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STRUCTURE AND FUNCTION OF THE AGING BRAIN

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In this opening chapter of *The Aging Brain*, we set the stage for the contributions that follow by providing a broad overview of the latest advances in our understanding of how the brain changes, both structurally and functionally, across the adult lifespan. We leave domain-specific aspects of brain aging to the subsequent chapters, where contributors provide more targeted accounts of brain change germane to their particular focus on the aging brain. Here we review the extant, and rapidly expanding, literature to provide a brief overview and introduction to structural and functional change that occur with typical brain aging. We begin the chapter by looking back to review some of the early discoveries about how the brain changes across the adult lifespan. We close the chapter by looking forward, toward new discoveries that challenge our core assumptions about the inevitability or irreversibility of age-related brain changes. These sections serve as bookends for the core of the chapter where, we review the latest research advances that continue to uncover the mysteries of the aging brain.

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INTRODUCTION: STUDYING THE AGING BRAIN

Whether in the lab or in the clinic, we now take for granted the ready access to measurement tools and the precision with which we are able to investigate lifespan changes in the structure and functioning of the human brain in vivo. However, the study of the aging brain is a relatively young endeavor. Early neuroscientific studies did not include, or perhaps even consider, systematic investigations of brain changes that may occur in later life. Indeed, a leading text on the history of neuroscience, *Origins of Neuroscience* (Finger, 1994), does not include a section on older adult brain development, and the term *aging* does not even appear in the subject index. Of course, this may be explained in part by the comparatively restricted range of the human lifespan before the turn of the 19th century. However, by the mid-20th century, researchers in the fields of medicine, neuroscience, and evolutionary biology began to recognize that the brain does not remain stable across the normal adult lifespan. Postmortem investigations began to report both gray and white matter volume loss as well as ventricular enlargement in older versus younger adults (for an early review, see Kemper, 1994). However, these early pathological and comparative neurological studies were plagued by small sample sizes and methodological constraints that affected measurement reliability (Good et al., 2001). By the latter decades of the 20th century, postmortem studies also began to identify broad topological patterns of age-related change in brain structure. Sensory cortices were seen be comparatively preserved, while more pronounced changes were evident in association cortices, including frontal and lateral parietal regions (Flood & Coleman, 1988). Following rapidly from these postmortem investigations, in vivo neuroimaging techniques, including computed tomography and two-dimensional magnetic resonance imaging (MRI), became more widely adopted. These methods were critical in advancing our understanding of the aging brain because they allowed the enterprise of brain research to essentially "scale-up," enabling the collection of brain volume measures from larger groups of participants that could then be more reliably compared across age cohorts. These imaging techniques, and in particular, the development of high-resolution, three-dimensional MRI neuroimaging methods in the late 1980s and early 1990s, as well as more sophisticated registration protocols necessary to spatially align individual brains to conduct group comparisons, opened the way for larger cohort and longitudinal studies that have become standard in the field today (Salat et al., 2004).

As with studies of structural brain aging, the earliest investigations of aging brain function in humans emerged in the middle decades of the 20th century. Indeed, as early as 1938, electroencephalogram (EEG) recordings were seen as offering "appreciable promise as a means to characterize

significant deviations from the 'natural' aging found in Alzheimer and other dementias" (Berger, 1938, as reviewed by Rossini, Rossi, Babiloni, & Polich, 2007, p. 376). In the latter part of the century, increasingly sophisticated methods emerged to investigate age-related changes in brain function. These included single photon emission computed tomography, positron emission tomography (PET), functional MRI (fMRI), and magnetoencephalography (MEG) techniques. In the early decades of the 21st century additional techniques, including intracranial EEG or electrocorticography methods, have enhanced the spatial and temporal resolution of functional brain measurements. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation techniques now allow for the temporary modulation of brain activity, enabling researchers to more directly investigate how changes in brain function are associated with cognitive functioning in later life (e.g., Freitas, Farzan, & Pascual-Leone, 2013; Rossi et al., 2004). As we will see at the end of the chapter, these brain stimulation techniques are also offering considerable promise as interventions or treatments to potentially alter the course of cognitive aging (e.g., Zimerman et al., 2013).

In the following sections of the chapter, we survey findings drawn from each of these techniques to provide a comprehensive overview of the current state of research on structural and functional brain aging. As we have seen, the study of the aging brain remains in its infancy. Brain imaging, allowing us to measure and record from the brain in vivo, is barely half a century old. Yet despite this brief history, much is now known about the myriad ways in which our brains change as we move through adulthood and into older age—and of course much remains to be discovered.

STRUCTURAL BRAIN CHANGES IN OLDER ADULTHOOD

Age-related changes in the structure of the brain have been examined across multiple, interacting levels, from cells and synapses to regions or structures and, more recently, large-scale brain systems or networks. Although structural brain changes measured using in vivo techniques almost certainly reflect cellular changes including dendritic branching, synaptic density, and demyelination of local and long-range axonal fibers, here we focus our review on measures of parenchymal (gray and white matter) and cerebrospinal fluid (CSF) volumes, both globally and regionally, and how local changes converge at the level of whole-brain networks. Consistent with the vast majority of research literature in this field, we also limit our primary focus to changes primarily involving cortical structures. However, age-related changes to subcortical structures are of increasing interest in understanding age-related changes in cognitive and affective behaviors (e.g., Samanez-Larkin &

Knutson, 2015) or as early markers of atypical brain aging (e.g., Schmitz, Spreng, & Alzheimer's Disease Neuroimaging, 2016), and we highlight these where possible throughout our review. Whereas earlier studies measured structural change almost exclusively in terms of volumetrics, more recent work has emphasized other features, including topological variability, rates of change, and interindividual differences. In this section we provide an overview of the changing structure of the brain in older adulthood at each level of analysis and across these multiple features of brain aging. Although not the primary focus of the chapter, this evolving, multidimensional perspective on structural brain changes in older adulthood is gaining prominence in the search for sensitive neural biomarkers that signal transition from normal aging to brain disease, a topic we discuss briefly in the final section.

From Postmortem to In Vivo: Early Findings

Early in vivo neuroimaging studies of structural brain aging focused primarily on global changes in tissue compartments including gray and white matter and CSF volumes (for a review, see Raz, 1996). These studies confirmed postmortem investigations that had reported global volume loss and ventricular enlargement in older relative to younger adults (Kemper, 1994). In addition to confirming these ex vivo findings, early neuroimaging investigations provided the first indication of topological variability, with changes occurring at different rates for different brain regions and tissue types. This pattern has been described as a mix of declines and relative preservation (Raz, 2000), and suggested that not all brain regions demonstrate a similar extent or rate of decline across the lifespan. As we will see, more recent work suggests an even more complex picture of structural brain aging, with different regions demonstrating significantly different, and often nonlinear, trajectories of change (Fjell et al., 2014).

Investigations of structural brain aging using in vivo neuroimaging methods began to increase rapidly toward the end of the last century as MRI technology became more readily accessible and numerous groups began efforts to map the trajectory of age-related brain changes with increasing topological specificity. However, these efforts were not without controversy. Many of the earliest in vivo studies adopted a cross-sectional approach, comparing measures of brain structure between younger and older adults. However, cross-sectional designs have been criticized for providing purely chronologically based estimates of brain age. In other words, measurements at a single time point can only characterize brain structure at that time point. Single-point measures are unable to describe age-related changes in brain structure (Raz & Lindenberger, 2011). There are two primary criticisms of cross-sectional designs. First, they are contaminated by cohort

effects, which confound group membership and age in difference calculations. Second, cross-sectional designs do not account for individual differences, which introduce significant variability in group-level estimates and likely deflate true estimates of structural brain change between age-groups. With the increasing accessibility of MR technology, research groups began to conduct longitudinal studies of age-related changes in brain structure. Although complex and costly, longitudinal studies hold the advantage of accounting for individual differences and controlling for cohort effects, providing what is arguably a truer estimation of age-related brain change. As a reflection of the differences in these two approaches, a recent study of age-related cortical thinning reported annualized rates of –0.30% using cross-sectional methods. This estimate stands in somewhat stark contrast to the estimated annualized rate of –0.59% using a longitudinal study method (Fjell et al., 2014). The difference represents a nearly twofold difference in annual change estimates. These results are consistent with an earlier study that used a combined cross-sectional and longitudinal design (Raz et al., 2005) and again reported deflated cross-sectional change estimates. Taken together, these studies urge caution in the interpretation of these estimated structural brain changes. Although cross-sectional studies of age-related brain change may be more feasible and cost-effective and may allow for larger study samples to be collected, these designs may nonetheless underestimate the magnitude of age-related brain changes.

Since the earliest in vivo investigations, the number of studies investigating structural brain changes associated with normal aging has increased exponentially. Taken together, the findings provide a complex picture, with often conflicting findings. In the following sections, we review the extant literature and distill the findings into the most commonly reported and replicated patterns of structural brain change in older adulthood. We begin by reviewing the most recent evidence for global changes in whole-brain and ventricular volumes and then summarize the current state of knowledge with respect to region-specific trajectories of change. The most common in vivo metrics for measuring changes in brain structure are volumetrics, cortical thinning, and surface area, and we limit our review almost exclusively to these measures. Because the health of cerebral white matter is assuming a place of increasing importance in the study of brain and cognitive aging, we review patterns of white matter change, including volumetrics, white matter integrity, and lesion burden in a separate section. Finally, we end this section of the chapter on structural brain aging with a brief review of structural brain networks. These covarying patterns of structural brain change appear to be potent predictors of the transition from normative to diseased aging and may in fact identify disease-specific structural network biomarkers.

Global and Regional Changes

Global Changes

Age-related changes in cerebral parenchyma and ventricular volumes have been reported from the earliest in vivo studies (reviewed in Raz, 1996). Interestingly, whereas gray matter, CSF and ventricular volume changes were consistently reported in these early studies, age-related changes in white matter volumes were generally not observed, although microstructural changes in white matter had been reported previously (Wahlund et al., 1990). Age-related changes in whole brain volumes were also reported in one of the first whole-brain, volume-based morphometry studies, with evidence that global gray matter volumes declined linearly and CSF volume increased linearly with age (Good et al., 2001). Again, consistent with earlier reports, no age changes were observed in global white matter volumes. In contrast, white matter volume changes were reported in an early longitudinal study from the Baltimore Longitudinal Study of Aging (Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Age-related declines on the order of 5.4, 2.4, and 3.1 cm^3 per year were reported for total brain, gray matter, and white matter volumes, respectively, whereas ventricular volume increased by 1.4 cm^3 per year. These findings were recently replicated in a larger sample from the same study cohort (Thambisetty et al., 2010).

Longitudinal investigations have characterized global (and regional) changes in brain structure in terms of annualized percent change estimates. Annualized percent change is a standardized metric for determining the rate and trajectory of age-related changes by calculating a per-year estimate of decline. Annualized percent change is typically calculated voxel-wise (volume-based morphometry) or vertex-wise (cortical thickness) for each participant across multiple time points, thus allowing for both global and regional estimates of change. Although different formulae for calculating annualized percent change have been reported, a typical approach involves calculating differences in volume (or thickness) between time points, which is then divided by the baseline volume (or thickness) estimate and the number of years between time points (e.g., M. E. Shaw, Sachdev, Anstey, & Cherbuin, 2016). Longitudinal studies of cortical thickness have reported annualized percent change ranging from –0.59 in a cohort with mean age of 75 (Fjell et al., 2014) to –0.35 for lifespan (Storsve et al., 2014) and young-old (60–66) samples (M. E. Shaw et al., 2016). In one of the few non-Western studies reported in the literature, annual change of –0.56% for total brain volumes were observed in the Singapore Longitudinal Aging Brain Study (Leong et al., 2017). These findings provide strong evidence that declines in parenchymal volume, and concomitant increases in CSF and ventricular volumes, are a hallmark of adult aging. Despite earlier cross-sectional

reports, longitudinal studies demonstrate convincingly that both gray and white matter tissue compartments decline with age. Although estimates and measures vary widely across studies, there appears to be convergence around the extent of parenchymal change, with annual loss estimates ranging from –0.30% to –0.56% per annum. Further, this rate of global decline appears to accelerate in late life from young-old (60–66 years; M. E. Shaw et al., 2016) to middle-old (~75 years; Fjell et al., 2014) and old-old (+90 years; Yang et al., 2016). Finally, although a full review of sex differences in age-related brain change is beyond the scope of this review, it is important to note that the majority of published reports (whether cross-sectional or longitudinal) and across both global and regional measures, show a steeper and more rapid trajectory of decline for men than women (e.g., Driscoll et al., 2009; Good et al., 2001; Pfefferbaum et al., 2013; Raz et al., 1997; M. E. Shaw et al., 2016; Sullivan, Rosenbloom, Serventi, & Pfefferbaum, 2004; Thambisetty et al., 2010).

Regional Changes

The earliest in vivo imaging studies reported global, or nonspecific, brain changes in late life (Jernigan, Press, & Hesselink, 1990). However, evidence from animal and human postmortem studies (Flood & Coleman, 1988; Kemper, 1994) and later in vivo imaging studies (e.g., Pfefferbaum et al., 1994; Raz et al., 1997) observed regional variability in structural brain changes occurring in late life. Indeed, as noted earlier, the extent of regional variability was described in these early studies as a "patchwork" of age-related change across the cortical mantle (Raz et al., 1997). This distributed or "heterochronous" (Salat et al., 2004) nature of structural brain changes across the lifespan has been observed repeatedly in both cross-sectional studies (Dotson et al., 2016; Fjell et al., 2009; Fleischman et al., 2014; Salat et al., 2004; Walhovd et al., 2010; Yang et al., 2016; G. Ziegler et al., 2012) and longitudinal studies (Fjell et al., 2015; Pacheco, Goh, Kraut, Ferrucci, & Resnick, 2015; Resnick et al., 2003; Scahill et al., 2003; M. E. Shaw et al., 2016; Storsve et al., 2014; Sullivan et al., 2004; Thambisetty et al., 2010).

In a targeted investigation of regional differences in brain atrophy using region of interest methods, the most robust age changes were observed in prefrontal gray matter (Raz et al., 1997). The authors interpreted this finding in the context of earlier postmortem and in vivo imaging studies, suggesting that anterior brain regions, particularly prefrontal and temporal regions, may undergo accelerated changes with age (for a review of these early studies, see Raz, 1996). Subsequently, longitudinal studies appeared to confirm this finding of greater susceptibility of prefrontal and temporoparietal association cortices to age-related decline (Fjell et al., 2014, 2015; Pacheco et al., 2015;

Resnick et al., 2003; Salat et al., 2004; M. E. Shaw et al., 2016). We discuss network-level changes in more detail here, but several studies have specifically identified regions of the default network, a collection of functionally interconnected brain regions situated primarily along the brain's midline, as showing increased susceptibility to age-related changes (Fjell et al., 2015; Storsve et al., 2014). Explanations for these regional atrophy patterns include the "last-in, first-out" hypothesis (Raz, 2000), suggesting that brain regions such as the prefrontal cortex (PFC), which reach full maturation later in life, may be the most vulnerable to early decline in late adulthood. Similarly, the extended development–sensory hypothesis suggests that all heteromodal association cortices atrophy earlier, followed by declines in primary sensory-motor and paralimbic cortices in later older adulthood (McGinnis, Brickhouse, Pascual, & Dickerson, 2011).

On balance, existing research is consistent with these hypotheses, with frontal and heteromodal association areas most commonly identified as undergoing more rapid decline than sensorimotor regions (Pfefferbaum et al., 2013; Raz et al., 2005; L. M. Shaw et al., 2009; Storsve et al., 2014; Thambisetty et al., 2010). This leads directly to the conclusion that accelerated volume loss is not simply a global feature of structural brain aging. Support for this idea was recently provided in a large cross-sectional study, with a smaller longitudinal validation cohort (Fjell et al., 2015). Brain regions followed one of several trajectories with critical change periods, or inflection points, occurring in late adolescence or middle adulthood. Structures including the hippocampus, brain-stem regions, cerebellum, and cortical white matter, showed stability (or increases) in cortical thickness, followed by steep declines in later life. Structures including the amygdala, putamen, thalamus, nucleus accumbens, and cerebellar cortex showed a pattern of near linear decline across the lifespan. A third category, which included estimates of global parenchymal and cortical volumes, followed a quadratic function with accelerating decline in later life (Fjell et al., 2015). Regional variability in rates of brain atrophy was also reported in two recent studies of young-old (Shaw et al., 2016) and old-old (Yang et al., 2016). In young-old, greater annualized percent change was observed in heteromodal than in primary sensory motor cortices, with inferolateral temporal and inferior parietal cortices showing particularly pronounced changes. In contrast, for old-old adults, accelerated changes were observed in medial temporal and occipital cortices, particularly in the 10th and 11th decades of life (Yang et al., 2016). Structural declines have also been reported in primary sensory-motor and occipital brain regions in old-old adulthood (Salat et al., 2004; Storsve et al., 2014). Together these findings are consistent with the "retro-genesis" hypothesis (McGinnis et al., 2011), with prefrontal and heteromodal cortices developing later and declining earlier than primary sensorimotor regions.

White Matter Changes

A recent postmortem investigation of structural brain changes in older adulthood reported reduced cerebral white matter volume in both anterior and posterior brain regions while failing to find age-related changes in cerebral gray matter (Piguet et al., 2009). These results prompted the study authors to suggest that "healthy brain aging is a process affecting predominantly white, not gray, matter" (Piguet et al., 2009, p. 1294). These findings hint at the importance of considering white matter changes as a core feature of structural brain aging. Interestingly, changes in global white matter volume were not commonly reported in early cross-sectional studies, although subsequent well-powered cross-sectional and longitudinal studies did report reliable age-related declines in overall white matter volumes (Pfefferbaum et al., 2013; Raz et al., 2005; Resnick et al., 2003; Walhovd et al., 2011). Consistent with reports of regional specificity in cortical volume and thickness changes, white matter changes also appear to follow an anterior–posterior gradient with the most rapid atrophy occurring in frontal white matter (Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; Raz et al., 2005; D. A. Ziegler et al., 2010). The vast majority of reports of white matter atrophy also describe a curvilinear pattern, with more rapid declines occurring in later older adulthood (Fjell et al., 2015; Maillard et al., 2009; Pfefferbaum et al., 2013; Walhovd et al., 2011; Yang et al., 2016).

Beyond volumetrics, white matter changes have also been characterized using diffusion imaging methods to assess the integrity of white matter fiber tracts in the brain. Several recent reports suggest that changes in white matter integrity may precede gray matter changes, thus providing a more sensitive marker of structural brain changes in normal aging (Arvanitakis et al., 2016; Hugenschmidt et al., 2008). Declines in white matter integrity have now been reported across numerous studies and again appear to follow an anterior to posterior gradient with the most rapid changes occurring in frontal white matter compartments (Bennett & Madden, 2014; Bennett, Madden, Vaidya, Howard, & Howard, 2010). A third metric for characterizing the health of cerebral white matter involves measuring the volume of white matter lesions. Lesions in the brain's white matter are thought to occur as a result of small cerebrovascular events, leading to alterations in axonal myelin and ultimately membrane permeability, resulting in axonal damage. White matter lesions are associated with cerebrovascular risk factors (Raz, Rodrigue, Kennedy, & Acker, 2007) and, given increasing rates of obesity and metabolic diseases in Western populations, likely represent one of the most rapidly growing forms of structural brain change in older adulthood. White matter lesion burden appears to rapidly increase in the oldest old with one recent report suggesting decelerating volume loss and accelerating lesion

volumes in this cohort (Yang et al., 2016). Further, the presence of cerebral small vessel disease, including atherosclerosis, deep white matter lesions, or subcortical lacunar infarcts is strongly associated with Alzheimer's disease (Yarchoan et al., 2012) and a nearly two-fold increased risk of dementia onset (Snowdon, 1997).

Changes in Structural Brain Networks

Over the past decade research investigating structural brain change in older adulthood has expanded beyond global and regional changes to consider distributed patterns of structural decline. Structural covariance is observed as interindividual differences in regional brain structure covarying with other brain structures across the population (Alexander-Bloch, Giedd, & Bullmore, 2013; Evans, 2013; Mechelli, Friston, Frackowiak, & Price, 2005). Across individuals, intrinsically connected functional brain networks, such as the default network, can be topographically represented in the structural patterns of cortical gray matter. Patterns of covariance in brain structure were first identified in postmortem studies (Andrews, Halpern, & Purves, 1997), and changes in structural covariance networks with age have now been reported in whole-brain in vivo studies (Alexander et al., 2006; Brickman, Habeck, Zarahn, Flynn, & Stern, 2007; Chen, He, Rosa-Neto, Gong, & Evans, 2011; DuPre & Spreng, 2017; Meunier, Achard, Morcom, & Bullmore, 2009; Montembeault et al., 2012; Spreng & Turner, 2013; Zhao et al., 2015).

As with global and regional measures of structural brain changes, structural covariance changes with age are more prominent between frontal brain and posterior cortices, reflecting a loss of long-range covariance in favor of increased local processing (Montembeault et al., 2012; Wu et al., 2012; Zhao et al., 2015). Another prominent feature of network-level changes is declining structural covariance within the default network, a collection of functionally connected brain regions implicated in mnemonic and associative processing (Andrews-Hanna, Smallwood, & Spreng, 2014). In one report, structural covariance patterns were identified from seed regions showing maximal atrophy across various neurodegenerative diseases. Structural covariance with these seed regions in young adults reflected atrophy patterns in a disease specific manner (Seeley, Crawford, Zhou, Miller, & Greicius, 2009). As one example, structural covariance of the default network in young showed high spatial coherence with the pattern of neurodegeneration observed in Alzheimer's disease. We recently reported similar patterns of reduced structural covariance within the default network, with changes observable over as little as 2 years in a normal aging cohort. Further, we observed that changes in default network structural covariance reliably predicted the transition from

mild cognitive impairment to Alzheimer's disease in a longitudinal sample (Spreng & Turner, 2013). Similar patterns of declining structural covariance have been reported in other large-scale distributed brain networks, including executive control networks, which have been implicated in those cognitive functions most affected by aging (Montembeault et al., 2012). Indeed, measures of structural covariance, when combined with estimates of cerebral blood flow, explained almost all age-related variance in cognitive performance in a recent report (Steffener, Brickman, Habeck, Salthouse, & Stern, 2013). This last observation speaks to the importance of measuring not simply independent trajectories of regional changes but covariance patterns describing how volume changes in distributed brain regions cohere across the across the lifespan.

Summary of Structural Brain Changes in Aging

With the advent of increasingly powerful in vivo neuroimaging techniques, the study of age-related structural brain changes represents a vast and expanding field. Given the scope of the review, we chose to focus on the broad trends that have been most reliably reported over the past 2 decades of structural neuroimaging research. Global changes in gray matter, white matter, and ventricular volumes are clearly a hallmark of normal brain aging. Heteromodal association cortices are more susceptible to late-life structural decline than primary-sensory motor regions, and rates of decline differ among cytoarchitectonic zones. Rapid declines occur in frontal and heteromodal association cortices in young-old, with comparatively shallow rates of decline observed in medial temporal lobe and primary sensorimotor regions. This is followed by more rapid changes in the medial temporal lobe and primary sensorimotor motor regions in old-old adulthood. White matter changes, whether measured as volume, integrity, or lesion burden, are also a prominent feature of brain aging and may in fact be a stronger predictor of cognitive decline and dementia than cortical changes. Finally, investigators are increasingly moving beyond region-specific metrics to identify whole brain patterns of structural brain change. Measures of structural covariance have proven to be powerful predictors of cognitive capacity in normal aging and as potent biomarkers of the transition from normal aging to neurodegenerative disease. Understanding these normative patterns of structural brain change is critical to expanding opportunities for detecting nonnormative brain aging using in vivo imaging methods. However, as we noted in our chapter introduction, age-related brain change is multidimensional, affecting both structure and function. In the next section, we turn our attention to changes in how the brain functions in older adulthood again considering how these are reflected globally, regionally, and at the level of interacting networks.

FUNCTIONAL BRAIN CHANGES IN OLDER ADULTHOOD

Functional neuroimaging methods have been used to study the aging brain for more than 3 decades. Much of the work over this period has used these methods to identify the neural correlates of cognitive functioning across myriad domains (e.g., sensory-motor, processing speed, memory, executive function). As with the research literature on structural brain changes, the findings characterizing functional changes in older adulthood are often varied and provide conflicting perspectives as to the nature and implications of observed differences in brain activation between age cohorts. In this section, we briefly review domain-specific brain changes, focusing on the findings of our recent meta-analytic reviews. We then review more domain-general patterns of functional brain changes in older adulthood and describe several of the leading theoretical perspectives in the field. As with our review of structural brain aging, we end this section by describing age-related functional brain changes at the level of large-scale, functionally connected brain networks. We have chosen to focus here on functional neuroimaging studies using MRI or PET measures of brain function. Although much research and numerous advances have been made using electrophysiological techniques, including EEG and MEG studies, we are unfortunately unable to cover these techniques within the scope of the review.

Domain-Specific Changes

The field of neurocognitive aging research has rapidly expanded over the past 2 decades. Although a comprehensive survey of the literature across this vast literature is beyond the scope of this chapter, we have published three meta-analytic reviews of studies investigating age-related functional brain changes. The first meta-analysis included 80 functional neuroimaging studies across four cognitive domains: perception, memory encoding, memory retrieval, and executive functioning (Spreng, Wojtowicz, & Grady, 2010). For perceptual tasks, older adults showed greater dorsolateral PFC as well as anterior insula and frontal opercular activation, whereas younger adults showed the predicted pattern of greater activity in sensory cortices, particularly occipital regions. For memory tasks, young adults showed greater right lateral PFC and medial temporal activity during encoding, whereas older adults preferentially engaged right PFC regions during memory retrieval. Age differences during executive control tasks were primarily observed in prefrontal brain regions. Specifically, older adults showed greater activation in more dorsal aspects of PFC bilaterally, whereas younger adults showed greater recruitment of right ventrolateral PFC regions. Across all domains, older adults engaged prefrontal regions to a greater extent than young adults.

In contrast, younger subjects, particularly those showing poorer task performance, engaged posterior sensory regions. Further, the enhanced pattern of PFC recruitment observed in the older adult cohorts was performance-dependent. Higher performing older adults showed greater left lateralized prefrontal engagement, while lower performing subjects engaged regions of right PFC.

In two follow-up meta-analyses, we examined age differences specifically in the domain of executive control processing. We examined patterns of age-related brain change associated with discrete executive control processes including working memory, inhibition, and task switching (Spreng, Shoemaker, & Turner, 2017; Turner & Spreng, 2012). Consistent with the findings of the earlier review, we observed a general pattern of increased functional brain activity for older versus younger adults. However, the specific nature of this enhanced functional recruitment was process specific. Task switching and working memory were associated with increased prefrontal recruitment bilaterally. In contrast, inhibition showed a "young-plus" pattern with age-related increases localized to regions typically implicated in young. Again, the most robust age difference observed across all three control processes was enhanced recruitment of prefrontal brain regions for older versus younger adults. This age-related difference in PFC activity was greater at higher levels of working memory demand, suggesting that increased recruitment of these regions may reflect greater reliance on, or strategic engagement of, working memory resources in older adulthood (Spreng et al., 2017).

Domain-General Changes: Neural Dedifferentiation

As reviewed in the preceding text, early functional neuroimaging studies of cognitive aging typically adopted a domain-specific approach, with investigators enumerating age-related changes in the neural implementation of specific cognitive task performance using cross-sectional study designs (for reviews, see C. L. Grady, 2008, 2012; Greenwood, 2007; Hedden & Gabrieli, 2004; Park & Reuter-Lorenz, 2009; P. A. Reuter-Lorenz & Lustig, 2005; P. A. Reuter-Lorenz & Park, 2014; Spreng et al., 2010; Turner & Spreng, 2012). Taken together, these studies also identified domain-general patterns of functional brain changes in aging, suggesting that all age-related cognitive changes may share, at least in part, a common neural substrate. Perhaps the most ubiquitous pattern observed across studies has been referred to as *neural dedifferentiation*, increased and more spatially distributed patterns of neural activity in older versus younger adults during cognitive task performance (Park, Polk, Mikels, Taylor, & Marshuetz, 2001). In one of the earliest functional neuroimaging investigations of cognitive aging, PET scanning

methods were used to measure changes in metabolism across brain regions while younger and older participants performed visuoperceptual tasks. Older participants displayed greater functional activation during task performance than younger participants. Moreover, unlike the lateralized pattern of functional activity within the prefrontal cortex observed in the young, older participants demonstrated greater bilateral activation (C. L. Grady et al., 1994). Since this seminal work, this pattern of decreased lateralization in functional brain response in aging has been replicated in numerous reports using both PET and fMRI methods, spanning a range of cognitive domains including memory encoding and retrieval (Cabeza, 2002; Cabeza, Anderson, Locantore, & McIntosh, 2002; C. L. Grady, 1996; McIntosh, 1999; Velanova, Lustig, Jacoby, & Buckner, 2007), visual attention (Cabeza, 2002; Cabeza et al., 2002; C. L. Grady, 1996; Madden et al., 2007; McIntosh, 1999; Velanova et al., 2007); working memory (Cabeza, 2002; Cabeza et al., 2002; Cappell, Gmeindl, & Reuter-Lorenz, 2010; C. L. Grady, 1996; Mattay et al., 2006; McIntosh, 1999; Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000; Velanova et al., 2007), and selective attention and inhibition (Colcombe, Kramer, Erickson, & Scalf, 2005).

The finding that cortical activation patterns become increasingly differentiated is now a leading account of functional brain changes in older adulthood and indeed of neurocognitive aging. Dedifferentiation has been operationalized in a number of ways. It has been described simply as nonidentical brain activity patterns between younger and elder populations (Zarahn, Rakitin, Abela, Flynn, & Stern, 2007) or as more diffuse and distributed cortical representations of cognitive activities (Craik & Bialystok, 2006). Other researchers suggest that it reflects a failure to engage specialized neural mechanisms during cognitive performance (Cabeza et al., 2002; Li, Lindenberger, & Sikström, 2001). Three forms of dedifferentiation have been described (Park et al., 2001). Contralateral recruitment refers to the age-related recruitment of brain regions homologous to those recruited in younger participants (e.g., C. L. Grady et al., 1994). Unique recruitment describes the engagement of additional (nonhomologous) brain regions (e.g., Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Madden et al., 2007; McIntosh, 1999). Finally, substitution reflects activation of entirely novel neural networks in older relative to younger adults, perhaps signaling strategy differences or functional reorganization (e.g., Rieck, Rodrigue, Boylan, & Kennedy, 2017; Turner & Spreng, 2015).

Evidence for dedifferentiated neural response in older versus younger adults suggests that reduced neural specialization may provide a neural marker of age-related cognitive decline. However, as a theory of neurocognitive aging, it is ambivalent with respect to whether these brain changes are compensatory or deleterious. In other words, does dedifferentiated neural

response reflect compensatory functional responses or inefficient processing in older adults? In general, decreased lateralization of functional brain activity (i.e., greater dedifferentiation) has been considered compensatory for cognitive performance in older adulthood. In an early report, older participants who performed better on a verbal memory task showed greater bilateral PFC activation than those who performed more poorly, suggesting that dedifferentiated neural activity was indeed a compensatory functional response to degraded neural circuitry in healthy aging (Cabeza et al., 2002). Dedifferentiation through substitution has also been positively associated with cognitive performance. During an incidental encoding task, older adults recruited medial temporal lobe regions less, and lateral PFC regions more, than their younger counterparts (Gutchess et al., 2005). Moreover, recruitment of lateral PFC and medial temporal lobe structures were inversely correlated in older but not younger participants. The investigators concluded that because the analysis was only conducted on "remembered" stimuli, dedifferentiation was compensatory for recognition performance in the older adults. Perhaps the most compelling evidence that dedifferentiation is compensatory was provided by the application of repetitive TMS (rTMS) to older and younger participants during an episodic memory task. Although memory retrieval was disrupted by rTMS to a right PFC region in younger participants, older participant performance was disrupted by rTMS applied to both right and left PFC, suggesting that greater bilateral recruitment (i.e., dedifferentiation) supported cognitive performance in these participants (Rossi et al., 2004).

In contrast to these compensatory accounts, several functional neuroimaging studies have reported that dedifferentiated neural response is associated with poorer, not improved, cognitive ability in older adults. In one of the few studies to directly contrast these competing behavioral accounts of neural dedifferentiation, functional compensation and neural inefficiency hypotheses were directly contrasted in a sample of healthy older and younger adults during performance of a delayed recognition task (Zarahn et al., 2007). The authors observed evidence of inefficient neural responding (i.e., greater activity for equivalent performance) in older relative to younger participants across a large area of cortex during encoding and maintenance epochs of the task. Moreover, the spatial patterns of response in younger participants were more similar to the pattern observed in higher performing than lower performing older adults, which is inconsistent with a compensatory account.

Dedifferentiation of neural response in older relative to younger adults has been one of the most ubiquitous findings in the neurocognitive aging literature. Moreover, this account of functional brain changes parallels a similar pattern of dedifferentiation in behavioral performance across

cognitive domains in older adulthood (Baltes & Lindenberger, 1997). Although there is strong empirical evidence demonstrating dedifferentiation of functional brain response in older adulthood, the data remain equivocal as to whether these changes are compensatory or associated with cognitive decline in later life. In the next section, we briefly review several leading theories of age-related changes in brain function that attempt to reconcile the compensation versus decline debate, while also providing more specific accounts of the topology and cognitive implications of age-related functional brain changes.

Theories of Brain Function in Older Adulthood

As with studies investigating structural brain changes, accounts of functional change across the adult lifespan are highly variable and report somewhat conflicting findings with respect to the patterns of change and their implications for cognitive function in later life. However, areas of broad convergence have emerged, and these have been characterized by several leading theories of neurocognitive aging.

Consistent with the evidence for functional dedifferentiation reviewed earlier, a series of studies investigating brain changes during episodic, working memory, and visual attention tasks, older adults demonstrated a robust pattern of reduced asymmetry in the pattern of activation across cerebral hemispheres (Cabeza, 2002). This pattern of overlapping, or dedifferentiated, neural response across cognitive tasks was described as *hemispheric reduction asymmetry in older adults* (HAROLD). Older adults demonstrating the HAROLD pattern of functional brain changes showed better performance on an episodic memory task than those who showed a more "young-like" pattern of asymmetry in the recruitment of prefrontal brain regions during the task, suggestive of compensation. Further, this pattern was observed across multiple cognitive domains including episodic memory, working memory, and visual attention (Cabeza et al., 2004).

Age-related functional brain changes have also been observed in response to increasing levels of task challenge leading to the *compensation-related utilization of neural circuits hypothesis* (CRUNCH) of cognitive aging (P. A. Reuter-Lorenz & Cappell, 2008; P. A. Reuter-Lorenz & Lustig, 2005). This theory posits that inefficiencies in neural processing may cause older adults to overrecruit neural resources to achieve the same level of cognitive performance as younger adults. As with HAROLD, increased, or dedifferentiated, recruitment patterns were seen as evidence for compensatory activity, necessary to overcome degraded or noisy neural signaling associated with broader neuronal tuning curves (e.g., Li & Rieckmann, 2014) or degraded signaling pathways (e.g., Bennett & Madden, 2014). The CRUNCH hypothesis

predicts two patterns of functional brain change that are commonly reported in older adulthood. At lower levels of task demand, increased recruitment is observed in the context of equivalent cognitive performance for older and younger adults. However, as task demands increase, older adults demonstrate lower levels of brain activity than younger individuals, and task performance declines. Thus, although considered a compensatory account, by incorporating levels of task demand, CRUNCH suggests that older adults show poorly modulated and inefficient neural recruitment patterns, with greater brain activity required per unit of cognitive output.

A third theory of neurocognitive aging integrates both structural and functional brain changes when considering the behavioral implications of dedifferentiated patterns of brain activity in older adulthood. The *scaffolding theory of aging cognition* (STAC) argues that changes in cortical volume, white matter integrity, and neurochemical signaling may be counteracted, at least in part, by the construction of neural "scaffolds" (Park & Reuter-Lorenz, 2009; P. A. Reuter-Lorenz & Park, 2014). Conceptually similar to the CRUNCH hypothesis, these scaffolds involve the functional recruitment of additional neural resources to offset these age-related structural brain changes. In this model, dedifferentiated patterns of brain response in older adulthood reflect a scaffolding process wherein additional neural resources are engaged to supplement task-specific recruitment patterns observed in younger adults (P. A. Reuter-Lorenz & Park, 2014). As reviewed in the earlier domain-specific section, these scaffolds, or patterns of enhanced recruitment, in older adults typically involve activation of anterior brain regions bilaterally, consistent with the *posterior to anterior shift in aging* (PASA) hypothesis (Davis et al., 2008) and the HAROLD models (Cabeza, 2002).

The final theory we review in this section on domain-general theories of functional brain aging is *neuromodulation*. This account of age-related functional brain changes argues that declines in the goal-directed modulation of neural activity is a central mechanism of neurocognitive aging (Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Gazzaley & D'Esposito, 2007). Consistent with this idea, reduced selectivity in neural responses in category-selective regions of visual association cortex in older relative to younger participants have been reported during a working memory task (Payer et al., 2006). Critically, this reduced selectivity in neural responses (i.e., noisier processing) was accompanied by enhanced activity in the PFC, suggesting greater PFC activity was necessary for older adults to modulate visual association regions in response to degraded perceptual representations. A similar pattern of age-related deficits in the modulation of neural responses based on task goals has been reported during selective working memory (Gazzaley et al., 2005). During the task, age-related reductions in goal-directed suppression of activity in the visual association cortex resulted in poor filtering

of goal-irrelevant stimuli, and, critically, these brain changes predicted subsequent impairments on a recognition memory paradigm.

Consistent with this idea, impaired modulatory capacity, as seen in older adulthood, has been shown to attenuate neural responsiveness to afferent signaling in posterior brain regions, producing poorly regulated and noisy information processing as evidenced both in computational modeling (Li & Rieckmann, 2014) and functional neuroimaging (Schmitz, Dixon, Anderson, & De Rosa, 2014) studies. Resultant reductions in signal-to-noise ratios degrade the integrity of mental representations, thus reducing the quality of information throughput to higher cognitive processes. According to the neuromodulation account, reduced modulatory capacity should preferentially impact those domains dependent on the highest levels of representational complexity, including episodic memory, selective attention, and working memory. These are indeed among the most vulnerable to age-related decline and show robust patterns of dedifferentiated brain response in prefrontal brain regions (cf. Spreng et al., 2010, 2017; Turner & Spreng, 2012).

Changes in Functional Brain Networks

With the advent of whole-brain, in vivo functional neuroimaging methods, and recent advances in computational resources and multivariate analytical methods, neurocognitive aging is increasingly studied through the lens of large-scale functional brain networks (Damoiseaux, 2017). Commonly reported patterns of age-related changes in neural networks, or functionally connected assemblies of spatially distributed brain regions, include changes occurring within specific brain networks, as well as alterations in the dynamic interactions among networks.

Investigations of network changes associated with normal aging have typically implicated the default network, a collection of functionally connected brain regions including the posterior cingulate cortex (PCC), medial PFC (MPFC), inferior parietal lobule, and the medial and lateral temporal lobes (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; C. L. Grady et al., 2010; Hafkemeijer, van der Grond, & Rombouts, 2012; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Sambataro et al., 2010; Sheline & Raichle, 2013; Turner & Spreng, 2012). The default network is activated during social or internally directed cognitive processes, including access to stored knowledge representations and experiences (Andrews-Hanna et al., 2014) and is typically suppressed during performance of externally directed tasks (Buckner, Andrews-Hanna, & Schacter, 2008). Age-related changes include reduced suppression (Hansen et al., 2014; Lustig et al., 2003; Persson et al., 2007) and decreased within-network connectivity during

both task (Geerligs, Maurits, Renken, & Lorist, 2014; C. L. Grady et al., 2010; Sambataro et al., 2010) and rest (Andrews-Hanna et al., 2007; Chan, Park, Savalia, Petersen, & Wig, 2014; Damoiseaux et al., 2008; Geerligs, Renken, Saliasi, Maurits, & Lorist, 2015). Recent evidence also suggests that the default network is more functionally connected to other brain networks in aging (Chan et al., 2014; Geerligs et al., 2015; Muller, Mérillat, & Jäncke, 2016; Sambataro et al., 2010; Sheline & Raichle, 2013; Spreng, Stevens, Viviano, & Schacter, 2016), and this connectivity is poorly modulated by task context (C. L. Grady, Sarraf, Saverino, & Campbell, 2016; Rieck et al., 2017; Spreng & Schacter, 2012; Spreng et al., 2016; Turner & Spreng, 2015).

Although changes involving the default network have been frequently reported, there is mounting evidence to suggest that the global network architecture of the brain is altered across the adult lifespan. This has been characterized as reduced network segregation and increased integration (Chan et al., 2014). As with patterns of brain activity (reviewed earlier), interactions among spatially distributed brain networks become increasingly dedifferentiated in older adulthood. In the context of functional brain networks, this means that with age, interactions between networks increase (i.e., they become less segregated or differentiated), while within-network connectivity declines. Measured across the whole brain, older adults display a less discrete network architecture both during cognitive task performance (Chan et al., 2014; Gallen, Turner, Adnan, & D'Esposito, 2016) as well as during rest, suggesting these functional network changes are also manifest within the intrinsic network architecture of the brain (e.g., Geerligs et al., 2015).

Similar patterns of network differentiation with age have been reported in a more circumscribed set of brain networks, including the default, dorsal attention, and frontal parietal control networks both during task and at rest (C. L. Grady et al., 2016; Spreng et al., 2016). Specific changes include reduced anticorrelations between dorsal attention and default networks and increased network interactions across all three networks, consistent with a network dedifferentiation account. We have also reported poor modulation of network interactions based on task goals. Older adults fail to decouple default and frontoparietal control networks in response to changing task context (Spreng & Schacter, 2012) and control demands (Turner & Spreng, 2015). These observations led us recently to propose the *default-executive coupling hypothesis of aging* (DECHA; Spreng & Turner, in press; Turner & Spreng, 2015; see Figure 1.1). This network neuroscience model of neurocognitive aging suggests that with age, older adults fail to flexibly decouple brain regions implicated in control processes from the default network, implicated in more associative cognitive processes. We have recently shown that increased coupling of these networks, as predicted by the DECHA,

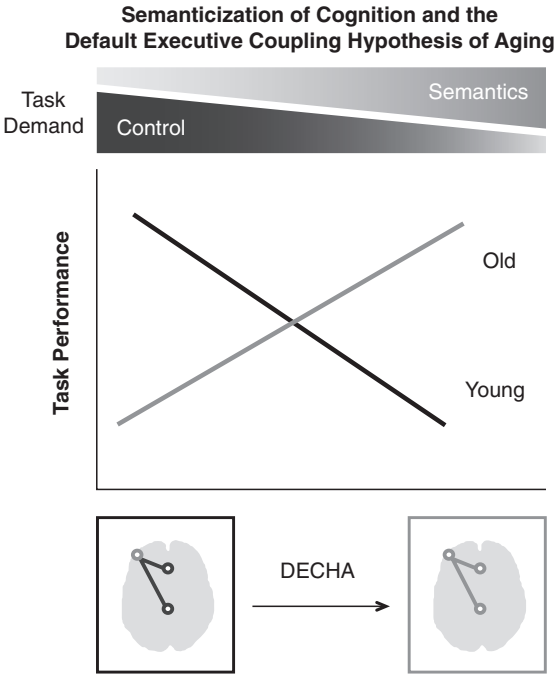

Figure 1.1. Default-executive coupling hypothesis of aging (DECHA): Integrated model of cognitive and brain aging. Behavior (top): Greater task demand for semantics impacts performance differently for younger and older adults. Brain (bottom): Default (midline circles) to executive (lateral circles) coupling increases from younger (black lines) to older age (lines). Data from Samanez-Larkin and Knutson (2015).

is associated with reduced fluid intelligence and increased reliance on semantic or crystalized knowledge in older adulthood (Spreng et al., 2018). Further, default coupling to the frontal–parietal control network defined more broadly, to include regions implicated in salience processing, may convey real-world benefits for older adults during tasks requiring access to prior knowledge such as creative problem solving (Adnan, Beaty, Silvia, Spreng, & Turner, 2019). Evidence both from cross-sectional (Rieck et al., 2017) and longitudinal (Ng, Lo, Lim, Chee, & Zhou, 2016) investigations provide support for this hypothesis and provide further evidence that these changes in network interactivity can predict individual differences in cognitive functioning. Taken together these network-based accounts of functional brain aging point to network neuroscience as an important new frontier in neurocognitive aging research.

Summary of Functional Brain Changes in Aging

In this section, we have reviewed the current state of knowledge with respect to changes in brain function that occur from younger to older adulthood. Domain-specific changes include greater recruitment of frontal brain regions during complex cognitive tasks, reduced hemispheric lateralization in anterior brain regions (e.g., Cabeza, 2002; C. L. Grady et al., 1994), and evidence for enhanced activation in regions typically engaged by young adults (Spreng et al., 2010, 2017; Turner & Spreng, 2012). Taken together, these domain-specific patterns of age-related brain changes reflect a global pattern of neural dedifferentiation, suggesting older adults have reduced capacity to recruit specialized neural circuits associated with discreet processing operations (Li et al., 2001). Leading theories of functional brain aging generally converge around the notion that these patterns of functional brain change are compensatory. Functional dedifferentiation reflects recruitment of additional neural resources, or scaffolds, to overcome the challenges posed by degraded neural signaling and communication associated with structural brain changes in later life. However, compensation comes at the cost of neural efficiency, with older adults expending greater neural resources per unit of cognitive output (cf. Zarahn et al., 2007). Finally, as with investigations of structural brain changes in older adulthood, researchers are increasingly studying age-related functional changes through the lens of distributed brain networks. Paralleling changes in regional activity, functional brain networks also appear to follow a dedifferentiation pattern in older adulthood, both with respect to the global network architecture of the brain and within more domain-specific cognitive networks. These network-level changes are marked by reduced within-network and increased between-network connections, as well as reduced modulation of network dynamics in response to changing task demands.

CONCLUSIONS AND NEW FRONTIERS

Summary of Structural and Functional Brain Changes

Over the past century we have learned much about the aging brain. With advances in in vivo imaging techniques, we now know that the cranial vault masks profound changes that occur in the structure of the brain across the adult lifespan. By some estimates, these changes may represent volume losses 0.3% per year through middle age, accelerating to almost 0.6% per year in older adulthood. We have also learned that these changes are not uniform across the cerebrum. The most profound and rapid losses occur in anterior and heteromodal association cortices, regions that are the last to

reach maturation in early adulthood. Further, not all tissue compartments undergo similar rates of decline. Although earlier studies suggested that white matter was not affected in normal aging, more recent work demonstrates that changes in the volume, integrity, and overall health of the brain's white matter may be the most significant predictor of the transition from normal aging to neurodegenerative disease. Perhaps most surprising given the extent and pace of structural brain change, is the relative paucity of evidence linking these changes to cognitive abilities in later life. A central factor in this incongruity may be the role of altered brain function in mediating the impact of structural changes. Functional brain changes include both domain-specific and nonspecific alterations in neural activation patterns that together point to a generalized pattern of neural dedifferentiation. Theories of neurocognitive aging, although differing somewhat with respect to specific causes and consequences, coalesce around the idea that older adults recruit additional neural resources to sustain cognitive output at a level equivalent to young, but at the cost of neural efficiency. Finally, we observed a growing trend in the literature to consider brain aging not only in terms of local changes but as alterations in large-scale and spatially distributed brain networks. Network patterns appear to mirror local changes, with the greatest declines observed in nodal connections involving anterior and heteromodal association cortices as well as an age-related shift toward a more dedifferentiated functional network architecture.

Emerging Challenges and Opportunities

Despite significant advances in our understanding of the aging brain, many challenges remain. Foremost among these is characterizing the interdependencies between structural and functional brain changes across the lifespan, and how these interactions influence the trajectory of age-related cognitive decline. In our review, we addressed structure and function separately, mirroring the vast majority of the research literature in the field. However, mapping the interactions and contingencies between changes in brain structure and function across the lifespan is almost certainly a precondition for developing predictive biomarkers that can reliably differentiate healthy versus pathological brain aging (for a recent effort to develop an integrated computational model of senescence across the lifespan, see Naik, Banerjee, Bapi, Deco, & Roy, 2017). Advances in multivariate and machine learning analytical tools are now opening the door for the inclusion of an array of structural and functional brain metrics in a single analytical model to predict the trajectory of cognitive aging. These methods are allowing researchers to move beyond characterizing group differences to pursue the development of person-specific biomarkers of age-related cognitive change.

However, progress in this direction will require large-scale studies to develop normative data sets, a daunting challenge given that variability is increasingly seen as a hallmark of neurocognitive aging (Garrett et al., 2013).

The vast majority of research in the field still consists of cross-sectional, extreme group designs. As discussed earlier, this approach can mask individual differences, and tends to underestimate the extent of age-related change. Large-scale longitudinal studies, such as the Betula Project, the Baltimore Longitudinal Aging Study, or Singapore Longitudinal Aging Brain Study, are beginning to address this issue. Further, open data initiatives are allowing for the aggregation of brain data across studies and centers resulting in unprecedented sample sizes (e.g., Human Connectome, UK Biobank projects). Combined with exponential advances in computational resources, these efforts hold significant promise for overcoming challenges posed by heterogeneity to drive the development of person-specific biomarkers, mapping structural and functional brain changes to individual trajectories of cognitive aging.

Finally, while big data initiatives hold considerable promise for biomarker development, efforts to develop a more mechanistic understanding of structural and functional brain aging are also informing the design of targeted interventions to alter the course of cognitive aging. We have drawn on the neuromodulation theory of functional brain aging (D'Esposito & Chen, 2006; Gazzaley & D'Esposito, 2007) to develop a targeted behavioral intervention protocol to enhance goal-directed modulation of brain activity, and executive control capacity, in older adulthood (Adnan, Chen, Novakovic-Agopian, D'Esposito, & Turner, 2017). Researchers are also drawing from network neuroscience models of brain aging to guide neurostimulation interventions to alleviate symptoms of psychiatric and neurological diseases, including diseases of aging. In one recent report, brain network analyses were used to detect regions on the cortical surface that were functionally connected to subcortical brain structures typically targeted in deep brain stimulation treatments (Fox et al., 2014). These analyses open the possibility of stimulating surface nodes (e.g., using TMS) to activate or suppress subcortical nodes noninvasively to alleviate symptoms of neurological or psychiatric disorders. Although only two of many examples, these reports highlight the potential translational implications of our increasingly sophisticated understanding of the aging brain. As this review has clearly demonstrated, the first 100 years of research exploring the structural and functional brain changes that occur across the adult lifespan have proven remarkably fruitful, enhancing our knowledge of the aging brain and highlighting the limitations and pitfalls inherent to human brain mapping. Undoubtedly the next century will offer myriad advances—and surprises—as we continue the quest to map the topology and trajectory of brain aging and leverage these discoveries to sustain and enhance cognitive functioning in later life.

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