with an increase in anterior regions, in both task and resting-state networks for older compared to younger adults (McCarthy et al., 2014; O'Connell & Basak, 2018; Zhang et al., 2017). This includes functional hub dynamics and dynamic connectivity changes with an age-related posterior-to-anterior shift (Zhang et al., 2017).

In a study that included both rest and a working memory task conditions, older adults had lower functional connectivity between prefrontal and ipsilateral parietal regions in both hemispheres and in both conditions (Li et al., 2009). In addition, the decrease connectivity was asymmetric, with the connectivity better preserved in the left hemisphere than in the right. The authors suggested that the right-sided shift in prefrontal activation indicated that the right prefrontal cortex needs to compensate for the reduced connectivity from the right parietal area. This possibility is supported by a greater reduction in right-side connectivity as the prefrontal activation shifts from the left to the right. A number of other imaging studies have found that older adults have reduced activity in occipitotemporal regions with increased activity in anterior regions (Chen et al., 2016; Chen et al., 2018; Lee et al., 2015).

In summary, although the HAROLD and PASA theories were originally developed to explain task-based performance in older adults, the results of the studies summarised here indicate with moderate certainty that older age is also associated with a more lateralised and high certainty a poster-anterior shift in functional connectivity during rest. The presence of these patterns at rest is compatible with the argument that the resting-state forms a baseline 'framework' of the brain, upon which task- and goal-directed activity builds (e.g., Raichle, 2011; Jamadar et al., 2016). The HAROLD- and PASA-like effects in resting-state connectivity suggest that older adults are able to recruit higher levels of activity contralaterally and in the anterior regions of the brain, possibly to compensate for functional deficits located in other regions or because of a loss of efficiency across the brain.

3.6 Dynamic Connectivity

3.6.1 Dynamic Resting-State Functional Connectivity is Different in Older Adults

Traditional analytic approaches to functional connectivity analysis implicitly assume that the functional connectivity over the course of the scan period is static¹. In other words, the correlation of time courses between regions is temporally invariant (or ‘stationary’) across the scan period. However, the brain itself is highly dynamic, and dynamically shifts between states across time (Lehmann et al., 1987; see reviews by e.g., Tang et al., 2012; Michel & Koenig, 2018). ‘Chronnectomic’ approaches to connectivity analysis examine the temporal dynamics of region-to-region coupling across the scan period (Calhoun et al., 2014; Liegeois et al., 2017). The most common approach to assessing dynamic functional connectivity is the ‘sliding-window’ approach, which involves segmenting the time-course from nodes into a set of temporal windows, inside which their connectivity is analysed (Bijsterbosch et al., 2020). Dynamic functional connectivity analyses have revealed that resting-state networks undergo fluctuations between states of higher integration and segregation, or modularity, both at rest and during tasks.

There are methodological considerations in the study of dynamic functional connectivity, not least of which is that temporal dynamics are better measured using fast neuroimaging methods like electroencephalography (EEG). While EEG provides millisecond temporal resolution, fMRI provides moderate temporal resolution between several hundred milliseconds (with multiband fMRI; Feinberg et al. 2010, 2013) and seconds. PET is even slower, with temporal resolution of a few seconds in fPET (Rischka et al., 2018; Jamadar et al., 2021), and equal to the scan duration in typical PET studies (Jamadar et al., 2021). Systematic review of EEG studies of dynamic connectivity in ageing is beyond the scope of this review, but see Courtney & Hinault (2021) for a recent review.

For fMRI-based studies of dynamic connectivity in ageing, relevant methodological considerations include the choice of the analytical approach, sliding-window length, and the measures used to assess connectivity within the windows. Metrics can include connectivity strength, spatial network organisation, topological variations, and graph metrics (see Preti et al., 2017 for a review). Indeed, across the 16 studies assessing age-related differences in dynamic functional connectivity, various analytic methods, window lengths and network measures have been used, which potentially impact

¹There are many conflicting definitions of the terms ‘static’ and ‘dynamic’ in the neuroimaging literature. We have clearly defined our use of the terms here, but see Jamadar et al. (2021) and Liegeois et al. (2017) for discussion of alternative definitions of the terms.

the conclusions that can be drawn across the studies (see Table S7). The number of studies is also relatively small, particularly those including participants across the full adult lifespan; hence we assess the weight of the evidence for age differences in dynamic functional connectivity as *moderate* (Table 2).

All seven of the studies (100%) that assessed dynamic within-network connectivity found altered dynamics in older adults compared to younger adults in all or some of the networks investigated (see Table S5 for details). Older adults showed reduced connectivity strength and reduced signal variability compared to younger adults (Chen et al., 2018a; Madhyastha & Grabowski, 2014; Park et al., 2017; Qin et al., 2015; Tian et al., 2018; Wen et al., 2020a). All eight of the studies (100%) that assessed dynamic between-network connectivity also found different dynamics with age (Chen et al., 2018a; Davison et al., 2016; Qin et al., 2015; Tian et al., 2018; Viviano et al., 2017; Wen et al., 2020a). Three studies examined other measures, such as segregation and integration (He et al., 2020), network stability (Mujica-Parodi et al., 2020), and network hub properties (Schaffer et al., 2014) and all found altered states in older adults compared to younger adults.

Eight studies assessed the nature and speed of transition between connectivity states, and all (100%) revealed age differences. The differences included a lower number of transitions between states (defined by specific connectivity patterns of networks), and slower transitions between states for older compared to younger adults (Chen et al., 2018a, 2018b; Viviano et al., 2017; Xia et al., 2018).

Dynamic functional connectivity becomes less efficient and more random with increasing age (Battaglia et al., 2020; Ezaki et al., 2018), with older adults also spending more time in functional connectivity states with weaker connectivity throughout the networks (Tian et al., 2018). Age-related changes in dynamic functional connectivity are likely representative of a reduction in the dynamic network changes that need to occur to adapt to an array of cognitive states or environmental demands.

Five studies also reported age-related dynamic connectivity differences using graph theory metrics, including reduced efficiency (Ezaki et al., 2018), alterations to the dynamic participation of nodes within hubs (Schaffer et al., 2014) and increased segregation and reduced integration during dynamic states (Davison et al., 2016; He et al., 2020). For example, Mujica-Parodi et al. (2020) examined network modular dynamics across the adult lifespan. To measure large-scale functional reorganisation, they calculated *module instability*, defined as the portion of nodes in a network module that switched modules between window periods of 24 seconds. They calculated the percentage of the

node that did not remain in the same module over time. In two large-scale fMRI lifespan datasets, age-associated degradation in network stability was sigmoidal, peaked at around age 60 years but started 13 years earlier. Differences were driven most by visual, auditory regions and basal ganglia, and negatively correlated with Mini Mental State Examination score (and accelerated with Type 2 diabetes). These results suggest that decreased network stability with age is evident around age 45 and is associated with poorer functional outcomes.

Schaeffer et al. (2014) used connectivity clustering to identify multi-network hubs and showed that, while hubs can belong to multiple networks, their degree of integration into these different networks varies dynamically over time. Hubs with a high degree of “connectedness” to other hubs in the network showed greater dynamic variation over time. The degree of hub integration into different networks was lower in older adults, suggesting that hubs may lose the capacity to flexibly connect and serve as “relay stations” that enable information integration. Older adults also showed a reduced ability to access changeable substates of dynamic resting-state networks that reflect a “rich club” organisation (Escrichs et al., 2021), suggesting an impairment in achieving changeable functional states that are key for efficient global communication across networks.

Effective task performance is likely best accomplished by a dynamic reduction in segregation, or greater integration, of the task-relevant systems that support the processing goals of the task. This suggests a “push–pull dichotomy” between segregation and integration in functional brain networks during rest versus task (Wig, 2017). This systematic review indicates with moderate certainty that older adults show a reduced ability to dynamically shift between states both during and in the transitions between states, and spend more time in weaker states of connectivity. When they do transition between states, they do so with reduced speed. Dynamic connectivity states likely become less complex and more random with increasing age. These changes are likely dysfunctional in terms of older adults being able to rapidly respond to a changing environment and oscillate between integration and segregation to manage complex environments and task demands.

3.6.2 Within-Subject BOLD Variability Is Lower in Older Adults

It was noted earlier that the theory of *coordination dynamics* (Tognoli and Kelso, 2014) proposes that “metastable” brain networks can shift flexibly between integrated and segregated configurations. In contrast, networks with high integration or segregation without variability cannot flexibly shift between states. In this theory, neurons activating the same way to stimuli over time would not adapt to changing demands or environmental conditions. Brain function variability enables stable output,

greater information coding capacity and protection to disruption (Grady & Garret, 2018). When variability is too low, there is reduced capacity for the system to shift between states. An optimal level of variability facilitates neural function, with too little or too much leading to a less efficient network system (Garret et al., 2010).

According to the coordination dynamics framework, age-related loss of brain network efficiency and deterioration in processing speed and cognitive performance are potentially mediated by a loss of brain variability. There is a relatively small literature of six studies (see Table S6) that investigated the age differences in the variability of the BOLD signal within-subjects during rest. The authors of these studies used different spatial scales and measures of the BOLD signal variability and did not consistently include participants across the full adult lifespan. Hence, the level of certainty of age differences in this literature is *moderate* (Table 2).

Of the six studies assessing within-subject BOLD variability, three studies (50%) reported lower BOLD variability or amplitude modulation in all or most networks of older compared to younger adults (Chen et al., 2017; Grady and Garret, 2018; Yang et al., 2018). Grady and Garret (2018) used the standard deviation of the BOLD signal to find reduced within-subject variability at rest among old adults. Age-related reductions in frequency and amplitude modulation of resting-state fMRI signals have also been found in the default mode network and salience network across the lifespan (Yang et al., 2018). When the brain was analysed at a voxel level (Garret et al., 2010) and parcellated into 90 regions, the pattern of variability in BOLD signal differed by spatial location, and showed both positive and negative correlations between the variability and global functional connectivity of the BOLD signal (Xie et al., 2020). These studies also suggest that a cortical–subcortical distinction may exist, with subcortical areas increasing in variability across age compared with cortical areas (also see Garrett et al., 2013).

Nomi et al. (2017) studied BOLD signal variability using the same database (Nathan Kline Institute) as several other authors (e.g., Betzel et al., 2014; Cao et al., 2014) investigating large-scale resting-state network typology and finding decreased modularity with age, based on decreased within-network and increased between-network connectivity. Nomi et al. (2017) found less variability in the BOLD signal with age in most networks and noted that it may be related to decreased modularity. This is because increased variability is thought to enhance functional specificity by facilitating switching between integrated and segregated states.

Several studies have also compared BOLD variability to mean BOLD measures as a statistical predictor of cognition in ageing. These studies suggest that signal variability within-subjects can be a powerful predictor of individual differences in cognition across the adult lifespan (Garret et al., 2011). In fact, some have found that BOLD variability within-subjects accounts for almost all the variance in age-related fMRI differences, and are largely uncorrelated with age-related mean-based BOLD patterns (Garrett et al., 2010). This suggests that brain signal variability potentially provides a largely independent measure to mean brain activity in cognitive ageing and that BOLD variability should be considered for wider use in fMRI studies.

Variability of the BOLD signal within subjects is also lower in older compared to younger adults in studies that included both rest and task conditions, (e.g., Garret et al., 2011, 2013; Guitart-Masip et al., 2016). Grady and Garret (2018) found BOLD variability was higher during internally-directed tasks, and higher still during externally-directed tasks. This pattern was also reduced with age, suggesting that reduced signal variability may reflect a reduced ability to switch between internal and external cognitive states. Younger age, and faster and more consistent response times to perceptual and attention tasks, have also been associated with greater variability, but less mean activity (Garret et al., 2011).

The relatively small number of studies reviewed in this section suggest that older adults may display less variability than younger adults in BOLD signal in most, if not all, large-scale resting-state networks at rest. Reduced BOLD variability in older adults likely reflects a state of reduced *metastability* to integrate functional regions and to produce neural fluctuations needed for optimal cognitive function and behaviour in response to complex environmental demands. Further research is needed to establish whether less variability in BOLD signal impacts functional performance in ageing and whether changes in variability patterns are a necessary condition for age-related connectivity changes to become evident (Garret et al., 2010).

3.7 Metabolic Connectivity Differences Are Evident in Older Adults

The concept of “metabolic connectivity” actually predates the concept of functional connectivity, with the first analyses of region-to-region covariance in neuroimaging signal conducted in FDG-PET data (Metter, 1984; Horwitz et al., 1984, 1986). Glucose metabolism provides the primary source of energy for brain function and maintenance, as well as the production of neurotransmitters (Mergethaller et al., 2013). The adult brain accounts for approximately 2% of total body weight but requires approximately 20% of total glucose supply (Clarke & Sokoloff, 1999). Moreover, the brain cannot store glucose and

so requires a readily available source via the arterial blood supply. Hence, there are complex and dynamic changes in the energy consumption of brain cells from moment-to-moment as the brain performs its vast array of functions (Yellen, 2018). Brain glucose metabolism is tightly coupled to cerebral blood flow and oxygen supply to the degree that local blood flow is highest in regions with the highest glucose metabolism. An intricate interplay exists between the brain, endocrine system, central and peripheral energy supply, and energy utilisation. This requires a highly responsive system that is well controlled by both feedback and feedforward processes that produce choreographed changes in the flow through biochemical pathways (Yellen, 2018).

Brain glucose metabolism has been well studied in ageing and shown to differ with age. For example, Kuhl et al. (1982) used FGD-PET to study brain glucose utilisation in subjects from 18 to 78 years of age, and found that whole-brain cerebral rate of glucose metabolism was, on average, 26% less at 78 years than at age 18 years of age. The difference was greater than that reported for mean cerebral oxygen utilisation. The lower cerebral glucose metabolism with age was seen most in frontal, temporal, and subcortical regions, as well as in the cingulate and insula (Nugent et al., 2014; Trotta et al., 2016), which are heavily involved in higher-order cognitive functions.

The brain's dependence on glucose, and changes in brain glucose metabolism with age, suggest that FDG-PET imaging is a potential biomarker for the early identification of cognitive ageing and neurodegenerative disease. Indeed, there is a broader literature on FDG-PET in older adults beyond connectivity and in age-related diseases, such as Alzheimer's disease. FDG-PET is typically used to measure neuronal activity, specifically the local concentrations of radioactive tracer that is metabolically trapped in neurons or glial cells after being metabolised in glucose-6-phosphat, with the slope of the time-activity curve used to measure glucose metabolism (Herzog et al, 2019). Voxel-based analyses and semi-quantitative measures of FDG uptake can be used for the identification of specific patterns of glucose uptake and the "metabolic connectivity" of brain regions.

Before discussing the studies summarised Table 2, several considerations should be noted about their design. First, the use of FDG-PET has historically been limited by poor temporal resolution, with studies acquiring single images that index the rate of glucose uptake across the entire scan period. As such, most studies purporting to study "metabolic connectivity" have actually measured metabolic *covariance* across subjects. Metabolic covariance is a poor predictor of metabolic connectivity (Jamadar et al., 2021). To be comparable to "functional connectivity" measures, it is necessary to measure the time-course of FDG-PET activity across the scan for each individual subject, and then

correlate those time-courses across regions to form a connectome. Recent advances in FDG-PET data acquisition have made it possible to measure the time course of FDG uptake over the course of a scan (Villien et al., 2014; Hahn et al., 2016; Jamadar et al., 2019); and this 'fPET' method has been applied to characterise metabolic connectivity in younger adults (Li et al., 2020; Jamadar et al., 2020; Jamadar et al., 2021). We showed that metabolic connectivity yields correlated, but unique information, to fMRI-based measures of functional connectivity. To date, the high temporal resolution fPET approach has not been applied to study resting-state metabolic connectivity in ageing, so existing studies use a combination of metabolic covariance measures, or correlation of network properties estimated using fMRI with FDG-PET based measures of glucose uptake or the cerebral metabolic rate of glucose (CRM_{GLC}).

The second consideration is that although there is a clear correlation between FDG-PET signal and glucose consumption in the brain, the measured concentration of FDG uptake is not a direct measurement of the metabolic function (Berti et al., 2013). Absolute quantification of brain glucose utilisation is a more complex procedure that is able to provide fully quantitative estimates of CRM_{GLC} . In order to extract the biological measurement of interest, PET data need to be evaluated using a mathematical model that takes into account both the delivery of the tracer to the tissue and its subsequent fate in brain tissue (Berti et al., 2013). However, this quantitative approach was not undertaken and reported in all studies reported here.

A small literature was identified as part of the systematic review that specifically investigated resting-state network using FDG-PET in healthy ageing (see Table S7 for details). Due to differences in the metrics reported, drawing clear conclusions about metabolic connectivity in ageing from these studies is difficult and certainty in the results is *low* (Table 2). However, the nine studies, together with other select research investigating brain glucose, point to glucose as a key player in "normal" age-related brain functional network changes and as a promising avenue for further research.

The metabolic basis for changes in functional network covariance and segregation was examined in eight studies, suggesting age differences across the adult lifespan (Arnermann et al., 2018; Azari et al. 1992; Horwitz & Duara, 1986; Liu et al., 2014; Manza et al., 2020; Moeller et al., 1996; Trotta et al., 2016; Zuendorf et al., 2003). For example, older subjects display reduced metabolic covariance within most networks, together with a more heterogeneous pattern of high and low correlations between-networks (Liu et al., 2014; also see Azari et al., 1992). A strong correspondence has also been found between large-scale resting-state network connectivity and glucose network covariance in younger

and older adults (Bernier et al., 2017; Di et al., 2012; Li et al., 2020; Tomasi et al., 2013, Tomasi et al., 2017) and in animals (Amend et al., 2019). Varied networks measures, analytic and parcellation approaches used across the studies limits assessment of consistency of age effects (see Table S7 for details).

Research has demonstrated the existence of “small world” properties in metabolic functional brain networks (Hu et al., 2015; Zhang et al., 2011), including in older adults (Di et al., 2017). The correlation between glucose metabolism and local and global connectivity is especially high for hubs with high between network connectivity, indicating a topology optimised for maximal communication speed with minimal energy consumption (Tomasi et al., 2013). Network hubs have greater metabolic rates compared to non-hubs (Liang et al., 2013; Dai et al., 2015). Moreover, older adults show increased clustering and decreased efficiency of metabolic networks; which implies a degeneration process in which the brain shifts from small-world segregated networks to a more local and less distributed organisation with age (Arneman et al., 2018). Longitudinal changes in metabolic covariance have also been found amongst older adults (Di et al., 2019). The orbital frontal cortex and anterior temporal lobe showed a significant reduced metabolic activity in ageing, and causally influenced many other regions, which were widespread and included regions that did not show age-related reductions in metabolic activity.

Preserved brain glucose metabolism may be a mechanism underlying “reserve” theories of ageing. In other words, efficient metabolism is neuroprotective as it supports the brain with the necessary energy it needs to function, whereas impaired metabolism inhibits this normal brain function (Bastin et al., 2012; Strahan & Mattson, 2012; Yoshizawa et al., 2014). Kim et al. (2015) examined the mediating role of education on functional covariance using regional cerebral glucose metabolism rates ($rCRM_{GLC}$). The results showed that participants with higher education also had higher $rCRM_{GLC}$ in the regions responsible for memory and language. A lower education level was associated with higher $rCRM_{GLC}$ in motor and somatosensory areas. Graph theory analyses indicated that individuals with higher education were more efficient and displayed greater small-world characteristics, i.e., relatively local clustering with sparse between network connections. These results suggest that glucose metabolism is a likely mechanism mediating changes in functional connectivity across the lifespan and may also contribute to the “reserve” found in people with higher education.

In summary, although the literature on metabolic connectivity is relatively small, it points to glucose as a potentially central player in age-related changes in brain network function that may contribute to

age-related changes in cognitive performance. Specifically, metabolic brain networks appear to show strong coherence with fMRI networks, including “small world” properties, although additional research using graph metrics is needed. Further research is also needed to confirm that ageing is associated with metabolic “dedifferentiation” of large-scale networks, and that glucose metabolism is tied to network connectivity. Like fMRI studies, metabolic connectivity studies suggest that hub networks associated with higher order cognitive processes are most vulnerable to age-related alterations, although additional work is needed to fully elucidate these changes across large scale resting-state networks.

4. Discussion, Methodological Considerations and Future Research Directions

4.1 The Systematic Review Findings Largely Support Theories of Cognitive Ageing

The literature reviewed here is largely consistent with theories of cognitive ageing. A less segregated, less modular and less efficient network organisation among older adults may reflect *dedifferentiation* and *compensation*, underpinned by more diffuse, nonspecific recruitment of brain regions. Older age is also associated with a more lateralised and a poster-anterior shift in functional connectivity during rest in line with the HAROLD and PASA theories of cognitive ageing. These differences in older adults’ functional networks likely reflect impaired *coordination dynamics*, namely, the ability to access *metastable* states between integration and segregation, with reduced signal variability compromising this dynamic shift.

At least some of the differences in functional network connectivity and efficiency with age are likely driven by changes in anatomical connectivity and energy demands. Age-related functional changes are paralleled by grey and white matter changes that alter the *scaffolding* of the brain and reduce the capacity for global network integration and decrease global efficiency. Although the literature reviewed here does not relate functional connectivity to measures of *cognitive reserve* directly, it does suggest that some of the individual variability in cognitive functioning in older adults can be accounted for by a differential deployment of specific brain networks or that preserved glucose metabolism contributes to the “reserve” found in certain older adult cohorts (e.g., higher education, professional careers). Future research is needed to elucidate whether the relationships between functional connectivity and cognitive performance may be influenced by cognitive reserve.

4.2 Limitations of Cross-Sectional Studies

One of the limitations of the studies reviewed so far is their cross-sectional nature, with approximately half of the studies comparing younger and older adults cohorts only, and half analysing age as a

continuous variable across the adult lifespan. Cross-sectional studies are highly informative about age-related differences in resting state networks and their underlying neural correlates. However, because they are correlational in nature, they are less informative about the causal relationship between age-related brain changes in the ageing process and associated alterations to function. In other words, cross-sectional studies allow the examination of age-related *differences* in connectivity, not age-related *changes*. Drawing conclusions about causal pathways in ageing requires longitudinal and causal analyses, which were rarely undertaken in the research reviewed here.

There are also other considerations in the research designs of the studies reviewed, such as comparability of measures of brain activity obtained from different age groups, and the choice of the study populations (see Rugg, 2014 for review). Cross-sectional comparisons raise the possibility that differences found between study groups reflect underlying cohort differences rather than age-related changes. For example, perhaps differences between younger and older adults are due to generational differences in psychosocial experiences (younger adults experiences a developmental environment with substantial technological integration not experienced by the older generation in their youth), rather than differences related to ageing per se. Or perhaps age-related differences reflect different cognitive strategies employed by younger and older adults during tasks or at rest. Cross-sectional studies cannot rule out these alternative explanations of age-related differences in behaviour and brain connectivity.

The influence of variables that also correlate with age and age-related diseases may confound fMRI-based measures of connectivity. Older adults show greater individual variability in cortical thickness, vascular integrity, and undergo metabolic and haemodynamic changes which affect neurovascular coupling and the MR signal independently from its effects on cognition, brain activity, and connectivity (D'Esposito, 1999; Gazzaley & D'Esposito, 2003; Ward et al., 2020). Between-group differences in neurovascular coupling and fMRI signal intensity is an important confound in cross-sectional studies of connectivity in ageing, and great caution should be taken when comparing fMRI activity or connectivity between groups (Samanez-Larkin & D'Esposito, 2008; Ward et al., 2020).

4.2.1 Longitudinal Studies also Show Reduced Connectivity in Older Adults

Longitudinal studies address at least some of the potential cohort differences by tracking changes within-subjects over time. Longitudinal studies suggest the age-related changes in large-scale networks, such as the fronto-parietal, sensorimotor network and default mode network, occur in as little as two to four years in older adults (Chong et al., 2019; Li et al., 2020; Ng et al., 2016; Oschman

and Gawryluk, 2020; Staffaroni et al., 2018; Zonnervel et al., 2019), with the fronto-parietal changes associated with reduce processing speed (Malagurski et al., 2020). Global network segregation, integration, and module distinctiveness also decrease over a two year period in older adults (but not younger adults) particularly in the higher-order cognitive hubs of the cingulo-opercular, default mode, salience and ventral attention networks (Chong et al., 2019). The strength of long-range connections in the default mode and dorsal attention networks decrease 6% and 3% per decade of life, respectively (Tomasi & Volkow, 2012). The reduction was even more pronounced at 12% in the posterior cingulate and ventral precuneus. Taken together, these studies suggest that changes in the higher-order networks occur as part of the ageing process and are consistent with the reduced resting-state activity in these networks when comparing older and young adults reported earlier.

4.2.2. The Need for Additional Studies Across the Entire Adult Lifespan

It was noted earlier that some studies do not include middle-aged individuals, which means that full adult lifespan differences in functional connectivity cannot be characterised from their findings. For example, inverted U or quadratic trajectories of age-related changes likely have an inflection point in the fourth and fifth decade of life, however studies that compare young and old groups only cannot investigate these trajectories. This issue is most evident for the network measures where we assessed the strength of the evidence to be moderate to low (e.g. within-subject BOLD signal variability, lateralisation), as a smaller number of studies was available for review. Additional research across the adult lifespan is needed to investigate whether quadratic relationships exist between these network measures and age.

4.3 Resting-State Studies are Consistent with Task Studies, although both Remain Valuable

Although there is considerable overlap between resting-state networks and task-based networks, patterns of connectivity can have meaningful differences across a range of domains and task (Davis et al., 2017). Brain regions can also be involved in multiple domains, with different patterns of connectivity depending on the task, and can vary based on task difficulty or load (Antonenko & Flöel, 2013). This suggests that comparing and contrasting rest and task-based networks in ageing remains important for understanding the complex interplay of functional networks. In fact, to account for the complex network reorganisations and mechanisms in ageing and their behavioural relevance, it is still valuable to consider the structural, functional and metabolic properties at both rest and during task performance.

4.4 Potential Physiological Confounds

The physiological properties that underlie the BOLD hemodynamic response are known to change with age. Thus, measures of BOLD-fMRI activity and connectivity are potentially confounded by physiological changes in age that affect the signal but may not affect neuronal activity. Factors like changes in neurovascular coupling, vascular integrity, breathing, haemoglobin, and head movement impact BOLD signal changes with age (Geerligs et al., 2017; West et al., 2019; Samanez-Larkin & D'Esposito, 2008; Gazzaley & D'Esposito, 2005). The magnetic resonance relaxation rate that underlies the BOLD response is also influenced by the levels of haemoglobin in the blood, which also vary across the lifespan, affects measures of connectivity and its relationship with cognitive measures (Ward et al., 2020). Age-related decrements in global and regional cerebral blood flow impact the measurement of brain activity throughout the brain (Samanez-Larkin & D'Esposito, 2008), and estimates of connectivity (Galiano et al., 2020). These underlying changes in neurovascular coupling with ageing mean that group differences in BOLD measures alone cannot always be interpreted as changes in neural activity.

Simultaneous MRI-PET scanning has showed utility in demonstrating the presence of bioenergetic coupling between glucose utilisation and rapid transmission of neural information, with some initial research showing utility in ageing, and a broader literature demonstrating its reduction in mild cognitive impairment and AD (Marchitelli et al., 2018). This approach offers great promise for understanding metabolic and functional connectivity or dysconnectivity between brain regions across the ageing and disease spectrum. It also means that it is now possible to calculate region-to-region metabolic connectivity within individuals, which opens the possibility of using this metric more widely as a biomarker in ageing and neurodegenerative disease. To date, this emerging field has not examined brain metabolic connectivity across the lifespan.

Some studies have indicated that structural changes that occur in ageing, rather than functional connectivity organisation, may mediate at least some of the brain metabolic changes in ageing (Bullmore & Sporns 2012; Chételat et al., 2013; Curiati et al., 2011; Hedden et al., 2016). As further research is undertaken on metabolic connectivity in ageing, it will be important to control for the changes in brain volume that also occur with age.

4. 5 Research is Needed to Further Elucidate the Shared Pathways in Ageing and Disease

There is a large body of research looking at brain changes along the spectrum from cognitive ageing to dementia (Titov, 2017), as well as in vascular and metabolic disease states (Love & Miners, 2016).

This research suggests that ageing and disease processes likely overlap, differing in degree rather than in the underlying mechanisms (Cole et al., 2019). For example, there is an increased risk of cognitive decline and dementia related to hypoglycaemia, glycaemic control, metabolic syndrome and insulin resistance (Arvanitakis et al., 2016; Bello-Chavolla et al., 2019; Akintola & van Heemst, 2015; Ekblad et al., 2017). Vascular dysfunction is also an important and early event in neurodegenerative disease and is believed to be responsible for more than 50% of cases of dementia worldwide (Sweaney et al., 2019). It manifests as infarcts and microbleeds, changes in perivascular spaces, subcortical hyperintensities, lacunar ischaemic stroke and haemorrhagic strokes (Shi & Wardlaw, 2016). It is also believed that these factors act as mediators, moderators or even accelerators of age-related cognitive decline (Raz & Rodrigue, 2006).

Although there is a large body of epidemiological evidence linking metabolic and vascular health to ageing and disease, the relationship to functional connectivity is still in its infancy. Some imaging studies have shown that connectivity is altered in states of metabolic and vascular dysfunction (e.g. Beissels et al., 2014a, 2014b; Carnevale et al., 2020; Cui et al., 2014, 2016; Debette & Markus, 2010; Giorgio et al., 2020; Izzo & Guzzardi, 2019; Liu et al., 2020; Manschot et al., 2006; Moran et al., 2017; Musen et al., 2012; Quvenco et al., 2020; Reijmer et al., 2015; Sang et al., 2018; Spielberg et al., 2017; Viviano et al., 2017). Given the rising rates of chronic diseases that impact vascular and metabolism in the periphery and brain, such as obesity (Afshin et al., 2017) and diabetes (Tao et al., 2015), it is likely that future research in cognitive ageing may find an important role of peripheral factors, particularly as age itself is a key risk factor for these diseases. Moreover, many of these diseases sit along a spectrum from health to clinical dysfunction and hence understanding their influence on cognitive ageing may also allow them to be used as early markers for age-related structural and functional changes. Of course, the concepts in psychophysiology that underscore the relationship between central and peripheral systems are not new (see Fabiani, 2015 for a review). However, with the increasing availability of tools to measure network function, assessing the relationships between mechanisms known to affect the brain and to change with age and disease states, such as cerebral blood flow, hormonal status and metabolism, presents important avenues for further research.

5. Conclusions

The brain undergoes significant structural, functional and metabolic changes with age, with associated alterations in cognition and behaviour. During the early years of life, there is a rapid

organisation of functional brain networks. A further refinement of the functional networks then takes place until around the third and fourth decade of life. A multifaceted interplay of potentially harmful and compensatory changes can follow in ageing. Moreover, these changes can lead to a variety of expressions of cognition and behaviour, depending on the time, location and extent of the changes. The strength of connections, the topology by which regions are connected, and the efficiency of the connections are important determinants in the function of the brain networks and their potential impact of cognition and behaviour across the adult lifespan. When investigated across the whole brain at rest, the literature suggests with high certainty that older adults display lower within-network connectivity and higher between-network connectivity than younger adults. These changes begin to occur as early as the third or fourth decade of life, with the trajectory of alterations varying by network. Some networks may remain relatively stable (e.g., primary processing) and others may vary substantially (e.g., associative regions).

The typology of the connections of a functional network also dictates how age-related changes or damage impact the networks and their associated functions. The literature suggests with high certainty that older adults show a more segregated, more modular and less integrated system of networks than younger adults, presenting as diffuse and less specialised configurations of functional connections. A lower level of global and local network efficiency is also reported consistently in older adults compared to younger adults, particularly in the higher-order networks. Alterations to a “rich club” network hub, such as the executive control or the default mode networks, have a diffuse impact across the system by reducing the communication between brain regions, a prerequisite for efficient and effective higher order cognitive functions. Their importance may lie primarily in the between-network connectivity that support long-range connections. They are known for their key role in efficient brain-wide information processing, functional integration of diverse cognitive functions, and are vulnerable to ageing. These functional network changes are likely driving at least part of the changes often seen in ageing in higher-order cognitive processes.

Results with high certainty were found for dynamic between-network connectivity and a posterior-anterior shift in functional connectivity at rest. A relatively small resting-state literature also suggests with moderate certainty a reduction in hemisphere lateralisation in older age. On the other network measures reviewed, relatively consistent results were reported although certainty in the results is moderate to low due to smaller bodies of literature, various methods and fewer studies that include participants across the full adult lifespan. Studies assessing dynamic network connectivity found age

differences in all or some of the networks, both during and in the transitions between states, and occurring at a slower rate in older adults.

Functional networks based on glucose metabolism appear to show covariance differences across the adult lifespan, although the certainty of the evidence is low based on the available literature at this time. Nonetheless, metabolic brain networks have economical “small world” properties, and brain glucose metabolism is highly correlated with local and global connectivity, especially for hubs with high between-network connectivity. This and a broader literature on brain glucose suggests that it is a key contributor to age-related changes in connectivity and cognitive performance and warrants further study.

Simultaneous MR-PET measurements have also been used recently and shown underlying synchrony between hemodynamic processes and glucose uptake. Their high sensitivity and regional specificity offer promise for functional and multimodal brain imaging. To date, they have not been widely applied across ageing and cognitive decline and present a promising avenue for future research. There also appears to be a complex interaction between brain glucose, age and peripheral physiology, including cardiovascular and metabolic factors that are well documented in cognitive ageing, and for which age is a major risk factor. With a rise in these conditions in the global population, future research will also need to further characterise the role of these peripheral factors in cognitive ageing.

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