6 Brains, Hearts, and Minds: Trajectories of Neuroanatomical and Cognitive Change and Their Modification by Vascular and Metabolic Factors

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ABSTRACT Aging is accompanied by substantial reductions in brain volume, alterations in structural properties of the white matter, shifts in iron metabolism, and selective cognitive declines. Although it is assumed that brain changes precede and mediate cognitive aging, empirical support for this assumption is sparse. Cross-sectional studies cannot provide an adequate solution to the age-brain-cognition (ABC) triangle, and multiwave longitudinal investigations that can reveal mediation and moderation relationships among these variables are rare. Moreover, the trajectories of neural and cognitive aging and the distribution of variance in the ABC triad can be influenced by multiple factors reflecting vascular and metabolic risk and the propensity for neuroinflammatory response. To complicate matters further, the BC part of the trilateral relationship is not necessarily described by the brain's unidirectional effects on cognition. Rather, empirical evidence suggests that those are frequently connected by bidirectional paths. In addition, vascular, metabolic, and inflammatory risk factors modify and moderate the trajectories of age-related change. Although the extant literature is still scant, certain trends can be discerned, and the paths to elucidating the neural mechanisms of age-related changes through studying neuroanatomical changes in the context of the brain energy crisis can be outlined.

I list not prophecy; but let Time's news
Be known when 'tis brought forth.
—Shakespeare, *Winter's Tale*

Act IV, Scene 1

Whoever came up with the "time takes its toll" cliché knew what they were doing, for it is incontrovertible that in adult mammals, changes in virtually all systems and organs accompany the passage of time. Advanced age is associated with reduced lean mass and bone density, limited respiratory fitness, increased insulin resistance, low-grade chronic inflammation, lowered energy expenditure, and elevated vascular risk factors (Manini, 2010; Margolick & Ferrucci, 2015). Conceptualization of the multifarious aging process as a slow-rolling energy crisis (de la Torre, 2008) aligns with the dominant views of modern gerontology: the free radical accumulation model (Garaschuk, Semchyshyn, & Lushchak, 2018; Harman, 1956) and the disposable soma theory (Kirkwood, 1977). These theories converge on the conceptualization of postreproductive aging as an unprogrammed stochastic wear-and-tear process, driven by shifting of the dynamic equilibrium between the benefits of reactive oxygen (ROS), nitrogen (RNS), and carbonyl (RCS) species—RONCS (Garaschuk et al., 2018)—and the declines they cause through damaging mitochondria and inducing energetic deficit.

The inability to meet energy demands may underpin the differential age-related changes, and despite its universality, aging preferentially affects organs and systems with the highest energy requirements—the muscles, the liver, and the brain (Manini, 2010). The latter, while constituting only 2% of body weight, draws more than 20% of the organism's total energy (Attwell & Laughlin, 2001), most of which supports the brain's information-processing capability through maintaining neurotransmission (Howarth et al., 2012), while the remainder is allocated to building and maintaining structural components.

At any moment, the size and structural composition of the brain is determined by multiple forces and actors that make a veritable Robinson Crusoe list of things

good and evil. Nature is a mighty seamstress toiling over alterations in the never-quite-perfect fabric of the brain, shortening and extending and widening and narrowing to meet the demands, within genetic constraints, of many biological processes and environmental experiences. On the one hand, neuropil volume grows through the expansion of dendritic arborization, synaptogenesis, myelin synthesis, angiogenesis, astrocyte proliferation, and neurogenesis. On the other hand, attrition and shrinkage of neurons, synapse stripping by microglia, dendritic spine retraction, demyelination, and loss of astrocytes offset the expansion. The complexity of forces at play makes inferring neurobiological mechanisms of cognitive aging from gross structural changes extremely challenging and calls for evaluating their molecular and metabolic underpinnings. Although animal models exploring the fundamental physiology of aging are plentiful, their translation to noninvasive studies of the human brain is lagging.

The Free-Radicals-Induced Energetic and Neural Decline in Senescence (FRIENDS; Raz & Daugherty, 2018; figure 6.1) model inspired by the free-radical (Harman, 1956) and the energy crisis (de la Torre, 2008) theories casts the gradual decline in the availability of energy resources as the core phenomenon of cognitive aging. The age-related waning of mitochondria is exacerbated by endothelial dysfunction that impairs the delivery of energy substrates and the removal of byproducts and debris of cellular decay (e.g., Singer et al., 2014). Whereas maintaining ion pumps is critical for neurotransmission and is unlikely to slow down and accommodate the dwindling energy supply, the upkeep of the metabolically expensive myelin sheath (Bartzokis, 2011), cellular membranes, and dendritic spines (Morrison & Baxter, 2012) is affected by energetic scarcity. Moreover, endothelial dysfunction may directly impair the maintenance of the myelin sheath (Rajani et al., 2018). Thus, brain connectivity is disrupted (Damoiseaux, 2017), and it becomes a progressively noisier system. Noise propagates in the information-processing networks (Myerson et al., 1990) and is likely to affect them in proportion to their complexity. Aging, therefore, is bound to induce a differential failure of those cognitive skills that depend on novel connections and the reconfiguration of existing networks rather than those that rely on existing "greased paths."

Despite significant advances in the understanding of the mechanisms that translate brain cellular activity into cognitive operations undergirding complex reasoning, the specifics of the associations between brain aging and age-related cognitive changes remain unclear, and elucidating the mechanisms of brain aging is a critical priority for understanding and mitigating senescent cognitive declines. Yet, because it is an integral part of the organism, clarifying the brain's role in age-related cognitive changes is impossible without describing the contributions of other organismic components that affect its properties and the trajectories of change (Fjell et al., 2014; Kennedy & Raz, 2015; Raz & Rodrigue, 2006). Below, I survey the current literature on age-related changes in brain structure and their relation to cognitive changes, as well as the role of various risk factors in shaping individual trajectories of neurocognitive aging. Functional brain changes are reviewed in chapters 5 and 7 of this volume.

Postmortem Studies

Neuroanatomical postmortem studies have demonstrated that the brains of older adults are smaller and lighter than those of their younger counterparts and exhibit significantly larger cerebrospinal fluid cavities (Kemper, 1994). Older brains evidence shrinkage, dysmorphology and the selective attrition of neurons (Pakkenberg et al., 2003), the impairment of neurogenesis and synaptogenesis, sparser dendritic spines (Morrison & Baxter, 2012), and lower myelin content in the cortex and subcortical white matter (Kaes, 1907). Iron content is elevated in older brains, especially in the basal ganglia, the substantia nigra, and the red nucleus (Hallgren & Sourander, 1958). With iron as a key player in mitochondrial energy production (Zecca et al., 2004), its excessive deposits may signal the disruption of energy metabolism with age as well as set off multiple paths to age-related neurodegeneration (Ashraf, Clark, & So, 2018). Postmortem studies, though indispensable in elucidating the natural history of mammalian aging, represent only a cross-sectional snapshot of the brain state. They reveal nothing about the temporal dynamics and individual differences in change, which became accessible only with noninvasive neuroimaging techniques.

Aging of the Brain Structure: In Vivo Evidence

For the past three decades, noninvasive neuroimaging has produced a substantial body of cross-sectional studies of age differences in the brain's gross structural properties. The findings from in vivo studies agree with the postmortem record. They document age-related differences in almost all brain regions, including smaller total and regional volumes, a thinner cortex, and larger cerebral ventricles in persons of advanced age compared to their younger counterparts (Raz, 2000). Meta-analyses of the extant studies and mega-analyses of aggregated samples show differential age-related alterations across brain regions: stronger

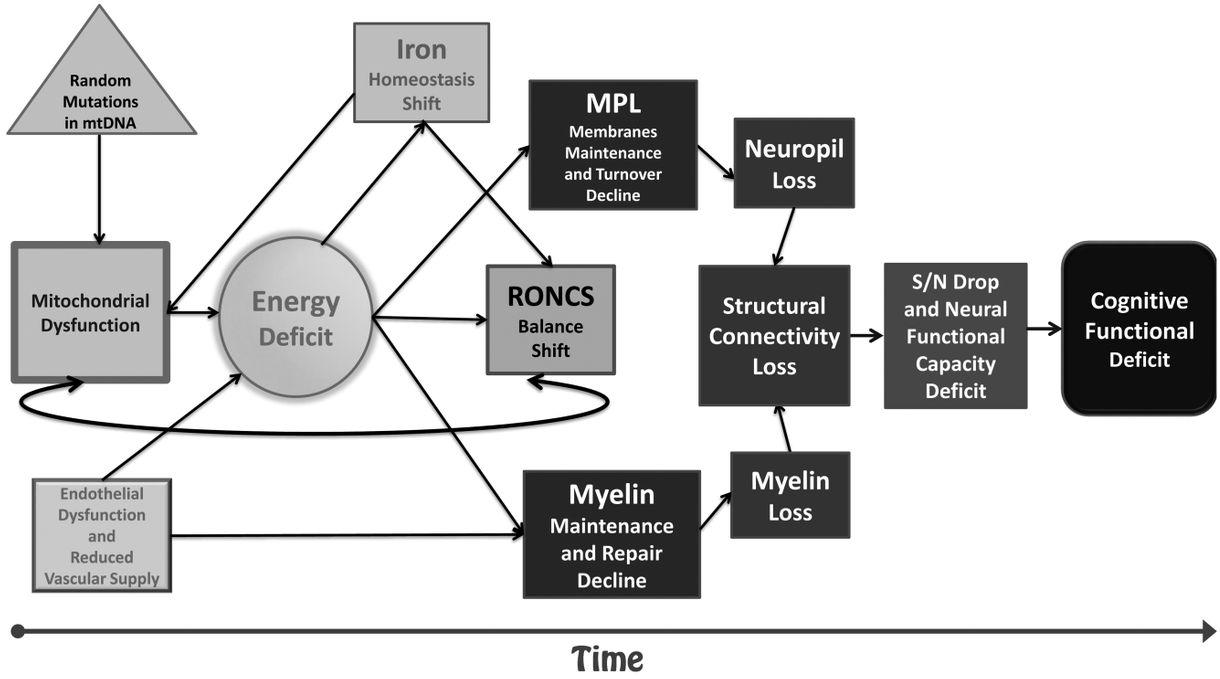

FIGURE 6.1 The FRIENDS model of cognitive aging. Random mutations accumulate in the mitochondrial DNA, and mitochondrial function declines with age. That decline results in the gradual reduction of energy substrates (ATP and NADH). The sequestration and transport of iron are affected, and the accumulation of iron, in turn, exacerbates mitochondrial declines. Endothelial dysfunction impairs the delivery of glucose and oxygen to the end organs in the brain and may directly stunt the regeneration of myelin. An energy crisis and further mitochondrial dysfunction ensue. Impaired mitochondrial respiration and the accumulation of iron lead to a shift in the homeostasis of RONCS and their excess further damages the mitochondria. This cascade of events further reduces the energy available for the maintenance of cell membranes and myelin and for supporting synaptic plasticity. Myelin and neuropil are gradually diminished, and connectivity among the brain regions is lost. That loss impairs the fidelity of neural communication, and the information-processing capabilities of the brain networks are degraded; the system becomes progressively noisier. Noise in the information- processing system affects all cognitive operations, with the more energy-dependent of them faring the worst of all. (See color plate 4.)

age associations in the prefrontal cortex, cerebellum, and neostriatum compared to the primary sensory cortices (e.g., Driscoll et al., 2009; Fjell et al., 2009; Raz et al., 1993, 1997, 2004; Walhovd et al., 2011; see Raz, 2000 for a review).

Despite their multiple advantages—for example, the feasibility of large-sample data collection and the potential for covering a life-span age range—cross-sectional studies have an irreparable flaw: they yield no true estimates of change and individual differences in change trajectories (Hofer & Sliwinski, 2001; Lindenberger et al., 2011) due to the violation of ergodicity assumption (McArdle, 2009; Molenaar, 2004). These limitations are particularly severe in studies that evaluate the brain's role in mediating age influence on cognition (Raz & Lindenberger, 2011). Therefore, I limit the discussion to longitudinal studies and call upon cross-sectionally sourced findings only when longitudinal data are unavailable.

Longitudinal studies of the cerebral ventricles and the whole brain reveal expansion of the former (e.g., McArdle et al., 2004) and shrinkage of the latter time (Raz & Rodrigue, 2006). Age-related shrinkage happens even in selected samples of healthy adults (Anblagan et al., 2018; Callisaya et al., 2013; Crivello et al., 2014; Fjell et al., 2013; Hua et al., 2016; Leong et al., 2017; Opfer et al., 2018; Pfefferbaum et al., 2013; Persson et al., 2014; Rast et al., 2018; Raz et al., 2005, 2010, 2013; Squarzoni et al., 2018; Yuan, Voelkle, & Raz, 2018) within time windows as narrow as six months (Raz et al., 2013). Brain volume change over at least two occasions has been estimated at 0.15% per annum in middle-age adults (Opfer et al., 2018) and .21% (Takao et al., 2012) and .51% in a broad-age sample (Storvse et al., 2014), steadily increasing to .56% (Leong et al., 2017), .61% (Opfer et al., 2018), .55%–.77% (Sigurdsson et al., 2012), .80% (Aljondi et al., 2018), and up to .83% (Crivello et al., 2014) in samples of older participants. Notably,

however, in some highly selected samples the total brain atrophy rates were modest even at the tenth decade of life (Mueller et al., 1998; Pressman et al., 2016).

Despite a general agreement on trends, specific findings vary across studies. The discrepancies may stem from differences in brain measurement methods, sample age ranges, and an admixture of individuals with vascular and metabolic risk factors, as well as frequency of assessments and the time elapsing between measurements. Most longitudinal studies of regional brain volumes reveal significant shrinkage of the neostriatum, cerebellum, posterior cingulate cortex, and tertiary association cortices. Lesser but still significant volume loss is noted in the fusiform, insular, anterior cingulate, and parahippocampal cortices, with minimal changes or no decline observed in the primary visual and somatosensory cortices (Crivello et al., 2014; Driscoll et al., 2009; Jiang et al., 2014; Kim et al., 2018; Leong et al., 2017; Persson et al., 2014; Pfefferbaum et al., 2013; Shaw et al., 2016; Storsve et al., 2014, see Kennedy & Raz for a review). Shrinkage of the hippocampus and the entorhinal cortex may follow a nonlinear course, with faster shrinkage in older participants (Crivello et al., 2014; Doré et al., 2013; Gorbatch et al., 2017; Jiang et al., 2014; Leong et al., 2017; Persson et al., 2014; Pfefferbaum et al., 2013; Raz et al., 2005, 2010; Storvse et al., 2014; see Kennedy & Raz [2015] for a review). Other regions (e.g., the prefrontal white matter) exhibit age-accelerated changes in some samples (Raz et al., 2008), whereas in other studies a mixed pattern of acceleration and deceleration is noted, with age-accelerating changes in the temporal and the occipital and deceleration in the prefrontal and the anterior cingulate cortices (Storsve et al., 2014). Notably, cross-sectional designs underestimate age-related changes in cortical volume and thickness (Fjell et al., 2014; Kim et al., 2018; Pfefferbaum & Sullivan, 2015; Rast et al., 2017; Raz et al., 2005; Sigurdsson et al., 2012).

The magnitude of regional declines varies even across studies on the samples drawn from the same population, and some age trends are less replicable than others. Importantly, however, significant individual variability of change is observed in virtually all regions and in all studies that statistically modeled individual differences. For example, substantial shrinkage of the prefrontal cortex and the white matter (Raz et al., 2005) was not observed in other samples studied in the same lab with the same methods (Persson et al., 2014; Raz et al., 2010), whereas shrinkage of the cerebellum, the hippocampus, and the orbitofrontal cortex, accompanied by a relative stability of the primary visual cortex, was consistently replicated (Persson et al., 2014; Raz et al., 2005, 2010). Cortical thickness trajectories approximate the course of age-related reduction in regional volumes (Storsve et al., 2014; Thambisetti et al., 2010; Yuan et al., 2018; but see Pacheco et al. 2015 for prominent thinning of the primary motor cortex), with the measures of cortical surface yielding lower estimates of age-related change (Storsve et al., 2014). Cortical thinning and volume shrinkage are tightly correlated, but the cortical surface changes at a slower pace (Storvse et al., 2014). The shape of age-related change—linear, quadratic, or accelerated/decelerated exponential—is still unclear, as very few studies included more than one follow-up assessment, thus precluding the trajectory evaluation.

In summary, structural brain aging is heterochronic and individualized. The fact that some persons show minimal change, whereas others exhibit steep declines, spurs the search for influential factors mitigating age-related change and shaping individual trajectories of aging with minimal decline (Lindenberger, 2014). Determining the factors that induce individual variability in the brain aging of healthy adults is a challenge, as by definition, healthy samples are selected for the absence of detectable pathology and have restricted variance in negative modifiers of the brain structure. Nonetheless, several factors have been implicated in moderating the trajectories of brain aging. Physiological and genetic variations associated with vascular, metabolic, and neuroinflammatory risks and affecting endothelial function and energy expenditure while increasing the RONCS burden—the *vascular health triad* (Wadley, Veldhuijzen van Zanten, & Aldred, 2013)—appear particularly important. Arterial hypertension, even when medically controlled, is linked to the accelerated shrinkage of several brain regions, such as the hippocampus (Raz et al., 2005), raising a possibility that this detrimental effect stems not from elevated blood pressure per se but from the concomitant vascular changes. In many samples, gray matter shrinkage is exacerbated by an age-related elevation in vascular risk (Bobb et al., 2014; Kim et al., 2018; Raz et al., 2005, 2007, 2008),and in inflammation (Metti et al., 2015), as well as by genetic variants associated with an increased risk for Alzheimer's disease (AD; Donix et al., 2010; Harrison et al., 2016; Hua et al., 2016; Li et al., 2016; Moffat et al., 2000; but see Persson et al., 2014; Raz et al., 2010; Squarzoni et al., 2018 for negative findings), inflammation (Persson et al., 2014), and endothelial dysfunction (Zannas et al., 2014).

Carriers of the ApoE ε4 allele, a risk factor for AD, show faster shrinkage of the medial-temporal (Moffat et al., 2000), prefrontal, and cingulate (Rast et al., 2017) regions. Amyloid deposits are associated with faster rates of regional shrinkage, especially in the

medial- temporal regions, occipital cortices, and precuneus (Doré et al., 2013). Alterations in the one-carbon metabolic cycle expressed in reduced levels of vitamins B_{12} and B_6 and elevated homocysteine (Hooshmand et al., 2016), as well as genetic variants associated with high levels of the latter (Persson et al., 2014), have been linked to accelerated shrinkage of the parahippocampal gyrus and the cerebellum.

In some samples, genetic and physiological vascular risks synergistically accelerate the thinning (Rast et al., 2017) and shrinkage (Bobb et al., 2014; Raz et al., 2007) of brain regions that are usually less vulnerable to aging. In other studies, however, the effects of vascular risk are negligible (Raz et al., 2010; Taki et al., 2013). It may take a combination of negative modifiers, such as older age, lower socioeconomic status, elevated vascular risk, and the presence of the ApoE ε4 allele to predict variability in regional shrinkage (e.g., Persson et al., 2016). Of note, most of the participants in large-scale, population-based studies of brain aging had hypertension, especially in samples limited to older adults: more than 80% in the AGES-Reykjavik Study (Sigurdsson et al., 2012), 75% in the Three-Cities Study (Crivello et al., 2014), 48% in the Seattle Longitudinal Study (Rast et al., 2017), and 46% in the Baltimore Longitudinal Study of Aging (Pacheco et al., 2015) but only 32% in the Singapore Brain Aging Study (S-LAB; Leong et al., 2017) and 20%–33% in the Detroit Longitudinal Study (Persson et al., 2014; Yuan et al., 2018). Thus, separating "pure" aging from the effects of cardiovascular and metabolic risk factors is a challenging undertaking.

Selective attrition of the participants is an important caveat in interpreting longitudinal findings, with attrition rates of 35% and below considered favorable (Ritchie, Bastin, et al., 2015). Some studies achieve better retention, with losses of only 12% in the Massachusetts General Hospital Aging Study (McArdle et al., 2004), 21% in the PATH Study (Shaw et al., 2016), 22% in the Three-Cities Study (Crivello et al., 2014), 24% in the Singapore Longitudinal Study (Leong et al., 2016), and 32% in the Norwegian Cognition and Plasticity through the Lifespan Study (Storsve et al., 2014). In many others, however, the loss of participants over the course of the first two waves was greater: 36% in (Jiang et al., 2014), 39% in the Aberdeen 1936 Birth Cohort Study (Sandu et al., 2014), 41% in Yuan et al. (2018), 43% in the Dallas Lifespan Brain Study (Peng et al., 2018), 46% in Persson et al. (2014), 49% in the Women's Health Initiative Memory Study (Vaughan et al., 2014), 52% in Moscufo et al. (2018), and 67% in the Aging Study of the Memory and Aging Center of the University of California, San Francisco (Pressman et al., 2016). Particularly problematic is a nonrandom nature of missingness (Lindenberger, Singer, & Baltes, 2002): returning participants tend to have more years of formal schooling (Gorbatch et al., 2017), score higher on cognitive tests (Persson et al., 2014; Ritchie, Bastin,, et al., 2015; Yuan et al., 2018), and evidence greater gray matter volumes (Ritchie, Dickie, et al., 2015) in comparison to the dropouts. Although longitudinal models can handle missing data (McArdle, 2009), one must always be careful in identifying the contributors to incompletely random missingness and including these variables in the models.

The neurobiological and cytoarchitectonic foundations of differential gray matter shrinkage remain unclear, but the understanding that emerges from rare studies combining histology with antemortem and *ex-vivo* neuroimaging indicates the relative contributions of various components of the cerebral cortex to the structural properties assessed by MRI. For one, in vivo cortical thickness measures are unlikely to reflect neuronal density (la Fougère et al. 2011). The most probable determinant of the gray matter volume is neuropil—the myelinated and unmyelinated axons, dendrites, and their collateral branches that constitute about 55% of the gray matter bulk, whereas neuronal bodies and glia account for 9%–11% each (Kassem et al., 2013). The role of neuropil volume changes as a core phenomenon in differential brain shrinkage gained support from MRI studies in rodents that revealed coupling between gray matter volume changes observed on MRI and changes in the volume of neuropil components, such as dendritic arborization and spine density (Kassem et al., 2013; Qiu et al., 2013).

Unlike the highly localized and relatively modest addition of neuronal bodies via neurogenesis, local variations in dendritic arborization and axonal density and diameter are common, widespread, and related to stress, hormonal cycle timing, and interactions with the environment (Kassem et al., 2013; Qiu et al., 2013). Another potential contributor to cortical volume loss is intracortical myelin (Courchesne & Plante, 1996; Raz, 2000). In the context of age-related shrinkage, this idea has yet to be tested directly, but it is supported by indirect evidence. Staining cortex for myelin reveals an inverted-U relationship between age and the extent of staining, which is greater in brains from young and middle-aged persons in comparison to infants and older adults (Kaes, 1907). Moreover, the age differences in myelin staining are greater in tertiary association than in primary sensory cortices (Kaes, 1907), and the magnitude of regional age differences and age-related shrinkage correlates significantly with myelination precedence rank (Flechsig, 1901). Brain structures

that myelinate earlier show smaller age-related differences and slower change, with 36%–38% of the variance in the age effects explained by the myelination rank of the region (Raz, 2000; Raz & Kennedy, 2009). Thus, the key to understanding age-related changes in the gray matter volume may lie in elucidating the lifespan course of myelination and white matter microstructural development.

Age-Related Differences and Changes in White Matter Structure and Organization

White matter is an agglomeration of axons that constitute the brain's long-distance communication infrastructure. Compared to the gray matter, it contains less interstitial fluid and has a sparser blood supply. Although the cortical and white matter myelin content varies by region and tract, most of the white matter axons have myelin sheaths of varying thickness, with myelin envelopes enhancing the speed and fidelity of neurotransmission and promoting an energetic, a transporting, and a neurotrophic function (see Beaulieu, 2014 and Saab, Tzvetanova, & Nave, 2013 for reviews). Myelin, which comprises multiple proteins and lipids, constitutes approximately 50% of the white matter and 35% of the total brain weight (Bartzokis, 2011; Saab et al., 2013). Myelin is energetically expensive to synthesize and maintain, which in the context of its sparse vascularization under the constraints of a reduced blood supply is problematic (Norton & Cammer, 1984). With age, the deficit may become more acute, as in older mammals the synthesis of myelin de novo is reduced due to a phagocytosis impairment that hampers the clearing of myelin-related debris (Hill, Li, & Grutzendler, 2018; Rawji et al., 2018).

Older adults without cognitive impairment show a slow reduction in the white matter volume starting in late middle age (Raz & Rodrigue, 2006), but measuring the white matter volume is a coarse way of gauging its role in cognitive aging. Nonetheless, several MRI approaches to assessing the structural properties of the white matter in intact humans have been developed. The earliest observations of aging brains revealed multiple hyperintense spots on T_2-weighted MRI scans, white matter hyperintensities (WMHs), dubbed *leukoaraiosis* or "white dilution" (Hachinski, Potter, & Merskey, 1987). The volume of WMHs has been linked primarily to advanced age with contributions from cerebrovascular disease (Pantoni & Garcia, 1997; Wardlaw, Valdés Hernández, & Muñoz-Maniega, 2015), metabolic syndrome (Portet et al., 2012), and neuroinflammation (Raz, Yang, Dahle, & Land, 2012; Wright et al., 2009).

WMHs reflect a broad range of changes in the white matter **s**tructure: demyelination, microinfarctions, ischemia, hypoperfusion, as well as cerebrospinal fluid (CSF) and interstitial fluid leakage through weakened blood-brain and CSF-brain barriers (Fernando et al., 2006; Haller et al., 2013; Pantoni & Garcia, 1997; Sam et al., 2016; Wardlaw et al., 2015). In healthy older adults, WMH volume increased moderately over time (e.g., Debette & Marcus, 2010; Gorbatch et al., 2017; Moscufo et al. 2018; Raz, Yang, Rodrigue, et al., 2012; Silbert et al., 2008; Sudre et al., 2017). The progression may be greater in those with a relatively high WMH load (Silbert et al., 2008) and is exacerbated by genetic and physiological indicators of vascular disease and inflammation as well as amyloid accumulation (Raz, Yang, Dahle, et al., 2012; Sabayan et al., 2015; Scott et al., 2016; Sudre et al., 2017; Wolfson et al., 2013). Because the WMH burden reflects many diverse pathological influences, it has limited use for understanding nonpathological age-related cognitive changes. It is necessary, however, to consider WMHs' effect on normally appearing white matter (NAWM) (Sam et al., 2016).

Currently, the most popular way of evaluating white matter microstructure is diffusion tensor imaging, or DTI (Basser, Mattiello, & Le Bihan, 1994; Salat, 2014), based on measuring the apparent diffusion characteristics of the brain water, representing them in a three-dimensional diffusivity tensor, and summarizing the tensor properties in four scalars: fractional anisotropy (FA), reflecting diffusion asymmetry along the principal axes; mean diffusivity (Md), the apparent diffusion coefficient averaged across three major axes; axial diffusivity (Ad), which represents diffusion along the main axis; and radial diffusivity (Rd), which is an average of the apparent diffusion coefficients of two minor-axes eigenvalues across the plane perpendicular to the main axis. Because DTI-derived indices reflect many aspects of cellular composition and fiber organization (Jones, Knösche, & Turner, 2013), as well as the brain orientation in the magnet (Basser et al., 1994), they are insufficiently specific.

Cross-sectional DTI studies have revealed age-related differences in all DTI-derived indices across most brain white matter tracts (Salat, 2014). These studies have suggested a pattern of differential aging similar to that revealed by cross-sectional investigation of the cortex: greater age differences in the anterior regions and in the association pathways compared to the posterior areas and the projection tracts (Cox et al., 2016; Salat, 2014). These age-related differences are in line with the first-in-last-out hypothesis (Raz, 2000; Raz et al., 1997), which posits that late to mature regions are more vulnerable to age-related declines than those that reach

their developmental peaks early. Most of the DTI studies have not considered the influence of WMH on regional diffusion properties, and those that did found that WMHs alter diffusion properties, as observed on MRI (Vernooij et al., 2008), underscoring the importance of combining WMH assessment with DTI examination of the cerebral white matter.

Longitudinal investigations of white matter aging are still rare. The most consistently reported finding is widespread FA declines (Barrick et al., 2010; Bender & Raz, 2015; Bender, Prindle, et al., 2016; Gorbatch et al., 2017; Hakun et al., 2015; Moscufo et al., 2018; Riekmann et al., 2016; Ritchie, Bastin, et al., 2015; Sexton et al., 2014; Sullivan, Rohlfing, & Pfefferbaum, 2010; Vik et al., 2015; Storsve et al., 2016; Teipel et al., 2010). In one sample, age predicted a faster reduction over time, suggesting accelerated change (Storsve et al., 2016). In four studies, an increase in Rd over time was observed (Barrick et al., 2010; Moscufo et al., 2018; Sexton et al., 2014; Storsve et al., 2016). With only NAWM examined, two longitudinal studies of healthy adults revealed a more complicated pattern of age-related change: declines in Ad within association and projection fibers but increases in Ad in anterior regions of the corpus callosum, with FA and Rd changes showing even less consistent patterns (Bender & Raz, 2015; Bender, Prindle, et al., 2016). Latent change score analyses revealed significant individual variability in a sample with a broad adult age range (Bender & Raz, 2015) but not among middle-age and older adults (Bender, Prindle, et al., 2016).

As in regional volumes and cortical thickness, age differences in white matter diffusion properties are influenced by the burden of age-related risk factors (e.g., Burgmans et al., 2010; Kennedy & Raz, 2009). White matter changes are exacerbated by vascular (Aribisala et al., 2014) and metabolic (Bender & Raz, 2015) risk and by genetic variants associated with an increased risk for AD (Riekmann et al., 2016) and vascular dysfunction (Taylor et al., 2010). These influences are expected to moderate the relationships between changes in the brain and cognition, just as they do for the cortical volumes. The main limitation of the DTI studies is the lack of neurobiological specificity in interpreting the findings (Beaulieu, 2014; De Santis et al., 2014). For example, the most widely used DTI-derived indicator, FA, may reflect axonal degeneration and demyelination, as well as in reorganization of healthy white matter and alteration of a local configuration of fibers.

Several promising techniques have been developed to discern distinct components of the white matter. Myelin content can be estimated via multiecho T_2-weighted sequences yielding a T_2 relaxation curve. The contribution of its shortest echo, which presumably represents myelin-trapped water, is myelin water fraction (MWF; Mackay et al., 1994). The method produces reliable MWF estimates within specific white matter tracts (Arshad, Stanley, & Raz, 2017) and, unlike DTI-derived indices, shows the inverted-U age differences similar to postmortem findings (Arshad, Stanley, & Raz, 2016). The same method estimates nonmyelin contributions to the T_2 signal that may reflect axonal size and density in a given brain region (Arshad et al., 2016, 2017; MacKay et al., 1994). Other methods of estimating myelin content are a multicomponent-driven equilibrium single-pulse observation of the T_1 and T_2 (mcDESPOT; Deoni et al., 2008) and R_1 relaxation rate (Yeatman, Wandell, & Mezer, 2014). To date, however, there are no longitudinal studies of MWF in normal aging.

To account for multiple contributors to the white matter microstructure, new approaches model multiple compartments (intra- and extracellular, intra-axonal water, and CSF) and quantify the distribution of axonal calibers (Assaf et al., 2008), as well as neurite density and orientation dispersion (Zhang et al., 2012). These methods require data acquisition with at least two B values. Currently, the test-retest reliability of these methods is unclear, and there are no longitudinal studies of normal aging with these techniques.

In sum, brain structural properties change with age, with the rate and magnitude of change varying across individuals and brain regions. The heteromodal association cortices, cerebellum, neostriatum, and medial-temporal regions show the steepest declines in volume, whereas the primary sensory regions appear more stable over time. Individual trajectories of structural brain aging are modified by multiple vascular, metabolic, and neuroinflammatory risk factors. The picture is less clear with respect to the white matter microstructure and composition, although age-related changes in water diffusivity and fiber organization, as well as multifarious pathological alterations, also occur under the influence of multiple risk factors. Because of the absence of longitudinal studies, the time course of changes in white matter components—for example, myelin—is unknown.

Changes in structural properties of the aging brain have been described above in terms of the brain components that are innate and have been present since the late stages of embryogenesis, as well as brain entities that "do not belong"—additions to the normal white matter known as WMHs. In the same vein, we can describe another component of the aging brain structure that, although necessary in some amount, does not "belong" to the normal brain tissue—iron. Unlike pathological entities (WMHs), iron is critically

important for normal brain function, and its role as a negative modifier of aging and a biomarker of decline reflects its transformation from a friend to a foe.

Brain Iron Homeostasis and Aging

Iron, acquired through the ingestion of nutrients, plays three vital roles in the brain: binding oxygen to the hemoglobin, aiding the synthesis of adenosine triphosphate (ATP) in mitochondria (Mills et al., 2010), and maintaining myelin (Todorich et al., 2009). The first, accomplished by heme iron, is not relevant to the topic of this review, but the other two, performed by nonheme iron, merit discussion. In the normally functioning, younger brain, iron, a powerful oxidant, is safely sequestered in ferritin and transported into the cell and across the mitochondrial membrane, on demand, while bound to transferrin (see Zecca et al. [2004] for a review). With time the sequestration gradually fails, most likely through an increase in autophagy (Ashraf et al., 2018), and free iron accumulates in the neural tissue (Hallgren & Sourander, 1958). A shift in iron homeostasis entails the accumulation of ROC (Harman, 1956), with ensuing oxidative stress impairing basic cellular machinery, including the main energy generator—the mitochondria (for reviews, see Raz & Daugherty, 2018; Zecca et al., 2004). Mitochondrial ferritin is pivotal for the emergence of a labile iron pool that contributes to oxidative stress and the release of proinflammatory cytokines (e.g., interleukin -1beta, IL-1β and tumor necrosis factor alpha, TNFα). Autophagic destruction of the ferritin envelope causes the release of iron into the intracellular space and can trigger cell death by ferroptosis, a newly characterized form of cell elimination that is distinct from apoptosis and necrosis (Ashraf et al., 2018). The role of iron as a good-turned-bad force in the aging brain makes estimating iron content in vivo important for elucidating the structural brain changes described above.

Because of its strong paramagnetic properties, iron induces significant local changes in tissue susceptibility, which can be evaluated through MRI techniques sensitive to the relaxation properties of the iron-rich particles. One such technique, susceptibility weighted imaging (SWI), allows for the estimation of iron content in vivo (Haacke et al., 2005; Langkammer et al., 2012). Cross-sectional studies of iron deposits in healthy adults concur with postmortem investigations in establishing age-related differences in the iron content of the striatum and substantia nigra (Daugherty & Raz, 2013). In addition, elevated iron has been estimated in several cortical areas of healthy older adults (Buijs et al., 2017; Rodrigue, Haacke, & Raz, 2011).

At the time of this writing, little is known about the time course of iron accumulation in the brain. Two longitudinal studies demonstrated an increase in iron content of the striatum in healthy adults in a wide age range (Daugherty et al., 2015; Daugherty & Raz, 2016). Moreover, an increase in estimated striatal iron content precedes and predicts regional shrinkage within a two- (Daugherty et al., 2015) and a seven-year (Daugherty & Raz, 2016) time window. These studies originated in the same lab, and if the discrepancies among samples with respect to volumetric findings is a rule, studies from various populations may produce different results.

Structural Brain Changes and Cognition

As interesting as brain findings can be, the primary interest of the cognitive neuroscience of aging is the role of the brain in cognitive changes. In gauging the relationships between structural brain changes and cognition, several questions are worth examining. First, are changes in the brain and cognitive performance coupled, and what is the magnitude and direction of that association? Second, do changes in the brain precede cognitive alterations, follow them, or exhibit a bidirectional influence? Third, if such associations exist, how are they affected by invariant (genetic), stable, or time-dependent risk factors and positive modifiers, such as exercise and cognitive activity? Fourth, are associations between brain and cognitive changes specific to cognitive domains and types of cognitive operations and stimuli, or do they represent a reflection of generalized neural and cognitive change? Finally, if such relationships exist, do reasonably general mechanisms drive them? The extant literature, alas, reveals the dearth of data pertinent to these questions. Nevertheless, we will try to marshal the available evidence while formulating recommendations for future studies.

Are changes in the brain and cognition coupled? The relationship between rates of change in brain characteristics and cognitive performance can be inferred from studies that assess participants on at least two occasions, although the breadth and validity of such inferences could be improved by increasing the number of assessments. The extant longitudinal studies targeting temporal dynamics of the aging brain and cognition have focused mostly on the quintessential age-sensitive ability—memory or global cognitive measures, such as the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). In a seminal study that established the best-practice analytic approach to elucidating change in the age-brain-cognition relationship, the

expansion of lateral ventricles over seven years was coupled with a decline in an aggregated index of memory (McArdle et al., 2004). Several studies have linked shrinkage of the prefrontal cortex and white matter and medial-temporal structures to declines or a reduced ability to benefit from repeated testing on cognitive tests (Aljondi et al., 2018; Daugherty & Raz, 2017; Gorbatch et al., 2017; Kramer et al., 2007; Leong et al., 2017; Persson et al., 2016; Raz et al., 2008; Rodrigue & Raz, 2004). In some samples, hippocampal shrinkage was coupled with a decline in memory (Fjell et al., 2013; Gorbatch et al., 2017; Leung et al., 2016), but in others no such coupling was observed (Anblagan et al., 2018; Persson et al., 2016). A decline in verbal memory was also coupled with a loss of total cerebral volume, shrinkage of frontal and parietal white matter, and ventricular expansion (Leung et al., 2016). Hippocampal shrinkage and ventricular dilation were linked to a decline in executive functions, and general brain shrinkage, as well as frontal, parietal, and temporal (but not occipital) gray matter atrophy, were associated with poorer global cognition (Leung et al., 2016).

An increase in subcortical WMH volume has been linked to declines in episodic memory (Silbert et al., 2008), whereas a total WMH increase over approximately four years was coupled with a decline in language performance but not in memory, and even that only in persons with low language skills (Zahodne et al., 2015). An increase in mean diffusivity in the inferior longitudinal fasciculus was coupled with a decline in executive (Stroop) performance (Fjell et al., 2017). Greater axial diffusivity in the cingulum and uncinate fasciculus at baseline predicted episodic memory decline over three years, whereas none of the regional gray or white matter volumes showed significant associations (Lancaster et al., 2016).

Underscoring the need for examining the bidirectionality of brain-cognition associations, some studies found higher baseline cognitive scores predicting reduced brain shrinkage over time (Persson et al., 2016; Ritchie, Bastin, et al., 2015; Yuan et al., 2018). The meaning of these findings remains unclear. They may reflect better brain maintenance (see chapter 7) as proposed by studies of health and intelligence (Gottfredson, 2004; Kraft et al., 2018) or stem from the effects of cognitive activity that can alter local brain volumes (Draganski, Kherif, & Lutti, 2014). The latter is a less plausible explanation, as brain changes induced by cognitive activity are highly localized, and their durability is uncertain (Wenger et al., 2017).

The impact of white matter changes on cognition is even less clear because of ambiguity in the neurobiological interpretations of the DTI-derived indices and the dearth of longitudinal studies. In one sample, a change in Md but not FA was coupled with working memory decline (Charlton et al., 2010), whereas in very old persons, declines in perceptual speed correlated with FA reduction (Lövdén et al., 2014), and in septuagenarians, FA decline co-occurred with a drop in fluid intelligence (Ritchie, Bastin, et al., 2015). However, in an adult life span sample, greater gains in associative memory were coupled with a reduction in FA and an increase in Rd—that is, presumably negative changes (Bender, Völkle, & Raz, 2016). This finding of cognitive gains associated with a *reduction* in FA has been replicated in a different sample for a different cognitive domain (speed of processing) and a shorter time window (Kievit et al., 2018).

Other properties of the brain tissue, such as iron content, are rarely investigated in longitudinal studies of cognitive change. To date, two results from a two-occasion longitudinal study have been reported. An increase in caudate iron was coupled with lesser repeated-testing gains in verbal working memory (Daugherty, Haacke, & Raz, 2015) and less improvement in navigation performance (Daugherty & Raz, 2017) over a two-year follow-up.

In sum, although the general link between cognitive and brain changes is supported by the extant data, evidence of consistent coupling between localized changes in brain characteristics and specific cognitive functions is lacking.

What is the temporal order relationship between brain and cognitive changes? An important question, especially in the context of the prediction and mitigation of cognitive declines, is whether changes in the brain precede cognitive alterations, follow them, or exhibit a bidirectional influence. To date, the dearth of multioccasion longitudinal studies has hampered obtaining the answers to this question. In semilongitudinal studies with repeated brain but not cognitive assessment, the entorhinal (Rodrigue & Raz, 2004) and hippocampal (Cohen et al., 2006) shrinkage rate was associated with memory scores at follow-up. In studies with a single MRI assessment and repeated measurements of cognition, associations between local brain properties and cognition emerged. Persons with thinner parahippocampal, temporal, and parietal association cortices (Pacheco et al., 2015) or lower fornix Ad and volume (Fletcher et al., 2013) exhibited greater decline in cognitive performance and were more likely to have a diagnosis of cognitive impairment at follow-ups. People who benefited more from the repeated administration of associative memory tests had larger volumes of the CA3 hippocampal subfield and the

dentate gyrus, whereas no relationship was noted for the CA1 subfield or subiculum (Bender, Daugherty, & Raz, 2013). Smaller baseline volumes of the prefrontal white matter, hippocampus, parahippocampal gyrus, and cerebellum predicted a failure to gain from repeated testing of fluid intelligence over two years (Persson et al., 2016). Smaller volumes of the cerebellum, parahippocampal gyrus, lateral prefrontal cortex, and caudate nucleus, as well as greater hippocampal iron content, predicted a greater decline in navigation performance or reduced gains from repeated testing over two years (Daugherty & Raz, 2017). In sum, elucidating temporal dynamics and lead-lag relationships between aging of the brain and cognition remains an important goal for the future, with little evidence available thus far.

What are positive and negative modifiers of the relationships between the brain and cognition in adult development? Many risk factors shape the trajectories of brain aging. However, considerably less is known about their moderating and mediating of the relationship between age-related changes in the brain and in cognition. Although most longitudinal studies include many individuals with age-related vascular risk factors, the influence of the latter on the outcome is rarely examined. Assessment of vascular and metabolic risk influence on brain-cognition associations yielded mixed results. Elevated higher pulse pressure moderated the relationship between baseline hippocampal iron and prefrontal volumes and improvement in navigational performance over time (Daugherty & Raz, 2017). Volumes of the hippocampal subfield CA1 which is sensitive to age-related vascular risks, correlated with gains from retesting on a verbal free-recall task in hypertensive individuals but not in their normotensive counterparts (Bender et al., 2013). Thus, answering this question awaits proper longitudinal studies.

Summary, Conclusions, and Future Directions: A "To-Do List" for the Cognitive Neuroscience of Aging

This survey of the extant literature on age-related cognitive changes and their neuroanatomical correlates converges on the following points:

1. Aging, even in its most benign forms, is accompanied by a decline in brain health markers: regional brain volumes, white matter diffusion properties, and iron content.
2. These changes occur within a relatively short time and can be reliably assessed by current MRI methods.
3. Age-related changes in the brain are differential: Heteromodal association cortices and association white matter fibers age faster than primary sensory cortices and projection fiber systems. In some regions, such as the medial temporal lobe, the change accelerates with age.
4. All examined brain properties exhibit individual differences even without average change. Individual variability may be missed if appropriate statistical models are not applied.
5. The rate of age-related cognitive change varies across cognitive domains, but assessment of cognitive performance over time is hampered by repeated exposure to tests that may dampen individual differences. However, when individual differences in cognition are observed, they tend to correlate with brain change.
6. The coupling of age-related changes in the brain and cognition is relatively weak, is inconsistent across brain regions and cognitive domains, and requires adequate statistical power to detect. Because a typical longitudinal study of cognitive aging and its brain correlates is underpowered and there is little agreement about cognitive measures, it is difficult to assess the true strength of these associations.
7. A more consistent pattern of results is observed when baseline brain characteristics are assessed. A faster rate of cognitive change is linked to less favorable initial brain characteristics.
8. The relationship between the brain and cognition is probably bidirectional. Better cognitive performance at baseline predicts lesser shrinkage of relevant brain regions. Such reciprocal influence of brain and behavior may stem from specific neural mechanisms, as well as general phenomena, cognitive reserves, and brain maintenance. Disentangling these influences is currently impossible because of a lack of multioccasion studies with adequate statistical power. The "reversed causality" hypothesis, tested only in a handful of longitudinal studies, requires greater attention.
9. Metabolic, vascular, and inflammatory risk factors modify the trajectories of aging. Physiological and genetic risks exacerbate the declines and may alter the relationship between changes in the brain and cognition. Due to significant variability in sample composition, genetic findings are inconsistent, even for well-established, risky genetic variants.

Several obstacles still stand in the way of better understanding the brain-cognition relationship in the context of aging:

1. Although neuroanatomical changes happen fast, studying the vicissitudes of the aging brain structure necessitates long-term multioccasion longitudinal designs. The scarcity of such longitudinal studies impedes our understanding of the temporal dynamics of cognitive aging. This imperative for more longitudinal research, however, is difficult to fulfill because of formidable logistic obstacles, which can be overcome only with a substantial investment of money, time, and human power.
2. Noninvasive neuroimaging provides many exciting opportunities for evaluating brain structural properties. However, no single property, such as regional cortical thickness or regional myelin content, is sufficient for describing and tracking age-related brain changes and their relation to cognition. Multimodal imaging, which is gaining popularity, may advance the field by integrating various aspects of the brain structure and gauging the temporal relations among distinct properties, such as myelin and iron content, neurite density, axonal size, and volume.
3. The study of cognition can benefit from focusing on the construct rather than individual indicators. A single test of recall is just one indicator of memory as a construct. The assessment of cognitive performance at the construct level is, regrettably, quite rare. Even the best of single indicators in any cognitive domain has only modest reliability—a fault that can be addressed, at least to some extent, by employing latent variable analyses driven by an appropriate theory. Moreover, the extant studies vary widely in their selection of indicators, thus impeding comparison and analyses of the findings. Greater uniformity in cognitive measures, with greater attention to their psychometric properties, is needed to harness the collective power of multiple cohorts.
4. Assessing brain properties relevant to aging cannot be isolated from measuring other changes in the organism. Yet few studies assess metabolic and vascular risk systematically, and many do not model its contribution to the variance in brain and cognitive changes. Moreover, like cognitive abilities, risk factors are constructs and are only partially reflected in single indicators, such as systolic blood pressure or blood glucose.
5. To take the need for comprehensive risk-factor assessment further, significant commonality among these negative modifiers of aging should be considered. Lower socio-economic status, poorer educational attainment, lower cognitive performance since the earliest stages of development, and the increased prevalence of behaviors and lifestyles that are detrimental to health, coupled with health-care disparities, high levels of chronic stress, and differential exposure to environmental pollution, can serve as cumulative and conjoint force multipliers that accentuate even seemingly minor genetic and physiological differences. Until modifiable aspects of this risk-factor consortium are addressed, attempts to isolate the effects of its specific components on brain aging and cognition may be futile.
6. The mechanisms of brain aging and its relationship with cognition remain poorly understood. Despite significant progress in elucidating pathways to aging in cellular and animal models, assessing the applicability of these models to humans is hampered by the limitations of noninvasive imaging methods. Evaluation of the cellular mechanisms (Garaschuk et al., 2018, Harman, 1956) and the effects of a cellular energy crisis (de la Torre, 2008) on the human brain can benefit from the development of suitable neuroimaging proxies. For example, the accumulation of iron and changes in the R_1 relaxation rate may serve as indirect but sensitive indicators of free radical damage. Tying changes in brain volume and cortical thickness to changes in neurotransmitter levels and their modulation, as well as energetic and metabolic changes, is vital for understanding the mechanisms of cognitive aging. This can be accomplished by applying methods like ^{31}P (Lin & Rothman, 2014) and functional ^{1}H magnetic resonance spectroscopy (fMRS; Stanley & Raz, 2018).
7. Further refinement of manual and computer-aided analyses of smaller volumes, such as hippocampal subfields, may advance the understanding of the brain-cognition relationship in normal aging. The hippocampus is not a uniform structure, and its components or subfields differ dramatically in cytoarchitectonic properties, connectivity, vascularization, response to stress, and sensitivity to vascular and inflammatory risk factors (Amaral, Kondo, & Lavenex, 2014; Insausti, 1993; McEwen, 1999; Raz et al., 2015; Shing et al., 2011). Although cross-sectional studies hint at important differences in the strength of associations between age, subfield volumes, vascular risk, and cognition in healthy adults, longitudinal studies are still lacking. A concerted effort aimed at developing reliable and valid

manual and computer-aided protocols (Wisse et al., 2017) will increase the likelihood of obtaining valuable knowledge about the relationship between structure and cognition in normal aging. Improved spatial resolution and shorter acquisition times will be attained with greater use of high-field (7T) scanners and further modifications of the existing sequences.

8. Assessing the RONCS role in the normal aging process may elucidate the neural mechanisms of cognitive aging. Testing their activity and effects in vivo (e.g., the FRIENDS model) posits a challenge because it requires simultaneous assessments of the brain load of RONCS, the state of myelin and neuropil, and cognitive performance. For each of these items, only indirect measures are available. Myelin content can be estimated by MWF, although current methods do not differentiate between myelin and its debris. Neuropil volume is most likely represented by the regional gray matter volumes measured from T_1-weighted MRI scans. Two indirect indices have been proposed to address the challenging problem of assessing the excess free radicals in vivo. First, measures of local brain iron content linked to mitochondrial dysfunction and a shift in RONCS homeostasis can be obtained via MRI in intact humans (Ashraf et al., 2018; Betts et al., 2016; Daugherty & Raz, 2015; Langkammer et al., 2012). Another promising candidate is R_1 relaxation time, which when abnormally prolonged can be shortened by the acute administration of antioxidants (Berkowitz, 2018).
9. Because animal models are crucial to testing hypotheses about the molecular underpinnings of human brain aging and cognitive change, the translational harmonization of animal neuroimaging studies with human investigations is critically important. With notable exceptions (Kassem et al., 2013; Qiu et al., 2013), such studies are still rare. Translationally harmonized studies should reproduce the precision of human neuroimaging tools, human construct-level measures of cognitive performance, and human longitudinal designs, in addition to taking advantage of the invasive procedures available in animal models.

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