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Chapter 20

Aging of the frontal lobe

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Abstract

Healthy aging is associated with numerous deficits in cognitive function, which have been attributed to changes within the prefrontal cortex (PFC). This chapter summarizes some of the most prominent cognitive changes associated with age-related alterations in the anatomy and physiology of the PFC. Specifically, aging of the PFC results in deficient aspects of cognitive control, including sustained attention, selective attention, inhibitory control, working memory, and multitasking abilities. Yet, not all cognitive functions associated with the PFC exhibit age-related declines, such as arithmetic, comprehension, emotion perception, and emotional control. Moreover, not all older adults exhibit declines in cognition. Multiple life-course and lifestyle factors, as well as genetics, play a role in the trajectory of cognitive performance across the life span. Thus many adults retain cognitive function well into advanced age. Moreover, the brain remains plastic throughout life and there is increasing evidence that most age-related declines in cognition can be remediated by various methods such as physical exercise, cognitive training, or noninvasive brain stimulation. Overall, because cognitive aging is associated with numerous life-course and lifestyle factors, successful aging likely begins in early life, while maintaining cognition or remediating declines is a life-long process.

INTRODUCTION

Many cognitive functions are mediated by neural processes within the prefrontal cortex (PFC). A wealth of evidence suggests that PFC anatomy and physiology decline with age, resulting in multiple cognitive deficits. The goal of this chapter is to give an overview of how alterations in PFC structure and function underlie various cognitive deficits in healthy (i.e., nonpathologic) aging. Specifically, cognitive functions discussed here include sustained attention, selective attention/inhibitory control, working memory, and multitasking. Not all age-related declines in cognitive abilities are discussed. This chapter begins with several theories of cognitive aging, particularly as it pertains to the PFC, in order to orient the reader toward the general themes that will emerge from the subsequent sections. Next, brief overviews of age-related changes in neuroanatomy and neurochemistry are presented, followed by sections summarizing alterations in cognitive functions, retained cognitive functions, and finally pathways to remediate cognitive decline in aging. Together, current research has attributed multiple age-related deficits in cognitive function to deficiencies in PFC anatomy and physiology. However, there is great heterogeneity across the older population, in that some older adults do not exhibit cognitive deficiencies. Importantly, those that do exhibit cognitive decline may remediate deficient cognitive function by capitalizing on neuroplasticity that is retained across the life span.

THEORIES OF COGNITIVE AGING

There are many hypotheses, theories, and models that attempt to explain the multifaceted changes that occur in normal "healthy" aging. Here, several of these

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hypotheses/theories/models are summarized to highlight anatomic and physiological changes commonly associated with aging and the PFC. To begin, one of the most commonly observed research findings, and stereotypes of aging, is that older adults are slow to respond. This slowing is observed in both behavioral responses as well as neural processing, which affects multiple stages of cognitive function (processing speed theory of aging) (Salthouse, 1985, 1996). Age-related slowing has been associated with declines in the structural integrity of white matter tracts (Rabbitt et al., 2007b; Turken et al., 2008) as well as loss of brain volume (Rabbitt et al., 2007a). The consequence of these anatomic changes, coupled with diminished dopamine in the aging brain, is thought to lower the neural signal-to-noise ratio (i.e., more neural noise) (neural noise hypothesis) (Li et al., 2001; Li, 2005; Voytek et al., 2015). Therefore, increased neural noise demands more computational time to properly evaluate neural signals, thereby slowing cognitive functions and contributing to age-related declines in task performance (Crossman and Szafran, 1956; Welford, 1981).

Once generalized slowing is accounted for, many age-related declines in cognitive performance persist. Notably, older adults exhibit deficient inhibitory control, which serves to block the processing of irrelevant information, delete no longer relevant information, and restrain prepotent responses (inhibitory deficit hypothesis) (Hasher and Zacks, 1988; Hasher et al., 1999). Thus lowered inhibitory control ability is thought to underlie age-related declines in working memory, learning, and comprehension abilities (Hasher et al., 2007). Whereas slowed processing speed is thought to be pervasive throughout the aging brain, deficient inhibitory control has been attributed to alterations in the structure and function of the PFC (PFC function theory of aging) (Dempster, 1992; West, 1996). Alterations in PFC, particularly dopamine levels, result in deficient executive control abilities that affect attention, inhibitory control, and working memory function (context processing theory) (Braver and Barch, 2002). Notably, deficient PFC function affects top-down attention-related abilities to modulate neural activity in sensory cortex (e.g., Zanto et al., 2011b). The PFC-mediated top-down modulation of sensory cortex activity serves to alter both the speed and magnitude of neural responses to stimuli, based on the stimuli's relevance to task goals (Gazzaley et al., 2005a). Thus age-related declines in top-down modulation can yield deficiencies in both inhibitory control and processing speed (Gazzaley et al., 2008), and help explain widespread impairment associated with cognitive aging (top-down modulation model) (Gazzaley and D'Esposito, 2007; Gazzaley, 2012).

Despite reports of age-related declines in PFC anatomy and physiology and their relationship to multiple deficient cognitive functions, aging research does not always agree on whether specific cognitive functions decline with age. There are many examples of conflicting reports and even when age-related declines in performance are reported, there is great heterogeneity in that many older adults exhibit comparable performance to younger adults (although average group performance is often lower than average younger adult performance). Fortunately, cognitive neuroscience research has shed light on this conundrum, by suggesting compensatory neural mechanisms may be recruited to retain task performance following alterations in anatomy and/or physiology. For example, older adults exhibit decreased occipital neural activity and increased PFC activity as a means to compensate for declines in perceptual processes that occur in occipital regions (posterior-to-anterior shift in aging (PASA) model) (Davis et al., 2008). During more cognitively demanding tasks that require the use of unilateral PFC in younger adults, older adults may recruit contralateral PFC regions to yield comparable performance (hemispheric asymmetry reduction in aging model) (Cabeza, 2002). Thus, as task demands increase, older adults utilize more cognitive resources to retain performance.

Cognitive resources are limited and older adults may utilize compensatory neural mechanisms until their resource limit is reached (cognitive reserve theory) (Stern, 2002) (compensation-related utilization of neural circuits hypothesis) (Reuter-Lorenz and Lustig, 2005) (scaffolding theory of aging and cognition) (Park and Reuter-Lorenz, 2009). Importantly, this limitation in cognitive resources helps explain the heterogeneity of cognitive performance in the aged population—in that some older adults have more cognitive reserve than others, and hence, perform various cognitive tasks on-par with younger adults. Factors that relate to cognitive reserve include (but are not limited to) intelligence, education, occupational complexity, and physical fitness. These factors, coupled with data indicating that cognitive decline in aging is exacerbated by retirement (Rohwedder and Willis, 2010), suggests the ability to utilize cognitive reserve follows a "use-it-or-lose-it" model. As described in the "Improving Frontal Lobe Structure and Function" section, the brain retains neuroplasticity across the life span, and many (if not all) age-related cognitive deficits may be remediated by engaging the brain through physical and cognitive exercise or potentially noninvasive brain stimulation.

In summary, there are many hypotheses, theories, and models to account for cognitive aging and those described here reflect a sample rather than an exhaustive

list. The majority of these explanations of cognitive aging are complementary in that they each tend to address specific aspects of changes that have been observed in older adults and, together, help form a more cohesive picture of cognitive aging. Of particular interest, these hypotheses, theories, and models account for many of the recurrent themes throughout this chapter, such as the impact of deficient PFC anatomy and physiology on cognitive function, compensatory recruitment of neural regions to uphold performance, and limitations of cognitive capacity/reserve.

NEUROANATOMIC CHANGES

How brain weight changes across the life span has been extensively studied and may help explain how cognitive control abilities change with age. It is thought that by 90 years of age, brain weight has decreased by 11%–14% of maximum achieved weight in early adulthood (Dekaban, 1978; Jernigan et al., 2001). In a meta-analysis of 56 longitudinal magnetic resonance imaging studies, it was estimated that whole brain volume declines after age 35 at a rate of approximately 0.2% per year and this rate gradually increases to 0.5% annual brain volume loss by age 60 (Hedman et al., 2012). Yet, age-related declines in gray and white matter are not homogeneous throughout the brain. Compared to younger adults, older adults exhibit lower gray and white matter volumes in PFC, medial temporal, and parietal cortices (Gordon et al., 2008; Raz et al., 2010). Moreover, within the older adult group, increased age correlated with decreased gray and white matter within the same regions (Gordon et al., 2008), underscoring the role of age in brain volume loss. Given the prominent roles of the PFC, medial temporal, and parietal cortices in cognition (Bressler and Menon, 2010; Park and Friston, 2013), it is not surprising that older adults exhibit declines in a variety of cognitive functions, as detailed in the following sections.

NEUROCHEMICAL CHANGES

Multiple neurotransmitter changes occur in aging, but this chapter will focus on dopamine because catecholamine-producing neurons, especially those manufacturing dopamine, appear to be more sensitive to age-related changes than, for example, serotonergic or GABAergic neurons (Carlsson, 1987). Notably, older adults exhibit loss of dopamine-producing neurons in the substantia nigra (Fearnley and Lees, 1991) as well as reduced dopamine receptor and transporter density (Seeman et al., 1987; Volkow et al., 1994). Yet older adults exhibit increased dopamine synthesis capacity (Braskie et al., 2008), which may serve as a compensatory mechanism to maintain cognitive function. Indeed, optimal levels of dopamine in the PFC need to be maintained for cognitive stability (Cools and D'Esposito, 2011) and alterations in the dopamine system have been associated with multiple age-related declines in cognition, as detailed later. Thus multiple theories of cognitive aging have attributed age-related deficits in cognition to a deficient dopamine system, particularly as it pertains to PFC function (e.g., Braver and Barch, 2002; Hasher et al., 2007; Park and Reuter-Lorenz, 2009).

GENETIC FACTORS

Given the relevance of dopamine on cognitive aging, much research into genetic factors influencing cognition has focused on catechol-*O*-methyltransferase (COMT), which is an enzyme that catalyzes the degradation of dopamine, and brain-derived neurotropic factor (BDNF), which regulates the release and uptake dynamics of presynaptic dopamine. Unfortunately, research into the effects of COMT and BDNF on cognitive aging can be seemingly inconsistent, which may be a consequence of multiple interacting factors (Jagust, 2009). Notably, COMT and BDNF can affect cognitive ability differentially based on age (Degen et al., 2016; Noohi et al., 2016) and cognitive task type (Noohi et al., 2016; Rostami et al., 2017), which includes challenges on the dopaminergic system (Barkus et al., 2016) or genetic network profile (Noohi et al., 2016; Sapkota and Dixon, 2018). Aside from COMT and BDNF, many other studies have focused on polymorphisms in and around inflammatory genes as a source of nondemented cognitive decline in aging. Some of these studies indicate interleukin 1 beta, tumor necrosis factor alpha, and C-reactive protein may play a role in domain-specific cognitive decline (reviewed in Stacey et al., 2017). In a recent study of ~3500 healthy older adults, two genes associated with synaptic transmission and neural circuits formation, *STAU1* and *SEMA3F*, have been implicated in age-related cognitive decline (Tasaki et al., 2018). Finally, it is worth noting that apolipoprotein E and the single nucleotide polymorphisms clusterin (CLU), complement receptor 1, and phosphatidylinositol-binding clathrin assembly protein (PICALM) are related to age-related cognitive decline and also present a risk for Alzheimer's disease (Poirier et al., 1993; Jun et al., 2010). Moreover, carriers with each of the at-risk alleles (i.e., APOE ϵ4+, CLU C+, CLU1 A+, PICALM T+, COMT G+, BDNF A+) intensify the trajectory of cognitive decline and potential for dementia (Sapkota and Dixon, 2018), which underscores the importance of the genetic network profile. Together, much more research is needed to fully understand the role of these genes on

specific cognitive functions, their power to predict age-related cognitive decline, and how they might interact within a larger genetic network profile.

COGNITIVE CHANGES

Perception

The focus of this chapter is to summarize age-related changes in the structure and function of the frontal lobe and its effects on cognition. However, it is worth noting that perceptual processes associated with sensory cortical regions are also altered in aging and thought to be related to alterations in PFC function. While it is unclear whether both perceptual and PFC-mediated cognitive functions share a common source of age-related decline or have a cause and effect on each other (Baltes and Lindenberger, 1997; Roberts and Allen, 2016), it is of current interest to note that PFC activity may increase in older adults to compensate for some perceptual declines. Perceptual declines in aging may arise from several sources. For example, deficient peripheral sensory mechanisms are common among aged adults. However, once peripheral changes are accounted for (e.g., visual acuity or hearing loss), perceptual deficits in aging persist, such as the ability to discriminate color, motion, or sounds (Strouse et al., 1998; Zanto et al., 2010b). The persistence of these perceptual deficiencies in older adults is related, at least in part, to a reduction in the selective use of specialized neural regions, known as dedifferentiation. Dedifferentiation is manifest via reduced neural activity and a broadening of tuning curves in stimulus-selective regions (Park et al., 2012). Of current interest, PFC and parietal regions known to be involved in attentional control may be recruited to uphold performance in response to sensory processing declines, such as dedifferentiation (Lee et al., 2011; Burianova et al., 2013).

The differential networks utilized by older adults support a PASA model (Davis et al., 2008) that proposes age-related sensory cortical (posterior) declines may be compensated by the recruitment of PFC (anterior) regions to retain performance abilities. Indeed, optimal visual target detection performance in younger adults is associated with increased activity in visual cortex, whereas high-performing older adults exhibit a greater reliance on PFC activity (Madden et al., 1997, 2007b; Allen and Payne, 2012). As described in the following sections, the age-related shift from sensory toward PFC processes has been observed in numerous cognitive domains, including spatial target detection (Madden and Hoffman, 1997; Madden et al., 2007a; Li et al., 2013; Geerligs et al., 2014), feature target detection (O'connell et al., 2012; Cashdollar et al., 2013; Alperin et al., 2014; Zhuravleva et al., 2014), working memory (Rypma and D'Esposito, 2000; Grossman et al., 2002), and episodic memory (Cabeza et al., 1997; Madden et al., 1999; Anderson et al., 2000). Yet, not all studies observe age-related frontal increases (Grady et al., 1995; Milham et al., 2002), and so it is unclear under what circumstances older adults may exhibit increased PFC activity.

Whereas increased reliance on PFC regions may reflect compensation for deficient sensory processes in aging, evidence also indicates that older adults may utilize increased PFC activity to compensate for its own dysfunction or inefficient processing within some PFC regions (see "Selective attention" section). Alternatively, the differential networks utilized by older adults may reflect a lifetime optimization process that reduces sensory complexity (such as dedifferentiation) to enable an energy efficient means of generalizing sensory experiences (Moran et al., 2014; Gilbert and Moran, 2016). Although multiple age-related declines may result in compensatory PFC activity, it is clear that deficient perceptual processes play a role in how older adults engage PFC resources.

Sustained attention

Sustained attention refers to maintaining vigilance, or tonic alertness, over time and has been associated with a cingulo-opercular network (Sadaghiani and D'Esposito, 2015) as well as dorsolateral PFC and inferior parietal lobe, particularly in the right hemisphere (Sarter et al., 2001). However, a recent study demonstrated that sustained attention ability is predicted by whole-brain functional connectivity during rest and that only 27% of high sustained attention network edges were located within frontoparietal regions (Rosenberg et al., 2015). Thus, additional research is necessary to elucidate the neuroanatomic substrate associated with sustained attention.

Previous studies of selective attention in aging yield conflicting reports that have hindered a definitive conclusion regarding the effects of age on sustained attention (for reviews, see Davies and Parasuraman, 1982; Giambra, 1993). Because sustained attention is typically assessed via paradigms that require participants to either respond to infrequent targets or withhold responses to infrequent targets, some of this heterogeneity may stem from differential contributions of top-down and bottom-up processes between tasks (Staub et al., 2013). Aside from task-based differences, several other factors may help account for this heterogeneity, particularly age, motivation, and task difficulty. Regarding age, equivalence in sustained attention performance between younger and older adults has been observed when the older adult population is aged 50–69 years (Berardi et al., 2001;

Carriere et al., 2010). Yet, in older adults aged 70+ years, deficient sustained attention is more consistently observed (Parasuraman and Giambra, 1991; Filley and Cullum, 1994; Mani et al., 2005). In addition to age, motivation is known to affect sustained attention ability (Oken et al., 2006; Esterman et al., 2016), and older adults have reported higher motivation and less mind wandering than younger adults during sustained attention tasks, which may help maintain equivalent performance (Staub et al., 2014). Finally, differences in sustained attention have also been reported under increased perceptual demands, such that age-equivalence may be observed with low perceptual demands but age-related declines become apparent as perceptual demands increase, thereby increasing task difficulty (Parasuraman et al., 1989; Mouloua and Parasuraman, 1995). Together, accounting for age, motivation, and task difficulty helps reconcile many of the disparate findings in the literature on sustained attention and aging.

It is worthwhile to note that, with increasing demands on sustained attention, older adults may retain accuracy at the expense of response time (Thomson and Hasher, 2017), suggesting a differential strategy in aging (Staub et al., 2015). In support of this, an impressive study with more than 10,000 participants assessed both strategy and sustained attention ability across the life span and demonstrated that increased age is associated with a more conservative strategy and lower sustained attention ability (Fortenbaugh et al., 2015). Therefore, it may be hypothesized that older adults compensate for sustained attention declines by adopting a more conservative approach that minimizes performance decrements. However, additional research will be required to test this hypothesis.

Unfortunately, there is limited research assessing age-related differences in the neural mechanisms underlying sustained attention. Studies using the attention network task have shown age-related declines in the ability to capitalize on alerting cues (Gamboz et al., 2010; Kaufman et al., 2016) (but also see Zhou et al., 2011), which may index sustained attention (Oken et al., 2006). Because the alerting attention network has been associated with PFC, parietal, and thalamic regions (Fan et al., 2005), this could indicate age-related declines in sustained attention may stem from deficiencies in these areas. Research using a change detection (delay match to sample) task corroborates the idea that impaired sustained attention in aging may be due to altered PFC function (Chao and Knight, 1997). Nonetheless, additional research is required to better characterize the anatomic and physiological changes in aging that underlie sustained attention ability.

Sustained attention is fundamental to multiple cognitive domains, so it is not surprising that sustained attention ability can differentiate healthy aging from mild cognitive impairment (López Pérez-Díaz et al., 2013). Moreover, deficits in sustained attention are associated with frailty in older adults (i.e., low gait speed, low grip strength, low physical activity, weight loss, exhaustion) (O'Halloran et al., 2014). Thus, assessments of sustained attention ability may serve to identify various pathologic changes in aging.

In summary, sustained attention ability is highly heterogeneous in the aged population, but accounting for age, motivation, and task difficulty may help predict when age-related deficits are observed. Although additional research is necessary to understand the anatomic and neurophysiological changes associated with age-related declines in sustained attention, current evidence points to a deficient cingulo-opercular network and other PFC and parietal regions. Because sustained attention is fundamental to multiple cognitive domains and is associated with physical frailty, it may serve to differentiate healthy from pathologic aging. However, sustained attention research is limited and much work remains before strong conclusions may be drawn regarding the effects of age on sustained attention ability.

Selective attention and inhibitory control

Selective attention refers to goal-directed focus on task-relevant information while ignoring other irrelevant information. Research in this cognitive domain typically focuses on a specific aspect of the attended/ignored information, notably spatial location, features, objects, and time. Regardless of the type of information that is selectively attended or ignored, regions within the prefrontal and parietal cortices are generally involved in these cognitive processes (Corbetta and Shulman, 2002; Fan et al., 2005; Zanto and Rissman, 2015).

Research using target detection paradigms often uses a cue to indicate where in space, when in time, or to what (feature/object) participants should covertly allocate attention. The response time difference between validly and invalidly (or neutrally) cued stimuli provides a measure of the selective attention (orienting) response. Compared to younger adults, older adults exhibit comparable selective attention ability following spatial (Nissen and Corkin, 1985; Hartley et al., 1990; Gottlob and Madden, 1998) or feature (O'connell et al., 2012; Alperin et al., 2014) cues. However, other research has shown age-related declines in selective attention following feature (Zanto et al., 2013) or temporal (Zanto et al., 2011a) cues.

Although there is some discrepancy regarding selective attention ability in aging during target detection, there is general agreement that older adults exhibit differential neural activity profiles. Notably, older adults

exhibit declines in visual sensory processing regions as indexed by lower regional cerebral blood flow (rCBF) measured with positron emission tomography (Madden and Hoffman, 1997) and lower blood oxygen level-dependent (BOLD) activity measured via functional magnetic resonance imaging (Madden et al., 2007a; Geerligs et al., 2014). Electroencephalography (EEG) data corroborate those findings such that older adults exhibit lower (Lorenzo-Lopez et al., 2002; Zanto et al., 2013) and slower (Curran et al., 2001) early components (i.e., <200 ms posttarget onset) of the event-related potential (ERP), as well as reduced attentional modulation of alpha (8–12 Hz) and slow wave (contingent negative variation) activity in anticipation of the target stimulus (Zanto et al., 2011a). Whereas older adults exhibit declines in visual sensory processing regions, they concomitantly exhibit increased PFC activity as evidenced by higher rCBF (Madden and Hoffman, 1997), BOLD activity (Madden et al., 2007a; Geerligs et al., 2014) and larger frontal P3 amplitude ($\sim$300 ms poststimulus onset) of the ERP (O'connell et al., 2012; Li et al., 2013; Alperin et al., 2014). These age-related increases in PFC activity are generally observed when older adults exhibit comparable target detection performance to younger adults. Indeed, increased PFC activity in older adults correlates with improved target detection performance, indicating PFC activity serves as a compensatory mechanism in aging to retain performance (Madden et al., 1997, 2007b). Interestingly, compensatory recruitment of PFC may begin to occur in young and middle-aged adults (Zysset et al., 2007; Peltz et al., 2011; Reuter et al., 2013). Yet, it is unclear how compensatory mechanisms are utilized across the life span, as what may be compensatory in older adults can have negative effects on performance in young adults who engage similar neural regions as older adults (Amer et al., 2016).

The question is then why some studies exhibit age-related declines in target detection and others do not. It should be noted that target detection paradigms are typically easy to perform, with accuracies often approaching ceiling performance. However, when target detection is more difficult (e.g., distractors with similar target features), older adults' target detection performance declines (slower detection and lower accuracy) (Wang et al., 2012). Importantly, this relationship between age-related declines and task difficulty is not exclusive to target detection paradigms. Data from both change detection (e.g., delayed match to sample) and discrimination paradigms have shown similar results when assessing selective attention ability in aging. Notably, older adults utilize frontoparietal attentional networks to compensate for visual processing deficiencies and retain task performance (Lee et al., 2011; Huang et al., 2012; Burianova et al., 2013), but with increased task demands, older adults do not increase frontoparietal attention network activity as do younger adults, which leads to declines in performance (Hedden et al., 2012; Prakash et al., 2012; Sander et al., 2012). In other words, frontoparietal activity in older adults during low-demand conditions appears similar to younger adults during high-demand conditions, which is thought to reflect an age-related limitation in flexibly recruiting additional attentional network regions in response to increasing cognitive demands (Prakash et al., 2009). These results support models of cognitive aging that indicate compensatory neural activity may be recruited in aging to retain performance but fails to help once capacity limitations are exceeded (Stern, 2002; Reuter-Lorenz and Lustig, 2005; Reuter-Lorenz and Cappell, 2008; Goh and Park, 2009). Thus age-related differences in selective attention performance may or may not be observed based on cognitive capacity and task difficulty.

It could be argued that age-related declines in selective attention ability may be the result of cognitive resources being used to compensate for perceptual or sensory processing deficiencies, thereby limiting available resources for selective attention abilities. However, when perceptual/sensory differences are equated between younger and older adults, selective attention abilities are still deficient in aging (Quigley et al., 2010; Zanto et al., 2010b). Thus age-related declines in selective attention cannot be fully attributed to limited resources compensating for perceptual/sensory declines. And these results receive support from neuroanatomic changes observed in aging. Specifically, age-related declines in behavioral performance under increased task difficulty have been associated with gray matter volume shrinkage in PFC and parietal regions known to be involved in attentional control (Muller-Oehring et al., 2013), as well as diminished white matter tract integrity connecting frontoparietal attention networks (superior and inferior longitudinal fasciculi) (Bennett et al., 2012). Despite a disproportionate age-related decline in PFC and parietal gray and white matter, occipital (visual sensory) cortex is unchanged in aging (Raz, 2005; Gordon et al., 2008). Therefore, if sensory processing deficiencies require compensation, neuroanatomic changes should be prevalent in sensory cortex and predict age-related performance declines. Yet, it is the PFC and parietal regions, which support selective attention processes, that exhibit such neuroanatomic decline in age and predict behavioral outcomes. Moreover, the reduced white matter integrity in PFC has been associated with compensatory activity in the PFC, supporting a "less wiring, more firing" model (Daselaar et al., 2015). Together, recruitment of PFC regions in aging may reflect, to some extent, compensation for its own dysfunction in selective attention.

Indeed, several models of cognitive aging propose deficient PFC function underlies age-related declines in multiple cognitive domains, including selective attention ability—particularly inhibitory control (West, 1996; Hasher et al., 2007; Gazzaley, 2012). The inclusion of irrelevant stimuli invariably increases task difficulty, and older adults exhibit deficient working memory performance that is related to a selective deficit in inhibiting sensory processing activity to irrelevant stimuli (Gazzaley et al., 2005b; Chadick et al., 2014). Importantly, this decline in suppressing irrelevant stimulus processing is related to decreased activity in PFC as well as decreased functional connectivity between sensory cortex and PFC (Campbell et al., 2012; Chadick et al., 2014). The consequence of not engaging PFC-mediated suppression networks is that older adults remember irrelevant information better than younger adults, meaning that they do not ignore distraction, but rather coencode relevant and irrelevant information (Gazzaley et al., 2005b; Schmitz et al., 2010; Clapp and Gazzaley, 2012). Thus older adults may exhibit deficient working memory performance due to overloading limited memory stores with irrelevant information (see "Working memory" section). Not only are older adults allocating attentional resources to irrelevant stimuli, but they also fail to disengage from irrelevant items in the environment (Cashdollar et al., 2013; Cona et al., 2013), which is the result of a deficient ability to dynamically allocate attention and switch between functional brain networks between PFC and sensory cortex (Clapp et al., 2011) (see "Multitasking and task switching" section).

Reduced inhibitory control in older adults is also associated with neuroanatomic differences. Specifically, older adults with lower inhibitory control exhibit lower white matter integrity in anterior corpus callosum, anterior corona radiata, and anterior limb of the capsula interna (Sullivan et al., 2006; Chadick et al., 2014; Wolf et al., 2014). These pathways connect dorsolateral PFC/anterior cingulate cortex with other frontal and subcortical regions. Moreover, reduced inhibitory control in older adults and concomitant activity suppression deficits in sensory cortex are related to decreased gray matter volume in medial PFC, as well as decreased white matter integrity in tracts subserving frontoposterior attentional networks (superior longitudinal fasciculus) (Chadick et al., 2014). Therefore, neuroanatomic changes in PFC regions are not only associated with deficient inhibitory control, but as mentioned previously, these are the same regions that predict age-related performance deficits under increased task demands. Considering that distractions are a means to increase task demands, this consistency across studies should not be surprising. What remains to be understood is the relationship between age-related changes in inhibitory control, neuroanatomy, and dopamine. Although dopaminergic modulation of PFC alters inhibitory control ability (Bloemendaal et al., 2015), and dopamine is affected in age (Carlsson, 1987), the causal relationship between anatomic, neurochemical, and physiological changes in aging is unresolved.

EEG research has shown that inhibitory control deficits in aging occur as alterations in both amplitude and latency of neural activity to irrelevant information, which spans multiple stimulus processing stages between 100 and 500 ms poststimulus onset (Gazzaley et al., 2008; Deiber et al., 2010; Finnigan et al., 2011). Interestingly, not only do these studies show age-related declines that are selective for inhibiting neural activity to irrelevant stimuli, but general slowing of neural activity during the same processing stages were observed—independent of stimulus relevance. Therefore, these results help link models that suggest age-related declines in cognition result from deficient inhibition (Hasher and Zacks, 1988; Hasher et al., 2007) or slowed processing speed (Salthouse, 1996; Salthouse and Madden, 2007). Yet, older adults may "lose the race before it starts" as older adults do not capitalize on predictive information that would help orient their attention toward (or away from) an impending relevant stimulus (or distractor) (Zanto et al., 2010a; Padgaonkar et al., 2017). Thus older adults do not properly engage neural mechanisms in anticipation of predictable stimuli (Bollinger et al., 2011; Zanto et al., 2011a), which is under PFC control (Coull et al., 2000; Bollinger et al., 2010). These results support models of cognitive aging that suggest multiple cognitive declines may stem from deficient expectation-based mechanisms (Zanto et al., 2011a) and/or a proactive-to-reactive shift in aging (Paxton et al., 2008; Dew et al., 2012). Regardless of whether these age-related declines occur prior to or during stimulus presentation, deficient attentional (top-down) control from the PFC is a common source of multiple cognitive deficits in aging (Gazzaley and D'Esposito, 2007; Gazzaley, 2012).

In summary, data from selective attention research highlights several important factors in cognitive aging. Notably, there is great heterogeneity in the aged population, in terms of performance and neural activity profiles. Thus research studies do not always agree on whether age-related declines in selective attention abilities exist. Yet, there is more agreement across studies that utilize difficult tasks, such as the inclusion of distractors, which result in more pronounced performance deficiencies among older adults. Neuroimaging data has shed important light on this relationship between performance and task difficulty. Specifically, older adults exhibit deficient sensory processes as well as a disproportionate decline in gray matter volume and white matter integrity in PFC and

parietal regions that support selective attention ability. The consequence of these changes is that older adults tend to recruit PFC regions to compensate for declines in perceptual and selective attention processes. However, when task demands exceed available cognitive resources, age-related performance deficits become apparent—such as an inability to ignore distraction.

Working memory

Working memory is a capacity-limited cognitive system that enables temporary storage and manipulation of information (Baddeley and Hitch, 1974) and the PFC exerts top-down control over working memory contents (D'Esposito and Postle, 2015). Whereas change detection tasks can be used to assess selective attention ability, they are more commonly used to assess working memory. The goal of a change detection task is to determine whether previously presented stimuli that are held in working memory for a brief time have changed in some way, such as a shift in features, spatial location, or orientation. Thus, change detection tasks include delayed match to sample tasks, location matching, N-back, or same/different tasks.

Research studies in working memory typically demonstrate age-related deficits (Babcock and Salthouse, 1990; Rypma and D'Esposito, 2000), which may emerge from middle age onward (Grady et al., 2006; Mattay et al., 2006). However, older adults exhibit heterogeneous working memory ability, in that group-level working memory deficits may be attributed to a subgroup with poor performance, while others exhibit performance comparable to younger adults (e.g., 119). These high-performing older adults often exhibit recruitment of additional PFC and parietal regions to serve as a compensatory mechanism that maintains performance during change detection tasks (Rypma and D'Esposito, 2000; Lee et al., 2011; Burianova et al., 2013; Macpherson et al., 2014). Notably, there is a hemispheric asymmetry reduction in older adults (HAROLD model), with younger adults exhibiting unilateral PFC activity during working memory processes, while high-performing older adults recruit contralateral (i.e., bilateral) PFC to achieve the same goals (Cabeza et al., 2002). The recruitment of compensatory neural activity in aging has been observed during both working memory (Dixit et al., 2000; Reuter-Lorenz et al., 2000; Piefke et al., 2012) and inhibitory control processes (Nielson et al., 2002; Langenecker et al., 2004). Thus, similar to selective attention/inhibitory control processes, heterogeneity in working memory performance across the aged population appears to be related to the ability to recruit compensatory neural mechanisms, particularly within the PFC.

Due to the role of dopamine in working memory maintenance during distraction (Bloemendaal et al., 2015), it has been hypothesized that deficient dopamine underlies lower working memory performance in aging (Braver and Barch, 2002; Park and Reuter-Lorenz, 2009). Moreover, compensatory PFC activity may also be related to dopamine levels. The Val(158) Met polymorphism in the gene for catechol *O-methyltransferase* (COMT) regulates levels of dopamine in the PFC (Tunbridge et al., 2004). Older adults with the Met variant presumably have greater dopamine levels and exhibit neural activity profiles similar to younger adults during a change detection task (Sambataro et al., 2009). Older adults with the Val variant presumably have lower dopamine levels and exhibit increased dorsolateral PFC activity and functional connectivity with parietal regions. Unfortunately, no correlation was assessed between this increased activity and performance, so it is unclear whether this PFC activity was compensatory. While it is plausible that reduced dopamine requires increased neural activity to compensate for performance decrements, other research indicates reduced dopamine in aging is associated with decreased PFC activity. Specifically, lower dopamine synthesis capacity in the aged caudate nucleus is related to lower PFC activity and lower working memory performance (Landau et al., 2009). Similarly, by blocking dopamine D1 receptors in young adults, activity in PFC and parietal regions were reduced and resulted in lower working memory performance, comparable to older adults (Fischer et al., 2010). Thus, additional research will be required to understand the interaction between dopamine and compensatory PFC activity. Nonetheless, mounting evidence indicates age-related deficits in working memory stem from low dopamine levels and altered PFC function.

Similar to selective attention, age-related performance deficits in working memory are most pronounced under increased task difficulty (Ansado et al., 2012, 2013; Piefke et al., 2012; Prakash et al., 2012; Sander et al., 2012), such as when distractors are present (Hasher and Zacks, 1988). Under low task demands, older adults exhibit functional connectivity between lateral PFC and other network modules similar to younger adults under high task demands (Gallen et al., 2016b). As task difficulty increases, age-related deficits become more apparent concomitant with deficient top-down control signals from dorsolateral PFC (Heinzel et al., 2017), which arise from lower dopamine levels (Nyberg et al., 2014). Importantly, older adults recruit compensatory mechanisms until a resource ceiling is reached (Toepper et al., 2014) and working memory load-dependent modulation of neural activity is related to dopamine binding potential in the caudate nucleus and dorsolateral PFC (Backman et al., 2011a, b).

Therefore, older adults with lower dopamine appear to have a lower ceiling for cognitive resources, which limits the extent neural activity may be recruited to compensate for increased task demands and subsequently yields lower task performance—though this hypothesis is yet to be directly tested. Nonetheless, when task difficulty exceeds resources, older adults may still exhibit increased PFC and parietal activity relative to younger adults, but performance deficits are no longer compensated (Grady et al., 2008; Ansado et al., 2012, 2013; Piefke et al., 2012). This neural recruitment in aging without a performance benefit is considered failed compensation or inefficient processing (Grady, 2012) and support models that indicate compensatory mechanisms are only useful when sufficient cognitive resources are available, such as during low task demands (Stern, 2002; Reuter-Lorenz and Lustig, 2005; Park and Reuter-Lorenz, 2009). However, recent evidence indicates recruitment of bilateral dorsolateral and anterior PFC is a domain-general strategy in response to cognitive challenge and not necessarily exclusive to cognitive aging (Höller-Wallscheid et al., 2017). Therefore, although older adults are more likely to exhibit compensatory PFC activity during low-task demands, younger adults with lower working memory capacity may also exhibit a similar neural activity profile.

Although the PFC has been associated with working memory processes, age-related deficits in working memory ability have, paradoxically, not been attributed to declines in PFC anatomic structure. Specifically, the volume of PFC gray matter and white matter hyperintensities do not correlate with working memory deficits in aging (Gunning-Dixon and Raz, 2003; Arvanitakis et al., 2016). While a previous report has indicated a relationship between working memory and white matter hyperintensities, this study used tasks that challenged both working memory and executive (attentional) control processes (DeCarli et al., 1995). A recent study that also demonstrated a correlation between working memory and gray and white matter within PFC did so by assessing the impact of distraction on working memory performance (i.e., distractability), but no such relationship was observed with overall working memory performance (Chadick et al., 2014). Thus, anatomic changes in the PFC more likely impact selective attention processes that exert top-down control over the contents of working memory, rather than affecting the contents of working memory per se.

In summary, there is a significant amount of overlap between the cognitive processes and neural networks that support working memory and selective attention (Cowan, 1995; Gazzaley and Nobre, 2012; Kiyonaga and Egner, 2013). Thus age-related declines in working memory exhibit many of the same deficient characteristics as selective attention/inhibitory control. Notably, age-related deficits in working memory are attributed to deficient (or inefficient) function within the PFC and that heterogeneity in working memory ability is partially accounted for by the ability to recruit compensatory neural activity to uphold performance. As task demands exceed limited resources available, age-related declines in working memory become apparent and are therefore most pronounced under high task demands. Although it remains unclear how age-related differences in dopamine levels may underlie deficiencies in selective attention/inhibitory control or compensatory recruitment of neural activity during working memory, mounting evidence attributes changes in dopamine level as a contributor to alterations in PFC function and working memory performance in aging.

Multitasking and task switching

Multitasking refers to dividing attention between multiple skills, tasks, or cognitive sets, while task switching refers to a type of multitasking that involves shifting between multiple skills, tasks, or cognitive sets. Thus it is intuitive that age-related deficiencies in multitasking are related to lower performance on the component tasks (Todorov et al., 2014). Yet, multitask abilities in older adults are lower than in younger adults, even when performance is normalized by the individual component task performance (Anguera et al., 2013). Similar to results from single-task studies, slowed processing speed plays a role in multitasking deficits (Allen et al., 1998; Glass et al., 2000). However, when generalized slowing is accounted for, age-based multitasking performance deficits persist (Hartley and Little, 1999; Glass et al., 2000; Verhaeghen et al., 2003). Notably, age-related performance declines in multitasking become pronounced with increased task difficulty (McDowd and Craik, 1988), which corroborates the idea from single-task studies that many age-related deficits in cognitive performance stem from limited cognitive resources. However, multitasking deficits in aging are not always sensitive to task demands (Verhaeghen and Cerella, 2002), and age-related differences in multitasking performance may stem from deficient attentional control more so than competition for limited cognitive resources (Bier et al., 2017). It is possible that limited resources highlight age-related differences in multitasking when younger adults have cognitive resources to spare, but as task difficulty exceeds available resources in both age groups, younger and older adults may show similar additive multitasking costs, despite generally lower performance in aging due to slowing and/or deficient attentional control. Although this hypothesis needs to be tested, it is likely that age-related differences in multitask performance stem from multiple sources that include generalized

slowing, deficient attentional control, and limited cognitive resources.

Neuroimaging research has provided additional insight into the nature of age-related changes in multitask ability. Notably, older adults may recruit PFC and parietal regions as a compensatory mechanism to uphold multitasking performance abilities (Fernandes et al., 2006; Hartley et al., 2011; Wild-Wall et al., 2011) and, in particular, during task switching (DiGirolamo et al., 2001; Smith et al., 2001; Goffaux et al., 2008). Furthermore, older adults with the lowest task switch costs exhibit the highest dopamine synthesis capacity as well as smaller neural activation increases during switch trials (Berry et al., 2016). Thus, striatal dopamine synthesis and frontoparietal efficiency contribute to maintained multitask performance in aging. But when age-related performance deficits are observed, older adults exhibit lower PFC engagement (Anguera et al., 2013) as well as lower functional connectivity (Madden et al., 2010) and white matter integrity (Jolly et al., 2017) within PFC and parietal cortex networks. Moreover, when older adults are required to disengage a secondary task and reengage a primary task, they fail to dynamically allocate attention and switch between functional brain networks involving PFC and sensory cortex (Clapp et al., 2011). Thus age-related differences in multitasking ability is related to differences in the neural networks underlying attentional control, particularly within the PFC. This age-related reduction in attentional (top-down) modulation of neural activity occurs during early processing stages (i.e., $<$400 ms) but is retained at later stages (Malcolm et al., 2015), suggesting the deployment of attentional control is slowed in aging. Thus age-related multitasking deficits support models of cognitive aging that attribute cognitive deficiencies to slowed processing speed (Salthouse, 1996; Salthouse and Madden, 2007), as well as deficient attentional control through diminished communication between PFC and sensory cortex (Gazzaley, 2012). Although some research indicates limited resources also play a role in age-related multitasking deficits, additional research will be necessary to understand whether compensatory neural recruitment may occur until task demands exceed available resources, as predicted by limited resources models (e.g., Stern, 2002; Park and Reuter-Lorenz, 2009).

In summary, age-related deficits in multitasking ability are related to lower performance on the individual component tasks, but they do not account for all age-related declines in multitasking ability. Sources of multitasking decline stem from deficient processes that also affect single-task performance, but are exacerbated during multitasking, which is affected by slowed processing speed, lower attentional control, and limited cognitive resources. Neuroimaging research has demonstrated that deficient function in PFC and parietal regions underlie these age-related differences in multitasking. Overall, research on multitasking performance in aging is limited and additional work is needed to fully understand the contribution of each of these sources of multitasking dysfunction and how they relate to neural activity declines in specific cortical regions.

RETAINED COGNITIVE FUNCTIONS

Under low task demands, many cognitive functions appear to be comparable between younger and older adults. As described in the previous sections, age-equivalence has been reported during sustained attention, selective attention, inhibitory control, and working memory tasks, which may in part be attributed to cognitive reserves that enable compensatory neural mechanisms to uphold performance. It is worth noting that, while many age-related cognitive declines have been attributed to a deficient dopaminergic system, cognitive reserve has been associated with the noradrenergic system (Robertson, 2013) modulating a right hemisphere frontoparietal network (Robertson, 2014).

Age-equivalence in inhibitory control and working memory ability appear most often when the attended stimulus is in a different modality than the ignored stimuli, particularly when visual stimuli are attended and auditory stimuli are ignored (reviewed in Guerreiro et al., 2010). It could be argued that multisensory integration processes do not compete as much for limited cognitive resources, thereby enabling older adults with lower resources to perform on par with younger adults. Indeed, age-related declines in multisensory integration only seem to appear during more cognitively demanding tasks, such as multitasking (de Dieuleveult et al., 2017). However, not all manipulations of task difficulty yield age-related declines in performance. When task difficulty is manipulated by increasing the intensity and familiarity of the distractors, age-equivalent performance is maintained (Rouleau and Belleville, 1996; Belleville et al., 2003). Thus older adults appear to retain the ability to detect and remember stimuli when distraction is in a different modality (i.e., retained multisensory integration ability), but age-related differences can become apparent under increased task demands, likely due to limited cognitive reserves for the demanding task(s).

Yet, different cognitive abilities peak at different stages of life. In an impressive sample of 48,537 participants across the life span, many cognitive abilities were shown to peak in early adulthood, with several abilities peaking in midlife or later (Hartshorne and Germine, 2015). Cognitive functions that utilize PFC and exhibit peak ability in mid-to-late life include arithmetic, comprehension, and emotion perception. Whereas emotion

perception peaks in midlife and exhibits modest declines in advanced age (Ruffman et al., 2008; Hartshorne and Germine, 2015), emotional control remains stable or is even enhanced with age (Gross et al., 1997; Carstensen et al., 2000). It is interesting to note that, despite age-related changes in the anatomy and physiology of the PFC, several cognitive functions subserved by the PFC are relatively maintained or improved with age. Although cognitive functions associated with the PFC are the focus of this chapter, it is worthwhile to also note that the medial temporal lobes exhibit similar age-related declines as the PFC, and yet some cognitive functions subserved by the medial temporal lobes remain intact or peak in mid-to-late life, such as declarative memory (Salthouse, 1982; Hartshorne and Germine, 2015). It is possible that these retained cognitive functions in age, and the varying ages at which different cognitive functions peak, reflect a motivational shift across the life span, supporting theories that posit older adults are motivated by emotion-related goals while younger adults are motivated by knowledge-based goals (socioemotional selectivity theory) (Carstensen et al., 2003). Although additional research is necessary to test this hypothesis, the implication is that cognitive functions that are consistently engaged across the life span (such as vocabulary and emotional control) are the ones to be maintained (i.e., use it or lose it). As described in the next section, this certainly seems to be the case.

In summary, under low task difficulty, many cognitive functions exhibit age-equivalent performance, including sustained attention, selective attention, inhibitory control, working memory, and multisensory integration. Regardless of task difficulty, several other cognitive functions are retained or modestly affected in age, including arithmetic, comprehension, emotion perception, and emotion regulation. Because some of these cognitive functions peak in mid-to-late life, reports of age-equivalence in these domains should be interpreted with caution if the age of the studied groups lies on either side of the age of peak performance. Therefore, when attempting to determine age-related declines in cognition, the type of cognitive task and the individual's age must be taken into account.

IMPROVING FRONTAL LOBE STRUCTURE AND FUNCTION

Despite the many cognitive functions that decline with age, there is mounting evidence that the brain retains neuroplasticity throughout the life span and many (if not all) deficient cognitive functions may be maintained or recovered (Greenwood and Parasuraman, 2010; Merzenich et al., 2014). One well-documented means to maintain or improve cognitive function in advanced age is through physical exercise (for reviews, see de Asteasu et al., 2017; Zubala et al., 2017). Physical exercise and, most notably, cardiorespiratory and resistance training (Kelly et al., 2014) have been associated with increased gray and white matter volume, particularly in the PFC (Colcombe et al., 2006; Erickson et al., 2014); physical exercise improves cognitive functions associated with the PFC, including inhibitory control (Dustman et al., 1984), working memory (Fabre et al., 2002) (but also see Smith et al., 2010), and multitasking/-task switching ability (Hawkins et al., 1992). These exercise-based improvements in cognition are associated with increased activity in PFC and parietal cortex (Colcombe et al., 2004) as well as increased neural specificity (i.e., less dedifferentiation) in sensory cortex (Kleemeyer et al., 2017).

In addition to physical exercise, cognitive exercise (also referred to as cognitive training) may also help counteract age-related declines in various cognitive abilities (for reviews, see Lustig et al., 2009; Brehmer et al., 2014; Lampit et al., 2014), which tends to improve the trained cognitive function, with some transfer of benefit to cognitive domains that rely on the trained function. For example, perceptual training in older adults can improve not just perceptual abilities but transfer to improved visual working memory performance due to more efficient sensory processing in visual cortex (Berry et al., 2010). Cognitive speed of processing training in older adults not only accelerates cognitive processing, but translates to improved everyday abilities such as driving performance (Ball et al., 2007), which has been attributed to speeded multitasking abilities (Edwards et al., 2013). Moreover, auditory cognitive training that emphasizes speed of processing enables faster and less variable neural responses within the brainstem of older adults, and these benefits extend to improved working memory performance (Anderson et al., 2013), likely because processing speed is thought to underlie multiple cognitive domains, including working memory (Babcock and Salthouse, 1990; Salthouse, 1996). Thus cognitive training appears to benefit not just the trained cognitive function, but other cognitive modalities that rely on the trained function.

Given that cognitive training appears to be beneficial for the trained cognitive domain, targeting age-related deficiencies such as inhibitory control should be most beneficial. Indeed, distraction-training in aged humans and aged rats shows improved inhibitory control concomitant with sharpened sensory receptive fields (in aged rats) and decreased PFC activity to distractors (in aged humans) (Mishra et al., 2014). Moreover, this training resulted in a transfer of benefit to working memory and sustained attention abilities (Mishra et al., 2014). Similarly, age-related declines in multitasking

performance are prominent, and multitasking training in older adults improves performance (Allen et al., 2014; Kray and Feher, 2017) concomitant with PFC activity profiles similar to younger adults (Erickson et al., 2007; Anguera et al., 2013). Furthermore, multitasking training yields a transfer of benefit to working memory and sustained attention abilities (Basak et al., 2008; Anguera et al., 2013). Although transfers of benefit to untrained cognitive domains are desirable, it is unclear in which scenarios cognitive training will enhance untrained domains, as a transfer of benefit is not always observed or is minimal (Verhaeghen et al., 1992; Gross et al., 2012). It is likely that cognitive training and transfers of benefit are most effective when targeting cognitive functions in need of improvement (Zinke et al., 2011, 2014).

Although cognitive training is easy to implement broadly across the population, some participants appear to be better candidates than others. Individual characteristics such as age, education and baseline performance help predict training-based gains (Zinke et al., 2014), which vary in predictive power according to task (Borella et al., 2017b). Moreover, implementing a particular strategy may yield greater training gains (Borella et al., 2017a). Therefore, if strategy is not guided by the experimenter/clinician, those with less optimal strategies may benefit less. Interestingly, older adults who benefit the most from cognitive training exhibit more segregated brain subnetworks (i.e., more modularity) prior to training, particularly when those subnetworks underlie the trained cognitive function (Gallen et al., 2016a). Because brain modularity is thought to reflect an energy-efficient way to organize and communicate information in a flexible and adaptive manner (Liao et al., 2017), it could be hypothesized that older adults with high modularity not only show the greatest training-based improvements, but also exhibit the greatest transfers of benefit. It should also be noted that cognitive training increases striatal dopamine (Backman et al., 2011a, b), so it could be further hypothesized that older adults with low levels of dopamine may benefit most from cognitive training.

While more research is needed to understand individual differences in response to cognitive training, additional research will also be needed to fully understand how long physical exercise or cognitive training benefits may last after training has ceased. Research has reported posttraining benefits that last from 6 months (Anguera et al., 2013; Anderson et al., 2014) to 2 years (Ball et al., 2007). Yet, it would not be surprising to see longer-lasting effects, depending on the level of practice or expertise. Several studies have demonstrated professional career can mitigate age-related declines in cognition, though the benefits appear limited in scope to cognitive domains related to the profession (Morrow et al., 1994; Cavallini et al., 2009; Nunes and Kramer, 2009). Similarly, other life-course factors serve as determinants of cognitive aging, such that engaging in leisure activities in midlife are positively associated with cognitive ability level, while physical activity in late life is associated with less cognitive decline (Gow et al., 2017). Additional life-course factors that predict cognitive decline in advanced age include low education (Albert et al., 1995), hypertension (de Frias et al., 2014), less self-efficacy (Albert et al., 1995), low/no alcohol use (Zanjani et al., 2013), reduced cardiovascular capacity (Alagiakrishnan et al., 2006), diabetes mellitus (Arvanitakis et al., 2004), metabolic syndrome (Yaffe et al., 2004), inflammation of interleukin 6 and C-reactive protein (Yaffe et al., 2004), and unhealthy behaviors such as poor sleep quality (Nebes et al., 2009), smoking, and poor nutrition (Sabia et al., 2009). Given this, recent theories of cognitive aging emphasize lifestyle choices and life-course factors in determining resilience to cognitive decline in aging (STAC-r) (Reuter-Lorenz and Park, 2014). Thus early- and middle-aged adults should engage in healthy physical and cognitive lifestyles to reap long-term gains in (or retention of) cognition.

Whereas both physical and cognitive training can yield benefits for cognitive performance in advanced age, additional research will be required to understand any synergistic effects that may be gained by combining both physical and cognitive exercise. It may be that the combination of both physical and cognitive exercise will result in optimal cognitive gains, such that physical exercise increases the potential for neurogenesis/synaptogenesis while cognitive training guides it to induce more targeted changes (Fissler et al., 2013; Bamidis et al., 2014). Benefits of physical and cognitive exercise, such as education, are both predictive of preserved cognitive function in aging, but they operate via separable effects on cognition and brain structure (Gordon et al., 2008; Chapman et al., 2016). Fitness/exercise in older adults is associated with preserved gray matter in dorsolateral PFC, parietal, and medial temporal areas, as well as increased cerebral blood flow in medial temporal areas concomitant with improved memory performance. Conversely, cognitive training/education in older adults is associated with preserved white matter in inferior PFC as well as increased cerebral blood flow in PFC concomitant with improved executive function. Thus it is plausible that the combination of both physical and cognitive training will yield greater benefits than either one in isolation. Interestingly, while implementing regimented physical and cognitive exercises may help retain or regain various cognitive abilities in aging, recent research indicates a busy lifestyle may

also yield similar benefits on cognition (Festini et al., 2016), likely due to the inherent physical and cognitive challenges associated with a busy lifestyle.

Finally, it should be noted that noninvasive brain stimulation, such as transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation, may also be used to improve cognitive function in aging (reviewed in Hsu et al., 2015). While evidence remains somewhat limited, current reports suggest older adults may improve working memory (Park et al., 2014), inhibitory control (Kim et al., 2012), episodic memory (Flöel et al., 2012; Manenti et al., 2013), and semantic memory (Meinzer et al., 2013, 2014). Of note, many of these improvements in cognition arise from studies stimulating the PFC. For example, tDCS to right PFC improves visual processing speed in older adults (Brosnan et al., 2017). Unfortunately, the effects of noninvasive brain stimulation can be highly variable, and effects can be contingent on numerous parameters such as stimulus intensity, duration, anatomy, and cognitive state, to name a few (Rubens and Zanto, 2012; Woods et al., 2016). One study demonstrated that only older adults with a high education benefited from tDCS, whereas older adults with a low education exhibited declines in performance (Berryhill and Jones, 2012). However, education is associated with high cognitive reserves and another study indicated that older adults with low cognitive reserves benefit the most from tDCS (Brosnan et al., 2017). These somewhat conflicting results may be attributed to the sensitivity of tDCS effects on task-specific baseline performance (Learmonth et al., 2015), and are less contingent on education or cognitive reserve. Nonetheless, additional research is necessary to help account for these conflicting results and understand all the factors that may influence stimulation-based changes in cognition. Overall, noninvasive brain stimulation is a promising field of research with potential to improve or maintain cognition in advanced age. Importantly, supplementing cognitive training with noninvasive brain stimulation can yield benefits in older adults (Stephens and Berryhill, 2016) greater than cognitive training alone (Jones et al., 2015).

In summary, there are many ways to help maintain or regain PFC structure and function in advanced age. While the benefits of exercise are the best documented, mounting evidence indicates cognitive training and noninvasive brain stimulation may also yield beneficial effects. Additionally, many lifestyle and life-course factors can contribute to a decades-long decline in cognition. Therefore, engaging in physical and cognitive exercise as well as maintaining a healthy lifestyle can help maintain most (if not all) cognitive functions into advanced age.

SUMMARY

As examined, current research has attributed multiple age-related declines in cognitive function to deficiencies in PFC anatomy and physiology, with a particular role of suboptimal dopamine levels that may have a genetic basis. Here, evidence was reviewed indicating deficient perceptual, selective attention/inhibitory control, working memory, and multitasking abilities in aging. However, there is great heterogeneity across the aged population, with some older adults not exhibiting deficiencies—particularly when task difficulty is low. Cognitive reserve is thought to play a role in retaining task performance by recruiting additional cortical regions for compensation, typically within the PFC. When task difficulty exceeds cognitive reserve, age-related performance differences are most pronounced. Yet, despite changes in PFC, not all PFC-mediated cognitive functions exhibit declines with age, or they exhibit modest changes in advanced age, such as in arithmetic, comprehension, emotion perception, emotional control, and declarative memory. Many life-course factors predict the trajectory of cognition in aging and generally follow a "use-it-or-lose-it" model. Fortunately, the brain remains plastic across the life span and many (if not all) age-related declines in cognition can be remediated. Approaches to regaining or retaining cognitive function include healthy lifestyles, particularly physical fitness, as well as cognitive training and noninvasive brain stimulation techniques. Together, predicting the trajectory of cognitive aging, especially as it pertains to changes in PFC, is a complex multivariate problem, but the effects of age may be minimized or eliminated by lifestyle choices that can be made in early to mid-adulthood.

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