Top-Down Modulation and Normal Aging

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ABSTRACT: Normal aging is characterized by cognitive deficits that cross multiple domains and impair the ability of some older individuals to lead productive, high-quality lives. One of the primary goals of research in our laboratories is to study age-related alterations in neural mechanisms that underlie a wide range of cognitive processes so that we may generate a unifying principle of cognitive aging. Top-down modulation is the mechanism by which we enhance neural activity associated with relevant information and suppress activity for irrelevant information, thus establishing a foundation for both attention and memory processes. We use three converging technologies of human neurophysiology to study top-down modulation in aging: functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and transcranial magnetic stimulation (TMS). Using these tools we have discovered that healthy older adults exhibit a selective inability to effectively suppress neural activity associated with distracting information and that this top-down suppression deficit is correlated with their memory impairment. We are now further characterizing the basis of these age-related alterations in top-down modulation and investigating interventions to remedy them.

KEYWORDS: aging; top-down modulation; fMRI; ERP; EEG; attention; working memory

Individuals over 65 years of age currently make up more than 13% of the American population. Over the next 30 years, this percentage will double and the number of senior adults is expected to swell to 70 million *(U.S. Census Bureau, Decennial Census Data, and Population Projections, 2000)*. This dramatic increase in the size of the older population will have far-reaching societal consequences. Although neuroscience research has largely focused on severe forms of age-related intellectual deterioration seen in dementia, cognitive decline in nondemented seniors, or *cognitive aging*, is pervasive and can severely

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constrain an otherwise productive life. Cognitive deficits are a cause of great distress to many older adults who feel that their ability to lead a high-quality life is negatively impacted by this decline and it is often considered the most debilitating aspect of aging.[1] Exploring the neural impairments that underlie cognitive deficits, as well as the compensatory changes that allow many older adults to remain cognitively intact, is an important step in alleviating this burden and delaying or preventing the debilitating functional decline of dementia.

Insidious impairments in the cognitive abilities of many older adults is a well-documented phenomenon and a substantial body of research has revealed performance deficits in multiple cognitive domains, such as working memory (WM), episodic memory, and attention.[2,3] Despite heterogeneity in the nature and severity of decline between older individuals, common features have been observed on neuropsychological testing, for example, decreases in processing speed on many different tests.[4] In an attempt to account for common features, several hypotheses have been proposed. Three frequently cited hypotheses in the aging literature are: (1) *the processing speed hypothesis* in which performance deficits are attributed to generalized slowing of processing speed,[4] (2) *the executive deficit (frontal aging) hypothesis*, which proposes that executive abilities dependent on frontal lobe integrity are affected earlier and to a greater magnitude than other processes,[5] and (3) *the inhibitory deficit hypothesis*, which suggests a reduction in the efficiency of inhibitory mechanisms.[6] It is important to note that these hypotheses are largely based on neuropsychological data. We are now attempting to generate a parsimonious principle of cognitive aging by exploring alterations in *neural mechanisms* associated with aging.

The search for alterations in the brain that produce cognitive deficits has involved a variety of experimental approaches, including neurophysiological, neurochemical, and neuroanatomical methodologies. Although anatomical studies have revealed subtle age-related structural changes, such as alterations in dendritic arborization and spine count,[7,8] many studies have revealed no such changes, including preservation of neuronal number with aging.[9–14] Despite the lack of overwhelming evidence for structural alterations, there has been a steady accumulation of studies revealing physiological changes[15–19] and changes in neurotransmitter levels with aging.[20,21] These observations have led to an emerging view that changes in neural signaling, rather than structural alterations, account for age-related cognitive deficits. This principle has been a guiding force for the application of the more recently applied technologies of functional brain imaging to study age-related brain alterations. Functional neuroimaging techniques, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG), allow us to record correlates of brain activity in human research subjects during the performance of cognitive tasks and is thus particularly well suited to explore the neural basis of cognitive aging in humans.[22]

NEURAL MEASURES OF TOP–DOWN MODULATION

The experiments that we describe in this article review our recent attempt to generate unifying aging principles based on our view that neural alterations are likely not limited to localized brain regions, but rather in the functional connections between brain regions. This is consistent with the manner in which the brain generates higher-order cognitive abilities; cognition is an emergent process subserved by the integration of signals across distributed brain regions, or *neural networks*, rather than a product of independently functioning isolated brain regions.[23] By evaluating changes that occur in neural networks, we hope to identify an underlying cause of the diverse cognitive deficits associated with normal aging. To accomplish this, our experimental focus has been on the neural process of *top-down modulation*, selected both because it serves as a foundation for many cognitive abilities, such as attention, WM, and episodic memory, all of which are vulnerable in aging, and its very basis has been attributed to functional interactions between distant brain regions.

How we perceive stimuli in our environment involves an integration of two distinct influences: externally and internally driven attention. Sensory input from our surroundings often demand attention based on stimulus characteristics, such as novelty or salience (*bottom-up processing),* but we are also capable of directing attention toward or away from encountered stimuli based on our goals *(top-down modulation)*.[24–26] Top-down modulation underlies our essential ability to focus on what is task relevant and ignore irrelevant distractions by differentially *enhancing* and/or *suppressing* neural activity in sensory cortical regions depending on the relevance of the information to our goals. This modulation is achieved by neural connections subserving dynamic interactions between widely distributed brain regions at the "top" (prefrontal cortex [PFC]) and the "bottom" (visual association cortex [VAC]);[27–29,30] and has been described to occur both when a stimulus is present and when a stimulus is absent. Thus, it serves as a neural mechanism that underlies the processes of selective attention and memory encoding when a stimulus is present[25,31–33] and mental imagery, WM maintenance and anticipation when a stimulus is absent.[34–37] Although numerous functional imaging studies have examined age-related changes in neural activity associated with attention and memory,[22,38] our research is directed at specifically exploring alterations in top-down modulation with aging.

Our first goal to explore alterations in top-down modulation in aging was to define reliable measures of both top-down enhancement and suppression of neural activity in young adults. We chose to do this in the context of a visual WM task when information is presented that must be held in mind for a short period of time. In a commonly used task to study WM, the delayed-recognition task, a subject is first required to remember a stimulus presented during a "cue" period and then maintain this information for a brief "delay" interval when the stimulus is absent. Lastly, the subject responds to a "probe" stimulus to determine

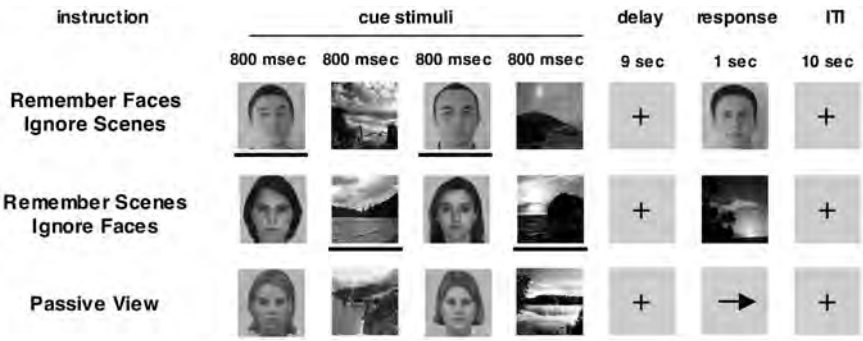

FIGURE 1. Experimental design of the selective WM task. Tasks differed in the instructions given at the beginning of each run and in the response requirements. Participants were instructed to (1) Remember Faces and Ignore Scenes, (2) Remember Scenes and Ignore Faces, and (3) Passively View both Faces and Scenes—with no attempt to remember or evaluate them. In the memory trials response period, a face or scene stimulus was presented (depending upon the condition), and participants were required to report with a button press whether the stimulus matched one of the previously presented stimuli. During the response period of the Passive View task, an *arrow* was presented and participants were required to make a button press indicating the direction of the *arrow*. (Adapted from Gazzaley *et al*.[39])

whether the information was successfully retained. Thus, the cognitive stages are segregated in time and can be investigated in relative isolation by recording during these distinct stages with microelectrodes in animals and event-related fMRI and EEG in human research subjects. We modified the classic delayed-recognition task to generate a *selective* WM task so as to directly study the processes of enhancement and suppression. To identify distinct measures of top-down enhancement and suppression we developed a paradigm consisting of three delayed-recognition tasks in which aspects of visual information are held constant while the task demands are manipulated (FIG. 1).[39] During each trial, participants observe sequences of two faces and two natural scenes presented in a randomized order. The tasks differ in the instructions informing the participants how to process the stimuli: (1) *Remember Faces and Ignore Scenes*, (2) *Remember Scenes and Ignore Faces*, or (3) *Passively View* faces and scenes without attempting to remember them. In each task, the period in which the cue stimuli are presented is balanced for bottom-up visual information, thus allowing us to probe the influence of goal-directed behavior on neural activity (top-down modulation). In the two memory tasks, the encoding of the task-relevant stimuli requires selective attention and thus permits the dissociation of physiological measures of enhancement and suppression relative to the passive baseline. Specifically, neural activity measures recorded in VAC that are greater in magnitude for the memory tasks compared to the passive baseline reflect enhancement, while activity measures below passive

baseline reflect suppression. In the memory tasks, following a 9-sec delay the participants are tested on their ability to recognize a probe stimulus as being one of the task-relevant cues, yielding a behavioral measure of WM performance. In addition, a postexperiment surprise recognition memory enables us to evaluate incidental long-term memory of the stimuli.

The experiments we performed using this paradigm employed both event-related fMRI and EEG on counterbalanced sessions to record correlates of neural activity while the subjects performed the task. This allowed us to capitalize on the high spatial resolution achievable with the fMRI blood oxygen level dependent (BOLD) signal and the high temporal resolution attained when recording electrical activity with EEG. Although both measures are thought to reflect cortical activity driven by local cortical processing and the summation of postsynaptic potentials on synchronously active, large ensembles of neurons,[40–42] changes in BOLD signal can be localized to cortical regions separated by millimeters and EEG can resolve activity changes in the millisecond range. Thus, these techniques offer complementary, but unique information to study the modulation of activity at the neuronal population level.

For fMRI, we used an independent functional localizer task to identify stimulus-selective regions in the VAC. This allowed us to assess the top-down modulation of activity in regions that are separable based on perceptual differences. We identified both face-selective regions and scene-selective regions in the fusiform gyrus and the parahippocampal/lingual gyrus, respectively,[43–45] and then used them as regions of interest to study activity modulation based on the goals of the task. For the purpose of this article, we will focus on the fMRI data from the left scene-selective region, since it yielded the most robust measures of top-down modulation. For EEG, we used a face-selective event-related potential (ERP), the N170, a component localized to posterior occipital electrodes and reflecting VAC activity with face specificity.[46]

Our fMRI and EEG data revealed that in young adults ($n = 17$, 19–30 years of age), top-down modulation of both activity magnitude (fMRI) and processing speed (ERP) occurs above and below the passive baseline depending on task instruction (FIG. 2). For the fMRI data, all younger subjects exhibited greater activity during the encoding period when attempting to remember scenes compared to ignoring scenes, despite viewing the same number of scenes in both conditions ($P < 10^{-5}$). In addition, 82% of the younger subjects enhanced activity above the passive view baseline when remembering scenes and 88% suppress activity below the passive view baseline when ignoring scenes (enhancement, $P < 0.005$; suppression, $P < 0.0005$). Comparable findings of significant enhancement and suppression were observed for the peak latency of the N170 component, revealing that top-down modulation occurs for both the magnitude of activity and the speed of cortical processing.[39] We thus established reliable measures of top-down enhancement and suppression that could then serve as functional biomarkers to study cognitive aging.

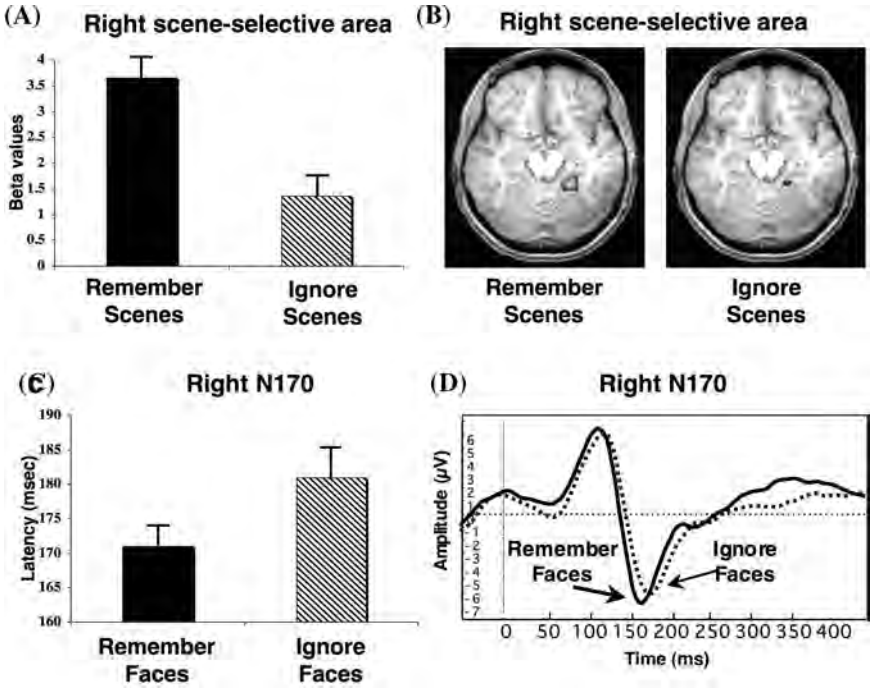

FIGURE 2. Activity data for *Remember* and *Ignore* conditions: fMRI and ERP. (**A)** Group data: Average beta values in the scene selective area revealing greater activity in Remember Scenes vs. Ignore Scenes condition. (**B**) A representative subject demonstrating the BOLD signal level within the masked scene selective in Remember Scenes vs. Ignore Scenes condition. (**C**) Group data: Average peak latency for the right N170 in PO8 electrode revealing earlier latency for Remember Faces vs. Ignore Faces. (**D**) Grand-averaged waveforms of the time-locked ERP to face stimuli revealing earlier latency for Remember Faces vs. Ignore Faces. *Error bars* indicate standard error of the mean. (Adapted from Gazzaley *et al*.[39])

TOP–DOWN MODULATION IN AGING

To evaluate if these modulation indices change with aging we repeated the identical fMRI study on healthy older adults ($n = 16$, 60–77 years of age) (FIG. 3).[47] As we observed in the younger subjects, the older subjects exhibited greater activity in the scene-selective region when attempting to remember scenes versus ignore scenes ($P < 0.0005$), revealing they were capable of top-down modulation. However, while 88% of the older participants enhanced activity above the passive view baseline (enhancement, $P < 0.0005$), only 44% suppressed activity (suppression, $P = 0.72$), revealing the absence of significant suppression of task-irrelevant information in the older population. To compare across age groups, we calculated three

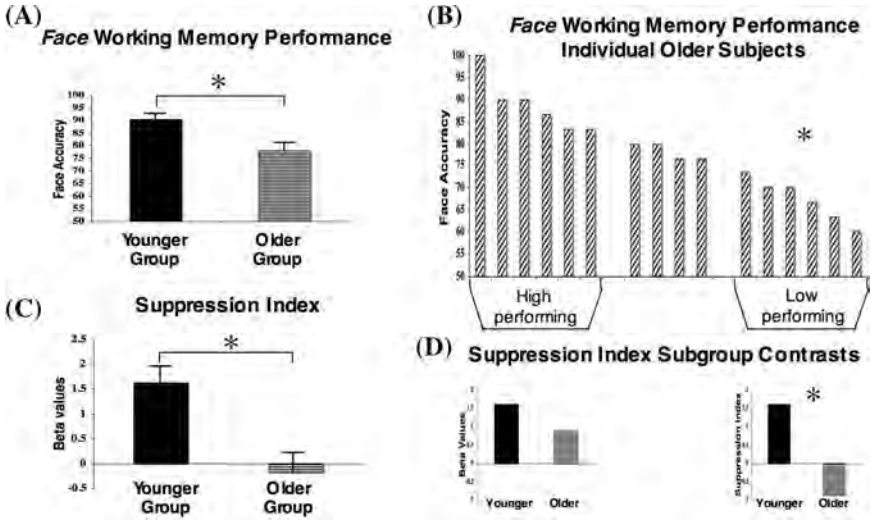

FIGURE 3. Relationship of suppression deficit and WM deficit. (**A** and **C**) Across-group comparisons of (**A**) Face WM accuracy ($^*P = 0.001$) and (**C**) suppression indices ($^*P < 0.005$). (**B**) Subgroups of the six high-performing and the six low-performing older individuals ($^*P < 10^{-5}$) on the Remember Faces condition. (**D**) A significant suppression deficit is only present in the low-performing older subgroup (* $P < 0.05$). *Error bars* indicate standard error of the mean. (Adapted from Gazzaley *et al.*[47])

modulation indices: overall modulation index (Remember Scenes–Ignore Scenes), enhancement index (Remember Scenes–Passive View), and suppression index (Passive View–Ignore Scenes). The use of these indices enabled across-group comparisons to be performed without directly contrasting BOLD signal magnitude between populations that might have vascular responsivity differences.[48] This analysis revealed the presence of an age-related decrease in the degree of overall modulation ($P < 0.05$). Critically, this age-related decrease in modulation can be attributed to a selective decrease in the subcomponent process of suppression ($P < 0.005$) (FIG. 2 D), as there was no significant difference in the enhancement subcomponent ($P = 0.27$). We have also replicated this finding and confirmed that it is a neural change and not a blood flow change by identifying a similar selective suppression deficit of the N170 latency shift in an EEG experiment on older subjects.[49]

In addition to exhibiting a decrease in the suppression index during encoding, as a population the older participants were cognitively impaired on the WM tasks in terms of both reduced accuracy and a slower reaction time compared to the younger population.[47] We further determined that only the subpopulation of older adults with a significant WM deficit on the task had a significant suppression deficit. This subpopulation also rated the scenes that were viewed

during the Ignore Scenes task as significantly more familiar than the younger participants rated them on the surprise postexperiment recognition test, revealing increased incidental long-term memory of distracting information and supporting our neural data that task-irrelevant scenes were not suppressed. To more directly evaluate the relationship between top-down modulation during encoding and subsequent WM recognition performance in the older subjects, we performed a Pearson's correlation between the suppression index and Remember Faces WM accuracy. The analysis revealed that the suppression index in older subjects significantly correlates with WM performance ($r = 0.53$, $P < 0.05$), such that the degree of top-down suppression during encoding predicts WM recognition accuracy, establishing the relationship between an age-related deficit in selective attention (specifically the suppression of task-irrelevant information), incidental long-term memory encoding, and interference during the WM task. Thus, while older adults are able to enhance sensory neural activity for relevant information, they are unable to sufficiently suppress neural activity for irrelevant information. The correlation between suppression indices and WM performance in the older adults implies that because of limited WM capacity, older individuals are overwhelmed by interference from failing to ignore distracting information, resulting in memory impairment.

The findings of these studies reveal that an age-related alteration in a basic neural process, such as top-down modulation, can influence multiple cognitive domains. In addition to revealing that an alteration in top-down modulation underlies cognitive aging deficits, our studies also contribute to the interpretation of an existing hypothesis of cognitive aging, the *inhibitory deficit hypothesis of aging*.[6] Behavioral evidence on the interaction between attention and WM processes in aging has suggested that age-related cognitive impairments are associated with increased sensitivity to interference from task-irrelevant information.[50,51] However, the premise that a specific deficit in attentional inhibitory processes negatively impacts WM performance has remained controversial due to the challenges in dissociating cognitive subcomponent processes, such as enhancement and suppression of neural activity, using behavioral measures alone.[52] Recent attempts at using physiological measures to evaluate inhibitory deficits in aging have supported the inhibitory hypothesis, but also failed to resolve the controversy by not establishing the specificity of an attention deficit to inhibition and not directly relating impaired attentional processing to WM deficits, which is necessary if this hypothesis truly reflects a unifying principle crossing cognitive domains.[19,53,54] Our findings serve to resolve controversy surrounding the inhibitory deficit hypothesis of aging by establishing specificity of an attentional deficit to the suppression of task-irrelevant information (i.e., a suppression deficit occurs in the setting of preserved enhancement) and directly relating this suppression deficit to WM impairment.

ONGOING STUDIES

The older individuals that participated in our aging studies were healthy, well educated, and cognitively intact compared to age-matched controls on extensive neuropsychological testing, allowing us to generalize these findings as a hallmark of normal cognitive aging. Encouragingly, the deficits we reported at the population level do not seem to be a universal characteristic of aging, as a subgroup of the older population with preserved suppression abilities also exhibited intact WM performance, reflecting the variability of the aging process and highlighting the importance of top-down suppression in cognition. This variability of neural and cognitive measures in the older population led us to question what is normal and consider two possible interpretations: (1) The impaired group represents what occurs during the normal aging process independent of neuropathology and the intact individuals (one third of the group) are examples of successful aging or (2) The intact group reflects the normal aging process and the impaired individuals (one-third of the group) are exhibiting the earliest signs of pathological cognitive impairment. Thus, our study raises the important question: Is this suppression deficit a harbinger of impending dementia? We are pursuing an answer to this question by following these older adults longitudinally and planning future studies in which we couple our fMRI functional biomarkers with other markers of Alzheimer's disease: hippocampal volumes, as assessed by structural MRI, *in vivo* amyloid PET imaging, and *ApoE* genotyping. Additionally, we are evaluating if there are within group differences between the older individuals that participated in this study, which might supply a clue to the heterogeneity of the population. For example, leukoariosis—white matter lucencies identified on FLAIR MRI—might be disproportionally present in the impaired subgroup, supporting an age-related relationship between white matter connectivity impairment, alterations in top-down modulation, and cognitive deficits.

Aside from focusing on questions related to the heterogeneity of the older population, our laboratories are also interested in understanding the neural basis of the modulation alterations in older adults that exhibit WM impairment. To assess this, we have initiated studies to explore the neural processes that underlie top-down modulation, so that we may better understand the changes that occur with age. Our studies are guided by the view that complex cognitive processes are not localized to brain regions functioning in isolation, but rather are emergent properties of neural networks interactions.[23,55–57] Top-down modulation is not believed to be an intrinsic property of sensory cortices, but rather mediated by cortical projections from higher-order cortical regions, often thought to be located in multimodal association cortex, such as the PFC and parietal cortex.[30] The extensive reciprocal connections between the PFC and virtually all cortical and subcortical structures situate the PFC in a unique neuroanatomical position to monitor and manipulate diverse

cognitive processes.[58,59] These anatomically defined networks establish the structural basis by which the PFC may exert top-down control, but there is also accumulating physiological evidence of PFC networks and their role in control processes. Neuronal recordings and neuroimaging data have revealed that top-down modulation of visual processing involves simultaneous activation of these regions.[37,60–63] In addition, we observe increased BOLD signal in PFC in the memory tasks of our paradigm relative to the passive view task, suggesting a role of these regions as a "top" in goal-directed VAC activity modulation. It is important to note that these studies, including our own data, reveal indirect evidence of functional interaction between these areas.[30,64] There are, however, two invasive studies in monkeys that support the PFC as a direct driving force of activity modulation in the VAC, where the visual information is represented and stored.[27,29] Additionally in humans, combined stroke–ERP studies have provided evidence of frontal cortex dependent top-down modulatory influences on VAC occurring in the first few hundred milliseconds of visual processing.[28]

Traditionally, most functional imaging studies have used univariate analyses, permitting only the independent assessment of activity within each brain region in isolation. However, there has been the steady development of multivariate approaches to analyzing neuroimaging data in a manner more directly in alignment with the network model of the cognition.[65–71] Multivariate analyses generate functional and effective connectivity maps of interacting brain regions, thus emphasizing the role of brain regions within the context of activity in other regions and the cognitive processes being performed. Several groups have begun to establish the presence of functional interactions between the PFC and posterior cortical regions during cognitive control processes, such as attention, WM, and visual imagery.[72–74] We have recently developed a new method to analyze event-related fMRI data sets in a multivariate manner.[67] We then applied this method to characterize the neural networks involved in maintaining a representation of an image in mind over a brief period of time (visual WM)[75] and the networks involved in incidental long-term memory.[76] We are now in the process of performing a functional connectivity analysis on the encoding phase of the selective WM task we have described. Preliminary evidence has revealed regions of robust functional connectivity between the PFC and VAC, further supporting the role of the PFC as a control region. We are also exploring age-related changes in these functional connections in an attempt to understand the basis of an age-related top-down suppression deficit.

The possibility that there is an impairment in PFC function with age and that this might be the underlying source of the top-down modulation deficit we identified in the older subjects is consistent with another well-established hypothesis of cognitive aging, *the frontal hypothesis*. Advocates of this hypothesis propose that early and prominent alterations in frontal lobe integrity underlie the cognitive deficits that occur with normal aging. However, as

with the inhibitory deficit hypothesis, controversy surrounds this claim.[2] For example, structural MRI studies have reported atrophy limited to the medial temporal lobes and frontal cortex,[77] generalized atrophy with age,[78] and no atrophic changes.[79] Similarly, functional imaging studies have revealed decreases in PFC activity, while others have revealed increases.[22] It has thus been challenging to use neuroimaging techniques alone to parcel out the significance of structural and functional changes in the aging brain. In an attempt to resolve this controversy, we are now directly exploring the role of the PFC in top-down modulation by employing a unique coupling of fMRI, EEG, and a "reversible lesion" technique offered by repetitive transcranial magnetic stimulation (rTMS).

Although fMRI permits us to identify brain regions of interest, it is inherently limited in that it is a correlational technique and thus unable to assess causality, necessity, and the exact role of a region within a network for a cognitive operation. To accomplish this, we need to manipulate function in a brain region and observe the effects of perturbation on neural activity in distant brain regions, as well as cognitive performance. TMS allows us to do this by applying a focal magnetic pulse to a subject's scalp, resulting in a brief electric current in the underlying cortex and synchronous neural firing.[80] When applied in a repetitive manner at low frequency the stimulation results in a transient disruption of neural activity in a defined region of cortex that lasts for a brief period of time after the TMS is performed.[81–84] The recent development of this technology now enables us to perform "virtual lesion" experiments in a safe manner in human subjects.[85] We recently performed a pilot study using 1Hz rTMS to transiently disrupt PFC regions in young adults that were preidentified with fMRI and assessed the consequences on cognitive performance and top-down modulation in sensory regions using EEG. This experiment used the same selective WM paradigm we used in our recent aging study. Our goals are to determine if by selectively disrupting PFC pathways in young adults, both neural measures of top-down modulation and cognitive performance can be made to mimic the pattern seen in older adults. The pilot study performed on four subjects revealed encouraging preliminary results. Transient disruption of fMRI-identified regions in the middle frontal gyrus resulted in an alteration of distant neural measures of top-down modulation. Specifically, the increase in P300 amplitude that occurs in the remember condition versus the ignore condition was diminished, and additionally, there was a significant slowing of the response time on the WM memory task.[86] This pattern of a decrease in P300 for the relevant information and slower response time is identical to a finding that we observe in the older subjects performing this task without rTMS.[87] A full-scale study is now under way to directly evaluate the causal role of the PFC in goal-directed modulation of visual cortex activity.

In addition to our efforts at manipulating PFC function directly with rTMS, we are also modifying the task demands in young adults performing the

selective WM task in a manner that taxes PFC function. There is an extensive literature on the role of the PFC in WM,[88] and so in an ongoing experiment we are assessing if having young subjects perform a nonverbal WM task concurrently with our visual WM task influences top-down modulation measures and differentially affects enhancement and suppression. To accomplish this, at the beginning of each trial, subjects are presented auditorily with six digits to memorize. On half of the trials the digit sequence was random (*high load*); on the other half the digit sequence was "1,2,3,4,5,6" (*low load*). After hearing the digits, the participants then performed the face/scene WM paradigm as previously described. Preliminary results revealed that the high digit load did not alter the participants' ability to enhance activity levels in the scene-selective region during the Remember Scenes task, but did result in increased BOLD signal associated with the irrelevant scenes in the Ignore Scenes task.[89] Thus, increasing the WM load in younger adults produced a selective suppression deficit identical to that seen in older adults performing the task without the increased load. This suggests that the age-related alteration in top-down modulation we recently documented may result from PFC changes in aging expressed as decreased WM resources with age. If further studies support that PFC alterations with aging underlie the top-down suppression deficit, this will serve to reconcile the *frontal* and *inhibitory deficit* hypotheses of aging.

CONCLUSIONS

Coupling the many tools of human neuroimaging technology with our recently developed cognitive paradigm has allowed us to reveal an age-related alteration in top-down modulation, a neural mechanism that underlies the diverse cognitive processes affected by aging. Our recent studies exploring alterations in neural networks that underlie these modulation alterations point to changes in PFC as a potential etiology. This is suggested by preliminary studies that have replicated aging top-down modulation changes in healthy young adults by increasing WM load, presumably taxing PFC function, and by transiently disrupting activity in the PFC regions with rTMS. This association between a suppression deficit and alterations in PFC control in aging may serve to reconcile the *inhibitory* and *frontal* hypothesis of cognitive aging and propels us along on our ultimate goal of defining underlying principles of cognitive aging. More research is needed that integrates the various technologies of human neurophysiology to capitalize on their unique strengths. Future studies are now planned to use neural measures as functional biomarkers to explore the therapeutic role of cognitive training and pharmacological treatment in improving cognitive abilities in older adults.

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