

Top-down modulation: The crossroads of perception, attention and memory

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ABSTRACT

Research in our laboratory focuses on understanding the neural mechanisms that serve at the crossroads of perception, memory and attention, specifically exploring how brain region interactions underlie these abilities. To accomplish this, we study top-down modulation, the process by which we enhance neural activity associated with relevant information and suppress activity for irrelevant information, thus establishing a neural basis for all higher-order cognitive operations. We also study alterations in top-down modulation that occur with normal aging. Our experiments are performed on human participants, using a multimodal approach that integrates functional MRI (fMRI), transcranial magnetic stimulation (TMS) and electroencephalography (EEG).

Keywords: top-down modulation, functional connectivity, attention, memory, perception, cognitive aging

1. INTRODUCTION

Our ability to selectively focus attention on sensory information relevant to our goals and ignore irrelevant information is essential for optimal performance on all cognitive operations. This ability is mediated by a neural process known as *top-down modulation*, which involves the enhancement and suppression of sensory cortical activity associated with relevant and irrelevant information, respectively. This goal-directed modulation of neural activity is not an intrinsic property of sensory cortices, but rather is manifest via long-range connections between distant brain regions, or *neural networks*. Top-down activity modulation occurs both when stimuli are encountered in the environment, such as during selective attention and memory encoding and when stimuli are absent and sensory representations are generated internally, as in mental imagery. Thus, top-down modulation establishes a neural basis for perception, selective attention and a critical foundation for successful memory storage. Research in our lab is focused on using the tools of cognitive neuroscience (functional MRI (fMRI), transcranial magnetic stimulation (TMS) and electroencephalography (EEG)) to understand the basic mechanisms of top-down modulation and how it is altered in normal aging.

1.1 Enhancement and suppression.

How we perceive stimuli in our environment involves an integration of two distinct influences: externally- and internally-driven attention. 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*)¹⁻³. Top-down modulation is a bi-directional process in that it underlies our ability to both focus our attention on task-relevant stimuli and ignore irrelevant distractions by differentially *enhancing* or *suppressing* neural activity in sensory cortical regions depending on the relevance of the information to our goals^{4,5}. Thus, by generating neural contrast via the enhancement and suppression, top-down signals bias the likelihood of successful representation of relevant information in a competitive system. It is well documented that interleaved inhibitory and excitatory mechanisms are present throughout the neuroaxis (e.g., spinal reflexes, cerebellar outputs and basal ganglia movement control). It is thus not surprising that top-down modulation entails both enhancement and suppression to regulate the impact that perceived sensory stimuli have on neural activity. This provides a powerful contrast for sculpting neural processes that support all higher order cognitive operations^{6,7}.

The physiological basis of top-down modulation relies on extensive evidence from single-unit physiology, functional neuroimaging and electroencephalography (EEG), which reveal that measures of neural activity are augmented in specialized sensory cortical regions—the presumed sites of neural representation—when attention is directed toward a

stimulus or stimulus attribute⁸⁻¹². Evidence of activity modulation has been generated for the auditory¹³, olfactory¹⁴ and somatosensory¹⁵ systems, but the modality most studied is vision. Physiological and neuroimaging studies have revealed that neural activity is enhanced in visual cortex when attention is directed toward behaviorally relevant visual stimuli¹⁶⁻¹⁹ and reciprocal suppression of activity occurs in visual regions that encode non-relevant stimuli^{12, 17, 20, 21}. In the *biased competition model*, this suppression is thought to occur due to competition of multiple stimuli for limited visual processing resources²². An important question has emerged as to whether enhancement and suppression are mechanistically distinct processes or are different levels of the same process. We have recently generated converging evidence from studying top-down modulation in older individuals^{5, 23} and manipulating cognitive demands in working memory (WM) tasks in young adults^{24, 25} that these two processes are differentially influenced, suggesting they have independent control processes, physiologically, anatomically and/or neurochemically²⁶.

1.2 The crossroads of attention and memory.

Attention and memory have traditionally been viewed as separate processes and are often studied independently. However, attention is a gateway to memory, in that stimuli that are ignored or passively viewed are not remembered as well as those that are the focus of attention. Furthermore, physiological evidence supports that selective attention is necessary to restrict the contents of capacity-limited memory to task-relevant representations²⁷, favoring successful memory performance by limiting interference from task-irrelevant representations²⁸. As has also been demonstrated, there is mechanistic overlap between these processes²⁹⁻³³. Additionally, we have recently shown that top-down modulation employed in the service of selective attention early in during memory encoding influences the effectiveness of storing information, as revealed by a direct correlation with subsequent memory performance³⁴.

1.3 Neural networks.

Theories of brain organization focus on two distinct, but complementary principles: *modularity*—the existence of neuronal assemblies with intrinsic functional specialization and, *connectivity*—the integration of signals from distant brain regions resulting in organized behavior. While the modular model may be reasonable to describe basic features of primary cortices, it is insufficient to explain complex, higher-order, cognitive processes, which are not localized to isolated brain regions^{35, 36}. In order to adequately explore the brain mechanisms involved in such processes, we should focus our experimental design and analyses on interactions between brain regions, or *neural networks*³⁷. The network approach is especially important for understanding top-down modulation, the very basis of which is believed to be dependent on communication between distributed regions.

It is widely thought that goal-directed activity modulation during visual processing is not an intrinsic property of visual cortices, but is achieved via connections between control regions in the prefrontal cortex (PFC), a *source* of the modulatory signal, and the visual association cortex (VAC), a *site* of modulation where visual information is represented (review; ²⁶). Tract-tracing studies in experimental animals offer a structural basis for this claim by revealing long-range reciprocal cortico-cortical connections between PFC and VAC³⁸⁻⁴³. Several of these pathways have also been described in humans using post-mortem dissection⁴⁴ and more recently using *in vivo* diffusion tensor magnetic resonance imaging⁴⁵. There is also accumulating neurophysiological evidence of PFC involvement in top-down modulation^{26, 46, 47}; neuronal recordings and neuroimaging have revealed that modulation of visual processing involves simultaneous activation of both PFC and VAC^{8, 48-51}. However, it is important to recognize that while these studies are suggestive, they are indirect evidence of functional interactions between these areas based on univariate statistics that measure activity in brain regions independently of one another.

2. METHODOLOGY

2.1 fMRI

Data Acquisition. MRI experiments were performed on either a Varian 4T scanner or a Siemens 3T Trio scanner equipped with echo-planar imaging. During each fMRI experiment, we collected 33 3 mm oblique axial T2*-weighted gradient-echo, echo-planar imaging (EPI) slices, with 2000 ms TR, 25 ms TE, 90 degree flip angle and 250mm x 250mm field of view in a 128 x 128 matrix. A color liquid crystal display (LCD) driven by a Pentium PC or Apple desktop computer was used to present stimuli and located at the head of the subject gurney. The subject views the screen through a mirror mounted on the head coil. E-Prime, Presentation or Matlab software was used to present stimuli and record

responses and response latencies. Specially constructed fiber-optic motor response recording devices are used to transmit subject behavioral data.

Data analysis. Using a multiple regression approach, we model BOLD signal changes occurring during each qualitatively distinct stage of the behavioral trials with a series of covariates that are entered into the GLM^{52, 53}. Each covariate comprises canonical HRF positioned appropriately to represent the *onset* neural activity associated with one of the task components. Parameter estimates are interpreted as indices of the extent to which their corresponding covariates of interest explain the data and thus the magnitude of the BOLD response. Statistical maps are generated by computing t-statistics associated with linear combinations of the covariates of interest. In our multivariate approach (beta series correlation analysis, a GLM is constructed in which every stage of every trial is modeled with a separate covariate⁵⁴. The resulting beta values (from correct trials only) were sorted according to the stage from which they were derived to form a “beta-series” for each stage. Stage-specific whole brain correlation maps were obtained by calculating the correlation stimulus-selective beta-series with that of all other brain voxels.

2.2 EEG

Data Acquisition. Electrophysiological signals were recorded with ActiveTwo 64 Channel EEG Acquisition System (CortechSolutions, LLC). Raw EEG data were referenced to the average off-line. Artifacts were removed through an independent component analysis and a voltage threshold of +/-50 mV.

Data Analysis: Artifact-free data epochs were signal-averaged using conventional procedures. Stimulus-locked ERPs, were extracted during the analysis process. We performed selective averaging based on different task periods. ERP peak latencies are obtained from appropriate scalp sites over pre-selected latency ranges. Mean amplitude measures were obtained over defined intervals are generally referenced to a 200-ms pre-stimulus baseline. Mean voltage measures were usually emphasized because they are less sensitive to the signal/noise ratio and spurious peak selection, but we examine both mean and peak values.

2.3 TMS

A Magstim Standard Rapid TMS Unit (Jali Medical Inc) was used to generate pulses with a 70 mm figure-of-eight induction coil. The magnetic stimulus had a biphasic waveform with a pulse width of about 300 μ s. TheBrainsight frameless stereotaxic software (Rogue Research, Montreal Canada) was used to co-register the participant’s head, coil and high-resolution T1-weighted MRI images into a common digital workspace. Spatial accuracy of this system is approximately 5 mm. Once the coil is localized over motor cortex, TMS pulse intensity and position are adjusted to identify 120% motor threshold. Then, the coil is positioned over a cortical site of interest. Repetitive TMS is triggered with a TTL pulse from a frequency generator while single pulse TMS is triggered by a TTL pulse from a photodiode fixated to the stimulus presentation monitor to ensure precise timing. The number of TMS pulses and the frequency of rTMS at 1 Hz is well within safety recommendations⁵⁵.

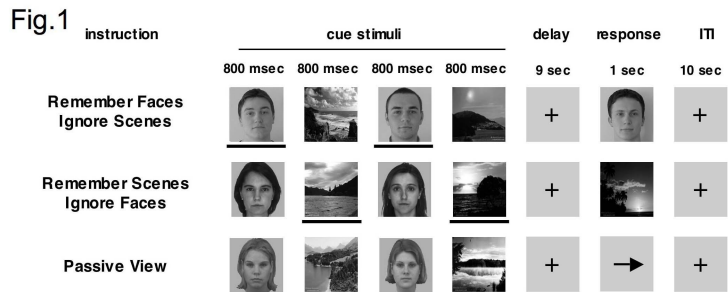
EXPERIMENTS AND RESULTS

This section reviews data from our lab addressing two goals: (1) Characterize neural indices of top-down modulation in young adults and their relationship to performance; (2) Assess age-related changes in top-down modulation and its impact on cognition.

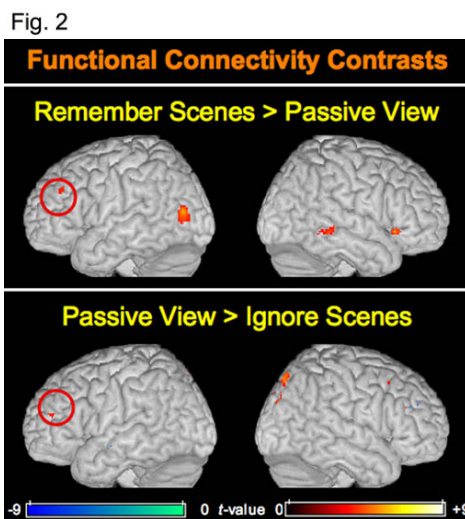
3.1 Characterize neural indices of top-down enhancement and suppression in young adults and its relationship to cognition.

Studies 1 & 2. These studies identified neural indices of top-down modulation using fMRI and EEG recordings^{21 56}. 18 young, healthy participants (18-30 y.o.) engaged in fMRI and EEG experiments on separate days. We identified distinct measures of top-down enhancement and suppression of VAC activity while the participants performed a novel selective, delayed-recognition WM experiment (Fig. 1). The paradigm consisted of three tasks in which aspects of visual information were held constant while task-demands were manipulated. During each trial, participants observed sequences of two faces and two natural scenes presented in a randomized order. The tasks differed based on instructions that informed 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. For each task, the period in which the cue stimuli were presented was balanced for bottom-up visual information, thus allowing us to assess the

influence of goal-directed behavior on neural activity in visual cortices relative to baseline passive view levels (i.e., top-down modulation). After a 9 second delay, participants were tested on their ability to recognize a probe stimulus as being one of the task-relevant cues, yielding accuracy and response time measures of WM performance. fMRI and EEG data provided converging evidence that both the *magnitude* of neural activity and the *speed* of neural processing are modulated by top-down influences. Furthermore, both *enhancement* and *suppression* occurs relative to the passive view baseline depending on task instruction. For fMRI data, BOLD signal in a scene-selective area located in the right and left parahippocampal gyrus was higher for Remember Scene trials and lower for Ignore Scenes trials (i.e. remember faces) when compared to the Passive View baseline condition. ERP analysis of the N1 latency (a face-selective potential⁵⁷) revealed the presence of both enhancement and suppression of the speed of face processing; the right N170 peak latency was earlier for Remember Faces and later for Ignore Faces than Passive View. Fourier transformation of the EEG data to the time-frequency domain revealed top-down modulation of spectral measures in posterior electrodes. Specifically, gamma band synchronization and alpha band desynchronization occurred for the relevant stimuli relative to passively viewed and ignored⁵⁸.



To explore the role of top-down control areas, we utilized a functional connectivity method that we developed to study network connectivity using fMRI data^{54, 59}. We were able to identify sources of these modulatory influences by examining how network interactions between the PFC and the VAC were influenced by attentional goals at the time of encoding. Our findings revealed a PFC region in the middle frontal gyrus that was more correlated with the VAC when scenes were remembered and less correlated when scenes were ignored, relative to passive viewing (Fig. 2). Moreover, the strength of the PFC-VAC coupling predicts the magnitude of attentional enhancement and suppression of VAC activity. Taken together, these findings suggest that PFC biases activity levels in posterior sensory cortices via attention-dependent modulation mediated by the strength of functional coupling with VAC.



Study 3. This study was designed to establish fMRI and EEG markers of top-down modulation when information was simultaneously competing for resources, as opposed to being temporally divided as in study 1 & 2³⁴. To accomplish this goal, we modified the paradigm so that participants were presented with overlapping, “double-exposed” images of faces and natural scenes, and were instructed to remember either the face or the scene while simultaneously ignoring the other stimulus. The rest of the paradigm was the same. The competition for resources in the setting of concurrent relevant and irrelevant information made the task significantly more difficult, thus leading to greater individual performance variability. This enabled us to establish for the first time a direct relationship between early activity modulation in sensory cortices during selective encoding and subsequent WM performance. Specifically, the degree to which participants modulated the early P1 (97-129 ms) component of the event-related potential (ERP) during selective stimulus encoding significantly correlated with their subsequent WM recognition accuracy.

Study 4. While studies 1 -3 used complex real-world stimuli, this study was designed to explore top-down modulation for features of lower-level visual stimuli (motion direction and color hue)²⁵. The design of this study was identical to that utilized in study 1, except instead of faces and scenes, participants were presented with four sequential circular apertures of dots: two were differently colored and stationary, while two were gray and moving coherently in different directions. Attention was selectively modulated by task instructions that guided participants to remember ‘color’ (ignore motion) or the direction of ‘motion’ (ignore color). In the EEG portion of this study, we discovered that top-down modulation of early visual processing (< 200 ms from stimulus onset; P1 and N1 modulation indices) was intimately related to subsequent WM performance, such that *the likelihood of successfully remembering relevant information was associated with limiting interference from irrelevant stimuli*. The consequences of a failure to ignore distractors on recognition performance were replicated for both types of feature-based memory. These results suggest that focus on relevant information is not the primary determinant of high-level performance, but rather, optimal WM performance is dependent on effectively filtering irrelevant information to prevent overloading a limited memory capacity.

Study 5. To assess neural networks involved in top-down control of color and motion processing during WM encoding, the paradigm from Study 4 was used with fMRI recordings (unpublished). fMRI data was subjected to beta-series correlations using V4 and V5 seeds to provide measures of functional connectivity. Additionally, source localization of the EEG recordings was conducted using sLORETA. Beta-series correlations of the fMRI data showed that when participants attended to the stimuli, a region in the PFC, the right inferior frontal junction (IFJ), was correlated with V4 and V5 for color and motion stimuli, respectively. Interestingly, no significant correlation was observed in PFC when participants ignored the irrelevant stimuli (i.e. V5 when attending color or V4 when attending motion). Source localization of the EEG signal generated by the contrast between attended and ignored stimuli at the time of the P1 and N1 indicated that the only potential frontal source involved in attentional modulation was the right IFJ during the time of the P1 to motion and the time of the N1 to color stimuli.

Study 6. In order to evaluate causality of the top-down control area identified in Study 5 (right IFJ) on feature processing, we performed a fMRI-guided repetitive TMS experiment with EEG recordings (unpublished). Participants performed the same experimental task as described in Study 4 in two separate visits. The first visit utilized fMRI to identify the right IFJ region in each participant that was potentially involved in top-down modulation of color and motion feature processing. The second visit involved the application of rTMS to the IFJ target region, and EEG and behavioral data was collected during the period immediately following rTMS, when IFJ function was disrupted by rTMS. Application of 1 Hz rTMS to the IFJ was found to disrupt color WM performance during the first half of the post-TMS time period (when the disruption was maximal) and result in loss of posterior markers of top-down modulation for EEG signals time-locked to the color cues in that same period. This established a causal role of the IFJ as a control region for the top-down modulation of color processing, and underscores the critical interactions between attentional modulation and working memory performance. Motion processing and performance were suspected to not be impacted by rTMS because the fMRI study revealed that for motion processing bilateral IFJ was involved, and thus it may be more immune to the effects of unilateral rTMS.

Study 7. This study was designed to assess the impact of different types of interference presented during a period of WM maintenance⁶⁰. In this study, EEG and fMRI data were recorded in separate experiments that each introduced different types of visual interference during a period of WM maintenance: distraction (irrelevant stimuli) and interruption (stimuli that required attention). The data converged to reveal that regardless of the type of interference, the magnitude of processing interfering stimuli in the visual cortex (P1 and N1 indices) predicted subsequent WM recognition accuracy for stored items. fMRI connectivity analyses suggested that in the presence of distraction, encoded items were maintained throughout the delay period via connectivity between the middle frontal gyrus and visual association cortex,

while memoranda were not maintained when participants were interrupted, but rather reactivated in the post-interruption period. These results elucidate the mechanisms of external interference on WM performance and highlight similarities and differences of distraction and multitasking.

Study 8. An EEG study was performed to test the hypothesis that the efficiency of processing interference is plastic, such that it can improve over a single session and result in a diminished impact on WM performance⁶¹. The experimental design described in Study 7 was modified so that lower-level features served as cues, interfering stimuli and probes (i.e., motion direction of flow fields of dots as cues and probes, and a rotating field of dots as distractors and interruptors). To optimize learning during EEG recordings, participants were given performance feedback on each trial. We show that both types of interference disrupted WM performance, but interference-induced disruption abated across a single experimental session via rapid learning. WM accuracy and response time improved in a manner that could be predicted by changes in early neural measures of interference processing in visual cortex (i.e. P1 suppression and N1 enhancement). These results suggest practice-related changes in processing interference exert a positive influence on WM performance, highlighting the importance of filtering irrelevant information, and the dynamic interactions that exist between neural processes of perception, attention and WM during learning.

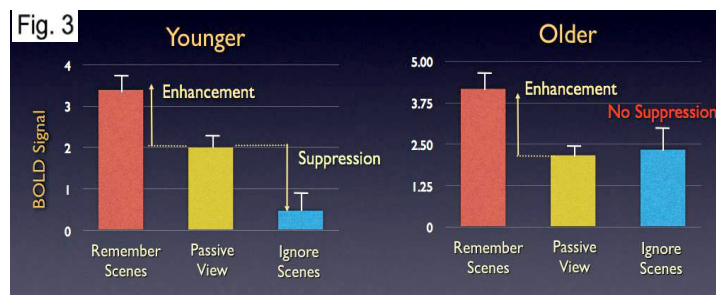
Study 9. Influence of manipulations of reward on top-down modulation⁶². Although there is an extensive literature on the interaction of reward motivation and WM performance, this largely consists of single-unit recordings in monkeys. We recently completed an fMRI study of young adults directed at evaluating the influence of reward motivation on top-down modulation. This study used a variant of the selective WM task in Study 1, in which trials were divided into no reward, low reward and high reward based on a point system. Points were worth money that was paid as a bonus after the experiment. We assessed whether differential WM performance, as indexed by reduced response times on the task, was associated with an amplification of enhancement and suppression indices. Response time analyses supported our hypothesis that rewarded trials result in an improvement in WM performance, such that response time was significantly faster on high and low reward trials relative to no reward trials (only true for memory tasks, not passive view). This study further revealed that both enhancement and suppression of activity in stimulus-selective VAC were amplified in trials with the highest reward level relative to non-rewarded trials. PFC also showed enhanced activity during high reward trials. Overall these results reveal that motivation for reward can play a pivotal role in driving cognitive performance, presumably through top-down signaling from prefrontal regions.

Study 10. While studies 1-9 explored neural measures of top-down modulation and the role of suppression of influence on WM performance, this study assessed its impact in the retrieval of long-term memory (LTM)⁶³. Twenty-seven participants first studied pictures that contained one to four images of a common object and then, after a one-hour delay, were probed with auditory cues that either matched a study object or were new. Immediately after hearing the cue (and within 2500ms), participants responded with a button press to indicate their recall of the number of the objects from the relevant studied picture (i.e., 1, 2, 3, 4 or new). Participants performed this experiment with their eyes held shut; or eyes open with constant gaze at a busy scenic picture. Behavioral results revealed that recollection accuracy was diminished by the mere act of having ones eyes open. An fMRI version of this study showed that impaired performance in the setting of open eyes was associated with a decrease in activity in the left hippocampus and a disruption of network involving the left inferior frontal gyrus (IFG), hippocampus and visual association cortex, which supported retrieval of contextual details based on visual imagery when eyes were closed. We conclude that bottom-up influences from irrelevant visual information interfere with top-down selection of episodic details, resulting in impaired recollection.

3.2 Assess age-related changes in top-down modulation and its impact on cognitive performance.

Study 11. Based on extensive behavioral literature revealing that older adults exhibit impairment in their ability to effectively inhibit irrelevant information⁶⁴, we explored the hypothesis that older adults would experience a selective inability to effectively ignore irrelevant stimuli that would be expressed neurally as a top-down suppression deficit⁵. Eighteen healthy older participants (60-77 years of age) with no cognitive deficits relative to age-matched controls were studied with fMRI in the face/scene WM experiment (study 1). Analysis of BOLD signal modulation in the most robust region of modulation, the left scene-selective area, revealed that in the setting of preserved enhancement of neural activity for relevant information, older adults demonstrated a significant deficit in top-down suppression of irrelevant items (i.e., activity while ignoring scenes was not significantly reduced relative to passive view (Fig. 3). In addition to exhibiting a suppression deficit during encoding, older individuals were impaired on WM performance in terms of both reduced accuracy and a slower RT compared to younger individuals. Regression analysis revealed a significant

correlation between the fMRI suppression index and WM accuracy, such that the degree of top-down suppression of irrelevant information directly correlated with recognition accuracy of the relevant information. It was these findings that inspired us to develop a training program targeted at improving top-down modulation abilities in older adults.



Study 12 & 13. In a follow-up to study 11, we utilized the identical paradigm but instead used EEG recordings to examine the relationship between the inhibitory deficit and the processing speed deficit of older adults^{58 65}. We replicated our previous findings of an age-related selective deficit in suppressing task-irrelevant information using EEG modulation indices, P1 and N1 ERPs. However, these data also showed that the suppression deficit only occurred in the early stages of visual processing, using alpha power as a reflection of later attentional processing. Thus, the employment of suppressive mechanisms are not abolished with aging, but rather delayed in time, revealing a decline in processing speed selective for the inhibition of irrelevant information. EEG spectral analysis of frontal regions, focusing on midline frontal theta, suggested that this resulted from excessive attention to distracting information early in the time course of viewing irrelevant stimuli. Subdividing the older population based on WM performance revealed that impaired suppression of distracting information early in the visual processing stream was associated with poorer memory of task-relevant information. Thus, these data reconcile two cognitive aging hypotheses by revealing that an interaction of deficits in inhibition and processing speed contributes to age-related cognitive impairment⁵⁸.

Because stimuli were presented in a random sequence, it remained unclear from the previous study whether the age-related suppression deficit was a result of a selective impairment in filtering irrelevant stimuli or a decline in recognition processing speed (i.e. the time to recognize information as relevant or irrelevant). To address this, we performed another EEG experiment in which older participants could anticipate the arrival of irrelevant stimuli prior to their appearance, which eliminated the need for them to rapidly to assess stimulus relevance. Using the same indices of top-down modulation, this study once again revealed the presence of a suppression deficit, suggesting that anticipation of ensuing irrelevant information does not alleviate older adult's suppression abilities⁶⁵.

Study 14. This fMRI study explored age-related changes in top-down modulation while information was simultaneously competing for processing resources (overlapped images of faces and natural scenes) (unpublished). We had hypothesized that suppression would be more automatic in this scenario and thus suppression abilities might be preserved with aging. However, an fMRI experiment once again revealed the presence of a selective-suppression deficit in the older adults, even in the setting of direct sensory conflict. Functional connectivity analysis revealed that network changes in dorsolateral prefrontal and anterior cingulate cortex networks were associated with the suppression deficit.

Study 15. To assess the presence of age-related changes in modulation for lower-level stimuli (direction of moving dots and color of stationary dots), we performed an EEG version of study 4 in older adults⁶⁶. Analysis revealed that the primary changes with aging in processing features was a delay in the speed of neural processing, specifically the early N1 component for color stimuli, and the selection negativity, a difference waveform peaking between 240-400 ms (attend-ignore), for both color and motion stimuli. Importantly, the latency of the peak of the selection negativity correlated with subsequent WM recognition RT. This study establishes the relationship between delays in neural processing speed and diminished WM performance with aging, even when corrected for perceptual differences and differences in motor processing speed.

Study 16. This EEG study utilized the same design as study 7, except it was performed in healthy older adults to assess age-related changes in top-down modulation for different types of interference and its impact on ongoing WM maintenance⁶⁷. As was true for young adults, both types of interference (distraction and interruption) disrupted WM

performance, but engagement in the secondary task (i.e., interruption) was more disruptive than distraction. However, we also observed an age X task interaction, such that WM performance of older adults was impaired out of proportion by the interrupting discrimination task, consistent with a literature on sensitivity to dual task engagement with aging. N1 modulation indices revealed that the amount of attentional processing for either type of interference once again predicted WM accuracy. However, while impairment observed with aging was explained by a suppression deficit of the distractors, age-related deficits induced by interruptors did not seem to be mediated by excessive attention to these stimuli relative to young adults. These results allude to distinct underlying mechanisms mediating the impact of different types of external interference on WM with normal aging.

CONCLUSIONS

The series of studies presented in this paper describe a multimodal approach, integrating fMRI, EEG and rTMS, to explore the nature of top-down activity modulation in visual cortices, the underlying neural networks, differential influences of enhancement and suppression on WM and LTM performance, and age-related changes in these processes. The studies on younger adults revealed robust markers of modulation with both fMRI and EEG in visual cortices. This activity modulation was demonstrated by functional connectivity analysis to be mediated via coupling between the sensory regions and cognitive control areas in the PFC. A study to assess causality of these control areas employed rTMS to disrupt PFC activity, revealing a direct influence on sensory activity modulation and WM performance. Suppression abilities were shown to be plastic in young adults, influenced by both practice and reward. Of further interest, it was demonstrated that suppression of irrelevant information, not focus on relevant information, was the primary determinant of successful WM performance. The collective results of studies on older adults revealed that they experience an inability to adequately implement top-down suppression mechanisms when confronted with irrelevant information (in the setting of preserved enhancement), leading to decreased WM performance. This occurs whether they are prepared *or* unprepared for the appearance of distractors, distractors are present during encoding *or* while maintaining information, *or* whether the interfering information is entirely irrelevant (distractions) *or* an element of a secondary task (interruptions). Older adults were also shown to have the ability to improve their suppression abilities with practice. The finding described here, and the neural markers that were used to understand these processes, are now being used to guide the development and assessment of therapeutic interventions (cognitive training, and pharmacological) to improve suppression abilities, with the ultimate goal of improving cognitive abilities and quality of life in older adults.

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