Top-down modulation in visual working memory

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Working memory (WM) is a construct that encompasses our ability to temporarily maintain and manipulate information that is no longer accessible in the environment for a brief period of time in order to guide subsequent behavior (Baddeley 1986). A majority of the research over the last thirty years directed at understanding the neural basis of WM has focused on characterizing the pattern of neural activity that occurs when active representations of recently presented information are maintained prior to an action guided by these maintained representations. This focus was launched with physiology studies that first discovered persistent activity in prefrontal cortex (PFC) neurons in monkeys during this processing stage (Fuster and Alexander 1971; Kubota and Niki 1971), and has continued to thrive with dozens of single unit recording studies in experimental animals (Chafee and Goldman-Rakic 1998; Funahashi, Bruce and Goldman-Rakic 1989; Fuster 1990; Miller, Li and Desimone 1991; Niki, Sakai and Kubota 1972; Watanabe and Niki 1985; Wilson, Scalaidhe and Goldman-Rakic 1993) and functional imaging studies utilizing WM paradigms in human subjects (Courtney, Ungerleider, Keil et al. 1997; D’Esposito, Postle and Rypma 2000; Jha and McCarthy 2000; Postle, Druzgal and D’Esposito 2003; Ranganath and D’Esposito 2001).

Recently, our laboratory has investigated the neural mechanisms underlying encoding processes, that is, the processes that influence what information is actively maintained, and what is not. It is clear that ability to actively maintain relevant information will depend critically on how well such representations are generated during encoding. Furthermore, active representations are susceptible to interference by distracting information (Miller, Erickson and Desimone 1996). In the real world, as compared to the artificial environment of WM tasks, multiple streams of information reach our awareness, some of it relevant, some not for the task at hand. Given the inherent capacity limitations of WM (Luck and Vogel 1997), it is essential that only representations of task-relevant information are generated and maintained in the first place. Thus, an important aspect of goal-directed behavior is understanding the neural mechanisms underlying how task-relevant versus task-irrelevant information is differentially processed.

To investigate the neural mechanisms underlying goal-directed behavior, we have focused on the process of top-down modulation. Human interaction with our environment involves a fluid integration of externally driven perceptual information that demands attention based on stimulus salience or novelty (bottom-up processes) and internally driven, goal-directed decisions concerning external stimuli or stored representations (top-down modulation) (Bar 2003; Frith 2001). Top-down modulation has been described both when a stimulus is present in the environment – e.g., selective attention and memory encoding (Bar 2003; Pessoa, Kastner and Ungerleider 2003; Treue and Martinez Trujillo 1999; Wojciulik, Kanwisher and Driver 1998) – and when a stimulus is absent – e.g., mental imagery, working memory maintenance and anticipation (Fuster 1990; Ishai, Haxby and Ungerleider 2002; Kastner, Pinsk, De Weerd et al. 1999; Miller,
Li and Desimone 1993). It underlies our ability to selectively focus on relevant stimuli and ignore distracting stimuli, establishing a foundation for attention and memory. Understanding the cognitive and neural mechanisms of top-down modulation are important for reconciling the large body of literature that exists for both attention and memory processes. It has long been acknowledged that these processes, especially WM and selective attention, are similar conceptually, but have traditionally been classified separately and studied independently. It is only recently that the mechanistic overlap of these processes has become the subject of a concerted research focus (Awh and Jonides 2001; de Fockert, Rees, Frith et al. 2001; Desimone 1996; LaBar, Gitelman, Parrish et al. 1999). Evidence has revealed that selective attention is necessary to restrict the contents of capacity-limited memory networks to task-relevant representations (Ploner et al. 2001).

The theoretical framework of the neural basis of top-down modulation relies on extensive evidence from single-cell physiology, functional neuroimaging and EEG data, revealing increased activity in specialized posterior cortical regions – the presumed sites of neural representation – when attention is directed toward a stimulus or stimulus attribute (Barcelo, Suwazono and Knight 2000; Corbetta, Miezin, Dobmeyer et al. 1990; Kastner and Ungerleider 2001; Moran and Desimone 1985; Pessoa, Kastner and Ungerleider 2003). Descriptions of top-down modulation of activity magnitude has been described for the auditory (Hillyard, Hink, Schwent et al. 1973), olfactory (Zelano et al. 2005) and somatosensory (Seminowicz, Mikulis and Davis 2004) systems, but the modality most studied has been vision. Physiological and neuroimaging studies have revealed that neural activity is enhanced in the visual association cortex (VAC) for behaviorally relevant visual stimuli (Duncan, Humphreys and Ward 1997; Fuster 1990; Hopfinger, Buonocore and Mangun 2000; Kanwisher and Wojciulik 2000). Reciprocal suppression of activity in visual regions that encode non-relevant stimuli has also been reported (Duncan, Humphreys and Ward 1997; Kastner, De Weerd, Desimone et al. 1998; Kastner and Ungerleider 2001). In this biased competition model, suppression occurs due to competition of multiple stimuli for limited visual processing resources (Desimone and Duncan 1995).

### Enhancement and suppression: defining neural measures

Our recent experiments have focused on studying top-down enhancement and suppression of neural activity while a stimulus is being presented in a WM task. Experimental paradigms directed at understanding the neural mechanisms of WM maintenance are often delay tasks, designed to temporally isolate WM component processes. In a typical delayed recognition trial, the 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 whether the information was successfully retained. Thus, the cognitive stages are segregated in time and can be investigated in relative isolation during these distinct stages with microelectrodes in animals and event-related fMRI in human participants. We have modified the classic delayed-recognition task to study the processes of enhancement and suppression directly. We identify distinct measures of top-down enhancement and suppression by utilizing a paradigm we developed consisting of three tasks in which aspects of visual information are held constant while task-demands are manipulated (Figure 12.1) (Gazzaley, Cooney, McEvoy et al. 2005a). 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. For example, measures of neural activity above passive baseline reflect enhancement, and activity below baseline is suppression. Also in the memory tasks, after a 9 s 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 post-experiment 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 functional MRI (fMRI) and electroencephalography (ERP) on counterbalanced sessions to record correlates of neural activity while the participants 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 (Chawla, Lumer and Friston 1999; Logothetis, Pauls, Augath et al. 2001; Silva 1991), changes in BOLD signal can be localized to cortical regions separated by millimeters and ERP 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.

Our original research focus was to identify neural measures of both the enhancement and suppression of neural activity associated with task-relevant and task-irrelevant information, respectively. Inherent to theories of top-down modulation is the concept that neural activity is modulated relative to a level of activity generated when a stimulus is passively viewed and no goal-directed decisions are performed, i.e. its bottom-up, perceptual influence. Neural activity in
response to viewing a stimulus may be differentially enhanced or suppressed relative to this level of activity if it is respectively attended or ignored. Despite this logic, modulation relative to a stimulus-present, neutral baseline has rarely been evaluated and comparisons are usually made between attend and ignore tasks or relative to a resting baseline without visual stimulation (Eimer 2000; Holmes, Vuilleumier and Eimer 2003; O’Craven, Downing and Kanwisher 1999; Pinsk, Doniger and Kastner 2004; Rees, Frith and Lavie 1997; Vuilleumier, Armony, Driver et al. 2001; Wojciulik, Kanwisher and Driver 1998). Without establishing a perceptual baseline level of activity, it is not possible to interpret top-down influences as representing enhancement or suppression. While modulation both above and below a perceptual baseline has not yet been reported with neuroimaging data, the presence of enhancement and suppression has been suggested in EEG studies of spatial attention documenting a decreased amplitude of the P1 component for ignored locations and increased amplitude of the N1 component for attended locations, both relative to a baseline obtained with ‘neutral’ trials when attention was unfocused or broadly focused (Luck and Hillyard 1995; Luck et al. 1994). The passive viewing task utilized in our experiment established a perceptual, bottom-up baseline from which activity in the remember tasks could be compared.

We chose to focus our first study on activity measures of enhancement and suppression obtained from visual association cortex of young healthy participants. For fMRI, we used an independent functional localizer to identify both stimulus-selective face regions and scene regions in the fusiform gyrus and the parahippocampal/lingual gyrus, respectively. For the purpose of this chapter, 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 ERP, we utilized a face-selective event-related potential (ERP), the N170, a component localized to posterior occipital electrodes and reflecting visual association cortex activity with face specificity (Bentin, Allison, Puce et al. 1996). Our fMRI and EEG data revealed top-down modulation of both activity magnitude and processing speed occur above and below a perceptual baseline depending on task instruction (Figure 12.2). Modulation of the processing speed as reflected by a shift in the latency of the N170 was a novel finding that revealed another aspect of top-down modulation. It suggested that in addition to modifying activity magnitude, top-down influences can modulate the time-course of neural activity, as reflected by a shorter time to reach maximal synchronized neural activity (Silva 1991). It has been proposed that amplification of activity magnitude improves signal/noise ratio, allowing more information to be extracted from relevant stimuli (Hillyard, Vogel and Luck 1998). Likewise, faster processing speed reflects an augmentation in the efficiency of neural processing, further facilitating information extraction.

It is well documented that the nervous system utilizes interleaved inhibitory and excitatory mechanisms throughout the neuroaxis (e.g., spinal reflexes, cerebellar outputs and basal ganglia movement control networks). It is thus not surprising that top-down modulation would utilize both enhancement and suppression to control the impact of sensory information on neural activity, providing a powerful contrast for sculpting these neural processes (Knight, Staines, Swick et al. Chao 1999; Shimamura 1997). Thus, by generating contrast via enhancing and suppressing activity magnitude and processing speed, top-down signals bias the likelihood of successful representation of relevant information in a competitive system.

A unique aspect of this study was that the relevant and irrelevant stimuli were presented sequentially. Most selective attention studies that have assessed activity modulation have used tasks in which multiple stimuli were presented simultaneously (O’Craven, Downing and Kanwisher 1999; Vuilleumier, Armony, Driver et al. 2001; Wojciulik, Kanwisher and Driver 1998), and so modulation was considered to be driven by competition for limited perceptual processing resources. In contrast, our findings reveal that modulation of activity magnitude can occur based
on task-relevancy that directs differential attention to sequentially presented stimuli, without competition for perceptual processing resources. Thus, we inferred that modulation was needed to resolve competition for limited working memory resources. This finding supports a more general model of top-down modulation in which goal-directed decisions modulate activity levels to resolve competition for limitations in cognitive resources, whether perceptual or mnemonic (Ranganath, DeGutis and D’Esposito 2004).

Enhancement and suppression: dissociable processes?

Using the selective WM paradigm we developed, we are able to generate distinct measures of top-down enhancement and suppression by calculating the fMRI BOLD magnitude and ERP component amplitude or latency difference between the remember condition and passive view (enhancement), or between passive view and the ignore condition (suppression). An important question that emerged was whether or not these two processes are mechanistically dissociable? If they have independent control processes, either anatomically or neurochemically, then they might be differentially affected by aging or disease. Our first attempt at addressing this was to

![Figure 12.2](image-url)
study top-down modulation using this paradigm in a population of healthy older participants (Gazzaley, Cooney, Rissman et al. 2005b). In this population, we predicted that we would see a shift in the balance between enhancement and suppression. It is well-established that many aspects of cognition decline with normal aging (Craik and Salthouse 2000). However, behavioural evidence exploring the interaction between attention and WM in aging suggests that age-related WM impairments are associated with increased sensitivity to interference from task-irrelevant information (Hasher and Zacks 1988; May, Hasher and Kane 1999; West 1999). We hypothesized that the older individuals may have a selective deficit in their ability to suppress task-irrelevant information. Such a select deficit would provide evidence for dissociable mechanisms of enhancement and suppression.

In a recent publication, we compared the fMRI BOLD signal magnitude between the tasks within each group of younger (n = 17, 19–30 years of age) and older participants (n = 16, 60–77 years of age) (Figure 12.3). Direct comparisons of BOLD signal across age groups revealed a significantly greater signal magnitude within the scene-selective region in the older group than in the younger group in the Ignore scenes condition (p < 0.005), while no age-related differences existed between the Remember scenes (p = 0.37) or Passive view conditions (p = 0.96). These comparisons reveal the presence of a selective age-related deficit in the suppression of task-irrelevant information. To further compare across age groups, we calculated three 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

Figure 12.3 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 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. (2005b) Nat Neurosci, 8(10), 1298–1300.)
This analysis confirmed 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 ($p < 0.005$), as there was no significant difference in the enhancement subcomponent ($p = 0.27$).

Furthermore, we 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 post-experiment recognition test, revealing increased incidental long-term memory of distracting information and supporting our neural data that task-irrelevant scenes were not suppressed. This established 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. This finding, in addition to yielding important information about normal aging, revealed that enhancement and suppression, as defined by our measures, are dissociable processes.

To further explore the dissociation between the neural mechanisms of enhancement and suppression, we have begun experiments to manipulate the cognitive demands of the task and evaluate its effect on these measures. In one experiment, we are attempting to determine if having participants perform a nonverbal working memory task concurrently with the visual selective attention working memory task will differentially affect enhancement and suppression measures. At the beginning of each trial, participants were 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 (Rissman, Gazzaley and D’Esposito 2005). The fact that increased WM load in younger adults produced a selective suppression deficit similar to that seen in older adults suggests that age-related changes in top-down modulation may, in part, result from decreased WM resources with age.

These data and the findings on older participants converge to suggest that enhancement and suppression processes are dissociable. In these studies, only the measure of suppression was influenced by aging and increasing memory load, while the enhancement index was unaffected. This suggests that they are differentially regulated and thus may have different anatomical and neurotransmitter control systems.

### Where is the top?

Identification of distinct and dissociable measures of top-down enhancement and suppression in visual association cortex raises the important question of which brain regions drive top-down modulation? It has been suggested that the top-down modulation is not an intrinsic property of sensory cortices, but rather is achieved by intricate neural connections subserving dynamic interactions between brain regions, or neural networks. Tract-tracing studies in monkeys reveal an intricate anatomic network of reciprocal corticocortical connections between regions in the prefrontal cortex (PFC) and parietal cortex and the visual association cortex (Cavada and Goldman-Rakic 1989; Petrides and Pandya 1999, 2002; Ungerleider, Gaffan and Pelak 1989; Webster, Bachevalier and Ungerleider 1994). Several of these pathways have also been described in humans with post-mortem dissection (Heimer 1983) and more recently with in vivo diffusion tensor magnetic resonance imaging (Makris et al. 2004). These anatomically defined networks...
establish the structural basis by which the PFC may exert control over diverse cognitive processes, and there is also accumulating neurophysiological 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 (Corbetta 1998; D’Esposito et al. 1998; E. K. Miller, Li, and Desimone 1993; Moran and Desimone 1985; Ungerleider, Courtney and Haxby 1998). In addition, we observe increased BOLD signal in prefrontal and parietal regions in the memory tasks of our paradigm relative to the passive view task, suggesting a role of these regions as a ‘top’ in the visual association cortex activity modulation. It is important to note that the majority of these studies, including our own, reveal indirect evidence of functional interaction between these areas based on univariate statistics, which measure the activity in brain regions independently of other regions.

A noninvasive approach to evaluate interactions between regions with preserved structure and function is via multivariate analysis, a statistical method that used to generate maps of functional connectivity between brain regions during different cognitive processes (Buchel and Friston 2000; Friston, Phillips, Chawla et al. 2000; K. J. Friston, Frith, Liddle et al. 1993; Lin et al. 2003; McIntosh 1998; Penny, Stephan, Mechelli et al. 2004; Sun, Miller and D’Esposito 2004). Multivariate analyses generate functional and effective connectivity maps of interacting brain regions by measuring the activity relationship between anatomically connected regions and the cognitive processes being performed. We have recently developed a new multivariate method, designed specifically to characterize functional connectivity in an event-related fMRI dataset and measure interregional correlations during the individual stages of a multistage cognitive task (Rissman, Gazzaley and D’Esposito 2004). The method, beta series correlations, employs a standard general linear model (GLM) approach as do most univariate analyses for estimating stage-specific activity (Friston et al. 1995), but adapts the model such that distinct parameter estimates are computed for each trial and then used as the dependent data in a correlation analysis. Another important aspect of the technique is the use of a ‘seed’ region to explore the network correlated with a selected region and thus associated with a particular cognitive process. We have recently validated this method as a suitable measure of functional connectivity (Rissman, Gazzaley and D’Esposito 2004) and characterized the brain regions that revealed significant correlation with a visual association cortex seed during the maintenance period of a WM task (Gazzaley, Rissman and Desposito 2004). This maintenance network included the dorsolateral and ventrolateral PFC, premotor cortex, intraparietal sulcus, caudate nucleus, thalamus, hippocampus and occipitotemporal regions. These findings support the notion that the coordinated functional interaction between nodes of a widely distributed network underlies the active maintenance of a perceptual representation.

We are now in the process of performing a comparable functional connectivity analysis on the encoding phase of the selective working memory task we have described. Preliminary evidence has revealed regions of robust functional connectivity between the PFC and visual association cortex seeds during the encoding period, further supporting the role of the prefrontal cortex as a control region. However, there are only minimal differences between the connectivity patterns in the PFC associated with enhancement versus suppression. Using this dataset and the beta series correlation analysis, we have further revealed that functional connectivity between a visual association cortex seed and both the hippocampus and a region of the PFC, the inferior frontal gyrus, correlated with incidental long-term memory recognition when evaluated across subjects: thus establishing the utility of connectivity measures to predict cognitive performance (Siebert, Gazzaley, Rutman et al. 2005).

Although there is accumulating evidence that the PFC mediates its influence over diverse mental processes by modulating the magnitude of neural activity in distant brain regions via the
long-range projections, the majority of the evidence, including most multivariate analyses, are
correlational. These studies only support the engagement of PFC in these cognitive processes
and do not establish the casual relationship between PFC and control via top-down modulation.
An optimal experimental design to directly assess the mechanism of PFC control involves the dis-
ruption of PFC afferents and physiological recordings of distant brain regions while the subject is
engaged in a control task. There have been several studies that have implemented such a lesion-
physiology design on experimental animals and humans. These studies support the conclusion
that top-down modulation, utilizing both enhancement and suppression, is a mechanism of PFC
control over diverse cognitive processes.

Research on experimental animals provided the first direct electrophysiological evidence of a
PFC role in modulating activity in sensory cortices. It was observed that cooling the PFC in cats
results in increased amplitudes of evoked electrophysiological responses recorded from the
primary cortex for all sensory modalities (Skinner and Yingling 1977). Conversely, stimulation of
specific regions of the thalamus that surround the sensory relay thalamic nuclei (i.e. nucleus
reticularis thalami) results in modality specific suppression of activity in primary sensory
(Yingling and Skinner 1977). Thus, these findings suggest the presence of an inhibitory pathway
from PFC that regulates the flow of sensory information via thalamic relay nuclei. This
prefrontal-thalamic inhibitory system provides a mechanism for modality specific suppression of
irrelevant inputs at an early stage of sensory processing.

In nonhuman primates, PFC mediated top-down modulation during a WM task was studied
by coupling single-cell recordings and cortical cooling in monkeys (Fuster, Bauer and Jervey
1985). This experiment revealed that PFC cooling results in both augmentation and diminution
of spontaneous and task-specific activity in inferotemporal neurons during the encoding (stimulus-
present modulation) and delay period (stimulus-absent modulation) of a visual delayed-
response task, suggesting the presence of both enhancing and suppressive PFC influences.
Furthermore, cooling was accompanied by WM performance deficits, thus establishing a
link between PFC-mediated top-down modulation and cognition. These findings have been
complemented by the elegant callosal lesion-physiology study of Tomita et al. (1999), which
revealed that top-down enhancement signals from the PFC to inferior temporal cortex during
visual memory recall are mediated not by subcortical pathways, but front-temporal corticocortical
projections and that this modulatory influence is necessary for successful memory recall. This
supports the assertion that representations are stored in posterior sensory regions and top-down
signals from the PFC trigger the activation of these memory representations (Miyashita 2004).
Coupled with the results of lesion-behavior studies (Hasegawa, Fukushima, Ihara et al. 1998)
and functional neuroimaging studies (Lee et al. 2002; Ranganath, Johnson and D’Esposito 2003),
these results establish a role of PFC-mediated top-down modulation in long-term memory.
Recent lesion-physiology studies in rodents have also revealed the presence of modulatory
PFC influences on the activity of hippocampal place cells (Kyd and Bilkey 2003) and perirhinal
neurons during a spatial delayed-response task (Zironi, Iacovelli, Aicardi et al. 2001).

In humans, combined lesion-ERP studies have provided evidence of PFC-dependent top-down
enhancement of visual association cortex activity occurring in the first few hundred milliseconds
of the visual processing for selectively attended stimuli (Barcelo, Suwazono and Knight 2000).
Moreover, electrophysiological alterations accompanying PFC lesions were associated with
deficits in visual detection ability. Comparable findings of PFC-mediated ERP enhancement
and performance dependence have been obtained during a selective attention auditory task
(Knight, Hillyard, Woods et al. 1981). There is also evidence in humans that the PFC exhibits
suppressive control over distant cortical regions. For example, ERP studies in patients with focal
PFC damage have revealed that auditory (Knight, Scabini and Woods 1989) and somatosensory
(Yamaguchi and Knight 1990) evoked responses are enhanced, suggesting disinhibition of sensory flow to these regions. These suppressive influences have also been extended to emotionally salient stimuli, as was recently demonstrated by enhanced ERPs recorded in response to mildly aversive stimuli in patients with orbitofrontal lesions (Rule, Shimamura and Knight 2002). Furthermore, there is evidence that PFC-mediated suppression extends to selectively ignored auditory stimuli (Chao and Knight 1998; Knight et al. 1981).

We are currently evaluating the causal role of the PFC in top-down modulation of activity in the visual association cortex by using the same selective working memory visual task in patients that have had a stroke to different regions of their frontal cortex. Although still preliminary, in comparison to control subjects, patients with damage to the left or right middle frontal gyrus, or to projections connecting the MFG with posterior regions, exhibit impaired top-down modulation of visual processing (Cooney, Gazzaley and D’Esposito 2005). In contrast, a patient with intact MFG exhibited robust top-down modulation despite damage to left insula, inferior frontal gyrus and premotor areas. These data suggest a direct role of the middle frontal gyrus in the visual cortex activity modulation we have recently characterized. Due to the limitations of this lesion technique, in terms of inability to control the anatomical localization of the lesions and the potential for plasticity in response to a chronic lesion, we have now completed a pilot study to evaluate the potential of using transcranial magnetic stimulation (TMS) to study the PFC role in top-down modulation. The goal of this experiment was to utilize repetitive TMS (rTMS) to transiently disrupt neural activity in prefrontal areas identified with fMRI in young adults performing our cognitive task, and then to evaluate cognitive performance and neural electrical measures in distant visual association cortex with EEG during the period of disruption, thus allowing the direct evaluation of prefrontal pathways in top-down modulation and cognition. The pilot experiment performed on four subjects revealed that transient disruption of fMRI identified regions in the middle frontal gyrus resulted in an alteration of distant neural measures of top-down modulation (amplitude increase of the p300 in the remember condition), as well as a significant reduction in speed of the response time on the working memory task. A complete study is now underway to directly evaluate the causal role of the PFC in goal-directed modulation of visual cortex activity (Miller, Gazzaley, McEvoy et al. 2005).

Conclusions

In summary, it is likely that such parallel enhancement/suppression control entails large-scale neural networks (Knight 1997), including an inhibitory PFC-thalamic gating network and a direct excitatory PFC projection to specific cortical regions. Alternatively, suppression might entail long-range excitatory prefrontal-cortical projections that then activate local inhibitory neurons (Carr and Sesack 1998), or perhaps involves the withdrawal of excitatory influences by the reallocation of resources. For a review of computational models of inhibitory control, see Houghton and Tipper (1996). Clearly more empirical research is needed to further our understanding of the mechanisms of top-down enhancement and suppression, as well as place these modulatory control mechanisms within the framework of PFC functional architecture and associated neural networks.

References


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