

Effects of aging on functional and structural brain connectivity[☆]

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ABSTRACT

Over the past decade there has been an enormous rise in the application of functional and structural connectivity approaches to explore the brain's intrinsic organization in healthy and clinical populations. The notion underlying the application of these approaches to study aging is that subtle age-related disruption of the brain's regional integrity and information flow across the brain, are expressed by age-related differences in functional and structural connectivity. In this review I will discuss recent advances in our understanding of how age affects our brain's intrinsic organization, and I will share my perspective on potential challenges and future directions of the field.

Introduction

Age-related differences in cognitive performance have been linked to differences in various magnetic resonance imaging (MRI) derived brain measures, such as regional grey matter volume and task-induced activation (Fjell et al., 2014; Kennedy and Raz, 2015). Since the introduction of functional and structural connectivity approaches (Biswal et al., 1995; Mori et al., 1999), MRI has also been used to assess age-related differences on a brain network level. A systems-level or network approach of brain structure and function provides an intuitive framework for understanding a complex dynamic system. Neural network theory suggests two fundamental features of brain function, namely functional segregation and functional integration (Sporns, 2013; Tononi et al., 1994). Functional segregation refers to highly clustered connectivity in clique-forming regions (also called modules or communities), and is defined as high connectivity among members (or nodes) of the modules and low connectivity with members of different modules. Functional integration refers to connections between modules that enable integration of information from different modules. For optimal network and cognitive function the balance between functional integration and functional segregation is essential (Sporns, 2013).

In this review I will discuss previous research that used MRI to study the effect of aging on brain networks in vivo, through functional connectivity measures derived from resting-state functional MRI and structural connectivity measures derived from diffusion MRI. I will furthermore address our current knowledge of the effect of age on the association between functional and structural brain networks, and

discuss current limitations and future directions. However, before starting the review of literature on the effect of age, I will first describe commonly used functional and structural brain network measures and their contribution to our current understanding of brain network organization.

Functional connectivity reflects the coherence between temporal fluctuations in the blood oxygen level dependent (BOLD) signal across brain regions. Functional connectivity measures are commonly derived from “resting state” functional MRI data, in which participants are not presented with a task but are asked to relax and let their mind wander, but can also be derived from task-evoked functional MRI (Smith et al., 2009). Functional connectivity studies have demonstrated a network organization in line with the functional segregation principle, i.e. multiple distinct functional connectivity networks, including default mode, executive control, attention, salience, sensorimotor, and visual networks (Damoiseaux et al., 2006; van den Heuvel et al., 2008; Zuo et al., 2010). The neural validity of resting state functional connectivity has been debated (Morcom and Fletcher, 2007), but comparisons of electrophysiological recordings and resting state functional MRI data provide support for a neural correlate of these connectivity patterns (Nir et al., 2008; Ossandón et al., 2011; Yuan et al., 2012).

Structural connectivity measures derived from diffusion MRI allow for in vivo tracking of white matter pathways. Diffusion imaging is based on the property of water molecules to more readily diffuse along the major axis of the fiber bundle than perpendicular to it (Moseley et al., 1990), allowing for estimation of fiber direction. Tractography approaches can be used to estimate structural pathways between brain regions, e.g. by calculating the number of streamlines or probability of

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connection (Jbabdi et al., 2015). Diffusion imaging is also used to estimate the integrity of tissue microstructure of pathways, most commonly by measures such as fractional anisotropy and mean diffusivity (Basser, 1995; Basser et al., 1994). These diffusion imaging measures have limitations, as pointed out by (Jones et al., 2013). Therefore, recent advances in diffusion imaging acquisition and analysis aim to improve estimates of tissue microstructure and fiber reconstruction (Raffelt et al., 2012; Wu et al., 2016; Zhang et al., 2012). Structural connectivity studies have shown that the brain has a structural core, with highly connected regions (hubs) (Hagmann et al., 2008) and that these hubs have a “rich club” organization, which indicates that they are more densely interconnected with each other than can be expected by chance (van den Heuvel et al., 2012; van den Heuvel and Sporns, 2011). The regions that are part of this structural core and rich club, namely the cingulate gyrus, cuneus, precuneus, superior frontal and parietal lobe, largely overlap with the regions of the default mode network (Cao et al., 2014; Stam, 2010; van den Heuvel et al., 2012). Therefore the default mode network may be important for facilitating functional integration, and changes in default mode connectivity may impact network function and cognitive function across multiple domains.

Effects of age on functional connectivity

Age related differences in functional connectivity based on cross-sectional research

Many studies have investigated the effect of age on functional brain connectivity by measuring differences within brain networks using either region of interest based correlations or data-driven techniques such as independent component analysis (ICA). Overall, the most consistent finding across all these studies is that older adults have lower functional connectivity between regions of the default mode network compared to younger adults, see (Dennis and Thompson, 2014; Ferreira and Busatto, 2013) for previous reviews on this topic. The default mode network is a set of brain regions including the posterior cingulate cortex, precuneus, medial prefrontal cortex, and lateral parietal cortex. These regions consistently show decreased activation compared to baseline during task performance (Raichle et al., 2001; Shulman et al., 1997) and strong functional connectivity during resting state functional MRI (Greicius et al., 2003). Default mode network activity is linked to various cognitive processes such as episodic memory, self-referential processing, and mind wandering (Buckner et al., 2008), and associations between lower default mode functional connectivity and worse performance on cognitive tasks of memory and executive function have been observed (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Wang et al., 2010). Age-related differences in functional connectivity have also been observed in other brain networks such as the dorsal attention, salience, and sensorimotor networks (Allen et al., 2011; Huang et al., 2015; Onoda et al., 2012; Tomasi and Volkow, 2012). However, to date none of these differences have been reported as consistently as those observed in the default mode network.

Over the past several years there has been a growing interest in the examination of age-related differences in between-network functional connectivity in addition to just within-network functional connectivity. For example, Spreng and colleagues (2016) examined age-related functional connectivity differences within and between default mode and dorsal attention networks. They found lower within-network functional connectivity and higher between-network functional connectivity in older adults compared to younger adults across multiple nodes of these two networks, see Fig. 1 (Spreng et al., 2016). Grady and colleagues (2016) observed a similar result of less within- and more between-network connectivity in older compared to younger adults. Out of three brain networks examined (i.e. default mode, dorsal attention, and frontoparietal networks), the default mode network

showed less within-network functional connectivity in older adults, while the frontoparietal network showed more between-network connectivity in older compared to younger adults. These two networks also showed an effect of age on network segregation (a measure of between-network correlations relative to within-network correlations described by Chan and colleagues (2014)), with older adults showing lower segregation than younger adults. No age effects were found for the dorsal attention network (Grady et al., 2016).

Whole brain approaches such as graph theory have also been applied to examine age-related differences in brain network features. In graph theory a network is defined as a set of nodes with edges between them and multiple measures can be calculated within this framework to assess specific network features. Some commonly used measures include: *modularity*: the extent to which the entire brain graph can be divided into modules/clusters; *global efficiency*: the inverse of the average shortest path length between nodes in the entire network; and *local efficiency*: the inverse of the average shortest path length between all nearest neighbors of a node. See (Bullmore and Sporns, 2009) for a review on graph theoretical analysis of structural and functional brain networks in healthy adults. Using a graph theoretical approach, Chan and colleagues (2014) determined whole brain functional connectivity and found that older age was associated with lower within network and higher between network functional connectivity. This was observed when collapsing all networks together but also among the individual networks, suggesting this pattern is not limited to specific networks but generalizable across systems. Furthermore, they showed that older age was associated with lower network segregation measured as between-network correlations relative to within-network correlations (Chan et al., 2014).

Two other studies (Cao et al., 2014; Geerligs et al., 2015) applied whole brain graph theoretical approaches to determine modularity and global and local efficiency. Both studies found lower modularity in older compared to younger adults. In addition, the Geerligs study found lower local efficiency in their older adult group compared to their younger group. The Cao study examined age as a continuous variable in a lifespan sample and found that differences in local efficiency across the lifespan followed an inverted U-shape trajectory, with lower local efficiency in children and older adults compared to younger adults. No differences in global efficiency were observed in either study. It is not surprising that both modularity and local efficiency showed the same effect (i.e. lower in older adults) as these two measures tend to be related; a system with denser local connections tends to be more modular. These findings are in line with the earlier discussed observations of lower network segregation in older compared to younger adults (Chan et al., 2014; Spreng et al., 2016). The network segregation measure used by Chan and colleagues (2014) resembles the graph theoretical participation coefficient, which measures the proportion of inter- and intra-network connections of a local network. Geerligs and colleagues (2015) examined the effect of age on the participation coefficient for each of their five large networks and found a higher participation coefficient in the visual and somatomotor networks in older compared to younger adults, i.e. a larger proportion of network nodes were connected with nodes outside than inside the network for older adults.

Overall, functional connectivity studies seem to largely converge on the observation of lower within- and higher between-network connectivity in older compared to younger adults. In addition older adults also seem to have lower network segregation, lower modularity and lower local efficiency. These findings suggest that older age affects functional network integration and segregation, and possibly also the balance between the two.

Seemingly contradictory to this finding of lower network segregation with older age is the observed effect of age on anatomical distance of connections by Cao and colleagues. In the same study as described above they report that the proportion of short-distance connections was higher with older age while the proportion of long-distance

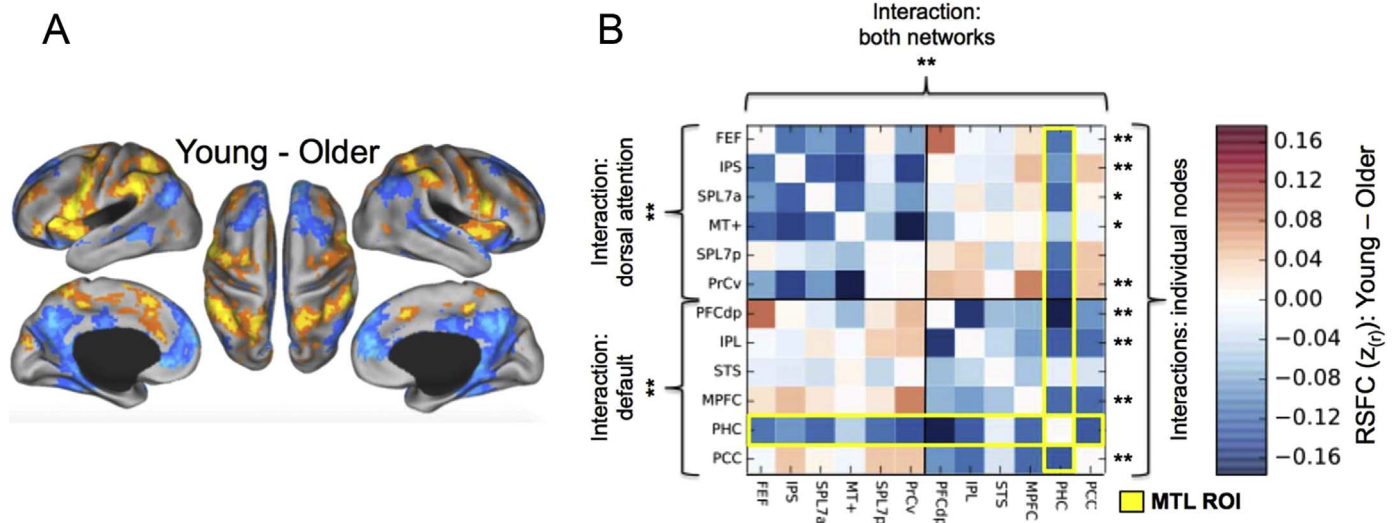


Fig. 1. Resting state functional connectivity differences between younger and older adults. (A) Functional connectivity of the posterior cingulate cortex. In older adults, the posterior cingulate cortex shows reduced functional connectivity with other regions of the default network (cool colors), but increased functional connectivity with regions of the dorsal attention network (warm colors), relative to young adults. $p < 0.05$; FDR corrected. (B) Contrasting the full correlation matrix of all regions of the default and dorsal attention networks for young vs. older adults demonstrates reduced (cool colors) within-network functional connectivity of both the default and dorsal attention networks, and increased (warm colors) between-network functional connectivity in older adults. Significant age (young vs. older) \times differentiation (within- vs. between-network functional connectivity) interactions were observed for functional connectivity when collapsed across both networks (top), for each network individually (left), and for the majority of individual regions of both networks (right). The medial temporal lobe (parahippocampal cortex; yellow outline) showed reduced functional connectivity with all other regions across both networks in older relative to young adults. ** significant crossover interaction; * significant interaction. Reprinted from Spreng et al. (2016), with permission from Elsevier.

connections was lower. This apparent increased sensitivity of long-distance connections to age is also implied by the findings of Sala-Llloch and colleagues (2014) who found higher average clustering and higher shortest path length with older age (Sala-Llloch et al., 2014). Even though these results appear contradictory the applied measures reflect different features of network organization and efficiency, therefore the Cao study was able to find both results in the same dataset. Future research may elucidate the relationship between anatomical distance, functional integration, functional segregation and network efficiency.

Whole brain or network approaches provide general network measures, and therefore do not always capture the different weights of nodes within the whole brain network structure. For example they do not take into account whether certain nodes are part of the structural core or “rich club”. Cao and colleagues examined rich club organization of functional brain networks and found that it is affected by age: showing an inverted U-shape pattern of a lower rich club

coefficient in children and older adults and a maximum rich club coefficient around 40 years of age, see Fig. 2 (Cao et al., 2014). This age-related difference in rich-club organization suggests an increase in network efficiency during development and early adulthood, and a decrease in efficiency with older age.

Functional connectivity changes in older adults derived from longitudinal research

The few longitudinal studies that investigated changes in functional connectivity in healthy older adults show mixed results. For example, Persson and colleagues (2014) did not find any longitudinal functional connectivity changes within the default mode network in older adults (Persson et al., 2014). It must be noted, though, that their functional connectivity measurements were derived from task-based and not resting state functional MRI data. Contrary to this null result, Ng and colleagues (2016) did find an age-related decline in functional

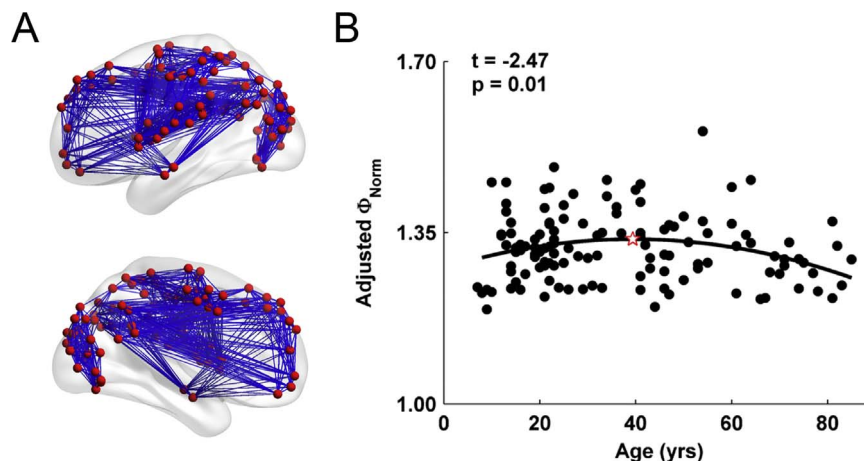


Fig. 2. The functional connectome's rich-club organization and its lifespan trajectories. (A) The rich-club origination of the group-averaged connectome. The red dots represent the hub regions, and the blue lines represent the connections between them. (B) Age-related change in the normalized rich-club coefficient. The dark dots represent the adjusted results of each subject after regressing out sex, head motion and data quality effects. The curve fits are shown by the dark lines; the red pentagram represents the peak age. Reprinted from Cao et al. (2014), with permission from Elsevier.

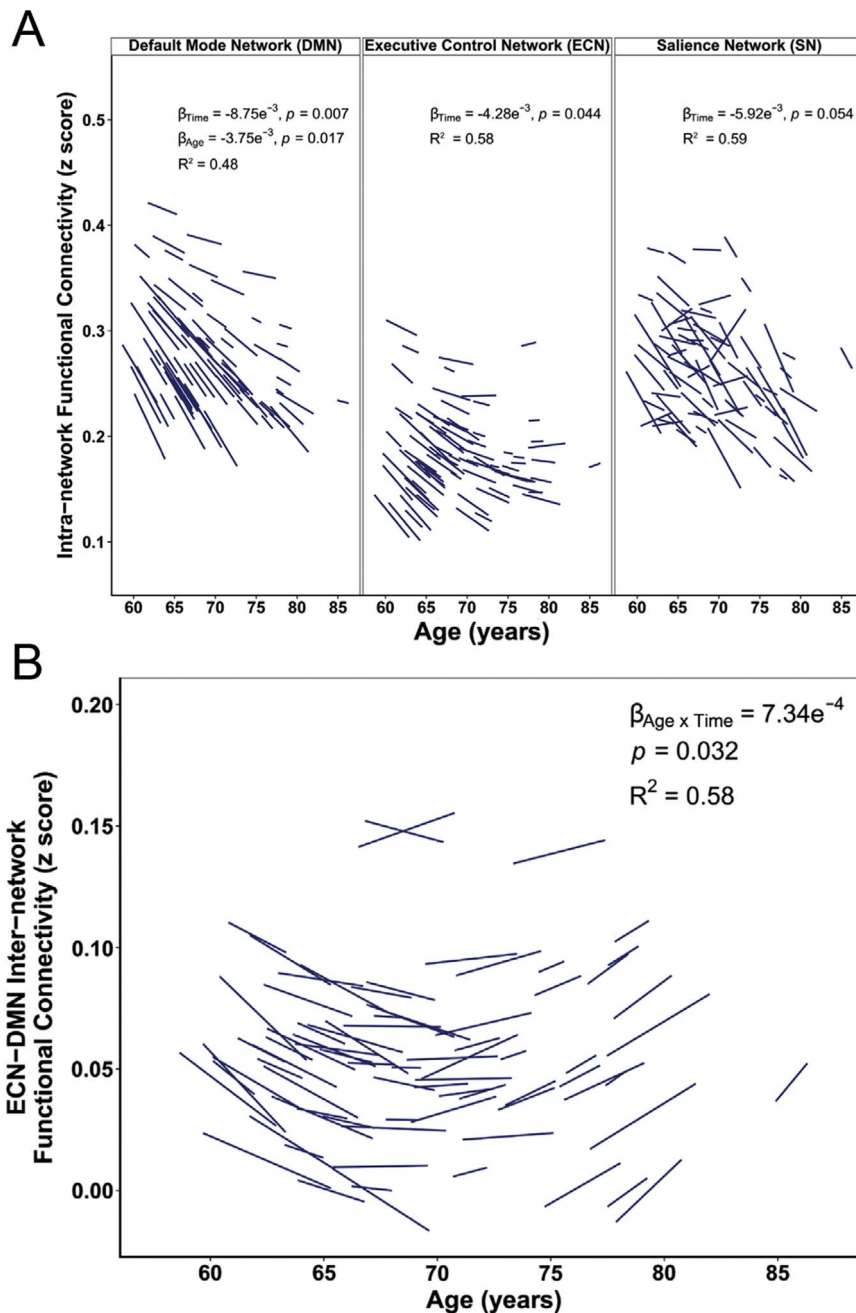


Fig. 3. Longitudinal changes in resting state functional connectivity in older adults. (A) Intra-network functional connectivity decreased with ageing. Spaghetti plots of the model-fitted longitudinal functional connectivity changes for each individual. Both default mode and executive control networks evidenced longitudinal decline in functional connectivity with ageing. Such decline was marginally significant in the salience network. Additionally, default mode functional connectivity showed a significant effect of age. (B) Age-dependent changes in inter-network functional connectivity between default mode network and executive control network with ageing. Spaghetti plot of the model-fitted longitudinal functional connectivity changes for each individual. Between-network functional connectivity involving the executive control and default mode networks showed a u-shaped trajectory whereby functional coupling between these networks initially decreased over time and later increased as with older participants. Reprinted from Ng et al. (2016), with permission from Elsevier.

connectivity within two networks of interest (the executive control and default mode networks) when evaluating changes in within and between network functional connectivity in healthy older adults over the span of 4 years (2–3 time points) using resting state functional MRI (see Fig. 3A). In addition, they found a u-shaped trajectory of age-related functional connectivity changes between executive control and default mode networks, showing an initial decrease in between-network functional connectivity followed by a subsequent increase as participants aged, see Fig. 3B (Ng et al., 2016).

This pattern of an initial decrease and subsequent increase in between-network connectivity may signify a similar process as the previously observed initial increase and subsequent decrease of within-

network default mode functional connectivity in participants on the Alzheimer's disease spectrum (Bai et al., 2011; Damoiseaux et al., 2012). These initial opposing functional connectivity changes could reflect a compensatory or over-recruitment mechanism, an initial strategy unable to be maintained over time, analogous to the proposed explanation for increased task activation in older adults in the extant task-based fMRI literature, see (Grady, 2012) for a discussion on this topic. If this pattern reflects a general mechanism of change in brain function this potentially explains some of the inconsistencies in the literature. Depending on where on the trajectory of change an individual's brain is, either higher or lower brain function compared to an earlier time-point (or younger individual in a cross-sectional

comparison) will be observed. More longitudinal studies spanning a larger time frame and multiple time-points are needed to confirm that age-related changes in brain function (i) follow this pattern of initial opposing changes in brain function, and (ii) align with the observed age differences from cross-sectional research.

Association between changes in cognitive function and changes in functional connectivity

Because most functional connectivity measures are derived from resting state functional MRI, there is no concurrent measure of cognitive function. A question that remains therefore is whether the observed age-related differences/changes in functional connectivity are associated with the well-established age-related decline in cognitive performance (Craink and Salthouse, 2011; Salthouse, 2010). Most cross-sectional studies published to date, but not all (Damoiseaux et al., 2016), found significant associations between cognitive performance and functional brain connectivity independent of age, such that participants with lower functional connectivity measures also have lower cognitive performance (Chan et al., 2014; Damoiseaux et al., 2008; Wang et al., 2010). How meaningful these findings are and how well they reflect age-related change remains to be determined as these type of analyses are limited by the well-known problem of cross-sectional mediation, see Hofer and Sliwinski (2001), Lindenberger et al. (2011), Lindenberger and Pötter (1998) for discussions. The commonality between age, brain measures and cognitive performance is too strong to allow a meaningful representation of age-related dynamics (Raz and Lindenberger, 2011; Salthouse, 2011). Longitudinal designs are a solution for this problem and allow examination of the relationship between brain measures and cognitive performance independent of age.

A study by Bernard and colleagues (2015) examined functional connectivity differences between memory decliners and non-decliners, where group membership was determined based on longitudinal measurements of memory performance. They found decreased functional connectivity in the default mode network, specifically between posterior cingulate cortex and parietal areas, in decliners compared to non-decliners (Bernard et al., 2015). A longitudinal study, examining older adults scanned twice with a 6-year interval, found a correlation (although only at an uncorrected statistical threshold) between change in default mode functional connectivity and change in recognition memory (Persson et al., 2014), suggesting that individuals with the largest reduction in default mode functional connectivity over time also had the largest decline in memory performance. Two other studies, including young, middle age and older adults followed for 3.3 years, found that decreased functional connectivity between sub-cortical (hippocampus, putamen and caudate) and cortical brain regions was related to decreased memory performance (Fjell et al., 2016b), and that decreased functional connectivity between putamen and cortical regions was related to decreased performance on a task of executive

control (Fjell et al., 2016a).

The largely consistent reports of an association between functional connectivity changes and changes in cognitive performance suggest that these brain changes may underlie the well-established age-related cognitive decline. In addition, they motivate further examination of functional connectivity as an early indicator of subsequent cognitive decline.

Effects of age on structural connectivity

The literature on age-related differences in structural connectivity is not as abundant as that on functional connectivity, but the observed results are largely consistent. Two studies that examined voxel-wise differences across a white matter skeleton both revealed relatively wide-spread decreases in fractional anisotropy in older compared to younger adults (Burzynska et al., 2010; Damoiseaux et al., 2009). Other studies that examined the organization of the brain into structural connectivity networks confirmed age-related differences in white matter connections. For example, Gong and colleagues (2009) estimated the probability of anatomical connections between the regions of the automated anatomical labeling template (Tzourio-Mazoyer et al., 2002) by using probabilistic tractography. This approach estimates the underlying fiber tract direction for all voxels between two regions of interest and calculates the probability of a connection between these regions (Behrens et al., 2007, 2003). They then used these measures to calculate graph theoretical indices such as local and global efficiency, and determined age-related differences across an adult life span sample. They found overall lower connectivity (i.e. higher network cost) and lower local efficiency with older age, but no differences in global efficiency (Gong et al., 2009).

Another study examined differences in diffusion based structural connectivity, defined as the number of interconnecting streamlines between two regions as the weights of the network edges, in a lifespan sample (Zhao et al., 2015). Their findings show an inverted U-shape trajectory for the association of local and global efficiency with age, and an U-shape trajectory for shortest path length and clustering coefficient. They did not find a significant effect of age on modularity but did observe a non-linear effect of age on connectivity within and between modules indicating lower connectivity in older adults. They also examined the networks rich club organization and found lower rich club organization in older adults, see Fig. 4. For adults aged 70 and older, this effect was mainly located in frontal brain regions (Zhao et al., 2015).

The pattern of age-related differences in structural network metrics, as shown by these two studies and others (Otte et al., 2015), is similar to the pattern observed in functional connectivity studies (see Section “Effects of age on functional connectivity”). The similar age-related trajectories between structural and functional connectivity may imply an association between structural and functional brain changes.

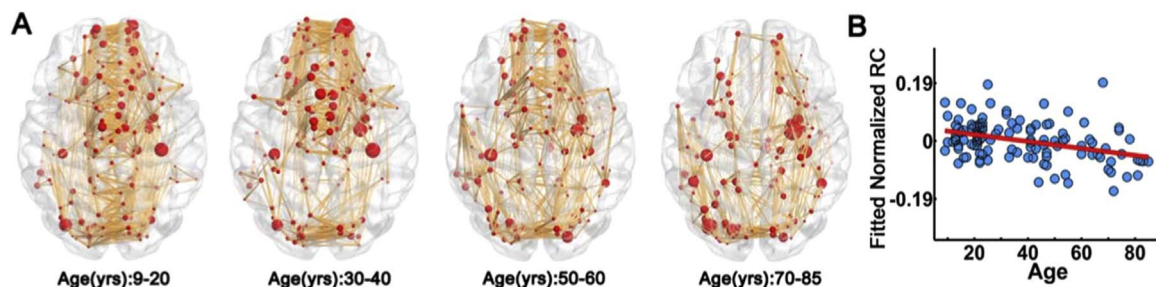


Fig. 4. The structural connectome's rich-club organization and its lifespan trajectories. (A) The rich-club organization of different age subgroups. The red nodes represent the hub regions with mean Z-scores of the nodal strength as nodal size. The orange lines represent the white matter connections between hub regions identified from the average matrix of different subgroups. (B) Lifespan trajectory of normalized rich-club with age. The blue dots represent the adjusted values after controlling for gender and brain size. Reprinted from Zhao et al. (2015), with permission from John Wiley and Sons.

Association between functional and structural connectivity in the aging brain

The extant literature suggests an association between structural and functional connectivity measures, and indeed previous work shows an association between functional and structural connectivity in an older adult population (Andrews-Hanna et al., 2007). However, strong functional connectivity between brain regions can exist in the absence of strong structural connectivity (Damoiseaux and Greicius, 2009; Zimmermann et al., 2016), possibly because of indirect structural connections. Several studies that assessed age-related structural and functional connectivity differences in the same dataset found that functional and structural connectivity are closely aligned and that they are both affected by age (Betzel et al., 2014; Fjell et al., 2016b; Zimmermann et al., 2016). Fjell and colleagues (2016b) examined the relationship between changes in subcortical to cortical functional connectivity and changes in structural connectivity, and found that in older adults a larger change in caudate functional connectivity was associated with a larger change in mean diffusivity of the cingulum bundle.

Betzel and colleagues (2014), who used the same dataset as a previously discussed study (Cao et al., 2014), found lower within- and higher between-network functional connectivity, and lower modularity in older adults. Their structural connectivity examination revealed a linear decrease with older age in both number of connections and total fiber count. When they combined measures of functional and structural connectivity they found that the relationship between age and functional connectivity depends on the path length of the connected nodes. The magnitude of the correlation between age and functional connectivity increased with increasing path length. This aligns with the observed higher between-network functional connectivity in older adults as the path length between nodes is likely greater between networks. It could also potentially explain the previously observed higher shortest path length for functional and structural connections in older adults (Sala-Llonch et al., 2014; Zhao et al., 2015).

Zimmerman and colleagues (2016) examined the effect of age on functional and structural connectivity and the correlation between the two in an adult life-span sample. They found lower functional and structural connectivity, and lower functional-structural correlation with older age across most parts of the brain. In an additional analysis the authors examined the within-module density index for each region, which measures how a region's functional network structure is related to its structural connectivity. They found that highly connected regions (i.e. hubs, including default mode areas) have a higher within-module density index in older compared to younger adults. Other regions, e.g. lateral occipital cortex and lingual gyrus, showed the opposite effect, i.e. lower within-module density index in older compared to younger adults (Zimmermann et al., 2016). This result seems to suggest more within-network connectivity in hub regions in older compared to younger adults. This is somewhat contradictory to findings from functional connectivity studies that find less within-network connectivity (Chan et al., 2014; Grady et al., 2016). Some of this discrepancy may possibly be explained by the relatively small sample size and the specificity of the effect to hub regions in the Zimmerman study compared to global network measures in the other studies. However, less within- and more between-network connectivity has also been observed specifically in the default mode network, which encompasses many of these hubs (Spreng et al., 2016).

Although most studies report an association between functional connectivity and structural connectivity not all do. Hirsiger and colleagues (2015) found a significant effect of age on structural connectivity of the cingulum bundle, but not on functional connectivity between the posterior cingulate and medial prefrontal cortex. Furthermore, they observed no significant relationship between functional connectivity and structural connectivity (Hirsiger et al., 2015). A possible explanation for this discrepancy is that this study examined

structural connectivity and functional connectivity of a specific area of the brain, whereas most other studies included the entire brain. In addition the age range of participants (64–85 years of age) was narrower than in most other studies. Another possible explanation could be related to unexplained variability across participants in other age-related brain health measures. For example, similar to the Hirsiger (2015) study, Reijmer and colleagues (2015) examined structural connectivity of the cingulum bundle and functional connectivity of the posterior cingulate and medial prefrontal cortex in clinically normal older adults. In addition they assessed the amount of white matter hyperintensities, which are high intensity areas on T2 weighted magnetic resonance images that are considered to reflect ischemic damage or demyelination (Fazekas et al., 1993). They found that structural and functional connectivity was significantly associated in older adults with low white matter hyperintensity burden, but not in those with high burden. Furthermore, among the adults with high white matter hyperintensity burden, a greater difference between structural and functional connectivity was related to worse performance on tasks of memory and executive function (Reijmer et al., 2015). This difference in the association of structural and functional connectivity was specific for the cingulum bundle and was not observed for the right inferior longitudinal fasciculus. Another study that examined structural connectivity of the fornix and functional connectivity between the hippocampus and thalamus revealed a significant association between functional and structural connectivity in healthy older adults but not in people with amnesic mild cognitive impairment (a well-established risk factor for Alzheimer's disease (Petersen, 2004)) (Kehoe et al., 2015). These examples indicate that inconsistencies in the healthy aging literature may be partially due to inclusion of pre-clinical populations, and thereby highlight the importance of early detection of age-related neurological disorders.

Current challenges and future directions

Cross-sectional versus longitudinal research designs

Just as in other research fields the vast majority of research findings in cognitive neuroscience are derived from cross-sectional studies. Cross-sectional designs evidently have some practical benefits, they are faster and more economical to complete than longitudinal designs. Nevertheless, the inherent limitations are particularly worrisome when applied to aging research. For one, age-related changes per definition cannot be measured with a cross-sectional design; only longitudinal studies can measure change. Also, cohort and period effects hinder interpretation of differences between age groups. Moreover, as mentioned in Sub-section “Association between changes in cognitive function and changes in functional connectivity”, the association between age, brain measures and cognitive function cannot be adequately examined as these type of analyses suffer from the problem of cross-sectional mediation (Hofer and Sliwinski, 2001; Lindenberger et al., 2011; Lindenberger and Pötter, 1998). Longitudinal designs minimize these problems and allow examination of age-related changes and the association between brain measures and cognitive performance independent of age. Longitudinal studies also enable determination of the order of certain age-related changes, which may help elucidate causal relationships between these changes, e.g. to establish whether changes in brain structure precede changes in brain function and cognition or the other way around. It is difficult if not impossible to imply directionality between these measures from cross-sectional studies. Determining directionality is important for early detection of age-related brain changes and adequately targeting possible interventions. Longitudinal studies are essential to verify the observed age differences in functional and structural connectivity from cross-sectional studies, and to clarify possible directionality between structural and functional connectivity differences and cognitive decline.

Whole brain approaches versus specific brain systems

As illustrated in this review, many of the recent studies examining the effect of age on functional brain connectivity used whole brain measures. While these measures provide great insight into network organization and reorganization over the lifespan, they may not always be the most sensitive approach to detect subtle differences or changes in specific brain connections. This could be especially important when investigating early onset of age-related diseases. There is evidence that specific neurodegenerative disorders affect specific brain networks (Seeley et al., 2009). Examining these specific networks in detail and incorporating knowledge from anatomical projections between brain regions may be necessary for early disease detection. Therefore, in addition to whole brain approaches specific hypothesis driven research is important to increase our understanding of age and disease related brain changes.

Whole brain parcellation and network membership

A current challenge of network analyses relates to the potential differences between network measures obtained using different parcellation and clustering schemes. It makes sense that the specific definition of network structure in a dataset will affect the network indices extracted from this data. Across the published studies multiple different parcellation and/or clustering approaches are used. These approaches differ in number of parcels or nodes (ranging from 2 to 4 digit numbers) and the number of clusters/networks defined. Furthermore, several studies used templates based on previously published parcellation and clustering schemes, e.g. from (Power et al., 2011; Yeo et al., 2011), while others used data-specific schemes. Even though some studies report consistent results between parcellation and/or clustering approaches (Cao et al., 2014), these comparisons are not exhaustive. There is currently no consensus on what the canonical network organization would be, or if there should be one altogether. Either way, more clarity on the effects of network definition on network measures is especially important when studying aging as network definitions may shift throughout the lifespan and thereby limit comparisons across age. Future work on the consistency of network measures across parcellation/clustering approaches and across the lifespan is needed to properly address this concern.

Multi-modal brain imaging

Another avenue for future research is to combine measures derived from different imaging techniques. Here we have discussed the direct comparison of functional connectivity derived from resting state functional MRI data with diffusion based structural connectivity measures. Other measures, such as grey matter volume and white matter hyperintensities that are known to change with age, may or may not affect brain connectivity. For example, it is rather commonly assumed that grey matter volume of a region can affect its functional connectivity. A plausible rationale for this may be that grey matter volume loss could result in contamination of voxels with cerebrospinal fluid, which would lower the voxels' temporal signal to noise ratio (Bodurka et al., 2005) and affect derived functional connectivity measures. Many studies include grey matter volume or density as a regressor in their analyses; however, such a relationship may not exist. Multiple studies examined grey matter volume and functional connectivity but did not find any evidence of an association (Damoiseaux et al., 2016; Fjell et al., 2016b; Persson et al., 2014). Increasing our understanding of the interactions of multiple brain indices will allow for a more sensitive assessment of age and disease related changes in brain structure and function.

Advances in image acquisition and analysis

Ongoing advances in image acquisition and analysis will continue to improve functional and structural connectivity measures. Higher field strengths, stronger magnetic gradients, and the application of multi-band accelerated echo planar imaging are just a few developments that have resulted in increased spatial and temporal resolution allowing for more sophisticated analysis techniques that better represent the brain's anatomy and functional dynamics, see (Smith et al., 2013; Sotiropoulos et al., 2013; Ugurbil et al., 2013). Examples of more sophisticated analyses enabled by the advances in image acquisition are the examination of functional connectivity dynamics at a sub-second resolution (Zalesky et al., 2014), and the examination of neurite orientation dispersion and density using diffusion imaging (Zhang et al., 2012). Recent advances also allow for decreased acquisition times of MRI sequences, which facilitate the application of these sophisticated methods to either older or clinical populations, which was previously challenging to achieve.

Conclusion

The existing literature suggests that our brain's functional and structural connectivity patterns change with older age. The observed differences/changes seem to particularly affect the default mode network, resulting in lower within-network connectivity in older adults. Furthermore, this decreased functional connectivity in older adults appears to be related to cognitive decline. Results from whole brain analyses suggest a central role for default mode regions in our brain system, as key members of the brain's "rich club". This "rich club" organization appears lower in older adults, possibly reflecting lower network efficiency and differences in brain dynamics. Network approaches also indicate a whole brain network-wide pattern of age-related functional and structural connectivity differences/changes, revealing lower within- and higher between-network connectivity and less system segregation in older adults. Overall, structural and functional connectivity seem to be strongly associated and similarly affected by older age. Network analyses have contributed to an increased understanding of age-related brain changes, but some important inconsistencies and challenges remain. Future research can address some of these issues by increasing the number of longitudinal studies, examining the effect of network definition on network measures, and comparing multiple brain indices within the same dataset.

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