

# Functional connectivity in aging

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### General introduction and outline of chapter

A large body of research shows that aging is accompanied by localized changes in brain structure and function. However, over the past decade the neuroimaging community has begun to recognize the importance of investigating the brain as a network. Brain regions don't function independently, rather they form an expansive

network that allows for communication between distant areas and enables complex cognitive functioning. Hence, age-related changes in the network structure might explain changes in cognitive functioning.

Characterizing this network by investigating the brain's functional connectivity has enabled new insights into brain organization. In this chapter, we will outline how the brain's functional connectivity is related to age and

how age-related differences in functional connectivity relate to age-related differences in cognitive functioning. We will address how neurodegenerative pathology influences functional connectivity and how, based on these measurements, biomarkers for clinical outcome might be developed in the future.

### Functional connectivity

Over the past decade, functional connectivity has emerged as a dominant MRI-based method for investigating human brain organization. The term was first introduced to the neuroimaging literature in an effort to clarify the various forms that connectivity could take. Unlike “structural connectivity,” referring to the anatomical paths between brain regions, and “effective connectivity,” referring to the causal influence of one region on the function of another, “functional connectivity” refers to a temporal relationship between the activity of two regions (Friston, 1994). For example, in the performance of a behavioral task such as finger tapping, regions whose activity covaries during tapping are described as functionally connected with one another. The observation that brain regions involved in the performance of a task are also correlated in their ongoing spontaneous activity, even during the baseline, resting state (Biswal, Yetkin, Haughton, & Hyde, 1995), has given rise to the methodology that is at the heart of this chapter.

Resting-state functional magnetic resonance imaging (fMRI) refers to the study of ongoing, spontaneous brain activity that is always present, but more easily studied when research participants are simply asked to relax in the MRI scanner and not do anything in particular. The field emerged from two distinct lines of research in the late-1990s, leading to substantial confusion regarding terminology that merits clarification at the outset. One line of inquiry was the aforementioned study of spontaneous brain activity, and the observation that regions involved in the same functional systems are correlated in their intrinsic activity at rest, referred to as “resting-state networks” (Beckmann, DeLuca, Devlin, & Smith, 2005; Damoiseaux et al., 2006; De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006) (see Fig. 3.1).

The other line of research addresses a set of brain regions that are more active during the baseline, “resting,” or “default” state than they are during task performance (Raichle et al., 2001; Shulman et al., 1997). These regions subsequently became known as the “default mode network” (Greicius, Krasnow, Reiss, & Menon, 2003), which is one of several “resting-state networks” (see Fig. 3.1),

and like all resting-state networks, it also exhibits characteristic activation patterns in response to task demands. In the case of the default mode network (DMN), one of its defining features is a consistent decrease in activity during goal-oriented externally demanding tasks.

### The default mode network

The DMN is a network of great interest to both cognitive and clinical neuroscience because of its involvement across a wide range of psychiatric and neurologic disorders as well as its distinct functional properties. As mentioned before, early studies described this network as a set of regions that showed more activity when research participants viewed a blank screen or fixation cross as compared to performing a cognitively demanding task—known as “task-related deactivation” (Raichle et al., 2001). In addition, regions of the DMN also demonstrate significant functional connectivity with each other (Greicius et al., 2003). There are different definitions of regions that are included in the DMN, however, the canonical regions that are robustly found in many different contexts include frontal (medial prefrontal cortex) and posterior (posterior cingulate cortex, precuneus) midline regions, and the lateral parietal cortex (see Fig. 3.1).

These initial findings led to the conclusion that the DMN represents a neutral, baseline, or “default mode” of brain function. Later studies further investigating its specific functional role linked DMN-regions to spontaneous cognition (daydreaming, mind wandering, self-referential processing, introspection) (Andrews-Hanna, Smallwood, & Spreng, 2014), and learning and memory (Daselaar et al., 2009). Beyond these involvements, the DMN is assumed to have a fundamental role in brain function. This is demonstrated by the fact that the DMN can be found in nonhuman animals like rats (Lu et al., 2012) and monkeys (Vincent et al., 2007). Furthermore, DMN also is visible during states of consciousness without spontaneous cognition, for instance, anesthesia (Greicius et al., 2008). It is assumed that DMN regions serve as hubs that integrate information from the entire brain network (Greicius et al., 2008; Raichle, 2015).

### Functional connectivity in aging

#### Within-network connectivity

Regions within the DMN become less functionally connected with age. This finding has been replicated across numerous studies using different methods. For

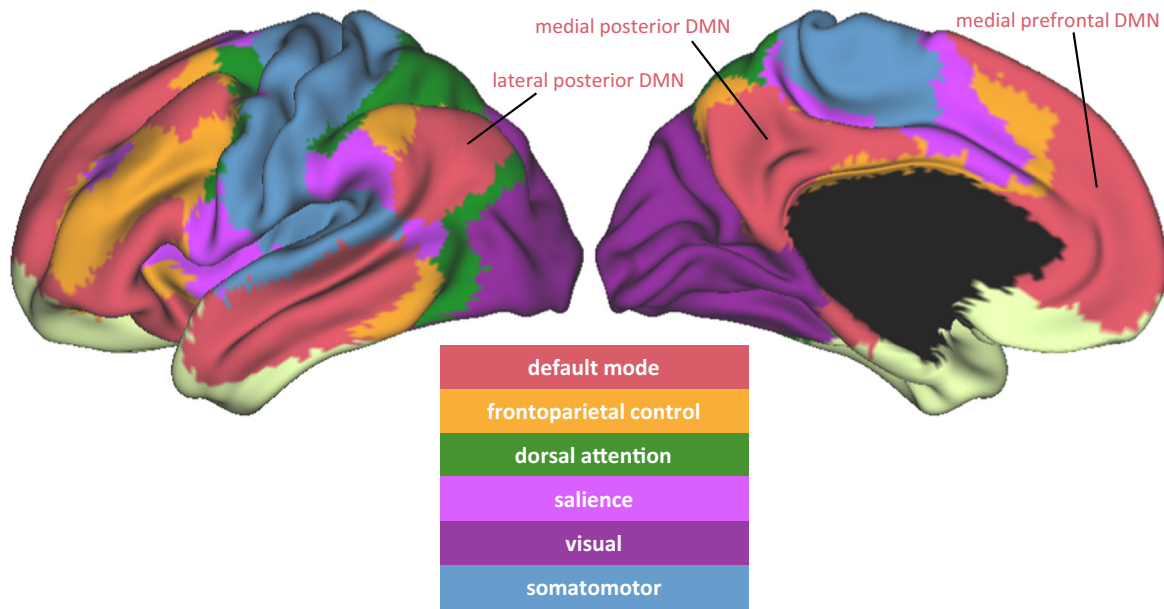


FIGURE 3.1 Aging-relevant canonical resting-state networks according to Yeo et al. (2011) rendered on the surface of the left cortical hemisphere. Left: lateral view; right medial view. Prominent default mode network-regions are highlighted.

instance, Andrews-Hanna et al. (2007) investigated age-related differences in the DMN by comparing a group of young adults and cognitively healthy older adults. Using a seed-based approach they quantified the connectivity between DMN seed regions and found that functional connectivity between most regions is significantly lower in older subjects. In an independent study, using a very different methodological approach, independent component analysis, Damoiseaux et al. (2008) compared DMN-connectivity for similar groups of subjects. They found two DMN components, one with a focus on posterior midline and lateral regions, one with a more anterior focus. The older group showed lower connectivity than the younger group in both components. Lower DMN functional connectivity in older subjects has been replicated in other cross-sectional group studies as well (Geerligs, Renken, Saliassi, Maurits, & Lorist, 2015; Grady, Sarraf, Saverino, & Campbell, 2016). Furthermore, the robustness of these findings was corroborated by a recent meta-analysis that aggregated data from 30 independent studies (Mak et al., 2017).

Age-effects in DMN connectivity have been shown not only in cross-sectional but also in longitudinal datasets, demonstrating changes in the connectivity of individual brains over time—known as “within-person” effects. Cross-sectional research designs aim to extrapolate from between-person effects to within-person effects, which is problematic (as discussed in more detail in the “Limitations” section). Therefore longitudinal research

designs can give unique insight into true within-subject change of functional connectivity. To date, only a few longitudinal studies investigate effects of aging within functional networks. For instance, Ng, Lo, Lim, Chee, and Zhou (2016) found that DMN connectivity in older adults (approximately between 60 and 87 years old) decreases over 4 years (within-person effect), in addition to replicating cross-sectional age-related differences (between-person effect). Using a slightly wider age-range (49–87 years), a similar study showed that change in within-DMN connectivity follows an inverted U-shape depending on age (Staffaroni et al., 2018). While participants below 66 years showed an increase in DMN connectivity over time, participants older than 74 years showed a decline. In contrast, other studies found stability over time (Persson, Pudas, Nilsson, & Nyberg, 2014) or at least no significant age-related change (Fjell et al., 2015) in DMN connectivity.

While the majority of research has assessed the overall strength of connectivity within the DMN as a whole, studies investigating the specific connectivity between pairs of DMN regions have found that connectivity between the anterior and posterior regions of the medial wall (e.g., medial prefrontal cortex, posterior cingulate cortex) are the most affected by aging (Andrews-Hanna et al., 2007; Mak et al., 2017).

The other portion of the DMN that is particularly susceptible to aging is the medial temporal lobe (MTL) subsystem, which most prominently includes the hippocampus. The MTL has strong connections to medial

“core” DMN regions and is often considered part of the DMN. The MTL is vitally involved in memory function and is, therefore a pivotal region for aging research. It is, for instance, very well established that hippocampal volume declines with age. That is true in cognitively unimpaired people (Fraser, Shaw, & Cherbuin, 2015), as well as in patients with dementia (Pini et al., 2016). Several additional studies, described below, investigate the connectivity within MTL regions and between MTL and other DMN regions.

Functional connectivity between MTL and other cortical DMN regions decreases with age. This effect has been shown by cross-sectional (Damoiseaux, Viviano, Yuan, & Raz, 2016; Salami, Pudas, & Nyberg, 2014), as well as longitudinal studies (Salami, Wåhlin, Kaboodvand, Lundquist, & Nyberg, 2016), but likely is specific to posterior parts of the MTL (Damoiseaux et al., 2016; Salami et al., 2016).

Such differences across the anterior–posterior axis of the MTL become further apparent when investigating connectivity within the MTL. One cross-sectional study found higher within-MTL connectivity in older adults (Salami et al., 2014), which later longitudinal work suggested shows a distinct pattern for anterior and posterior regions: while posterior MTL connectivity increases over time, anterior MTL shows an increase up to approximately age 55, followed by a decrease (Salami et al., 2016). In contrast, another cross-sectional study found lower connectivity with older age within the hippocampus of each hemisphere, as well as between left and right posterior hippocampus, but not anterior hippocampus (Damoiseaux et al., 2016).

While a large amount of aging research is focused on the DMN, there are other relevant networks as well. One of the major contributions of functional connectivity research to cognitive neuroscience has been the introduction of “resting-state networks,” which represent large-scale distributed functional systems (Smith et al., 2009). Numerous methods have been introduced to extract networks from resting-state fMRI activity, but the most prominent are independent component analysis (Beckmann et al., 2005), clustering approaches (e.g., Bellec et al., 2006; Yeo et al., 2011), and numerous other methods for delineating distinct networks (e.g., Power et al., 2011). All these methods decompose temporal fluctuations in brain activity into a set of distinct components, and while they differ in the specific analytic approaches, the extracted networks are highly consistent and reliable across methodologies (Shehzad et al., 2009; Zuo & Xing, 2014).

The resting-state networks that are of particular interest to aging research are predominantly located within association cortex, and in addition to the DMN include

frontoparietal control network, dorsal attention network, and salience network (see Fig. 3.1). In general, these networks also show age-related lower functional connectivity. It has to be noted that the investigation of these networks has produced a more mixed pattern of results than work concerning the DMN. The frontoparietal control network appears to have lower connectivity in old than in young subjects (Betzel et al., 2014; Fjell et al., 2015; Geerligs, Renken, et al., 2015; Grady et al., 2016). Similar results were obtained for the salience network (Betzel et al., 2014; Fjell et al., 2015). The dorsal attention network shows age-related lower connectivity in some studies (Andrews-Hanna et al., 2007), but not in others (Betzel et al., 2014).

The scarcely available work investigating within-person change in these networks also gives mixed results. Ng et al. (2016) found a significant decline in connectivity over time in the frontoparietal control network, but no significant change was found for the salience network. Fjell et al. (2015), while showing lower connectivity in the older group as compared to the young group for dorsal attention, salience, and control networks, found an opposing pattern when investigating within-person change in connectivity for the salience and the frontoparietal control network.

Having established that functional connectivity within higher-order networks generally is lower in old than in young people, the question of age-related differences in the interaction between these networks arises.

### Between-network connectivity

Initially, most aging studies investigated how the connectivity within specific functional networks is altered with advancing age. However, as the field progressed, more studies started to investigate connectivity *between* different networks. Based on the literature of task-related fMRI studies on aging, there are several reasons to expect that between-network connectivity is especially affected by aging. One of the recurrent findings in this literature is that older adults tend to show less functional specificity in the brain regions that are engaged during the performance of a task (Park et al., 2004; Rajah & D’Esposito, 2005). This could be a sign of neural reorganization, which might also be reflected in the functional organization of networks (Goh, 2011).

Based on these findings it would be expected that older adults also show stronger connectivity (or weaker “negative” connectivity, known as “anticorrelation”) between distinct functional networks that are involved in different cognitive processes. Indeed this is the pattern that has been observed in many studies. One of the first

studies to observe a distinction between the effects of age on within- and between-network connectivity was the work by Geerligs, Maurits, Renken, and Lorist (2014). They used a seed-based connectivity approach to investigate how connectivity between specific seed-regions and the rest of the brain was altered in older age while participants performed an oddball task. In line with previous studies, the results showed that older adults tended to show lower connectivity between the seed regions and other brain regions that were part of the same functional network.

However, higher connectivity was observed between the seeds and brain regions that were part of a different functional network. For example, they found higher connectivity with age between the DMN, the somatosensory, and the frontoparietal control network, as well as between the frontoparietal control network and the dorsal attention network. Other studies have replicated this pattern of results in resting-state data using different approaches (Betzel et al., 2014; Chan, Park, Savalia, Petersen, & Wig, 2014; Ferreira et al., 2016; Geerligs, Renken, et al., 2015). For example, Betzel et al. (2014) investigated connectivity between a predefined set of ROIs (regions of interest) and observed that ROIs that had previously been associated with the same network showed lower connectivity with advancing age, while ROIs associated with different networks mostly showed higher connectivity. This is one of many studies that have investigated connectivity within and between networks with advancing age. Unfortunately, due to differing methodological approaches, differing sets of network definition and ROI and differences in focus, it is difficult to pinpoint exactly which networks reliably show higher between-network connectivity in older adults. However, for some pairs of networks age-related connectivity differences are observed reliably. The dorsal attention network and the DMN are two networks that tend to show particularly strong negative connectivity or anticorrelations, potentially due to their engagement in externally directed (dorsal attention network) and internally directed (DMN) cognition. Spreng, Nathan Spreng, Dale Stevens, Viviano, and Schacter (2016) showed that the anticorrelations between these networks are lower in older compared to younger adults, in both task and resting state. Other studies have observed similar patterns of lower anticorrelations with advancing age (Ferreira et al., 2016; Geerligs, Renken, et al., 2015).

This higher connectivity between different networks can also be thought of as lower segregation. Hence, the presented studies indicate that segregation of networks at a young age decreases with age, rendering specialized networks less specialized, with potentially

detrimental effects on information processing. Indeed, Grady and colleagues (Grady et al., 2016) looked at interactions between the DMN, dorsal attention and frontoparietal networks and they observed that an index of segregation, the within-network connectivity versus the between-network connectivity, was lower in older compared to younger adults in all three networks during task performance and only in the DMN and frontoparietal networks during resting state. Using this same segregation index, Chan et al. (2014) showed that aging is associated with decreased segregation of both association cortex and cortex involved primarily in sensory-motor processing. However, their patterns of age-related differences in segregation differ; while sensory-motor systems showed a linear pattern of age-related lower segregation, a quadratic relationship was observed in association systems. One concern while interpreting these results is that other factors that occur more frequently in older age, such as cognitive deficits or mild cognitive impairment (MCI), may impact the observed effects of aging on connectivity. To this end, Ferreira et al. (2016) investigated a sample which was carefully screened for cognitive deficits and lifetime psychiatric disorders. They observed very similar higher between-network connectivity as previous studies, including a widespread pattern of higher connectivity between different networks with focally lower anticorrelations, involving mainly the connections between the DMN and the attentional networks.

The studies on between-network connectivity described so far all involved cross-sectional samples. A study by Ng et al. (2016) investigated connectivity between networks in a longitudinal sample. They observed that the change in connectivity between the DMN and the frontoparietal control network depends on age. While this between-network connectivity declines in participants between 60 and 70, it increases in participants older than 75. This finding indicates diminished segregation of networks may be a hallmark of aging.

## Whole-brain connectivity

In keeping with the tradition of cognitive neuroscience, network-based analyses focus on characterizing differences in connectivity on the level of functional systems. In contrast, a whole-brain approach aims to characterize the connectivity of the entire brain, by modeling it as a complex graph of connections. The whole-brain approach, therefore enables characterization of the general, brain-wide organization of functional connectivity. The characterization of the whole-brain

network of functional connectivity is called the “functional connectome.”

Graph theory, a branch of mathematics, serves as a framework to perform these investigations. In graph theory terms, a graph consists of nodes and edges. The functional connectome is reconstructed by, first, parcellating the brain into distinct regions (nodes), and second, for each pair of regions, calculating the functional connectivity between regions (edges) (for a graphical representation of nodes and edges see for instance Fig. 3.1 in van den Heuvel & Sporns, 2013). This results in a connectivity matrix, where each cell represents the functional connectivity between two brain regions. Based on this matrix, a wide array of graph theory metrics can be derived (Bullmore & Sporns, 2009).

Some of these metrics allow describing properties of functional segregation, for example, the strong connections within a module. A metric that has been investigated extensively in the aging field is local efficiency. It describes how well a node’s neighbors are connected. Local efficiency is high if a node’s neighbors are well-connected, and therefore local information flow is not heavily impeded by the loss of a node.

A consistent finding across many studies is that local efficiency is lower in older, as compared to young or middle-aged adults (Achard & Bullmore, 2007; Geerligs, Renken, et al., 2015; Sala-Llonch et al., 2014; Song et al., 2014). By investigating a large sample that spans nearly the entire life span, another study found a similar, but more complex, pattern of age effects on local efficiency (Cao et al., 2014). This study found that local efficiency shows a nonlinear relationship with age, in the form of an inverted U-shape. Cross-sectionally, local efficiency increases until the age of 30 and decreases in higher age. As local efficiency is conceptually similar to within-network connectivity, these results are well in line with the findings of decreased within-network connectivity with age.

The whole-brain approach, furthermore, allows a focus on regions that have an important role by enabling information flow between modules. These so-called hub regions are well-connected within modules, and also have strong connections to other hubs. Hence, hubs form a so-called “rich club” that allows distribution and integration of information across the entire brain. Since this organization only becomes apparent when describing brain connectivity on the whole-brain level, the whole-brain approach allows for a better description of its integrative organization.

One metric that captures this organization is the “rich-club coefficient.” The rich-club coefficient is

conceptually similar to local efficiency, but instead of local connections investigates the connections between hubs. In their investigation, Cao et al. (2014) identified hubs based on functional connectivity. They found them to be located mainly in regions of the default mode, attention and visual networks. Investigating the connectivity between hub regions, they found the rich-club coefficient to follow an inverted U-shape along the life span. Adults show higher values than children and old people with a peak at approximately 40 years. This finding indicates that global integration is worse in older age.

While the findings of lower local efficiency with age are fairly consistent, the complementary metric of global efficiency, which characterizes global parallel information flow, shows more mixed results. Many studies did not find age-correlations or differences in global efficiency (Cao et al., 2014; Geerligs, Renken, et al., 2015; Song et al., 2014), while some studies do (Achard & Bullmore, 2007; Sala-Llonch et al., 2014). It might be that parallel information flow is not diminished with age on a global scale, but that this process is confined to certain networks, which might explain conflicting findings. Future studies will need to shed more light on this issue.

Up to now, we described work regarding functional connectivity as static. However, an interesting question is not only how regions functionally connect, but also how this connectivity changes dynamically within seconds or minutes and how these dynamics differ depending on age.

## Dynamics

Functional connectivity is typically estimated using the time series over the course of the whole fMRI scan. However, computing connectivity this way may disregard informative fluctuations in connectivity over the duration of the scan. Indeed, recent work has shown that even in task-free, resting-state, functional connections change over the course of a scan (Allen et al., 2014; Chang & Glover, 2010). The first studies have now begun to investigate how aging affects these dynamics of functional connectivity. Some of these studies point to a loss of dynamics in the aging brain. Schaefer et al. (2014) looked at hubs and how they varied their participation in different networks over time. They showed lower whole-brain variation in network participation with advancing age. Chen et al. (2017) similarly showed lower variation of connectivity in older compared to younger adults, particularly in connections between different networks. Several studies investigated age-related dynamic

connectivity differences by grouping connectivity profiles of short windows into distinct whole-brain connectivity states (Allen et al., 2014). In line with previous findings one study observed that older adults had a lower rate of switching between distinct connectivity states (Xia et al., 2019). However, other studies observed no difference across the life span in the rate of switching between connectivity states (Viviano, Raz, Yuan, & Damoiseaux, 2017). Madhyastha and Grabowski (2014) found that older adults showed more variability of connectivity within the DMN than young adults. The flexibility of connectivity in different brain regions was investigated by Yin et al. (2016), who showed that flexibility of the right middle frontal gyrus was lower in older adults compared to younger adults, with the opposite occurring for the left supramarginal gyrus. So while some studies suggest a loss of dynamics and flexibility with age, other studies show no differences or even higher dynamics in older adults.

Xia et al. (2019) also investigated the occurrence of specific connectivity states in relation to age. They found that four out of the five detected states show age-related differences in their frequency of occurrence. Two states with either weak connectivity between networks or anticorrelations occurred more frequently in older adults. States with strong connectivity, particularly within the salience network and the visual network occurred more frequently in older adults. Similarly, Viviano et al. (2017) found two connectivity states that occurred more frequently in older than younger adults, these were a connectivity state which was similar to the average (regular) functional connectivity profile and a state with high default mode–ventral MTL connectivity. In addition, a state with low default mode–ventral MTL connectivity occurred less frequently in older than younger adults. In both studies, the differences in the occurrence of dynamic connectivity states mirrored the observed age-related differences in the average connectivity profiles. These results suggest that differences in the occurrence of specific connectivity states may explain some of the age-related differences in functional connectivity that have been observed previously.

The lack of consistency between studies so far may be associated with differences in methods used and the effects of confounds. Because dynamic connectivity estimates are based on shorter time segments they are more sensitive to nonneural factors, such as head motion, vascular signals, and respiratory signals or other sources of noise (Chang & Glover, 2010; Laumann et al., 2017). Group differences in dynamic connectivity may also be biased by autocorrelation and mean connectivity strength (Lehmann, White, Henson, Cam-Can, & Geerligs, 2017). In the case of estimating connectivity states, the choice of

settings (such as the number of states to estimate) can bias the results (Lehmann et al., 2017). Therefore future studies are needed to confirm the robustness and reliability of these findings and to investigate whether considering connectivity dynamics aids in our understanding of the mechanisms of age-related differences and change.

## Cognition and functional connectivity

Having established that functional connectivity is influenced by age, the question arises whether these effects are related to cognitive functioning. Most studies investigating this link focus on the cognitive domains of memory and processing speed in relation to functional connectivity of the DMN.

In cross-sectional studies, it has been shown that participants with higher DMN connectivity show better memory performance. This has been demonstrated for the connection between the frontal and posterior midline DMN regions (Andrews-Hanna et al., 2007), and the connection between the hippocampus and anterior DMN (Salami et al., 2014) or between hippocampus and posterior midline DMN regions (Salami et al., 2014; Wang et al., 2010). Interestingly, higher connectivity within the hippocampus seems to be related to worse memory performance (Salami et al., 2014). However, other studies, while finding age-related lower memory performance in old participants, did not find a link between memory and functional connectivity within the DMN (Damoiseaux et al., 2008) or the hippocampus (Damoiseaux et al., 2016). Looking beyond the DMN, it has been shown that higher functional specialization of different networks is associated with lower episodic memory performance (Chan et al., 2014). This was measured using segregation, an index of within- versus between-network connectivity. Interestingly this association between memory and segregation was particularly present for networks within association cortex (including the DMN, frontoparietal network, and dorsal attention network), and not for networks involved in primary sensorimotor functions.

In addition to the between-subjects analyses in cross-sectional study designs, the within-subjects analyses made possible in longitudinal designs are an important contributor to stronger evidence on brain–cognition links in aging that are not impeded by cohort effects (see “Limitations” section). Studies that simultaneously tracked changes in functional connectivity and memory have found a steeper decline in within-DMN connectivity to be related to a steeper decline in episodic memory performance (Fjell et al., 2015; Persson et al., 2014; Staffaroni et al., 2018). More generally, this pattern can also be found

for the connectivity seeded from hippocampus and basal ganglia regions, respectively, to widespread cortical regions: change in memory is positively related to change in functional connectivity (Fjell et al., 2016). Furthermore, changes in connectivity in the left posterior MTL also show a relationship to changes in memory scores, mirroring cross-sectional patterns in the hippocampus: greater functional connectivity increases go together with a steeper decline in memory (Salami et al., 2016).

Other studies track memory performance longitudinally and then investigate functional connectivity at the end of the observation interval. This approach allows for contrasting functional connectivity between subjects with declining and stable memory. Functional connectivity in regions of the DMN has been found to be lower in participants with declining memory than in participants with stable memory (Bernard et al., 2015). Furthermore, the reverse pattern can be seen for connectivity within the hippocampus: older adults with stable memory showed lower connectivity within the hippocampus, a pattern that makes them more similar to young adults (Salami et al., 2014).

Cross-sectional studies investigating associations between processing speed and functional connectivity indicate that lower DMN connectivity is associated with slower processing speed in older adults (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Hirsiger et al., 2016). However, connectivity of the hippocampus with DMN regions did not reveal a relationship to processing speed performance in an adult life span sample (Damoiseaux et al., 2016). A previous longitudinal study found a relationship between steeper processing speed declines and within-DMN connectivity (Staffaroni et al., 2018), however, another study did not find this link (Ng et al., 2016). The authors of the latter study also investigated between-network connectivity and found that a steeper decline in processing speed was associated with a steeper decline in between-network segregation between the DMN and the frontoparietal control network (Ng et al., 2016).

One mechanism to explain these conflicting results regarding the link between functional connectivity and cognitive functioning in healthy aging might be compensatory neuronal processes. According to the revised Scaffolding Theory of Aging and Cognition (STAC-r) (Reuter-Lorenz & Park, 2014), adverse changes in functional connectivity might be counteracted by compensatory processes, which might weaken or delay the effect of adverse brain changes on cognitive decline. Therefore simultaneously describing brain and cognitive changes might miss lagged relationships that can only be seen later in life, when compensatory mechanisms break

down. Investigating lagged relationships, however, requires research designs with at least three measurement occasions over multiple years, and while there exist a very few such studies, they have not yet investigated lagged relationships. In neurodegenerative disorders, however, compensatory processes might no longer be able to counteract changes in brain connectivity, hence, changes in connectivity might more directly result in cognitive decline.

### Functional connectivity in neurodegenerative disorders

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So far we have mainly discussed age-related differences and changes in functional connectivity observed in typical aging. Next, we will show how functional brain connectivity is influenced by age-related neurodegenerative disorders such as Alzheimer's disease (AD). The existing literature indicates that particularly the DMN, which has consistently shown lower functional connectivity with older age, seems further affected by AD. Most cross-sectional work indicates lower DMN connectivity in clinically diagnosed AD patients compared to cognitively unimpaired older adults (Badhwar et al., 2017; Binnewijzend et al., 2012; Greicius, Srivastava, Reiss, & Menon, 2004). However, longitudinal work suggests an initial increase of DMN functional connectivity that is later followed by a decrease in the same areas (Bai et al., 2011; Damoiseaux, Prater, Miller, & Greicius, 2012). These longitudinal studies furthermore suggest that areas within the DMN are affected relatively early at the MCI and early dementia stage, with additional brain networks affected as the disease progresses. The observed initial increase in connectivity may reflect a compensatory process, as outlined in the revised STAC-r model, a model that encompasses both typical and pathological aging (Reuter-Lorenz & Park, 2014). The STAC-r model poses that harmful effects of functional and structural brain changes on cognition can be muted by "compensatory scaffolding," such as recruitment of more neural circuitry. This compensatory process functions as an attempt to maintain typical cognition in response to numerous typical and pathological age-related neural insults. In AD this compensation process starting in the posterior DMN can also be viewed as a transient load-shifting process, which eventually will result in a cascading network failure, as described by Jones et al. (2016).

The important role of the DMN in AD is in line with the DMN's involvement in internally focused activities. Activities such as self-referential thinking and prospective memory encompass the same brain



regions that are active during successfully retrieving memories, that is, more brain activity in response to old items correctly identified as old compared to new items identified as new (Buckner, Andrews-Hanna, & Schacter, 2008). Furthermore, the DMN overlaps with observed brain patterns of gray matter volume loss and amyloid- $\beta$  deposition in AD (Buckner et al., 2005, 2008). Deficits in memory retrieval, gray matter atrophy and accumulation of amyloid- $\beta$  are all established indicators for AD. More specifically, the presence of amyloid- $\beta$  aggregations (plaques) in the brain is one of the defining pathological markers of AD, along with tau pathology (neurofibrillary tangles). The observed overlap of these AD markers to the DMN, and the observed lower functional connectivity in AD patients, indicates specific vulnerability of these brain regions to AD pathology.

Even though AD is the most common neurodegenerative disorder, it is not the only one. Since other neurodegenerative disorders present with different cognitive/behavioral deficits, do they also affect different brain networks? Seeley, Crawford, Zhou, Miller, and Greicius (2009) addressed this question and found that specific brain networks have selective vulnerability to specific neurodegenerative disorders. In line with previous research they observed gray matter atrophy within the DMN in AD, but in addition they observed different gray matter atrophy patterns in other neurodegenerative disorders. For example, in behavioral variant frontotemporal dementia the atrophy pattern overlapped with the salience network, and in progressive nonfluent aphasia it converged with the frontoparietal network (Seeley et al., 2009). In subsequent research they examined functional connectivity differences and observed divergent functional connectivity between behavioral variant frontotemporal dementia and AD, such that the former had lower salience network and higher DMN connectivity, whereas for the latter the opposite was true (Zhou et al., 2010), an effect that was later replicated in an EEG study (Yu et al., 2016).

### **Functional connectivity as a biomarker**

The evidence showing age effects on functional connectivity supports its potential application as a biomarker that might allow for predictions on an individual level. For instance, the “brain-age prediction” approach aims to provide an aggregated marker of brain health. Furthermore, functional connectivity seems to be affected early on in the course of

neurodegenerative disorders, long before neuropathology manifests itself in cognitive decline (Chen et al., 2016). Therefore connectivity might be useful in predicting future disease development.

### **Functional connectivity as a general biomarker for brain health**

Aging results in changes in brain function as well as in brain structure. Developing a biomarker for general brain health requires reducing the dimensionality of this high-dimensional pattern so that multiple three-dimensional brain maps are distilled into a small number of numeric values that allow for a more straightforward interpretation of brain aging. This biomarker can then be used to identify individuals with accelerated brain aging, or serve as an outcome measure in intervention studies. Machine learning methods have been used to try to identify such biomarkers. For example, a single person’s biological brain age can be estimated based on neuroimaging data and compared to their chronological age. This means that if a person is 50 years old and their brain looks like the brain of a typical 70-year-old, this can be taken as evidence for increased brain aging. The brain-age approach has been applied to a variety of neurocognitive and psychiatric disorders and could demonstrate that these patients have older appearing brains than typical individuals. Importantly, this approach can also be used to investigate the protective effects of lifestyle on brain aging (Cole & Franke, 2017).

The majority of extant studies that investigated brain aging relied on structural brain data, measuring, for instance, the amount of volume loss in the cortex and subcortical regions. More recent work extended this approach to include functional connectivity data (Liem et al., 2017). The combination of structural and functional connectivity data increased the prediction accuracy of the models and could therefore more fully characterize brain aging. This finding was validated further by showing that participants with mild or major cognitive impairment show progressively increasing functional and structural brain aging scores, indicating that accelerated brain aging is related to accelerated deterioration in cognitive functioning.

### **Connectivity as an early marker for neurodegenerative disorders**

The neurodegenerative process starts years, perhaps even decades, before measurable cognitive impairment (Vos et al., 2013). Therefore an effort is made to detect

neurodegenerative brain changes at an earlier stage by examining cognitively unimpaired older adults with heightened risk for dementia or AD, such as presence of genetic risk (e.g. APOE- $\epsilon$ 4 carriers), neuropathology (e.g. amyloid- $\beta$  and tau deposition in the brain), or subjective cognitive decline (i.e., a subjective concern of cognitive decline in the absence of objective impairment). Researchers have compared DMN connectivity in APOE- $\epsilon$ 4 carriers, which is the most prominent genetic risk factor for late-onset AD, to those with  $\epsilon$ 3-homozygotes, the neutral risk alleles. They found that participants with an at-risk genotype had lower DMN functional connectivity than the neutral risk group, even though they were not cognitively impaired (Machulda et al., 2011; Sheline et al., 2010). A longitudinal study in cognitively unimpaired older adults found that the at-risk group (i.e., APOE- $\epsilon$ 4 carriers) had more rapid loss of functional segregation between the DMN and the executive control network over time than the neutral risk group (Ng et al., 2018). These studies suggest that altered within and between DMN connectivity is an indicator of AD risk. Note that the APOE- $\epsilon$ 4 effect on DMN functional connectivity may be specific to women (Damoiseaux, Seeley, et al., 2012; Heise et al., 2014). This is in line with other research showing a faster cognitive decline in female MCI patients, and specifically in female APOE- $\epsilon$ 4 carriers, compared to their male counterparts (Lin et al., 2015). Lower DMN connectivity was also observed in cognitively unimpaired adults considered to have preclinical AD, that is, who have pathologic amyloid- $\beta$  +/-tau biomarkers (Jones et al., 2017; Mormino et al., 2011), and in individuals with subjective cognitive decline (Viviano et al., 2019). These studies indicate the potential for functional connectivity, mainly of the DMN, as a marker for early neurodegenerative disease detection and progression.

### Methodological considerations relevant to aging research

Cross-sectional and longitudinal study designs allow investigation of different effects. It is important to distinguish the effects of age-related differences (between-person effects) from the effects of age-related change (within-person effects). The majority of aging neuroscience studies use cross-sectional designs, sampling participants over a wide age range or young and old groups at one measurement occasion. However, interpreting these differences as a proxy for within-person changes is problematic, as, amongst other issues, these designs are confounded by cohort effects. For instance, since the

nutritional and educational environment changed over the last decades, differences between a 30- and an 80-year-old participant will not only reflect within-person changes over time, but also differences due to different environments in which the participants grew up. Within-person change can only be studied with longitudinal research designs, which have demonstrated different results as compared to cross-sectional studies (Pfefferbaum & Sullivan, 2015). However, since longitudinal studies are much more time- and resource-intensive than cross-sectional studies, and suffer from other drawbacks, like attrition (Chatfield, Brayne, & Matthews, 2005) or retest effects (Salthouse, 2016), the majority of studies rely on cross-sectional designs.

Divergent findings might also arise from conducting research on small samples, resulting in low statistical power (Button et al., 2013). While a study's sample size should always be taken into account when evaluating results, awareness of this problem has resulted in better-powered studies with larger samples in recent years (Poldrack et al., 2017).

Beside these general methodological issues, there are several considerations specific to investigating functional connectivity in aging. Computing functional connectivity involves choices between analysis approaches (e.g., correlation-based approaches versus independent component analysis), choices about which networks or ROI to focus on and choices about how to preprocess the data. Each of these choices can have a major impact on the results of a study. The studies described in this chapter vary widely in the approaches that are used. The effects of different analysis choices and preprocessing steps on age-related differences in connectivity were investigated in a recent study (Geerligs, Tsvetanov, Cam-Can, & Henson, 2017). They found that different preprocessing options can substantially alter the observed association between age and functional connectivity. In part, this is because fMRI data contains signals that do not have a neural origin. Some of these signals reflect head motion of participants in the scanner (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Even small amounts of head motion can significantly affect the fMRI data and these effects are very difficult to remove completely, even with very elaborate preprocessing pipelines (Power et al., 2014; Van Dijk, Sabuncu, & Buckner, 2012). In the context of aging, this is particularly concerning because older adults tend to move more when they are in the scanner compared to younger adults (D'Esposito, Zarahn, Aguirre, & Rypma, 1999; Geerligs, Rubinov, Cam-Can, & Henson, 2015). Another factor that is important in the context of aging is the impact of breathing and heart rate variability on the fMRI signal. Recent work has shown that these can

introduce substantial changes in the fMRI signal, and that these changes are shared between regions, thereby inducing apparent connectivity without any neural origin (Power, Plitt, Laumann, & Martin, 2017). Heart rate variability also decreases with age, and these changes can confound the observed associations between age and connectivity (Geerligs et al., 2017). These effects can be mitigated by specific pre- and postprocessing steps, but those are not commonplace yet.

Studies also vary in the networks or regions they focus on, which makes them difficult to compare. Even studies focusing on the same networks can use different ROIs. This is potentially important because misalignment of ROIs with true functional regions will cause greater heterogeneity in the signals within ROIs, which may lead to weakened functional connectivity estimates and seemingly lower segregation between brain systems (Geerligs et al., 2017). The location or number of true functional regions may change with age, causing misalignment with the ROIs used for analysis.

Given these confounds and limitations it is important to ensure that any conclusions that are drawn hold across a range of analysis choices and datasets. That is why it is encouraging to see that there are patterns of age-related differences that are observed consistently across studies, such as the consistent decline in connectivity within the DMN and the loss of network segregation with advancing age.

### Summary and future directions

Aging has pronounced effects on the brain's functional connectivity architecture. Connectivity within the DMN, as well as in other association networks is lower in older age, while the connectivity between different functional systems is higher. Together, these differences result in a loss of segregation between different functional systems. Nevertheless, findings regarding the association between connectivity and cognition remain sparse and unclear. This may be due to the limitations of the cross-sectional nature of most studies in the field, as well as to compensatory processes that older adults may engage to maintain higher levels of cognitive abilities. Future studies using longitudinal research designs, tracking study participants across several years and recording data about their brain and cognitive status, are imperative to further this area of research.

The field has largely advanced alongside the methodological innovation in data acquisition and analysis. Continuing innovation in describing brain connectivity will provide novel insights into the aging brain in the

future. Large, multisite datasets will help to disambiguate contradictory results from previous studies that often based their findings on small datasets, which might produce nonreplicable results.

### Acknowledgments

We are grateful to Dr. Susan Resnick for her insightful comments on this chapter. FL was supported by the University Research Priority Program "Dynamics of Healthy Aging" at the University of Zurich. LG was supported by a Veni grant [451-16-013] from the Netherlands Organization for Scientific Research.

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