Chapter 8

Executive Functions and Neurocognitive Aging

R. Nathan Spreng[1,2], Leena Shoemaker[3] and Gary R. Turner[3]
[1]*Department of Human Development, Cornell University, Ithaca, NY, United States,*
[2]*Human neuroscience Institute, Cornell University, Ithaca, NY, United States,*
[3]*Department of Psychology, York University, Toronto, ON, Canada*

INTRODUCTION

Executive functions (EFs) are integrative processes that guide goal-directed and purposeful behavior (Cicerone et al., 2011). These cognitive abilities are essential for maintaining functional independence in older adulthood (Cahn-Weiner, Boyle, & Malloy, 2002), yet show a consistent, near-linear, decline from middle adulthood onward. Indeed, EF loss is considered to be a hallmark of cognitive aging (Park, Polk, Mikels, Taylor, & Marshuetz, 2001). While the behavioral trajectory of executive functioning in older adulthood has been well characterized (Baltes & Lindenberger, 1997; Buckner, 2004; Hasher & Zacks, 1988; Miyake et al., 2000; Park et al., 2001; Salthouse, 1996), research is just beginning to link these cognitive changes to changes in brain structure and function. Establishing this link is becoming increasingly important as older adults, their families, and health care providers are looking to "brain science" for answers on how to slow the pace of cognitive decline. In this chapter we review how neurocognitive aging research is bridging this gap, leading to new approaches and strategies for preserving executive functioning—and prolonging functional independence—in later life.

More than a century and a half of neuropsychological research has implicated the frontal lobes of the brain in executive, goal-directed, control of behavior (Stuss & Levine, 2002). The advent of neuroimaging tools, enabling researchers to obtain in vivo measures of structure and function across the whole brain, has broadened this association, demonstrating that executive functioning is not simply the result of frontal lobe activity per se but rather an emergent property of interactions between the frontal lobes and posterior brain regions. Structural brain imaging research has shown that over the course of the adult life span, there is loss of cortical and white matter volume within

Executive Functions in Health and Disease. DOI: http://dx.doi.org/10.1016/B978-0-12-803676-1.00008-8

the frontal lobes of the brain, and these changes also follow a near-linear trajectory (Rodrigue, Kennedy, & Raz, 2005). This suggests that age-related declines in executive control may simply proceed in lock step with loss of frontal brain volume. However, brain structure is a poor predictor of cognition, with many older adults showing remarkable preservation of cognitive abilities despite significant brain volume loss (Snowdon, 1997). This dissociation between changes in brain structure and cognition has led researchers to investigate brain function as a potential mediator of age-related cognitive decline (Stern et al., 2005).

Many functional neuroimaging studies have now reported changes in brain function during cognitive task performance in older versus younger adults (Cabeza, 2002; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2014; Spreng, Wojtowicz, & Grady, 2010). Within the domain of executive functioning, research has primarily focused on age-related changes in brain activity associated with specific executive control processes, such as working memory and inhibition (see Turner & Spreng, 2012 for a review). More recently, researchers have recognized that goal-directed control of behavior involves constant, reciprocal, and dynamic communication between frontal cortices and posterior brain regions. As such, changes in functional connectivity, within or between functionally connected assemblies or networks, of brain regions may provide a more powerful marker of age-related declines in executive control (Gallen, Turner, Adnan, & D'Esposito, 2016; Grady, 2012; Spreng & Schacter, 2012; Turner & Spreng, 2015).

Here we review executive functioning and aging through the lens of functional brain changes that occur across the adult life span. We begin the chapter with an update of our metaanalytic review of all functional neuroimaging studies investigating age-related changes in *brain activity* across three executive control domains: working memory, inhibition, and task switching (Turner & Spreng, 2012). We next explore how research investigating changes in *functional connectivity* between brain regions is leading to increasing mechanistic accounts of age-related cognitive decline. In the concluding section of the chapter we review how these advances are informing the design of interventions to slow the pace of decline and enhance executive control functioning in older adulthood.

FUNCTIONAL BRAIN CHANGES AND EXECUTIVE FUNCTIONING: A METAANALYTIC REVIEW

As noted in the Introduction, studies of age-related functional brain changes have focused mainly on specific executive control processes. While there is no universally accepted schema for identifying component processes of executive control, one of the most influential has been the fractionated account proposed by Miyake et al. (2000). The authors used factor analytic methods to contrast a unitary versus a fractionated model of executive functioning in

younger adults. Their findings suggested that executive functioning was not a unitary cognitive construct but rather comprised three dissociable processes: updating in working memory, inhibition, and task switching. Other process-specific accounts of executive control have been proposed. One model suggests that task switching may not be a dissociable process but rather an emergent capacity drawing upon inhibition and working memory processes (Diamond, 2013). Others have argued that working memory capacity is superordinate, akin to fluid intelligence or G (Conway, Kane, & Engle, 2003; Duncan et al., 2000). Miyake et al. (2000) updated their original fractionation model identifying a common EF component that almost perfectly correlated with their original inhibition factor. The updated model now includes this unitary EF component and two dissociable subcomponents: task switching and working memory (see Friedman & Miyake, 2016; Miyake & Friedman, 2012 for reviews).

Despite these various schema, the majority of published studies of functional brain activity associated with executive control functions have investigated the three processes associated with the original fractionated account (Miyake et al., 2000). Indeed, in a metaanalysis of brain activity and executive control functions in young adults, more than three-quarters (349 of 457) of the studies reviewed investigated task switching (mental flexibility), inhibition, and working memory (Niendam et al., 2012). Therefore, we selected this original fractionated model as the basis for our prior metaanalytic review of functional brain changes associated with executive functioning in older adults (Turner & Spreng, 2012). At the time of our original review, there were too few published studies investigating age-related functional brain changes during task switching, so we limited our analysis to published studies involving either working memory or inhibition tasks.

Our original metaanalysis included 30 studies (19 working memory and 11 inhibition) that met criterion for inclusion (see Executive functions, brain activity and aging: An updated metaanalytic review, and Turner & Spreng, 2012). For younger adults, we observed increased activation in frontal and parietal brain regions associated with working memory, right lateralized activation in inferior frontal gyrus, and supplemental motor areas for inhibition tasks. These findings were consistent with the results of a large metaanalysis of executive functioning in younger adults (Niendam et al., 2012). When contrasted with young, aging was associated with greater recruitment of dorsolateral prefrontal cortex (PFC) bilaterally (right greater than left) during working memory tasks, consistent with previous reports (Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000; Smith, Jonides, Marshuetz, & Koeppe, 1998; Wager & Smith, 2003). Inhibition was associated with greater activity in the right inferior frontal gyrus, inferior frontal junction, and in the left medial superior frontal gyrus in older adults. We interpreted this pattern of increased recruitment as "young-plus," i.e., overrecruitment of regions associated with inhibitory control in younger adults (Simmonds, Pekar, & Mostofsky, 2008).

When we directly contrasted patterns of activity between working memory and inhibition in each age group, the spatial separation in the pattern of functional brain response across the two executive control processes appeared to be largely maintained from younger to older adulthood, consistent with a process-specific account of age-related functional brain changes. To our knowledge, this was the first quantitative review to report that functional brain changes associated with specific executive control processes may not follow a common trajectory across the adult life span.

From the time of our initial review, several more reports have been published investigating functional brain changes during working memory and inhibition in older and younger adults. Critically, in updating our review we were also able to identify a sufficient number of age-related task switching studies to include this executive process in our revised metaanalysis. We report the findings of this updated analysis in the next section.

EXECUTIVE FUNCTIONS, BRAIN ACTIVITY, AND AGING: AN UPDATED METAANALYTIC REVIEW

Here we report the findings of an updated metaanalytic review of all functional neuroimaging studies investigating age-related changes in brain activity associated with the three executive control processes: working memory, inhibition, and task switching (Miyake et al., 2000). We replicate the methods reported in Turner and Spreng (2012) and describe core aspects of the review procedure here for comprehensiveness. Additional details may be found in the original published report.

Metaanalysis Methods

Selection of Studies

Neuroimaging studies examining aging and executive functioning were selected using a systematic search process. To update our previous analysis (Turner & Spreng, 2012), search criteria for working memory and inhibition were reentered covering the time period from April 2010 to May 2016. To capture studies investigating task switching, we covered the full time period of our previous review (January 1982 to May 2016). Peer-reviewed articles, published in English, were selected from the search results of three separate databases: Medline, PsycINFO, and Science Citation Index. Searches were conducted using the following terms: (1) Keyword: "age" <OR> "aging" <OR> "ageing" <OR> "age-related" <OR> "older adults" <OR> "adult life-span"; AND (2) Keyword: "neuroimaging" <OR> "cerebral blood flow" <OR> "fMRI" <OR> "functional magnetic resonance imaging" < OR> "PET" <OR> "positron emission tomography"; AND (3) Population: "human." A second search specifically targeted EF with the added search term, Topic: "executive" <OR> "working memory" <OR>

"inhibition." To identify task switching studies, we conducted a third search with the following search terms: "task switching" OR reconfiguration OR "mental flexibility" OR "cognitive flexibility" OR "rule set" OR "reversal learning" OR "attention switching" OR "Wisconsin Card Sorting Task" OR "Trail making task." For this updated review, 9308 independent reports were identified across both searches.

Only studies that reported both healthy young and healthy old adult group results were included. Theoretical papers and reviews were excluded. Studies that reported combined group results and a region-of-interest analysis, reported only brain-behavior correlations, or did not report activation foci as 3D coordinates in stereotaxic space were excluded because these studies could not be meaningfully analyzed with our metaanalytic software (see below). For studies that contained multiple nonindependent contrasts, to limit the contribution of any one set of participants to the pool of foci, we selected the contrast with the lowest level baseline. We selected these lower level contrasts because functional brain activity is reduced in older relative to younger adults at higher levels of task challenge as performance limits are exceeded (Cappell, Gmeindl, & Reuter-Lorenz, 2010). Inclusion of only high-level contrasts would confound age-related brain changes with potential ceiling effects on behavioral tasks. For studies containing multiple independent samples, peak activation foci from each sample were included. Three papers for working memory and one inhibition study met criteria for inclusion and were added to those reported in our original publication. A total of 11 papers were identified as meeting our criteria for task switching (Table 8.1). Next, all experiments were allocated to working memory ($n = 22$), inhibition ($n = 14$), or task switching analyses ($n = 11$). In cases where allocation to either category was unclear, we assigned the study based on the author's characterization.

Creation of Activation Likelihood Estimation (ALE) Maps

The activation likelihood estimation (ALE) method provides a voxel-based metaanalytic technique for functional neuroimaging data (Laird et al., 2005; Turkeltaub, Eden, Jones, & Zeffiro, 2002). The software (GingerALE v1.1; BrainMap) computes statistically significant concordance in the pattern of brain activity across any number of independent experiments. Additionally, GingerALE can compute statistically significant differences in the pattern of brain activity between two sets of data from several independent experiments. ALE maps are derived based on foci of interest, which comprise statistically significant peak activation locations from published studies. Independent group analysis peak foci (Working memory/Inhibition/Task switching > Control task in Younger; WM/Inhibition/Task switching task > Control task in Older) were extracted from each study. Where studies reported within- and between-group peak foci (i.e., combined Younger/Older,

TABLE 8.1 Details of Metaanalysis Studies Included in the Review

Study Number	First Author	Year	Executive Control Process	Paradigm
Working Memory				
1	Anguera	2011	Spatial working memory	Delayed spatial rotation task
2	Bennet	2013	Verbal working memory	Sternberg task
3	Cabeza	2004	Verbal working memory	Delayed word recognition
4	Emery	2008	Verbal working memory	Letter-number sequencing
5	Freo	2005	Face working memory	Delayed match to sample
6	Grady	1998	Face working memory	Delayed match to sample
7	Grossman	2002	Verbal working memory	Sentence comprehension
8	Haut	2005	Verbal working memory	Letter-number sequencing (WAIS)
9	Holtzer	2009	Nonverbal working memory	Sternberg task (nonverbal)
10	Johnson	2004	Verbal working memory	Refresh task
11	Nagel	2009	Spatial working memory	Delayed spatial recognition
12	Otsuka	2006	Complex verbal working memory	Reading span
13	Park	2010	Nonverbal working memory	Delayed recognition
14	Paxton	2008	Verbal working memory	Continuous performance task (AX-CPT)
15	Podell	2012	Verbal working memory	Updating task
16	Raye	2008	Verbal working memory	Refresh task
17	Reuter-Lorenz	2000	Verbal working memory	Delayed latter recognition

(*Continued*)

TABLE 8.1 (Continued)

Study Number	First Author	Year	Executive Control Process	Paradigm
17	Reuter-Lorenz	2000	Spatial working memory	Delayed spatial recognition
18	Ricciardi	2009	Face working memory	Delayed match to sample
19	Rypma	2001	Verbal working memory	Sternberg task
20	Schneider-Garces	2010	Verbal working memory	Sternberg Task
21	Smith	2001	Complex working memory	Operation span (mathematical problem solving)
Inhibition				
1	Colcombe	2005	Response inhibition (sensory)	Flanker task
2	Jonides	2000	Response inhibition (sensory)	Delayed word recognition (with recency manipulation)
3	Korsch	2014	Response inhibition (sensory/motor)	Flanker task with response conflict
4	Lee	2006	Response inhibition (motor)	Simon task (with response conflict)
5	Madden	2002	Inhibition (distractor items)	Visual search
6	Mathis	2009	Response inhibition (semantic)	Stroop task (Incongruent vs neural)
7	Meinzer	2009	Response inhibition (semantic)	Category fluency
8	Mell	2009	Response inhibition (sensory)	Probabilistic object reversal
9	Milham	2002	Response inhibition (semantic)	Stroop task
10	Nielson	2004	Response inhibition (motor)	Go–no-go task

(*Continued*)

TABLE 8.1 (Continued)

Study Number	First Author	Year	Executive Control Process	Paradigm
11	Paxton	2008	Response inhibition (sensory)	Continuous performance task (AX-CPT)
12	Prakash	2009	Response inhibition (semantic)	Stroop task
13	Zhu	2010	Response inhibition (sensory)	Flanker task
14	Zysset	2007	Response inhibition (semantic)	Stroop task
Task Switching				
1	DiGirolamo	2001	Task switch (semantic)	Numerical (odd/even)
2	Esposito	1999	Set-shifting	Wisconsin Card Sorting Task
3	Gazes	2012	Task switch (feature)	Letter–color switch
4	Gold	2013	Task switch (feature)	Color–shape switch
5	Steffener	2014	Task switch (feature)	Letter–color switch
6	Jimura	2010	Task switch (semantic)	Semantic classification
7	Martins	2012	Set-shifting	Wisconsin Word Sorting Task
8	Nagahama	1997	Set-shifting	Wisconsin Card Sorting Task
9	Nashiro	2013	Set-shifting	Emotional reversal learning
10	Townsend	2006	Task switch (modality)	Auditory/visual attention task
11	Zhu	2014	Task switch (feature)	Color–shape switch

Younger > Older, and Older > Younger), foci from the combined task effects were allocated to both groups and task by age interaction foci (i.e., between-group effects) were allocated to each respective age group, consistent with previous methods (Spreng, Wojtowicz, et al., 2010). Nine separate ALE analyses were conducted in total, each yielding an ALE map and corresponding cluster report: (1−3) Working Memory in Younger, Older, and comparing Younger to Older; (4−6) Inhibition in Younger, Older, and comparing Younger to Older; (7−9) Task switching in Younger, Older, and comparing Younger to Older.

Before the analysis, coordinates reported in Montreal Neurological Institute space were converted to Talairach coordinates using the Lancaster transformation (Laird et al., 2010; Lancaster et al., 2007). In the approach taken by ALE, localization probability distributions for the foci are modeled at the center of 3D Gaussian functions, where the Gaussian distributions are summed across the experiments to generate a map of interstudy consistencies that estimate the likelihood of activation for each focus (the ALE statistic). The foci were modeled using a full-width half-maximum value of 8 mm^3. We then compared the summary of observations against a null distribution, determined through 5000 permutations of randomly generated foci identical in number to those being tested. To determine reliable differences in brain activity between younger and older adults, we tested the null hypothesis that the two sets of foci were randomly distributed and the observed difference between them was zero. For all analyses, the false discovery rate method was used to correct for multiple comparisons at $P < .05$ and subjected to a cluster size threshold of 100 mm^3 (Laird et al., 2005). Anatomical labels were applied to the clusters by using the Talairach Daemon and visual inspection of the ALE maps that were imported into FSLview v3.1 (Smith et al., 2004). Coordinates are reported in Talairach space (Talairach & Tournoux, 1988). All ALE maps were transformed from a volume image to an average multifiducial surface map using the Caret software (Van Essen, 2005) for presentation.

Metaanalysis Results

Younger Adults

Consistent with our original review, younger adults showed increased activation in frontal and parietal brain regions associated with working memory, and right lateralized activation in the inferior frontal gyrus and supplemental motor areas for inhibition tasks. Task switching was associated with left dorsolateral prefrontal, bilateral parietal, and dorsal anterior cingulate activation (see Fig. 8.1, Table 8.2). These findings are again consistent with a metaanalytic review of EFs in young adults (Niendam et al., 2012).

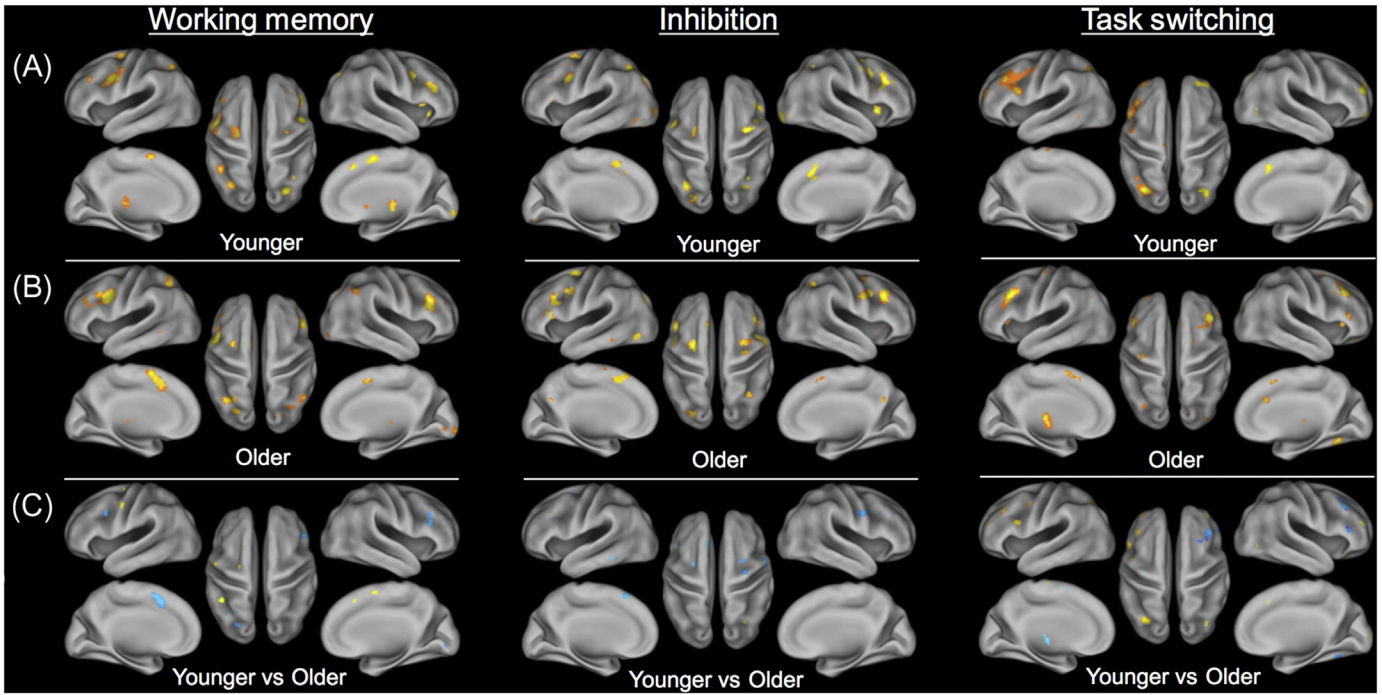

FIGURE 8.1 Reliable patterns of brain activity across all studies of working memory ($n = 22$), inhibition ($n = 14$), and task switching ($n = 11$). Clusters represent areas where activity was greater during executive function than baseline tasks. (A) Activation likelihood clusters for young adults. (B) Older adults. (C) ALE clusters displaying reliable differences between younger and older subjects (warm colors: Younger adults > Older adults; cool colors: Older adults > Younger adults). Activation likelihood clusters (false discovery rate, $P < .05$) are shown on an average multifiducial partially inflated surface map in Caret (Van Essen, 2005).

TABLE 8.2 Regions of Activation Demonstrating Significant Differences Between Young and Older Adults During Working Memory (A), Inhibition (B), and Task Switching (C)

Lat	Region	BA	x	y	z
A. Working Memory					
Young > Old					
L	Precentral gyrus	6	−42	0	28
L	Precentral gyrus	6	−50	−4	42
R	Frontal white matter		36	26	20
L	Anterior insula	13	−38	18	8
R	Inferior parietal lobule	40	32	−50	38
L	Inferior parietal lobule	40	−40	−38	38
L	Superior temporal gyrus	38	−44	20	−24
R	Caudate		14	−6	16
L	Caudate		−16	−2	18
Old > Young					
R	Middle frontal gyrus	46	46	26	22
R	Middle frontal gyrus	46	36	38	2
L	Inferior frontal gyrus	9	−36	8	30
L	Inferior frontal gyrus	47	−46	20	−4
R	Medial frontal gyrus	32	2	8	44
L	Medial frontal gyrus	32	−6	10	44
L	Precuneus	7	−24	−64	34
B. Inhibition					
Young > Old					
R	Inferior occipital gyrus	19	38	−76	0
Old > Young					
R	Middle frontal gyrus	6	28	−2	56
R	Middle frontal gyrus	6	48	2	32
R	Inferior frontal gyrus	9	54	8	36
L	Inferior frontal gyrus	44	−56	12	16
L	Superior frontal gyrus	6	−4	28	54
C. Task Switching					
Young > Old					
L	Superior frontal gyrus	10	−34	50	22
L	Middle frontal gyrus	9	−38	28	32

(*Continued*)

TABLE 8.2 (Continued)

Lat	Region	BA	x	y	z
L	Inferior frontal gyrus	9	−46	14	20
L	Precentral gyrus	6	−40	−2	36
R	Angular gyrus	39	30	−54	34
R	Superior parietal lobule	7	32	−64	44
L	Superior parietal lobule	7	−28	−62	44
Old > Young					
R	Middle frontal gyrus	8/9	38	28	38
R	Inferior frontal gyrus	46	46	32	12
R	Inferior frontal gyrus	13	38	24	10
L	Superior frontal gyrus	6	−4	8	54
R	Superior occipital gyrus	19	32	−78	24
R	Cerebellum		28	−50	−12

Lat, laterality; *L,* left; *R,* right; *BA,* Brodmann area; *X,* right/left coordinate; *Y,* anterior/posterior coordinate; *Z,* inferior/superior coordinate; *Vol,* volume.

Older Adults

(1) Working memory. Consistent with our previous report, older adults showed significantly greater activation than young in dorsal and anterior PFC brain regions bilaterally during working memory tasks (Fig. 8.1, column 1 and Table 8.2A). (2) Inhibition. Older adults showed more activity in the right inferior frontal gyrus, near the inferior frontal junction and in the left medial superior frontal gyrus, presupplementary motor area region during inhibition tasks. These results were consistent with the "young-plus" pattern we identified in our previous report (Fig. 8.1, column 2 and Table 8.2B). (3) Task switching. Activation differences during task switching in older versus younger adults were observed in right dorsolateral PFC and left superior medial brain regions (Fig. 8.1, column 3 and Table 8.2C).

Here we report the results of an updated metaanalytic review of age-related brain activation changes associated with the three executive control processes: working memory, inhibition, and task switching. In our previous report, working memory and inhibition showed dissociable patterns of brain activity in young, consistent with a fractionated account of executive functioning (Miyake et al., 2000). Not surprisingly, the addition of four studies to our initial review of working memory and inhibition did not significantly alter these findings. In a novel extension of this metaanalysis, activity

associated with task switching closely overlapped those regions of the PFC observed during working memory in young.

While these updated results support our earlier conclusion that executive functioning is dissociable into component processes with respect to brain function in younger adults, here we also observed a pattern of increasing overlap or dedifferentiated brain activity during working memory and task switching in older adults. These findings advance our understanding of executive functioning in the aging brain in two ways. First, they suggest that working memory may emerge as a superordinate control process in older adulthood. In both our previous study and in the current findings, we observed increased bilateral PFC activation during working memory for older adults. Here we also observed a similar pattern of bilateral PFC recruitment in older adults during task switching. Increased PFC activation during executive control processing has been reported previously for older adults (Reuter-Lorenz & Cappell, 2008; Spreng, Wojtowicz, et al., 2010). Although we did not observe a similar pattern of increased bilateral PFC activity for inhibition, there is evidence from studies of younger adults that more complex inhibition tasks are associated with increased recruitment of dorsolateral PFC regions, potentially reflecting increased working memory demand (Simmonds et al., 2008). The inhibition studies included in our review may have involved simpler or more "pure inhibition" demands and thereby did not tax working memory resources or engage dorsolateral PFC regions in young or older adults. However, the pattern of dedifferentiated brain activity between working memory and task switching suggests that the age-related recruitment of dorsolateral PFC observed for both control processes may reflect greater reliance on working memory resources to implement executive or goal-directed control of behavior in older adulthood.

A second important finding from this updated review was the observation of age-related increases in superior medial PFC (msPFC)/dorsal anterior cingulate cortex (dACC) for all three control processes. This region has been implicated in initiation tasks such as word generation in younger adults (Niendam et al., 2012). Lesions to this region have been associated with slowed processing particularly during more complex tasks reflecting inefficient access to stored representations or action schema necessary to guide responses in a goal-directed manner (Stuss et al., 2005). Overrecruitment of this region may reflect increased reliance on representational schema to support executive functioning in older adulthood, a hypothesis we have proposed in our recent work (Turner & Spreng, 2015; and see below).

Together, the results of the original and updated metaanalyses reviewed in this section provide a process-specific account of age-related changes in functional brain activity during executive functioning. Although we have interpreted these results as evidence for increasing reliance on working memory and internal representational schema, the findings do not provide a mechanistic account of how these changes are reflected in brain function. Put

another way, although brain activation maps tell us where executive functioning is "located" in older adults, they remain silent with respect to how executive control emerges from these activation patterns. Understanding how executive control is implemented in the brain is essential if we are to identify predictive neural markers of cognitive decline, or design brain-based, targeted intervention strategies. To better address this question, we next turn to investigations of how spatially distributed brain regions communicate through functionally connected networks. We postulate that age-related changes in the brain's functional network architecture may be an important neural mechanism associated with age-related decline in executive functioning.

BRAIN NETWORKS AND EXECUTIVE FUNCTIONS IN OLDER ADULTHOOD

Interactions among spatially distributed brain regions, or collections of regions, enable goal-directed modulation of neural activity based on goal states (Chao & Knight, 1995; Lorenc, Lee, Chen, & D'Esposito, 2015). Altered functional connectivity has been associated with poor goal-directed modulation of brain activity or interactivity, providing a putative neural mechanism of EF decline in older adulthood (Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005; Park et al., 2004; Payer et al., 2006). In this section we review how age-related changes in functional connectivity between frontal and posterior brain regions, and among distributed brain networks, lead to reduced goal-directed modulation of brain activity, providing a putative neural mechanism underlying EF decline in aging.

Goal-Directed Perceptual Processing

Age-related reductions in the modulation of neural activity in perceptual processing regions based on task goals have been associated with age-related declines in executive control (Gazzaley & D'Esposito, 2007). Payer et al. (2006) reported reduced selectivity in neural responses in category-selective regions of visual association cortex (VAC) in older relative to younger subjects during a working memory task. This reduced selectivity of neural response was accompanied by enhanced activity in PFC, which the authors interpreted as compensatory modulation of posterior brain regions in response to degraded perceptual representations. Gazzaley et al. (2005) reported a similar pattern of age-related deficits in the modulation of neural responses within the VAC. The authors observed age-related reductions in goal-directed modulation of perceptual cortices that resulted in poor filtering of goal-irrelevant (i.e., distracting) stimuli. In a follow-up study, Gazzaley, Sheridan, Cooney, and D'Esposito (2007) observed increased functional connectivity between lateral PFC and VAC regions during goal-directed

responding on a selective working memory task, suggesting that top-down modulation is implemented through functional connections between frontal and posterior cortices. This causal modulatory influence of PFC on posterior cortices has been confirmed in animal models (Fuster, Bauer, & Jervey, 1985), human lesion studies, and using transcranial magnetic stimulation methods (Lorenc et al., 2015).

In a recent review, Li and Reickmann (2014) reported that impaired modulatory influence from frontal cortices attenuates neural responsiveness to afferent signaling in posterior brain regions, producing poorly regulated (i.e., noisy) information processing. They emphasize the role of dopamine in modulating the integrity of neural representations through top-down (i.e., PFC-derived) biasing of goal-relevant versus irrelevant representations. This biasing mechanism serves to allocate limited cognitive resources to goal-relevant information processing, facilitating executive control of behavior.

In this neuromodulation account of executive functioning, increased engagement of lateral PFC brain regions, as we reported in our metaanalytic review above, may reflect increased demands for modulation of perceptual brain regions based on the current goals held in working memory. This provides a mechanistic account of goal-directed control in older adulthood. Degraded functional interactions between frontal and posterior brain regions lead to poor filtering of goal-relevant from irrelevant representations, producing a noisier cognitive landscape (Schmitz, Dixon, Anderson, & De Rosa, 2014). In this account, poor goal-directed modulation of perceptual processing regions results in poor suppression of irrelevant stimuli, leading to distractibility, poor concentration, and off-task behavior, which are the common symptoms of executive dysfunction.

Goal-Directed Modulation of Network Dynamics

In the previous section we discussed aging and executive functioning from the perspective of top-down, or goal-directed, control of perceptual processing. More recently, goal-directed control of behavior has been associated with interactions among spatially distributed brain regions that are intrinsically organized into large-scale, interacting networks (Corbetta & Shulman, 2002; Fox et al., 2005; Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Age-related changes in functional connectivity, or network interactivity, has been associated with age-related declines in executive functioning (Gallen et al., 2016; Geerligs, Renken, Saliasi, Maurits, & Lorist, 2015; Geerligs, Saliasi, Maurits, & Lorist, 2012; Grady, Sarraf, Saverino, & Campbell, 2016; Lustig et al., 2003; Madden et al., 2010; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Sambataro et al., 2010; Spreng & Schacter, 2012; Turner & Spreng, 2015). Our work has begun to explore how changes in network organization or

interactivity may impact goal-directed cognition in older adulthood. Specifically, how does goal-directed modulation of neural network dynamics change from younger to older adulthood and how do these changes manifest as age-related decline in executive functioning?

Numerous models of the brain's functional network architecture have been developed using both task (Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010) and resting-state (Power et al., 2011; Yeo et al., 2011) fMRI data. Our work has focused on a functional network model of goal-directed cognition that includes three interacting brain networks: dorsal attention, default, and frontal−parietal control (Spreng, Stevens, et al., 2010; Vincent et al., 2008). The dorsal attention network (DAN) is engaged during externally directed attentional tasks and comprised functionally connected brain regions including visual motion area, frontal eye fields, superior parietal lobule, intraparietal sulcus, and ventral premotor cortex. The default mode network (DMN) is hypothesized to be involved in accessing stored representations and is suppressed by externally oriented cognitive processes (Corbetta & Shulman, 2002). Anticorrelations between DAN and DMN networks are considered to be a core neural mechanism supporting executive functioning (see Grady, 2012, for review). The DMN network includes ventral medial PFC, posterior cingulate cortex, retrosplenial cortex, posterior inferior parietal lobule, and lateral temporal pole. A third, frontoparietal control network (FPCN), couples with these two networks to implement the cognitive control processes necessary to maintain goals, inhibit distractions, and shift behavior in the service of goal attainment (Spreng, Stevens, et al., 2010; Vincent et al., 2008). Critically, the FPCN network includes regions of the dorsolateral and dorsal medial PFC, as well as dACC; all regions identified as being overactive in older adults during EF tasks in our metaanalytic review.

DAN and DMN are associated with attention to perceptual features of the environmental or stored representational knowledge respectively. The FPCN is active for both attention states, suggesting that this network may play a modulatory role in shifting the focus of attention (Spreng, Stevens, et al., 2010). FPCN coupling could facilitate the updating of goal states, integrating information from the immediate environment with internal representations of past experience and future desires. Furthermore, coupling of FPCN with default and DAN could help to expand or stabilize the mental workspace by associating the contents of working memory with stored representations, mediated through FPCN−DMN coupling, or by facilitating external cueing strategies to refresh working memory, mediated through FPCN−DAN coupling. This dynamic network coupling may facilitate goal-directed control by increasing working memory capacity to maintain increasingly complex goal hierarchies.

In this model, neuromodulation occurs at the network level, with frontal and parietal brain regions of the FPCN implicated in the goal-directed modulation of neural processing in other brain regions, which are also organized into functional networks (e.g., DAN and DMN). Consistent with this network

modulation account, the FPCN is the only network containing dual-aligned nodes, brain regions functionally connected to both DAN and DMN regions facilitating attention to external stimuli or internal mnemonic representations, respectively (Spreng et al., 2013).

Drawing upon this interacting network model of goal-directed cognition, we investigated interactions among these brain networks in younger and older adults while they performed two planning tasks. The Tower of London task (Shallice, 1982) required participants to attend to perceptual features of an array to plan a series of actions that would transform the configuration of the array from the starting to a target goal state. In contrast, an autobiographical planning task (e.g., "How will I exercise more") required participants to attend to stored representational knowledge, such as recall of past behaviors, identification of potential hurdles, and desired goal states, to plan for a future goal (Spreng & Schacter, 2012; Spreng, Stevens, et al., 2010). Unlike younger subjects, older adults failed to modulate network dynamics based on changing task goals. Specifically, older adults failed to decouple default and frontal−parietal brain regions as the task goal shifted from the internal/personal to external/visuospatial task (Spreng & Schacter, 2012). This "stickiness" of DMN coupling may reflect reduced suppression of these brain regions during executive control tasks in older adulthood (Hansen et al., 2014; Lustig et al., 2003; Persson et al., 2007) or reduced differentiation among functional networks (Chan, Park, Savalia, Petersen, & Wig, 2014; Geerligs et al., 2015; Grady et al., 2016; Sambataro et al., 2010; Spreng & Schacter, 2012; Spreng, Stevens, Viviano, & Schacter, 2016).

While suppression and dedifferentiation explanations are consistent with our findings of poor goal-directed DN modulation, these accounts are more descriptive and do not speak to *how* network modulation is implemented in the brain or how this neural mechanism is altered in older adulthood. Our work provides a more mechanistic account, suggesting that goal direction is implemented through the dynamic modulation of FPCN, DAN, and DMN interactions. More specifically, we maintain that this interactivity is mediated through dual-aligned nodes of the FPCN, which modulate the activation (or suppression) of DAN and DMN regions and facilitate the transfer of information from the internal or external milieu to cognitive control regions (Spreng et al., 2013).

Thus far in this chapter we have demonstrated that older adults show increased recruitment of frontal brain regions and poor modulation of network interactivity during executive control tasks. Our recent work suggests that these two patterns may be linked. We end this section of the chapter by describing a novel network-based hypothesis of executive control functioning in older adulthood: the Default-Executive Coupling Hypothesis of Aging (DECHA)

Default-Executive Coupling Hypothesis of Aging

As we reported in our metaanalysis (see Executive Functions, Brain Activity, and Aging: An Updated Metaanalytic Review section), aging is associated

with increased activity in frontal brain regions during executive control processing. We also provided evidence of reduced DN flexibility during goal-directed cognitive tasks in a recent study investigating executive control functions during the Tower of London task (Shallice, 1982; and see above) across multiple levels of planning challenge (e.g., 3–6 move puzzles). Younger subjects demonstrated increased bilateral activation of frontal brain regions and increased DMN suppression as planning complexity increased. In contrast, older adults failed to modulate brain activity in these areas based on planning challenge, demonstrating increased PFC activity and reduced default suppression at lower levels of task challenge relative to younger subjects. Furthermore, while younger adults demonstrated increased functional connectivity between frontal brain regions during more complex planning tasks, older adults showed increasing connectivity between frontal and DMN brain regions (Turner & Spreng, 2015).

Based on these findings, we proposed the DECHA. This account suggests that increased prefrontal activation and increased frontal–default interactions cooccur and are functionally coupled during goal-directed tasks in older adults. This account reconciles two of the most persistent findings in studies of functional brain changes in older adulthood: enhanced bilateral prefrontal recruitment (reviewed in Executive Functions, Brain Activity, and Aging: An Updated Metaanalytic Review section) and altered network dynamics (reviewed in Brain Networks and Executive Functions in Older Adulthood section). Cognitively, we interpret these intersecting functional brain patterns as support for our earlier contention that sustaining stable representations in working memory is increasingly challenging in older adulthood, resulting in increased PFC activity. At the same time, as control processes decline with age (Park et al., 2001), working memory may become increasingly dependent on the vast accumulation of stored representational knowledge, which is implemented through increased frontal–default coupling.

In younger adults, we have shown that DN engagement can facilitate working memory when access to stored representations is goal relevant (Spreng et al., 2014). In older adulthood, age-related declines in working memory, or control processes generally, may increase reliance on stored representational knowledge, mediated by the DMN (Andrews-Hanna, Smallwood, & Spreng, 2014). As we discussed above, the increased frontal engagement observed in our metaanalysis suggests greater engagement of working memory resources. Increased default coupling may support the formation, maintenance, and stability of goal hierarchies in working memory by linking goal states with stored representational knowledge. Consistent with this hypothesis, dual-aligned nodes within the FPCN include both the msPFC and dACC that are functionally connected to the DMN (Spreng et al., 2013). Interestingly, these regions showed consistent age-related increases in activation for all three control processes included in our metaanalysis (see Executive Functions, Brain Activity, and Aging: An Updated Metaanalytic

Review section and Fig. 8.1). This may suggest that these regions within dorsal–medial PFC serve as a hub for access to, and/or transfer of, representational knowledge to lateral prefrontal brain regions in support of goal formation, updating, and maintenance in working memory.

Our exploration and validation of the DECHA model is ongoing, and mapping these functional brain changes to cognitive processes remains speculative. However, we believe that investigating process-specific changes in brain network activation, as well as alterations in functional network interactions, will lead to a more comprehensive understanding of the neural mechanisms supporting goal-directed cognition and how these change with age. In the concluding section of the chapter, we review some of our translational work, in which we are drawing upon these mechanistic accounts of age-related changes in executive functioning to develop and measure the efficacy of training interventions. We end with a brief review of future directions, promoting further research to elucidate the functional brain mechanisms associated with executive control in older adulthood and leading to more targeted intervention strategies to prevent or slow the pace of age-related decline.

AGING, BRAIN FUNCTION, AND EXECUTIVE CONTROL: CONCLUSIONS AND FUTURE DIRECTIONS

In this chapter we reviewed how age-related changes in executive functioning, a hallmark of cognitive aging, are associated with changes in brain function from young to older adulthood. We investigated this question from two perspectives. First we examined how aging is associated with process-specific changes in brain activity during executive or goal-directed cognitive control. In a metaanalytic review, contrasting brain activity associated with working memory, inhibition, and task switching in younger and older adults, we reported a common pattern of increased activation in lateral (working memory and task switching) and medial (all three processes) frontal brain regions. Second, we explored how age-related changes in functional connectivity among distributed brain regions may be an important neural mechanism underlying executive control decline in older adulthood. Specifically we reviewed evidence that reduced functional connectivity between frontal and posterior brain regions is associated with poor goal-directed filtering of perceptual inputs, leading to distractions and off-task behaviors, both of which are hallmarks of executive dysfunction. We also described how goal-directed modulation of brain network dynamics is reduced in older adulthood. Poor modulation of default and frontal–parietal control network coupling based on task context suggests that older adults may engage stored representational knowledge to support executive control in the face of declining control resources. Consistent with these findings, we have proposed a DECHA, suggesting that increased frontal brain activity and reduced

modulation of DN connectivity are functionally coupled and provide a core neural mechanism of executive control decline in older adulthood.

Characterizing the relationship between executive control and brain function in older adulthood is a complex endeavor. This work requires investigations of both brain activation and functional connectivity to elucidate the neural mechanisms associated with age-related cognitive decline. However, these efforts also hold considerable translational potential. Understanding how executive control is implemented in the brain, and how these mechanisms are altered in aging and brain disease, is opening new avenues for intervention design.

By identifying specific neural mechanisms and functional neural markers that characterize the implementation of executive control in the brain, we have designed a brain-based cognitive intervention to enhance goal-directed selective attention in brain-injured and healthy aging populations. The intervention, goal-based attention regulation (GOALS, Novakovic-Agopian et al., 2011), targets top-down neuromodulation through an active process of redirection of attention to goal-relevant stimuli, in effect, training participants to selectively filter "noise" (nonrelevant information). The intervention protocol have proven highly efficacious, improving executive control functioning (Novakovic-Agopian et al., 2011) and goal-directed modulation of brain activity in posterior visual cortices (Chen et al., 2011) in acquired brain injury patients. We are now investigating the efficacy of this intervention for enhancing goal-directed attention in healthy older adults with similarly encouraging results (Adnan, Chen, Novakovic-Agopian, D'Esposito, & Turner, in press; Turner et al., in press).

These rehabilitation studies highlight the significant translational potential of studying functional brain mechanisms to guide the design of more targeted and efficacious intervention protocols. Indeed, an emerging frontier in cognitive rehabilitation neuroscience involves the application of neurostimulation methods to alter brain function in place of, or as an adjunct to, standard behavioral or pharmacological therapies (Fox et al., 2014). These methods are critically dependent on a mechanistic understanding of how cognitive functions are implemented in the functional architecture of the brain. Planned studies in our laboratory will draw upon the DECHA model to guide neurostimulation protocols. For example, stimulating dual-aligned nodes of the FPCN (see Brain Networks and Executive Functions in Older Adulthood section) may serve to enhance information flow among brain networks, allowing more rapid integration of internally generated and externally perceived information, necessary to guide adaptive, goal-directed behavior. We believe that these neurostimulation methods represent an important new frontier in cognitive intervention research and that their success is critically dependent on a mechanistic understanding of how cognitive processes are implemented in brain's functional architecture.

To conclude, executive functioning is perhaps the highest cognitive achievement in human evolution. The capacity to guide our behavior by our goals, and overcome reflexive, automatic, or hard-wired reactions, frees us from rigid stimulus-response behaviors and enables us to flexibly navigate the challenges and obstacles on our way to a desired future. There is a certain irony, then, in the fact that our most advanced cognitive capacity is also the most vulnerable as we age.

With dramatic increases in life expectancy in most areas of the western world, the cost of age-related declines in executive functioning and associated loss of functional independence will rapidly mount, impacting the health care system, burdening families and care givers, and ultimately harming the health and dignity of older individuals. In this context, developing interventions to remediate, or slow the pace of, EF decline in older adulthood is of the utmost urgency. Here we have provided a comprehensive review of executive functioning, viewed through the lens of functional brain changes in older adulthood. We maintain that improving our understanding of how executive functioning is implemented in the aging brain offers the most direct, efficient, and efficacious approach to sustaining and enhancing this capacity well into advanced age.

REFERENCES

Adnan, A., Chen, A.J., Novakovic-Agopian, T., D'Esposito, M., & Turner, G.R. (in press). Brain changes following attention regulation training in older adults.

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences*, *1316*(1), 29–52.

Anguera, J. A., Reuter-Lorenz, P. A., Willingham, D. T., & Seidler, R. D. (2011). Failure to engage spatial working memory contributes to age-related declines in visuomotor learning. *Journal of Cognitive Neuroscience*, *23*(1), 11–25.

Baltes, P. B., & Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: A new window to the study of cognitive aging? *Psychology and Aging*, *12*(1), 12–21.

Bennett, I. J., Rivera, H. G., & Rypma, B. (2013). Isolating age-group differences in working memory load-related neural activity: Assessing the contribution of working memory capacity using a partial-trial fMRI method. *Neuroimage*, *72*, 20–32.

Buckner, R. L. (2004). Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. *Neuron*, *44*(1), 195–208.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging*, *17*(1), 85–100.

Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M., & Nyberg, L. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cerebral Cortex*, *14*(4), 364–375.

Cahn-Weiner, D. A., Boyle, P. A., & Malloy, P. F. (2002). Tests of executive function predict instrumental activities of daily living in community-dwelling older individuals. *Applied Neuropsychology*, *9*(3), 187–191.

Cappell, K. A., Gmeindl, L., & Reuter-Lorenz, P. A. (2010). Age differences in prefrontal recruitment during verbal working memory maintenance depend on memory load. *Cortex: A Journal Devoted to the Study of the Nervous System and Behavior*, *46*(4), 462–473.

Chan, M. Y., Park, D. C., Savalia, N. K., Petersen, S. E., & Wig, G. S. (2014). Decreased segregation of brain systems across the healthy adult lifespan. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(46), E4997–5006.

Chao, L. L., & Knight, R. T. (1995). Human prefrontal lesions increase distractibility to irrelevant sensory inputs. *Neuroreport*, *6*(12), 1605–1610.

Chen, A. J., Novakovic-Agopian, T., Nycum, T. J., Song, S., Turner, G. R., Hills, N. K., et al. (2011). Training of goal-directed attention regulation enhances control over neural processing for individuals with brain injury. *Brain*, *134*(Pt 5), 1541–1554.

Cicerone, K. D., Langenbahn, D. M., Braden, C., Malec, J. F., Kalmar, K., Fraas, M., et al. (2011). Evidence-based cognitive rehabilitation: Updated review of the literature from 2003 through 2008. *Archives of Physical Medicine and Rehabilitation*, *92*(4), 519–530.

Colcombe, S. J., Kramer, A. F., Erickson, K. I., & Scalf, P. (2005). The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. *Psychology and Aging*, *20*(3), 363–375.

Conway, A. R., Kane, M. J., & Engle, R. W. (2003). Working memory capacity and its relation to general intelligence. *Trends in Cognitive Sciences*, *7*(12), 547–552.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews. Neuroscience*, *3*(3), 201–215.

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cerebral Cortex*, *18*(5), 1201–1209.

Diamond, A. (2013). Executive functions. *Annual Review of Psychology*, *64*, 135–168.

DiGirolamo, G. J., Kramer, A. F., Barad, V., Cepeda, N. J., Weissman, D. H., Milham, M. P., et al. (2001). General and task-specific frontal lobe recruitment in older adults during executive processes: A fMRI investigation of task-switching. *Neuroreport*, *12*(9), 2065–2071.

Duncan, J., Seitz, R. J., Kolodny, J., Bor, D., Herzog, H., Ahmed, A., et al. (2000). A neural basis for general intelligence. *Science (New York, N.Y.)*, *289*(5478), 457–460.

Emery, L., Heaven, T. J., Paxton, J. L., & Braver, T. S. (2008). Age-related changes in neural activity during performance matched working memory manipulation. *Neuroimage*, *42*(4), 1577–1586.

Esposito, G., Kirkby, B. S., Van Horn, J. D., Ellmore, T. M., & Berman, K. F. (1999). Context-dependent, neural system-specific neurophysiological concomitants of ageing: Mapping PET correlates during cognitive activation. *Brain*, *122*(Pt 5), 963–979.

Fox, M. D., Buckner, R. L., Liu, H., Chakravarty, M. M., Lozano, A. M., & Pascual-Leone, A. (2014). Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(41), E4367–4375.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673–9678.

Freo, U., Ricciardi, E., Pietrini, P., Schapiro, M. B., Rapoport, S. I., & Furey, M. L. (2005). Pharmacological modulation of prefrontal cortical activity during a working memory task in young and older humans: A PET study with physostigmine. *The American Journal of Psychiatry*, *162*(11), 2061–2070.

Friedman, N. P., & Miyake, A. (2016). Unity and diversity of executive functions: Individual differences as a window on cognitive structure. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*.

Fuster, J. M., Bauer, R. H., & Jervey, J. P. (1985). Functional interactions between inferotemporal and prefrontal cortex in a cognitive task. *Brain Research*, *330*(2), 299–307.

Gallen, C. L., Turner, G. R., Adnan, A., & D'Esposito, M. (2016). Reconfiguration of brain network architecture to support executive control in aging. *Neurobiology of Aging*, *44*, 42–52.

Gazes, Y., Rakitin, B. C., Habeck, C., Steffener, J., & Stern, Y. (2012). Age differences of multivariate network expressions during task-switching and their associations with behavior. *Neuropsychologia*, *50*(14), 3509–3518.

Gazzaley, A., Cooney, J. W., McEvoy, K., Knight, R. T., & D'Esposito, M. (2005). Top-down enhancement and suppression of the magnitude and speed of neural activity. *Journal of Cognitive Neuroscience*, *17*(3), 507–517.

Gazzaley, A., & D'Esposito, M. (2007). Top-down modulation and normal aging. *Annals of the New York Academy of Sciences*, *1097*, 67–83.

Gazzaley, A., Sheridan, M. A., Cooney, J. W., & D'Esposito, M. (2007). Age-related deficits in component processes of working memory. *Neuropsychology*, *21*(5), 532–539.

Geerligs, L., Renken, R. J., Saliasi, E., Maurits, N. M., & Lorist, M. M. (2015). A Brain-Wide Study of Age-Related Changes in Functional Connectivity. *Cerebral Cortex*, *25*(7), 1987–1999.

Geerligs, L., Saliasi, E., Maurits, N. M., & Lorist, M. M. (2012). Compensation through increased functional connectivity: Neural correlates of inhibition in old and young. *Journal of Cognitive Neuroscience*, *24*(10), 2057–2069.

Gold, B. T., Kim, C., Johnson, N. F., Kryscio, R. J., & Smith, C. D. (2013). Lifelong bilingualism maintains neural efficiency for cognitive control in aging. *The Journal of Neuroscience*, *33*(2), 387–396.

Grady, C. (2012). The cognitive neuroscience of ageing. *Nature Reviews. Neuroscience*, *13*(7), 491–505.

Grady, C., Sarraf, S., Saverino, C., & Campbell, K. (2016). Age differences in the functional interactions among the default, frontoparietal control, and dorsal attention networks. *Neurobiology of Aging*, *41*, 159–172.

Grady, C. L., McIntosh, A. R., Bookstein, F., Horwitz, B., Rapoport, S. I., & Haxby, J. V. (1998). Age-related changes in regional cerebral blood flow during working memory for faces. *Neuroimage*, *8*(4), 409–425.

Grossman, M., Smith, E. E., Koenig, P., Glosser, G., DeVita, C., Moore, P., et al. (2002). The neural basis for categorization in semantic memory. *Neuroimage*, *17*(3), 1549–1561.

Hansen, N. L., Lauritzen, M., Mortensen, E. L., Osler, M., Avlund, K., Fagerlund, B., et al. (2014). Subclinical cognitive decline in middle-age is associated with reduced task-induced deactivation of the brain's default mode network. *Human Brain Mapping*, *35*(9), 4488–4498.

Hasher, L., & Zacks, R. T. (1988). Working memory, comprehension, and aging: A review and a new view. In G. H. Brower (Ed.), *The Psychology of Learning and Motivation* (pp. 193–225). San Diego, CA: Academic Press.

Haut, M. W., Kuwabara, H., Moran, M. T., Leach, S., Arias, R., & Knight, D. (2005). The effect of education on age-related functional activation during working memory. *Aging, Neuropsychology and Cognition*, *12*, 216–229.

Holtzer, R., Rakitin, B. C., Steffener, J., Flynn, J., Kumar, A., & Stern, Y. (2009). Age effects on load-dependent brain activations in working memory for novel material. *Brain Research*, *1249*, 148–161.

Jimura, K., & Braver, T. S. (2010). Age-related shifts in brain activity dynamics during task switching. *Cerebral Cortex*, *20*(6), 1420–1431.

Johnson, M. K., Mitchell, K. J., Raye, C. L., & Greene, E. J. (2004). An age-related deficit in prefrontal cortical function associated with refreshing information. *Psychological Science*, *13*(2), 127–132.

Jonides, J., Marshuetz, C., Smith, E. E., Reuter-Lorenz, P. A., Koeppe, R. A., & Hartley, A. (2000). Age differences in behavior and PET activation reveal differences in interference resolution in verbal working memory. *Journal of Cognitive Neuroscience*, *12*(1), 188–196.

Korsch, M., Fruhholz, S., & Herrmann, M. (2014). Ageing differentially affects neural processing of different conflict types-an fMRI study. *Frontiers in Aging Neuroscience*, *6*, 57.

Laird, A. R., Fox, P. M., Price, C. J., Glahn, D. C., Uecker, A. M., Lancaster, J. L., et al. (2005). ALE meta-analysis: Controlling the false discovery rate and performing statistical contrasts. *Human Brain Mapping*, *25*(1), 155–164.

Laird, A. R., Robinson, J. L., McMillan, K. M., Tordesillas-Gutierrez, D., Moran, S. T., Gonzales, S. M., et al. (2010). Comparison of the disparity between Talairach and MNI coordinates in functional neuroimaging data: Validation of the Lancaster transform. *Neuroimage*, *51*(2), 677–683.

Lancaster, J. L., Tordesillas-Gutierrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., et al. (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Human Brain Mapping*, *28*(11), 1194–1205.

Lee, T. M., Zhang, J. X., Chan, C. C., Yuen, K. S., Chu, L. W., Cheung, R. T., et al. (2006). Age-related differences in response regulation as revealed by functional MRI. *Brain Research*, *1076*(1), 171–176.

Li, S. C., & Rieckmann, A. (2014). Neuromodulation and aging: Implications of aging neuronal gain control on cognition. *Current Opinion in Neurobiology*, *29*, 148–158.

Lorenc, E. S., Lee, T. G., Chen, A. J., & D'Esposito, M. (2015). The Effect of Disruption of Prefrontal Cortical Function with Transcranial Magnetic Stimulation on Visual Working Memory. *Frontiers in Systems Neuroscience*, *9*, 169.

Lustig, C., Snyder, A. Z., Bhakta, M., O'Brien, K. C., McAvoy, M., Raichle, M. E., et al. (2003). Functional deactivations: Change with age and dementia of the Alzheimer type. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(24), 14504–14509.

Madden, D. J., Costello, M. C., Dennis, N. A., Davis, S. W., Shepler, A. M., Spaniol, J., et al. (2010). Adult age differences in functional connectivity during executive control. *Neuroimage*, *52*(2), 643–657.

Madden, D. J., Turkington, T. G., Provenzale, J. M., Denny, L. L., Langley, L. K., Hawk, T. C., et al. (2002). Aging and attentional guidance during visual search: Functional neuroanatomy by positron emission tomography. *Psychology and Aging*, *17*(1), 24–43.

Martins, R., Simard, F., Provost, J. S., & Monchi, O. (2012). Changes in regional and temporal patterns of activity associated with aging during the performance of a lexical set-shifting task. *Cerebral Cortex*, *22*(6), 1395–1406.

Mathis, K. W., & Molina, P. E. (2009). Central acetylcholinesterase inhibition improves hemodynamic counterregulation to severe blood loss in alcohol-intoxicated rats. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *297*(2), R437–445.

Meinzer, M., Flaisch, T., Wilser, L., Eulitz, C., Rockstroh, B., Conway, T., et al. (2009). Neural signatures of semantic and phonemic fluency in young and old adults. *Journal of Cognitive Neuroscience*, *21*(10), 2007–2018.

Mell, T., Wartenburger, I., Marschner, A., Villringer, A., Reischies, F. M., & Heekeren, H. R. (2009). Altered function of ventral striatum during reward-based decision making in old age. *Frontiers in Human Neuroscience*, *3*, 34.

Milham, M. P., Erickson, K. I., Banich, M. T., Kramer, A. F., Webb, A., Wszalek, T., et al. (2002). Attentional control in the aging brain: Insights from an fMRI study of the Stroop task. *Brain and Cognition*, *49*(3), 277–296.

Miyake, A., & Friedman, N. P. (2012). The nature and organization of individual differences in executive functions: Four general conclusions. *Current Directions in Psychological Science: A Journal of the American Psychological Society*, *21*(1), 8–14.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: A latent variable analysis. *Cognitive Psychology*, *41*(1), 49–100.

Nagahama, Y., Fukuyama, H., Yamauchi, H., Katsumi, Y., Magata, Y., Shibasaki, H., et al. (1997). Age-related changes in cerebral blood flow activation during a Card Sorting Test. *Experimental Brain Research*, *114*(3), 571–577.

Nagel, I. E., Preuschhof, C., Li, S. C., Nyberg, L., Backman, L., Lindenberger, U., et al. (2009). Performance level modulates adult age differences in brain activation during spatial working memory. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(52), 22552–22557.

Nashiro, K., Sakaki, M., Nga, L., & Mather, M. (2013). Age-related similarities and differences in brain activity underlying reversal learning. *Frontiers in Integrative Neuroscience*, *7*, 37.

Nielson, K. A., Langenecker, S. A., Ross, T. J., Garavan, H., Rao, S. M., & Stein, E. A. (2004). Comparability of functional MRI response in young and old during inhibition. *Neuroreport*, *15*(1), 129–133.

Niendam, T. A., Laird, A. R., Ray, K. L., Dean, Y. M., Glahn, D. C., & Carter, C. S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive, Affective & Behavioral Neuroscience*, *12*(2), 241–268.

Novakovic-Agopian, T., Chen, A. J., Rome, S., Abrams, G., Castelli, H., Rossi, A., et al. (2011). Rehabilitation of executive functioning with training in attention regulation applied to individually defined goals: A pilot study bridging theory, assessment, and treatment. *The Journal of Head Trauma Rehabilitation*, *26*(5), 325–338.

Otsuka, Y., Osaka, N., Morishita, M., Kondo, H., & Osaka, M. (2006). Decreased activation of anterior cingulate cortex in the working memory of the elderly. *Neuroreport*, *17*(14), 1479–1482.

Park, D. C., Polk, T. A., Hebrank, A. C., & Jenkins, L. J. (2010). Age differences in default mode activity on easy and difficult spatial judgment tasks. *Frontiers in Human Neuroscience*, *3*, 75.

Park, D. C., Polk, T. A., Mikels, J. A., Taylor, S. F., & Marshuetz, C. (2001). Cerebral aging: Integration of brain and behavioral models of cognitive function. *Dialogues in Clinical Neuroscience*, *3*(3), 151–165.

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., & Smith, M. R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(35), 13091–13095.

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: Aging and neurocognitive scaffolding. *Annual Review of Psychology*, *60*, 173–196.

Paxton, J. L., Barch, D. M., Racine, C. A., & Braver, T. S. (2008). Cognitive control, goal maintenance, and prefrontal function in healthy aging. *Cerebral Cortex*, *18*(5), 1010–1028.

Payer, D., Marshuetz, C., Sutton, B., Hebrank, A., Welsh, R. C., & Park, D. C. (2006). Decreased neural specialization in old adults on a working memory task. *Neuroreport*, *17* (5), 487–491.

Persson, J., Lustig, C., Nelson, J. K., & Reuter-Lorenz, P. A. (2007). Age differences in deactivation: A link to cognitive control? *Journal of Cognitive Neuroscience*, *19*(6), 1021–1032.

Podell, J. E., Sambataro, F., Murty, V. P., Emery, M. R., Tong, Y., Das, S., et al. (2012). Neurophysiological correlates of age-related changes in working memory updating. *Neuroimage*, *62*(3), 2151–2160.

Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., et al. (2011). Functional network organization of the human brain. *Neuron*, *72*(4), 665–678.

Prakash, R. S., Erickson, K. I., Colcombe, S. J., Kim, J. S., Voss, M. W., & Kramer, A. F. (2009). Age-related differences in the involvement of the prefrontal cortex in attentional control. *Brain and Cognition*, *71*(3), 328–335.

Raye, C. L., Mitchell, K. J., Reeder, J. A., Greene, E. J., & Johnson, M. K. (2008). Refreshing one of several active representations: Behavioral and functional magnetic resonance imaging differences between young and older adults. *Journal of Cognitive Neuroscience*, *20*(5), 852–862.

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Current Directions in Psychological Science*, *17*(3), 177–182.

Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., Marshuetz, C., et al. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *Journal of Cognitive Neuroscience*, *12*(1), 174–187.

Reuter-Lorenz, P. A., & Park, D. C. (2014). How does it STAC up? Revisiting the scaffolding theory of aging and cognition. *Neuropsychology Review*, *24*(3), 355–370.

Ricciardi, E., Pietrini, P., Schapiro, M. B., Rapoport, S. I., & Furey, M. L. (2009). Cholinergic modulation of visual working memory during aging: A parametric PET study. *Brain Research Bulletin*, *79*(5), 322–332.

Rodrigue, K. M., Kennedy, K. M., & Raz, N. (2005). Aging and longitudinal change in perceptual-motor skill acquisition in healthy adults. *Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *60*(4), P174–181.

Rypma, B., & D'Esposito, M. (2000). Isolating the neural mechanisms of age-related changes in human working memory. *Nature Neuroscience*, *3*(5), 509–515.

Rypma, B., Prabhakaran, V., Desmond, J. E., & Gabrieli, J. D. (2001). Age differences in prefrontal cortical activity in working memory. *Psychology and Aging*, *16*(3), 371–384.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, *103*(3), 403–428.

Sambataro, F., Murty, V. P., Callicott, J. H., Tan, H. Y., Das, S., Weinberger, D. R., et al. (2010). Age-related alterations in default mode network: Impact on working memory performance. *Neurobiology of Aging*, *31*(5), 839–852.

Schmitz, T. W., Dixon, M. L., Anderson, A. K., & De Rosa, E. (2014). Distinguishing attentional gain and tuning in young and older adults. *Neurobiology of Aging*, *35*(11), 2514–2525.

Schneider-Garces, N. J., Gordon, B. A., Brumback-Peltz, C. R., Shin, E., Lee, Y., Sutton, B. P., et al. (2010). Span, CRUNCH, and beyond: Working memory capacity and the aging brain. *Journal of Cognitive Neuroscience*, *22*(4), 655–669.

Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *298*(1089), 199–209.

Simmonds, D. J., Pekar, J. J., & Mostofsky, S. H. (2008). Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia*, *46*(1), 224–232.

Smith, Jonides, J., Marshuetz, C., & Koeppe, R. A. (1998). Components of verbal working memory: Evidence from neuroimaging. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(3), 876–882.

Smith, E. E., Geva, A., Jonides, J., Miller, A., Reuter-Lorenz, P., & Koeppe, R. A. (2001). The neural basis of task-switching in working memory: Effects of performance and aging. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(4), 2095–2100.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, *23*(Suppl 1), S208–219.

Snowdon, D. A. (1997). Aging and Alzheimer's disease: Lessons from the Nun Study. *The Gerontologist*, *37*(2), 150–156.

Spreng, R. N., DuPre, E., Selarka, D., Garcia, J., Gojkovic, S., Mildner, J., et al. (2014). Goal-congruent default network activity facilitates cognitive control. *The Journal of Neuroscience*, *34*(42), 14108–14114.

Spreng, R. N., & Schacter, D. L. (2012). Default Network Modulation and Large-Scale Network Interactivity in Healthy Young and Old Adults. *Cerebral Cortex*, *22*, 2610–2621.

Spreng, R. N., Sepulcre, J., Turner, G. R., Stevens, W. D., & Schacter, D. L. (2013). Intrinsic architecture underlying the relations among the default, dorsal attention, and frontoparietal control networks of the human brain. *Journal of Cognitive Neuroscience*, *25*(1), 74–86.

Spreng, R. N., Stevens, W. D., Chamberlain, J. P., Gilmore, A. W., & Schacter, D. L. (2010). Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *Neuroimage*, *53*(1), 303–317.

Spreng, R. N., Stevens, W. D., Viviano, J. D., & Schacter, D. L. (2016). Attenuated anticorrelation between the default and dorsal attention networks with aging: Evidence from task and rest. *Neurobiology of Aging*, *45*, 149–160.

Spreng, R. N., Wojtowicz, M., & Grady, C. L. (2010). Reliable differences in brain activity between young and old adults: A quantitative meta-analysis across multiple cognitive domains. *Neuroscience and Biobehavioral Reviews*, *34*(8), 1178–1194.

Steffener, J., Barulli, D., Habeck, C., & Stern, Y. (2014). Neuroimaging explanations of age-related differences in task performance. *Frontiers in Aging Neuroscience*, *6*, 46.

Stern, Y., Habeck, C., Moeller, J., Scarmeas, N., Anderson, K. E., Hilton, H. J., et al. (2005). Brain networks associated with cognitive reserve in healthy young and old adults. *Cerebral Cortex*, *15*(4), 394–402.

Stuss, D. T., Alexander, M. P., Shallice, T., Picton, T. W., Binns, M. A., Macdonald, R., et al. (2005). Multiple frontal systems controlling response speed. *Neuropsychologia*, *43*(3), 396–417.

Stuss, D. T., & Levine, B. (2002). Adult clinical neuropsychology: Lessons from studies of the frontal lobes. *Annual Review of Psychology*, *53*, 401–433.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain (M. Rayport, Trans.)*. Stuttgart: Georg Thieme Verlag.

Townsend, J., Adamo, M., & Haist, F. (2006). Changing channels: An fMRI study of aging and cross-modal attention shifts. *Neuroimage*, *31*(4), 1682–1692.

Turkeltaub, P. E., Eden, G. F., Jones, K. M., & Zeffiro, T. A. (2002). Meta-analysis of the functional neuroanatomy of single-word reading: Method and validation. *Neuroimage*, *16*(3 Pt 1) 765−780.

Turner, G.R., Novakovic-Agopian, T., Kornblith, E., Madore, M., Adnan, A., D'Esposito, M., et al. (in press). Goal-oriented attention regulation (GOALS) training in older adults.

Turner, G. R., & Spreng, R. N. (2012). Executive functions and neurocognitive aging: Dissociable patterns of brain activity. *Neurobiology of Aging*, *33*(4), 826 e821-813.

Turner, G. R., & Spreng, R. N. (2015). Prefrontal engagement and reduced default network suppression co-occur and are dynamically coupled in older adults: The Default-Executive Coupling Hypothesis of Aging. *Journal of Cognitive Neuroscience*, *27*(12), 2462−2476.

Van Essen, D. C. (2005). A population-average, landmark- and surface-based (PALS) atlas of human cerebral cortex. *Neuroimage*, *28*(3), 635−662.

Vincent, J. L., Kahn, I., Snyder, A. Z., Raichle, M. E., & Buckner, R. L. (2008). Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *Journal of Neurophysiology*, *100*(6), 3328−3342.

Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory: A meta-analysis. *Cognitive, Affective & Behavioral Neuroscience*, *3*(4), 255−274.

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., et al. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125−1165.

Zhu, D. C., Zacks, R. T., & Slade, J. M. (2010). Brain activation during interference resolution in young and older adults: An fMRI study. *Neuroimage*, *50*(2), 810−817.

Zhu, Z., Hakun, J. G., Johnson, N. F., & Gold, B. T. (2014). Age-related increases in right frontal activation during task switching are mediated by reaction time and white matter microstructure. *Neuroscience*, *278*, 51−61.

Zysset, S., Schroeter, M. L., Neumann, J., & Yves von Cramon, D. (2007). Stroop interference, hemodynamic response and aging: An event-related fMRI study. *Neurobiol Aging*, *28*(6), 937−946.