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Effects of Cholinergic Enhancement on Visual Stimulation, Spatial Attention, and Spatial Working Memory

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Summary

We compared behavioral and neural effects of cholinergic enhancement between spatial attention, spatial working memory (WM), and visual control tasks, using fMRI and the anticholinesterase physostigmine. Physostigmine speeded responses nonselectively but increased accuracy selectively for attention. Physostigmine also decreased activations to visual stimulation across all tasks within primary visual cortex, increased extrastriate occipital cortex activation selectively during maintained attention and WM encoding, and decreased parietal activation selectively during maintained attention. Finally, lateralization of occipital activation as a function of the visual hemifield toward which attention or memory was directed was decreased under physostigmine. In the case of attention, this effect correlated strongly with a decrease in a behavioral measure of selective spatial processing. Our results suggest that, while cholinergic enhancement facilitates visual attention by increasing activity in extrastriate cortex generally, it accomplishes this in a manner that reduces expectation-driven selective biasing of extrastriate cortex.

Introduction

The integrity of cholinergic afferents to cerebral cortex is necessary for normal stimulus discrimination, selection, and vigilance (Robbins, 1998). During periods of high attentional demand, acetylcholine is released diffusely throughout neocortex (Phillis and Chong, 1965) to modulate processing within both sensory and prefrontal-parietal cortices (Sarter and Bruno, 1997). Thus, cholinergic input to visual cortex has been shown to sharpen stimulus representations through a combination of signal amplification and noise suppression (e.g., Sato et al., 1987; Murphy and Sillito, 1991). Additionally, cholinergic afferents to prefrontal and parietal areas have been shown to be critical for spatial orientation (e.g., Davidson and Marrocco, 2000; Chiba et al., 1999) and sustained attention (e.g., McGaughy and Sarter, 1998), especially in the presence of distractors (Gill et al., 2000).

The above effects have been characterised in terms of cholinergic modulation of bottom-up and top-down processes, respectively (Sarter et al., 2001). An issue that remains unaddressed is the manner in which cholinergic modulation of these two types of processes combine. There remains uncertainty as to whether top-down modulation of sensory cortices is enhanced with cholinergic stimulation (as might be expected given the facilitatory effects of acetylcholine on attention generally [Sarter et al., 2001]) or whether it is suppressed, so as to favor bottom-up activity (suggested by cell layer recording studies in sensory cortices [Hasselmo and Cekic, 1996; Kimura et al., 1999] and computer modeling of cholinergic effects [Yu and Dayan, 2002]).

One method to investigate this is with functional imaging, which has demonstrated consistent neural correlates of both bottom-up and top-down activity within human visual cortex (e.g., Hopfinger et al., 2000). Although previous studies have reported modulation of visual cortical activity as a result of cholinergic drug administration, none have compared the effects of cholinergic modulation on occipital activation between conditions of sensory stimulation and attention while keeping stimulus constant. The anticholinesterase physostigmine has been reported to increase extrastriate cortex activity selectively during the encoding phase of a face working memory (WM) task (Furey et al., 2000a) in which stimulus properties differed between phases. However, a more recent fMRI study (Lawrence et al., 2002) observed that nicotine enhanced occipital activity similarly during two levels of difficulty of a rapid visual information-processing task. Consequently, enhancement of occipital cortices may reflect a direct effect of nicotine on visual-evoked responses. We have also shown that physostigmine modulates neural correlates of attention in visual cortex differently between face and nonface stimuli (Bentley et al., 2003), which may reflect a bias of acetylcholine toward processing stimuli of high intrinsic valence (e.g., Acquas et al., 1996).

A related question regarding cholinergic function relates to its role in memory processes. Behavioral dissociations between attention and WM following cholinergic manipulation (in humans, e.g., Sahakian et al., 1993; Park et al., 2000; and animals, e.g., Voytko et al., 1994) support hypotheses that acetylcholine may mediate memory and attentional processes independently (e.g., Everitt and Robbins, 1997; Ernst et al., 2001; Jones et al., 1992). However, it is likely that memory performance is at least partially cholinergically modulated by virtue of cholinergic effects on attentional aspects of such tasks (see Sarter et al., 2003). Hence, selective effects of physostigmine on WM encoding (Furey et al., 2000a) would be expected to reflect the actions of acetylcholine on attention more generally, and where neural processes are shared between attention and WM (e.g., Awh et al., 1999; LaBar et al., 1999), we would expect these to be modulated by cholinergic manipulation in a similar fashion.

In the present study, we aimed to distinguish the effects of physostigmine on brain activation attributable

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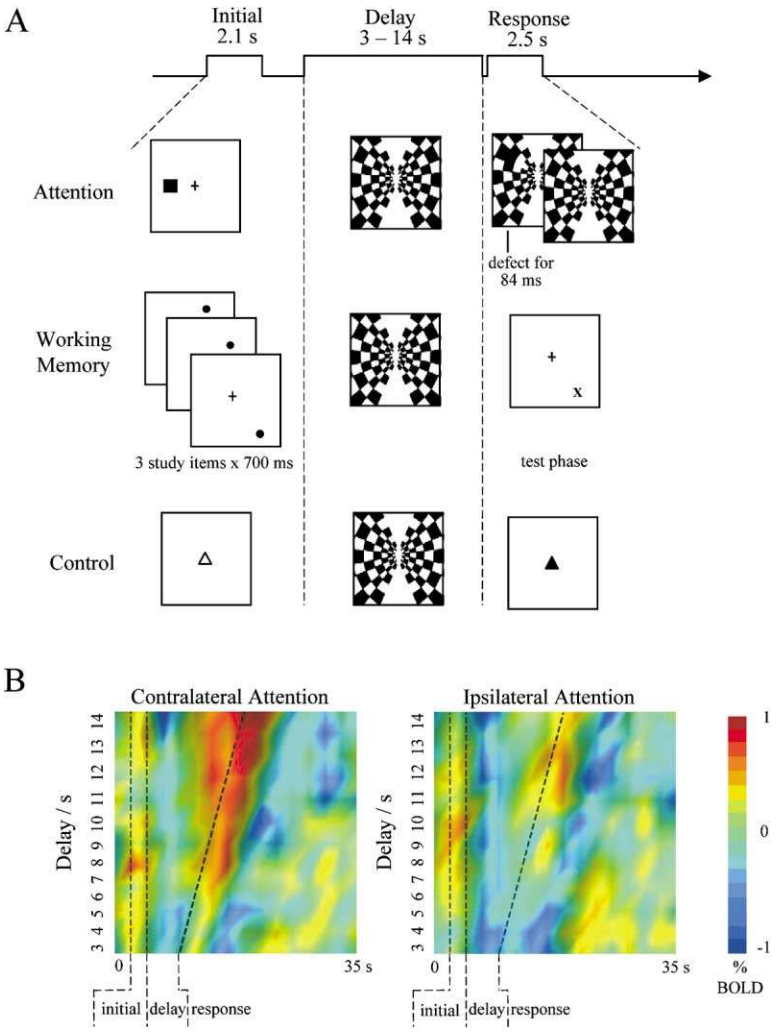

Figure 1. Task Design and Peristimulus-Evoked BOLD Responses

(A) Schematic time course of three tasks. Each task type consisted of task-specific stimuli at the beginning and end of every trial and a variable intervening delay period (3–14 s of alternating checkerboard) that was identical in stimulus across tasks and in which no motor response occurred. Transients at trial start and end were modeled separately from delay period for each task type, with each task phase being convolved with its own canonical hemodynamic response function.

(B) Adjusted data from occipital cortex (averaged over bilateral peaks plotted in Figure 5, under placebo) showing changes in BOLD response across attention trials for varying delay periods, temporally realigned to each trial onset. Trials were divided according to whether the initial cue was in the visual hemifield contralateral or ipsilateral to the occipital side from which the data was acquired. Note the increasing amplitude and duration of BOLD activity with delay duration reflects delay period activity (higher for attention to contralateral than ipsilateral space), unlike responses to cue or target that are delay independent. Effects reported in this paper reflect the degree to which data fits a standardized delay-*dependent* regressor for each trial type, similar to the actual profile of activity observed here for contralateral attention (see Experimental Procedures).

to the *main effect* of attention from that due to stimulus alone. An additional and orthogonal question was to determine whether the *differential* occipital activation engendered by selective spatial attention (e.g., Martinez et al., 1999) and spatial working memory (Awh et al., 1999) toward either hemifield (versus the opposite hemifield) is itself modulated by physostigmine. We expected that the degree of differential response between right and left occipital cortices would either increase or decrease, depending on whether cholinergic enhancement positively or negatively modulated top-down spatial biasing of sensory cortices, respectively. Finally, we examined for brain regions that show either a dissociation or similarity in response to physostigmine between attention and working memory, including separate analyses of WM encoding and delay periods. Since our experimental design aimed to control for sensorimotor effects between conditions, we limited our analysis of cholinergic modulation of attention to the period of maintained attention between cue and target (which approximates to the construct of "sustained attention"; see Sarter et al., 2001).

Results

Behavioral Data

RT and accuracy measures for each subject were submitted to separate repeated-measures ANOVAs with factors of treatment (drug or placebo) and condition (attention, WM, and control; Figure 2). RT: subjects were faster under physostigmine relative to placebo over all conditions [$F(1,17) = 4.6$; $p < 0.05$; RTs comparing drug to placebo for attention, WM, and control were 428 versus 443 ms; 1014 versus 1047 ms, and 435 versus 457, respectively], but there was no treatment $\times$ condition interaction. A main effect of condition was also apparent [$F(1,17) = 107$; $p < 0.001$], which could be predominantly accounted for by WM being slower than attention and control ($p < 0.01$). Accuracy: there was no main effect of treatment for accuracy. However, a treatment $\times$ condition interaction was evident [$F(1,17) = 5.7$; $p < 0.05$], which reflected physostigmine improving accuracy in attention (86% versus 79% for valid trials; $p < 0.05$) but not in WM (86% versus 87%) or control (98% versus 98%). An improvement in attention accuracy by drug

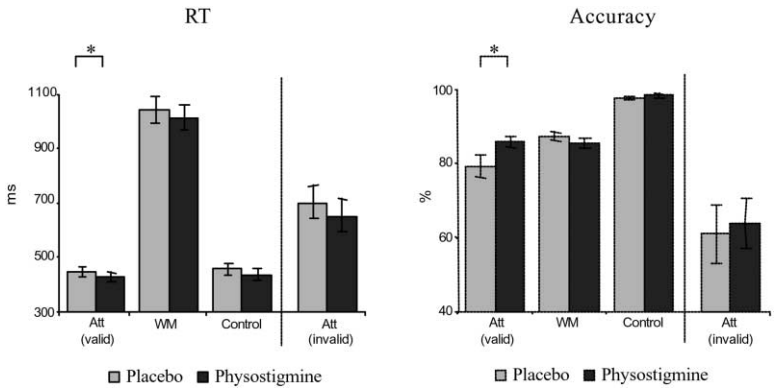

Figure 2. Behavioral Results

Performance compared across conditions (attention, working memory, and control; valid and invalid cue trials are shown separately) and treatments (placebo and physostigmine). For RTs, a main effect of group existed, suggesting faster responses under physostigmine (individual paired t tests for each task revealed a significant effect only for attention). For accuracy, subjects performed better under physostigmine during attention but not working memory or control (at ceiling), as suggested by a treatment × condition interaction. *$p < 0.05$.

was also apparent if invalid trials were included or if no upper time limit for responses was set. A main effect of condition was apparent [$F(1,17) = 48$; $p < 0.001$], with scores in control being higher than attention and WM ($p < 0.01$) and WM being higher than attention ($p < 0.05$; but see interaction with treatment above).

Within the attention condition, a selective spatial processing bias toward cued versus uncued hemifields was indicated by a faster performance (RT = 435 versus 678 s; $p < 0.01$) and greater accuracy (83.3 versus 62.6; $p < 0.01$) during validly versus invalidly cued trials. There was no treatment × validity interaction. Finally, we found

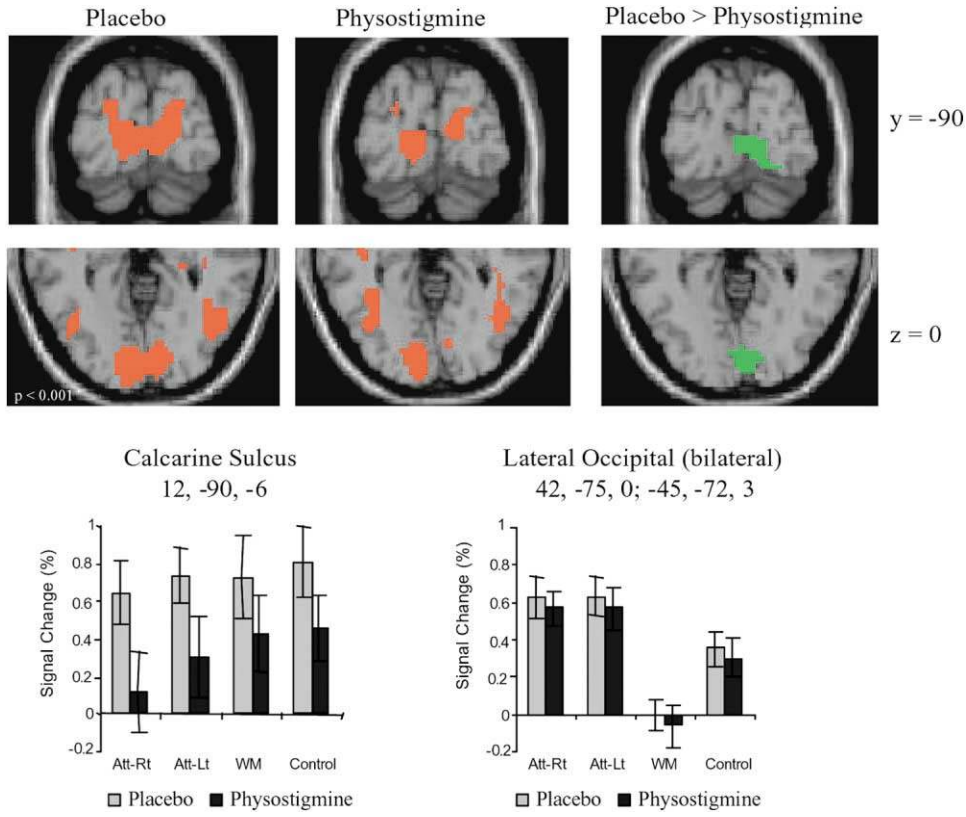

Figure 3. Effect of Physostigmine on Visual Stimulation

Regions within occipital cortex showing main effect of visual stimulation (i.e., delay period activity across all tasks) versus baseline, under placebo, physostigmine, and when comparing treatments for this effect (no occipital areas were greater under physostigmine than placebo for the main effect of visual stimulation). Graphs plot percent signal change from baseline for the three conditions (separating attend right and attend left conditions) in regions showing a main effect of visual stimulation under placebo. Primary visual cortex (calcarine sulcus) showed greater stimulus-evoked activity under placebo than physostigmine, which did not differ significantly across conditions. This effect was unlikely to be due to a general vascular effect of drug, as it was not seen in either lateral occipital cortex that also showed main effects of visual stimulation under placebo (these regions can also be seen to show an effect of condition due to failure of activation during WM but not attention or control).

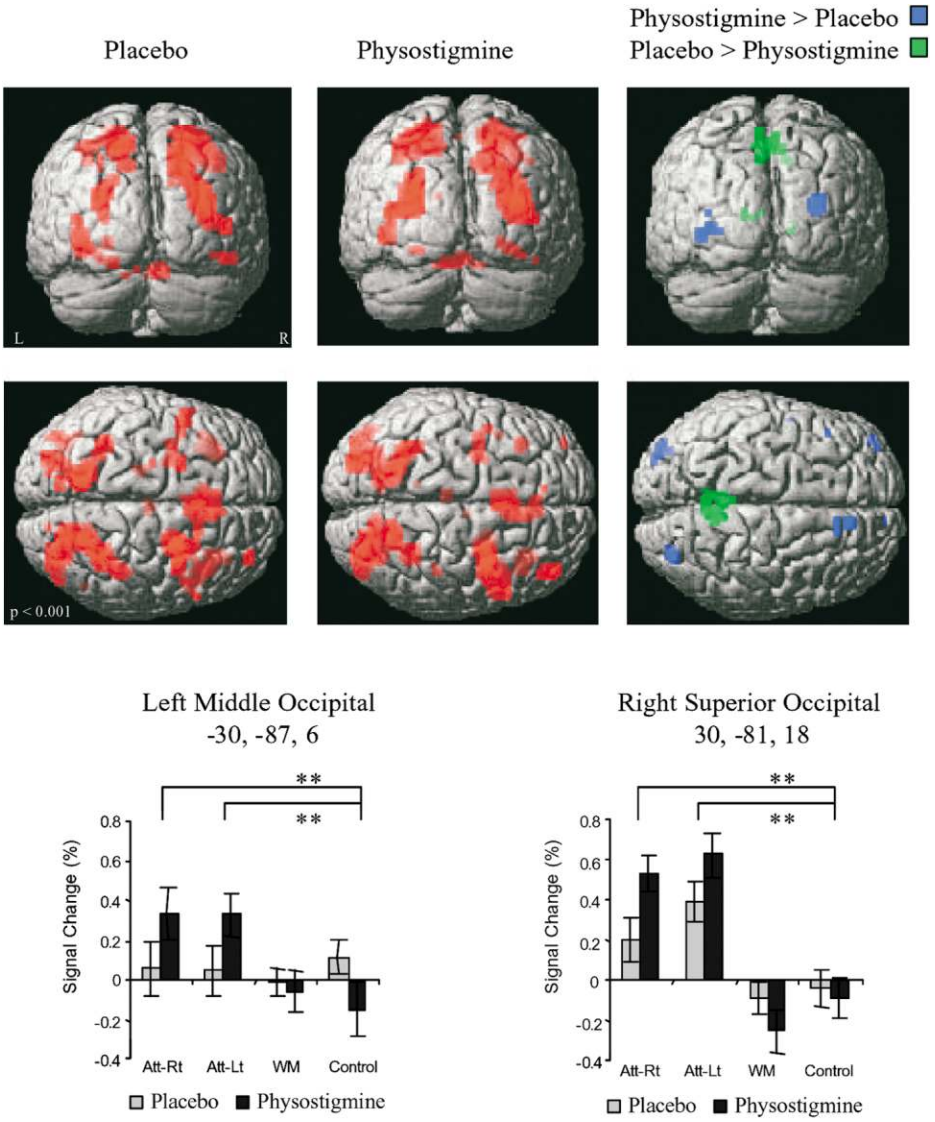

Figure 4. Effects of Physostigmine on Spatial Attention versus Control

Surface rendering of regions showing activity during delay periods of attention versus control tasks, under placebo, physostigmine, and when comparing the two treatments for this effect. Graphs plot percent signal change from baseline for the three conditions (separating attend right and attend left conditions) in regions from right and left occipital cortices showing enhancement of the attention versus control effect under physostigmine. Both of these regions showed an enhancement of attention relative to control activity on both attend right and attend left trials (**$p \leq 0.001$, uncorrected). The superior-medial parietal region showing less activation under physostigmine for the same contrast is also shown in yellow in Figure 6A.

no difference in the false alarm rate between treatments (overall mean = 4.6%; 1.1%, and 1.6%, for attention, WM, and control, respectively).

fMRI Data: Effects of Physostigmine on Visual Stimulation

We first examined for visual regions showing stimulus-evoked activation to the alternating checkerboard across all three conditions (attention, working memory, and control delay periods) versus baseline. Under both placebo and physostigmine, robust stimulus-evoked activations were evident in primary visual and lateral occipital cortices ($p < 0.05$, whole-brain corrected). A treatment effect was evident in primary visual cortex, with physostigmine reducing stimulus-evoked activation compared to placebo (12, −90, −6; $Z = 4.01$; $p < 0.001$, uncorrected; i.e., main effect of drug, with no treatment × condition interaction; Figure 3, graph 1). Lateral occipital cortices did not show a treatment effect (Figure 3, graph 2; treatment × region interaction comparing primary visual and lateral occipital regions was $p < 0.005$), suggesting that physostigmine did not simply change hemodynamic responsiveness across occipital cortex.

Table 1. Regions Showing Effect of Attention versus Control, under Placebo, and Interaction of This with Physostigmine

Brain Region	Peak Coordinates			Z Score
Placebo: attention delay > control				
R superior occipital	30	−78	18	5.29
L superior occipital	−24	−75	30	4.10
L fusiform gyrus	−39	−66	−6	4.20
R superior parietal	30	−51	57	4.48
L superior parietal	−15	−66	54	5.60
L inferior prefrontal	−36	21	−3	5.10
	−48	6	33	4.39
R inferior prefrontal	30	27	−12	4.30
Medial prefrontal	0	15	51	4.50
R dorsolateral prefrontal	24	0	57	4.49
L pulvinar	−6	−21	0	4.42
Drug > placebo: attention delay > control				
R superior occipital	30	−81	18	4.84*
L middle occipital	−36	−87	0	3.57*
L anterior prefrontal	−36	54	−6	3.81
R superior prefrontal	18	3	−9	3.69
Placebo > drug: attention delay > control				
R supero-medial parietal	6	−54	57	3.95*

Regions showing main effect of spatial attention under placebo are restricted to those in which clusters are significant at $p < 0.05$ (whole-brain corrected; SPM thresholded at $p < 0.001$, uncorrected). Treatment × condition interactions are thresholded at $p < 0.001$, uncorrected; *$p < 0.05$, corrected for whole-brain, or 12 mm radius spheres centred on MNI coordinates derived from appropriate contrast in Hopfinger et al., 2000. Simple effects of attention > control for strongest treatment level are also significant at $p < 0.001$, except L anterior prefrontal ($p < 0.01$) and R supero-medial parietal ($p < 0.005$).

fMRI Data: Effects of Physostigmine on Spatial Attention

Spatial Attention versus Control

Under placebo, spatial attention versus control activated prefrontal, superior parietal, and superior occipital cortices (Table 1 and Figure 4; note that the contrast is limited to delay periods of both conditions, in which stimulus was identical and no motor response occurred). The direct comparison of this effect between physostigmine and placebo revealed that these regions were differentially modulated by cholinergic enhancement. Specifically, extrastriate occipital and prefrontal cortices showed enhanced differential activity (blue in Figure 4), while superior-medial parietal cortex (green in Figure 4; yellow in Figure 6) showed reduced differential activity, during attention relative to control, under physostigmine versus placebo. The drug-induced increases in occipital activity with attention, relative to control, were also significant ($p < 0.001$) when analyzing attend-right and attend-left trials separately (i.e., contralateral and ipsilateral to cued direction; ** in Figure 4).

Right versus Left—Spatial Attention

We next addressed the orthogonal question of whether physostigmine influenced the differential activation of right versus left occipital cortices (and vice versa) as a function of attended location. Under placebo, being cued to either hemifield (versus the opposite hemifield) activated contralateral occipital cortex during the subsequent delay period in which a uniform stimulus was presented (Table 2 and Figure 5A; Figure 1B demonstrates how this effect reflects activity of the variable-length *delay period* rather than of the fixed-length initial cue). Physostigmine was found to reduce the effect of selective spatial attention on differential occipital activation in both right and left occipital cortices. Post hoc simple-effect analyses at the peaks of this treatment × laterality interaction revealed that drug enhanced activity (versus baseline, or control) on each occipital side during ipsilateral cue ($p < 0.05$; * in Figure 5A) but not contralateral cue (not significant) trials.

Hence, during both attend-right and attend-left trials, physostigmine enhanced the degree of activation (relative to control) in both ipsilateral and contralateral extrastriate occipital cortices, consistent with a drug-induced enhancement of accuracy across both valid and invalid trials. However, physostigmine was also found to increase activation in (adjacent) extrastriate cortex that was greater on the side ipsilateral than contralateral to the cued hemifield, resulting in a net *reduction* in lateralization of occipital activity.

We next determined whether the physostigmine-induced decrease in occipital lateralization bias with selective spatial attention was associated with a reduction in a behavioral measure of selective spatial processing. Taking each subject's difference in accuracy between valid and invalid cued trials as an invalidity effect, we found a highly significant correlation between drug-induced decrease of this behavioral measure and attenuation in occipital activity lateralization reported above ($r = 0.70$; $p = 0.001$; Figure 5B; effect averaged over bilateral occipital peaks of treatment × laterality interaction). In other words, subjects showing greater activation on the occipital side ipsilateral (versus contralateral) to that cued, under drug, were more sensitive at detecting invalidly (relative to validly) cued targets, under drug. Furthermore, those occipital regions manifesting a physostigmine-induced enhancement specifically during ipsilateral attention (versus control) showed a correlation of this effect with drug-induced improvement in accuracy of invalid trials ($r = 0.51$, $p < 0.05$; Figure 5C;

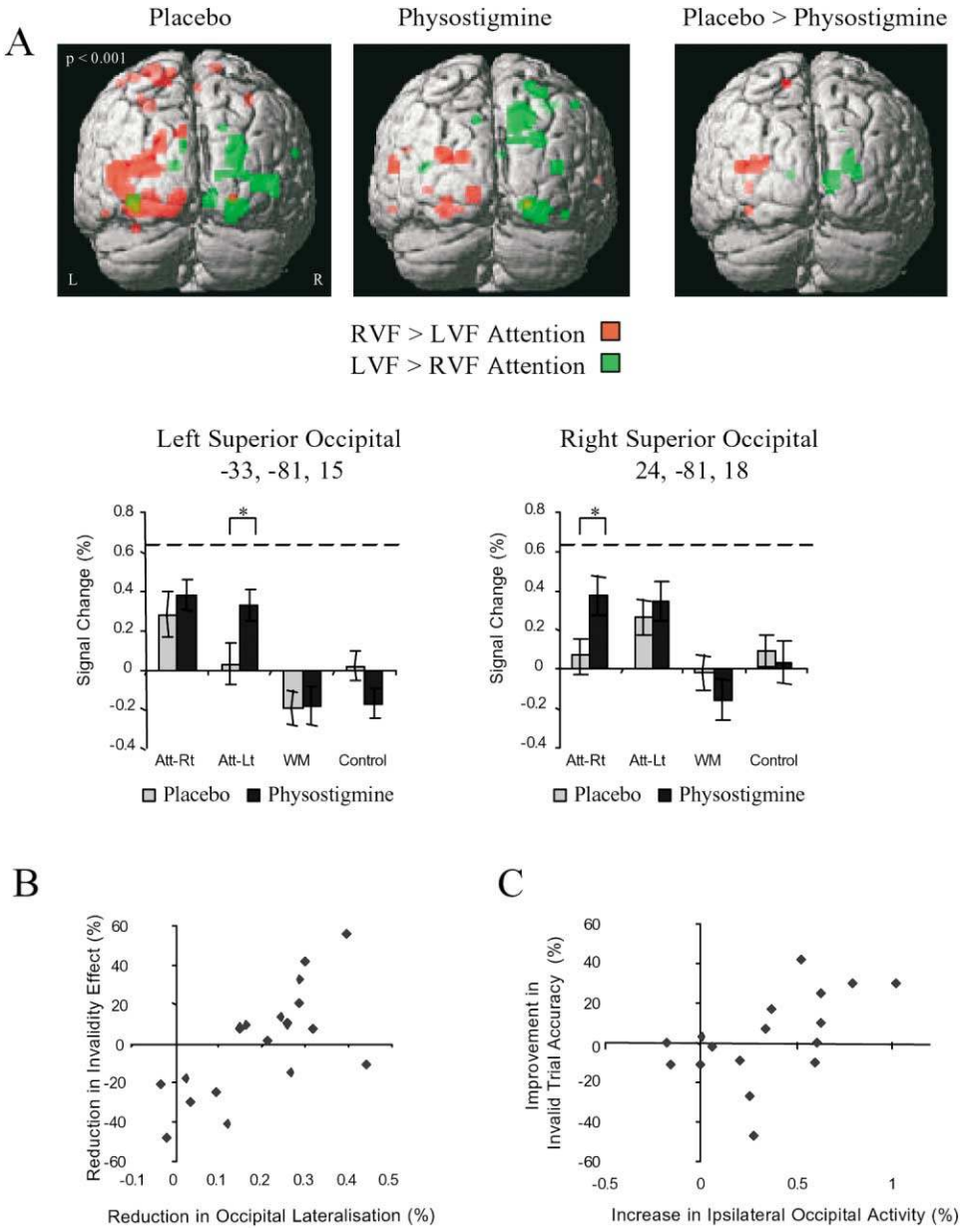

Figure 5. Effects of Physostigmine on Right versus Left Spatial Attention and Vice Versa

(A) Surface rendering of visual regions showing activity during delay periods of attend-right versus attend-left and vice versa for placebo, physostigmine, and the difference between treatments for these effects. Graphs plot percent signal change from baseline for the three conditions (separating attend-right and attend-left conditions) in regions from right and left occipital cortices showing reduced differential activity to attend-left versus right (and vice versa) under physostigmine relative to placebo. The physostigmine-induced reductions in differential activity occurred as a result of physostigmine increasing activity during ipsilateral attended trials (*$p < 0.05$) rather than due to drug-induced effects during contralateral attended trials (not significant). Dashed line indicates peak activity observed in right superior occipital region from Figure 4 (which was significantly greater than the peak activity depicted here). RVF, right visual field; LVF, left visual field.

(B) Scatter plot illustrates relationship between physostigmine-induced reduction in occipital lateralization and a behavioral measure of physostigmine-induced reduction in stimulus selectivity. Values on x axis calculated as Placebo[contralateral − ipsilateral activity] − Physostigmine[contralateral − ipsilateral activity], averaged over both occipital peaks showing treatment × laterality interaction. Values on y axis calculated as Placebo − Physostigmine Invalidity Effect, where Invalidity Effect = valid trial − invalid trial accuracy.

(C) Scatter plot illustrates relationship between physostigmine-induced enhancement of delay period activity in occipital cortex ipsilateral to cue location and accuracy on invalid trials. Values on x axis calculated as Placebo[ipsilateral − control activity] − Physostigmine[ipsilateral − control activity], averaged over both occipital peaks showing equivalent treatment × condition interaction.

effect averaged over bilateral occipital peaks showing treatment × task interaction: −33, −87, 0 and 30, −81, 18). These BOLD-behavioral correlations, together with the fact that the peak signal estimates of both superior occipital regions in Figure 5A were less ($p < 0.05$) than those observed elsewhere in superior occipital cortex

Table 2. Regions Showing Effect of Lateralized Attention, under Placebo, and Interaction of This with Physostigmine

Brain Region	Peak Coordinates			Z Score
Placebo: RVF > LVF attention				
L middle occipital gyrus	−42	−78	12	4.14
Placebo: LVF > RVF attention				
R middle occipital gyrus	45	−75	3	3.72
R fusiform gyrus	24	−69	−12	3.89
R lingual gyrus	9	−81	−9	3.53
L fusiform gyrus	−36	−93	−9	3.91
Placebo > drug: RVF > LVF attention				
L middle occipital gyrus	−33	−81	15	3.83
Placebo > drug: LVF > RVF attention				
R middle occipital gyrus	24	−81	18	3.53

RVF, right visual field; LVF, left visual field. Contrasts are thresholded at $p < 0.001$, uncorrected. All regions are significant at $p < 0.05$, corrected for 12 mm radius spheres centered on MNI coordinates derived from similar contrasts in Martinez et al., 1999 (except for L lingual gyrus). Simple effects of attention laterality for strongest treatment level are also significant at $p < 0.001$ at all coordinates.

(e.g., Figure 4), argues against the possibility that a ceiling in the hemodynamic response could explain the treatment × laterality interactions.

fMRI Data: Effects of Physostigmine on Spatial Working Memory

Spatial Working Memory versus Control

The effect of working memory versus control (delay-periods), under placebo, engendered activation in parietal and prefrontal cortices (Table 3). A similar network was also activated by attention versus control (delay-periods), under placebo, as shown by a conjunction analysis over the two tasks (i.e., regions significantly active in both attention and WM: red in Figure 6A). However, whereas superior-medial parietal cortex had shown an attenuated differential response to attention versus control under physostigmine versus placebo (yellow in Figure 6A), there was no drug-induced modulation of this area with WM versus control (treatment x condition interaction comparing attention and WM just

Table 3. Regions Showing Effect of Working Memory versus Control, under Placebo, and Interaction of This with Physostigmine and Showing the Effects of Both Lateralized Attention and Lateralized Working Memory, under Placebo, and Interaction of These with Physostigmine

Brain Region	Peak Coordinates			Z Score
A.				
Placebo: spatial WM[1] > control				
R superior parietal	6	−60	57	4.28*
L superior parietal	−24	−57	66	3.43
R dorsolateral prefrontal	27	3	60	4.16*
L inferior prefrontal	−33	18	3	3.38
R inferior prefrontal	48	21	−6	3.35
Drug > placebo: spatial WM > control				
No areas reached significance				
Placebo > drug: spatial WM > control				
L inferior prefrontal	−33	18	0	3.13
B.				
Placebo: RVF > LVF (attention & WM)[2]				
L superior occipital gyrus	−18	−87	27	5.46*
L inferior temporal gyrus	−42	−63	0	5.05*
L fusiform gyrus	−15	−84	−15	4.88*
L occipital pole	−12	−96	−6	3.43
Placebo: LVF > RVF (attention & WM)				
R occipital pole	12	−102	−3	4.37*
R inferior temporal gyrus	45	−66	−3	3.85
Placebo > drug: RVF > LVF (attention & WM)				
L middle occipital gyrus	−39	−78	12	4.97*
L fusiform gyrus	−33	−72	−12	4.33*
L superior occipital gyrus	−18	−87	24	4.02
Placebo > drug: LVF > RVF (attention & WM)				
R occipital pole	12	−102	−3	3.63*
R inferior occipital gyrus	36	−87	−3	3.11

Contrasts are thresholded at $p < 0.001$, uncorrected; *$p < 0.05$, corrected for whole-brain or for 12 mm spheres centred on MNI coordinates derived from similar contrasts in Rowe and Passingham, 2001 (working memory) and Martinez et al., 1999 (attention laterality). Simple effects of laterality for attention and WM under the strongest treatment level were significant at $p < 0.001$, uncorrected, at all coordinates.

[1] Effects presented in this table are restricted to *delay* periods of each task; see text for WM *encode* phase.

[2] This contrast represents the conjunction of (RVF > LVF attention) and (RVF > LVF WM).

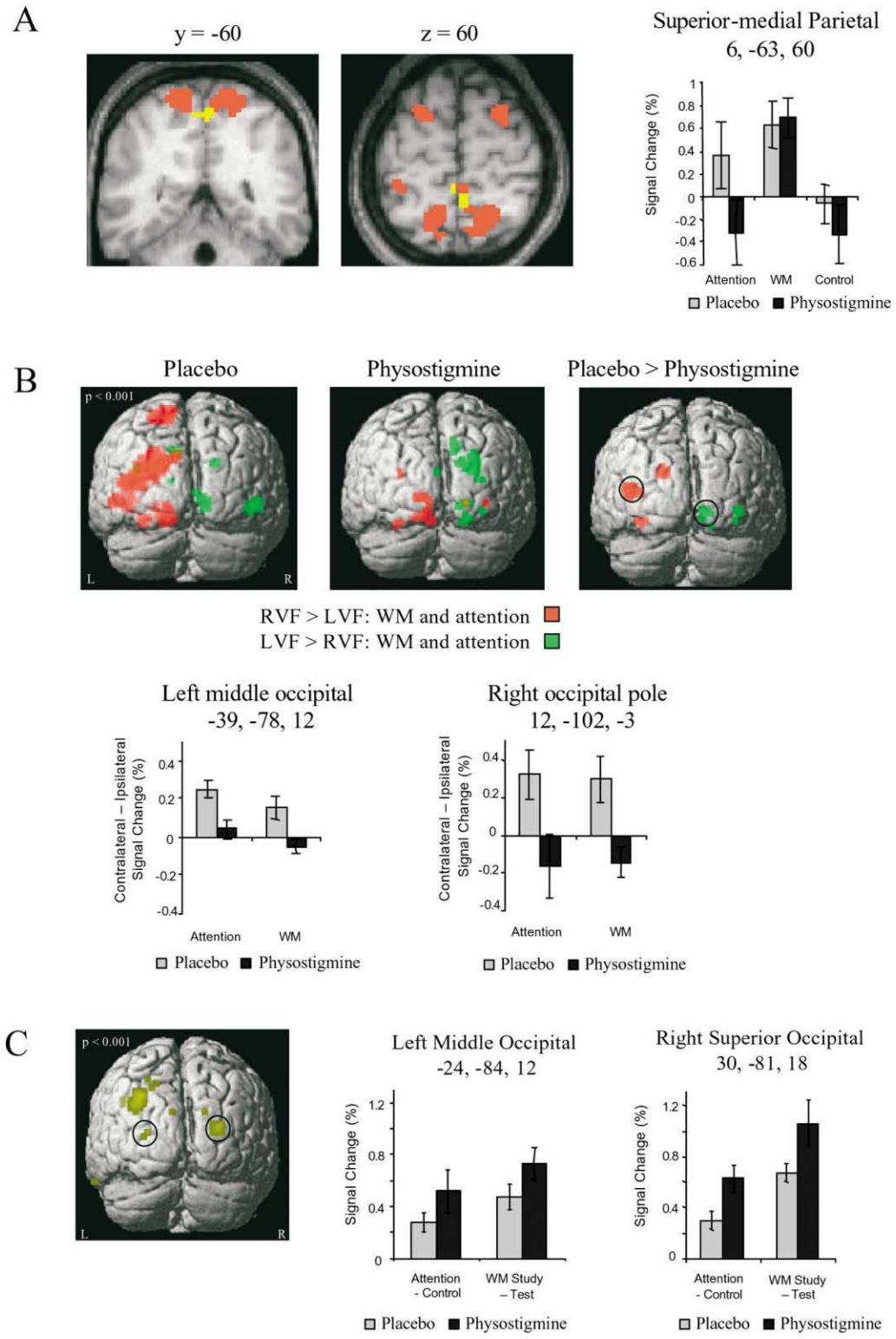

Figure 6. Dissociation and Commonalities of Physostigmine Effects on Spatial Attention and WM

(A) Regions within superior parietal and prefrontal cortices showing increased activity to the conjunction of attention and working memory, relative to control, under placebo (red). Superimposed is that parietal region showing greater differential activity to attention versus control, under placebo relative to physostigmine (yellow). This region was not modulated by physostigmine during WM in spite of showing an even greater effect of WM relative to control under placebo. Graph plots percent signal change from baseline for the three conditions in superior-medial parietal region showing a treatment × condition (attention or WM) interaction ($p < 0.005$). Values have been mean corrected with respect to occipital regions (across groups) to facilitate interregional comparison.

(B) Surface rendering of visual regions showing activity during delay periods of both WM-right versus left (i.e., whether study items were

fell short of conventional significance: 6, −63, 60; $Z = 2.77$; $p < 0.005$, uncorrected). Additionally, those occipital regions showing physostigmine-induced enhancement during attention versus control (Figure 4) showed no drug-modulation during WM-delay (treatment x condition interactions comparing attention and WM peaked at 33, −84, 18 and −27, −84, 21; $Z \geq 3.33$; $p < 0.001$, uncorrected). The only area showing an effect of drug on WM-delay (versus control) was in left inferior prefrontal cortex that showed less differential activation under physostigmine (a treatment x condition interaction comparing attention and WM also occurred in this region: physostigmine increased responses to attention versus WM: −39, 21, 3; $Z = 3.49$; $p < 0.001$, uncorrected).

Right versus Left—Spatial Working Memory

Subjects demonstrated selective occipitotemporal activation both on the side contralateral to that in which study items had been presented during the WM task and contralateral to the side that had been cued during the attention task, as revealed by a conjunction analysis over the delay periods of both tasks under placebo (Figure 6B, left, and Table 3). We hypothesized that if spatial attention and spatial WM employed a common occipital mechanism (see Awh and Jonides, 2001), then any cholinergic modulation of differential occipital activation observed with the contrast of attended location would also be found with the contrast of WM location. A between-treatment comparison of regions showing differential activation to laterality of both attention and WM (i.e., right versus left and vice versa, for both types of task) revealed that physostigmine reduced the degree of selective contralateral occipital activation for both tasks, in right and left hemispheres (Figure 6B, right, and Table 3; neither area showed a treatment × condition interaction).

Encoding

A previous WM study (Furey et al., 2000a) found that physostigmine enhanced extrastriate occipital activity selectively with face encoding (i.e., study versus test phases), which was interpreted as an effect of cholinergic enhancement on attention. We were able to test for this possibility in our experiment by examining for regions that showed drug-induced enhancement during both WM study (versus WM test) and attention delay (versus control delay), using a conjunction analysis over both types of effect. This revealed that bilateral occipital (30, −81, 18 and −24, −84, 12, $Z \geq 3.45$) and superior parietal (27, −63, 33, $Z = 4.01$; $p < 0.001$, uncorrected, for all) cortices showed enhanced activity under physostigmine selectively during both WM encoding and attention (Figure 6C). No visual regions showed the opposite contrast (i.e., reduction of both contrasts by drug).

Subjective, Physiological, and Eye Position Data

Subjects felt less alert after physostigmine relative to placebo, comparing subjective rating scores (Bond and Lader, 1974) between 0 and 40 min postinfusion (68% versus 75% alert, respectively; $p < 0.01$). This replicates an effect observed in a separate study employing an identical physostigmine protocol (Bentley et al., 2003). Subjects were also more likely to develop dry mouth ($n = 8$), dizziness ($n = 7$), and nausea ($n = 6$; all $p < 0.05$; mean intensity out of 6 = 1, 0.6, 0.4, respectively) under drug. There were no significant effects of drug on cardiovascular measures. Mean saccade frequency was 8% in attention, 3% in working memory, and <1% in control delay periods; median eye position was <0.5° from fixation in all sessions. There were no treatment effects for either eye position measure.

Discussion

The present study examined for similarities and dissociations in behavioral and brain responses to cholinergic enhancement between spatial attention, spatial working memory, and visual stimulation. By designing all tasks with a variable-duration, stimulus-identical delay period we were able to compare pharmacological actions between the cognitive effects of interest (viz. the delay components of each task) while eliminating sensorimotor differences between conditions or treatments (see Experimental Procedures). Furthermore, the design enabled us to test hypotheses regarding the effects of cholinergic enhancement on top-down biasing of sensory cortices during attention and WM (e.g., Yu and Dayan, 2002) and on the similarity of cholinergic actions between attention and WM encoding (e.g., Sarter et al., 2003).

Physostigmine enhanced accuracy for attention but not WM while causing a speeding of response independent of task. Effects of physostigmine on BOLD activity that were *selective* for attention rather than WM or control delay periods were evident in extrastriate occipital and prefrontal cortices (physostigmine increased the effect of attention versus control) and superior-medial parietal cortex (physostigmine decreased the same effect). Conversely, effects of physostigmine on brain responses that were *similar* across tasks were found in primary visual cortex (physostigmine reduced responses to attention, WM, and control-delay periods). Furthermore, cholinergic modulation of attention and WM was similar in the two following respects: physostigmine reduced selective occipital activation during both attention and WM-delay periods (as a function of preceding cue or study item laterality) and increased activations during both WM-encoding and attention-delay in the same extrastriate regions.

presented in right or left visual field) and attend-right versus left and vice versa, as revealed by a conjunction analysis of laterality effects over both tasks, for placebo, physostigmine, and the between-treatment effect. Graphs plot percent signal change difference between trials in which attention or WM were directed contralaterally versus ipsilaterally to each occipital side. Plots are from those coordinates showing the maximal treatment × laterality interaction (ringed) and demonstrate similar physostigmine-induced reductions in selective occipital activation with both attention and WM.

(C) Surface rendering of visual regions showing physostigmine-induced enhancement of both attention delay (versus control delay) and WM encode (versus WM test) contrasts. Graphs plot percent signal change difference for both contrasts under placebo and physostigmine, in those occipital coordinates showing the maximal treatment effect on both contrasts (ringed).

We discount any explanation of our findings in terms of general effects of drug on blood oxygenation level-dependent (BOLD) responses. First, all task effects were corrected for session means, which themselves did not differ by treatment across any of the areas highlighted (nor were there treatment effects on global activity or blood pressure). Second, certain treatment × condition interactions (Figures 4–6) can only be explained by recourse to an effect of drug on specific cognitive processes. In the case of drug effects across all tasks (Figure 3), we note that the effect reported was specific to only one part of visual cortex, arguing against a general change in occipital BOLD responsiveness. Finally, while a BOLD response ceiling could potentially explain a reduced occipital lateralization under drug, we argue against this on the basis of a behavioral correlation with this effect and the observation that peak responses within the interaction were significantly less than those in contiguous occipital regions.

Cholinergic Modulation of Visual Stimulation and Spatial Attention

Our findings of cholinergic modulation of occipital cortex that occurred both selectively with attention (in extrastriate cortex) and independent of task (in striate cortex, during visual stimulation) support a model in which acetylcholine acts on both task-driven (top-down) and stimulus-driven (bottom-up) sensory processes (see Sarter et al., 2001). The observed depression of visual-evoked BOLD activity by physostigmine in early visual cortices is consistent with previous functional imaging studies (Bentley et al., 2003; Mentis et al., 2001; Grasby et al., 1995; Thiel et al., 2001) and may reflect effects of acetylcholine in primary sensory areas on filtering noise (e.g., Sato et al., 1987; Murphy and Sillito, 1991) and inhibiting feedback from higher centers (Hasselmo and Cekic, 1996; Kimura et al., 1999).

Where physostigmine acted on extrastriate occipital cortex selectively during attention, this may have occurred by one (or both) of two means. First, cortical acetylcholine release is boosted more during attention than other conditions (e.g., Himmelheber et al., 2000), which would allow physostigmine to have a greater observed local effect. Although the response profile in calcarine sulcus argues against this (i.e., nonselective physostigmine modulation), this may reflect the fact that primary, relative to higher, sensory areas possess greater concentrations of cholinergic receptors (Mash et al., 1988; Prusky et al., 1988), and hence, the cholinergic responsiveness of primary sensory regions may be expressed at lower concentrations of acetylcholine. Second, physostigmine may have acted upon higher processing centers (as we found in superior parietal and prefrontal cortices) specifically engaged by attention, which may then indirectly augment activation in sensory regions (Gill et al., 2000; Sarter et al., 2001).

In a recent fMRI study employing the rapid visual information-processing task, nicotine was observed to enhance extrastriate occipital cortex similarly under two levels of difficulty (Lawrence et al., 2002). While this seems to contradict our findings of selective actions of physostigmine on attention, it is notable that the two conditions in the Lawrence et al. study employed task-relevant stimuli presented for an equally brief duration (attention varying as a function of target number and semantics), whereas in our study targets differed markedly in properties between attention and control. Hence, the enhancement of occipital activation by procholinergic modulation may depend upon the difficulty of detecting task-relevant stimuli as well as on attentional demand. We caution that the use of nicotine, in smokers, in Lawrence et al. makes these two studies not strictly comparable.

Cholinergic Modulation of Spatial Working Memory

In contrast to the wide effects of physostigmine on attention-delay (versus control), physostigmine's modulation of working memory-delay (versus control) was restricted to inferior prefrontal cortex (see also Furey et al., 2000a). Notably, physostigmine reduced the effect of attention-delay but not WM-delay in superior-medial parietal cortex, in spite of both conditions activating this region similarly under placebo. This pattern of activity could be explicable, as for occipital cortex, either in terms of differing acetylcholine release between conditions or as a difference in input to parietal cortex from other regions (occipital and prefrontal cortices were more extensively activated under attention than WM). Physostigmine also enhanced activity selectively with attention-delay but not WM-delay in occipital and prefrontal cortices.

These selective actions of physostigmine on delay period activity during attention but not WM parallel the observed behavioral effect: accuracy improved with drug under attention but not WM, in spite of both tasks showing similar baseline performance levels (under placebo, attention was performed slightly less accurately but faster than WM). Our pattern of neuroimaging results may also underlie results of studies in animals (Chappell et al., 1998; Baxter et al., 1996; Herremans et al., 1996) and humans (Heishman et al., 1994), including Alzheimer's disease (Sahakian et al., 1993; Jones et al., 1992), in which cholinergic manipulations produced relatively selective effects on attention rather than short-term memory. Where cholinergic drugs have been observed to exert specific effects on WM, these may have been due to the employment of more demanding tasks than used here (Robbins et al., 1997; Rusted and Warburton, 1988) or due to testing smokers (Park et al., 2000).

In a face-WM study by Furey et al. (2000a), using a drug protocol identical to ours, extrastriate cortex was found not to exhibit cholinergic modulation during WM-*delay* (as we found) but was positively modulated by physostigmine during WM-*encoding*. One interpretation was that physostigmine was acting specifically when enhanced attention needed to be paid toward a stimulus (see also Sarter et al., 2003). Our results lend support to this idea by finding extrastriate occipital regions that enhanced their response under physostigmine both during attention-delay and WM-encoding but not during WM-delay or control-delay.

Cholinergic Modulation of Task-Driven Occipital Lateralization

Previous studies have demonstrated selective activation of retinotopic occipital cortex depending on the

location at which either attention (e.g., Martinez et al., 1999) or working memory (Awh et al., 1999) is directed, independent of stimulus. Since acetylcholine has been proposed to be a critical modulator of top-down (task-driven rather than stimulus-driven) effects (see Sarter et al., 2001), we expected to find either an increase or decrease in selective occipital activation during the delay period of both tasks, depending on whether the net effect of acetylcholine was to increase or decrease, respectively, top-down biasing of sensory processing. We emphasize that this effect is orthogonal to the main effect of physostigmine on attention versus control (that was increased under drug). Our results show that physostigmine reduced the degree of occipital lateralization associated with both attention and WM, in both hemispheres. For attention, this effect was due to physostigmine increasing activation disproportionately more on the side ipsilateral than contralateral to the previously cued hemifield (i.e., it favored activation more on the occipital side representing the visual hemifield in which targets were less expected). Furthermore, the actions of physostigmine on occipital lateralization and activation of ipsilateral occipital cortex were correlated with concordant behavioral effects (viz. with a reduction in performance discrepancy between valid and invalid trials and an increase in invalid trial accuracy, respectively), suggesting that cholinergic modulation of occipital lateralization had effects on selective spatial processing.

The results provide a neural explanation for psychopharmacological studies showing that cholinergic neurotransmission inversely correlates with the cost engendered by invalid cues (Stewart et al., 2001; Phillips et al., 2000; Witte et al., 1997; Chiba et al., 1999) and are relevant to the hypothesis that the hypercholinergic state is associated with heightened processing of irrelevant information, e.g., as in anxiety (Berntson et al., 1998). Preferential enhancement of sensory-cortical responses to behaviorally irrelevant (relative to relevant) stimuli under physostigmine has also been observed in a fear-conditioning paradigm (Thiel et al., 2002), suggesting that cholinergic modulation of attentional processing may have subsequent effects on learning. Together, these findings speak to models (Yu and Dayan, 2002; Hasselmo and Cekic, 1996) in which the role of neocortical acetylcholine is to favor feedforward (or stimulus-driven) over feedback (e.g., expectation or task-guided) sensory processing, especially during periods of uncertainty. Our observation of preferential enhancement on the occipital side ipsilateral to cued direction under physostigmine (with no occipital enhancement under low-attention control) could be explained in terms of reduced feedback to sensory cortices (e.g., Hasselmo and Cekic, 1996; Kimura et al., 1999) if it were the case that such feedback suppression occurred preferentially on the inhibitory pathways that underlie selective spatial attention (e.g., Chelazzi et al., 2001).

Conclusions

Physostigmine reduced visual-evoked activity in striate cortex (possibly relating to neurophysiological evidence for net noise suppression) while enhancing activation selectively with maintained attention (relative to delay periods of other conditions) in extrastriate cortex. However, while the overall level of extrastriate cortex activation was raised under physostigmine with attention, the expectation-driven selectivity of activation in the same region was reduced. These last two (orthogonal) effects were associated with consistent behavioral effects: subjects' scores were higher with physostigmine over all attention trials, but subjects showing greater drug-induced reduction in occipital lateralization showed a relatively greater benefit during invalid than valid trials. Hence, while attentional engagement of higher visual cortex may increase under cholinergic enhancement, the retinotopic selectivity of occipital activation that characterises selective spatial attention may itself diminish (at least in the hypercholinergic state, given that our subjects were healthy young adults).

Our study also identified differences and similarities between cholinergic modulation of attention and working memory. Selective effects of physostigmine on attention delay period activity in extrastriate occipital and superior-medial parietal cortices paralleled a pharmacological dissociation on accuracy between tasks. However, physostigmine exerted effects on extrastriate cortex that were similar between attention and WM, specifically with analyses of WM encoding rather than delay (see also Furey et al., 2000a) and with task-driven lateralization of occipital responses. These findings support proposals that cholinergic effects on short-term memory are mediated primarily through attentional aspects of such tasks (e.g., Sarter et al., 2003) and, more generally, provide additional evidence for there being neural processes common to attention and working memory (Awh and Jonides, 2001).

Experimental Procedures

Subjects

Eighteen right-handed volunteers (13 female, 5 male; mean age = 23.4 ± 1.0) with no history of medical or psychiatric disease gave written informed consent. No subject was on medication or a smoker. Each subject participated in two sessions separated by 7–10 days, performed at similar times of the day. Subjects received a physostigmine or placebo (saline) infusion on different sessions, with treatment order being counterbalanced across subjects. Three further subjects that were scanned were excluded due to excessive saccades (>50% trials).

Drug Treatment

A double-blind placebo-controlled drug administration technique was used. Each subject received an intravenous cannula into the left cubital fossa and an infusion of either physostigmine or saline, depending on session. Dosage and rate of physostigmine infused was identical to that used in a recent study (Furey et al., 2000b), providing stable levels of plasma drug concentration and butyryl-cholinesterase inhibition as well as a significant and stable effect on cognitive performance for 40 min, following a 40 min loading period. The same drug protocol has also been found to result in changes in task-specific occipital activity using fMRI, with working memory (Furey et al., 2000a) and perceptual attention (Bentley et al., 2003) tasks.

During the drug session, subjects were first given 0.2 mg intravenous glycopyrrolate (peripheral muscarinic receptor antagonist) before an intravenous infusion of physostigmine was commenced (1.93 mg/hr for 10 min, followed by 0.816 mg/hr for 40 min). Subjects then performed the task in the scanner while receiving a constant rate of drug for a further 40 min (<1.3 mg physostigmine in total delivered). In the placebo session, an equivalent volume of saline was administered in all steps. On both sessions, blood pressure was

checked before and at 40 min into infusion, while pulse-oximetry was performed continuously. Subjects were given a questionnaire at 0 and at 40 min postinfusion that allowed a ranked measurement (0–6 scale) of seven recognized adverse reactions to physostigmine and glycopyrrolate as well as a list of visual analog scales for estimating subjective feelings (Bond and Lader, 1974).

Task

On each session, subjects performed three tasks (spatial attention, spatial working memory, and visual control; Figure 1) in different blocks and repeated once (e.g., AWCAWC). To minimize order effects, treatment and task order were completely counterbalanced across subjects, with task order being repeated across sessions. Furthermore, on each session, subjects were given half-hour practice with feedback, outside the scanner, prior to drug delivery, and were also given 10 min inside the scanner, prior to actual task, to accustom subjects with scanner environment and noise. There were 52 trials of each condition per session, with an ITI of 0.5–3.5 s.

In the attention task, subjects were cued to either right or left visual hemifields (for 2.1 s) before being presented with a 12 Hz alternating, polarized checkerboard (18° height × 22° width; vertical wedges removed) for 3–14 s (mean = 7.8 s; approximate Poisson distribution). After this delay period, two adjacent "squares" on either the right or left side of the checkerboard (6° eccentricity; 3° wide, within 45° arc about horizontal meridian) reversed in polarity (the target, appearing as a "hole" within the checkerboard) for 84 ms, before being replaced by the normal checkerboard for a further 2.5 s. Subjects were required to attend to the cued side covertly (i.e., while fixating centrally) and to press either right or left buttons, depending on target side, immediately on seeing the target, with the right hand. By only including responses within 1.5 s of target (accounting for >95% responses), a measure of accuracy could be obtained (since <27% accuracy could occur by subjects simply pressing after the commonest delay period). Targets either appeared on the same (valid trials: 80%) or opposite (invalid trials: 20%) side to that cued.

Working memory trials began with a study phase in which three points were presented successively (for 700 ms each) in one of 24 equally spaced locations in either right or left visual hemifields (each equivalent to half the checkerboard area). Subjects were then required to rehearse the locations of the three points while fixating centrally during presentation of a 3–14 s alternating checkerboard (parameters as for attention task). Following this period, a probe point appeared anywhere in the display (for 2.5 s), and subjects had to indicate whether its location was the same as one of the three studied points (test phase). The WM task is adapted from a blocked fMRI study (Awh et al., 1999) in which lateralized occipital responses (regions of interest) were found contralateral to the visual field in which studied items were presented during a spatial but not object WM task.

Visual control trials resembled attention and WM trials in temporal composition, with a 3–14 s delay period of alternating checkerboard, during which subjects fixated centrally. However, trials began with a central cue for 2.1 s and ended with a prominent central triangle on a plain background for 2.5 s, at which subjects had been instructed to press the first key, with no emphasis on speed (hence requiring minimal attention).

The use of variable-duration delay periods enabled us to model this temporal component of brain activity (in which the stimulus remained identical across conditions and there was no motor response) separately from transients at either end of the delay period (which varied between conditions and group—the latter due to drug effects on response). By employing a wide range of delay durations and modeling the delay periods of false alarm and saccade trials separately, the modeled time series of transients and delay periods (derived from convolving successive stimulus boxcars with the hemodynamic response function) are sufficiently decorrelated to enable efficient estimation of the independent effects of each task component (see also Rowe and Passingham, 2001). Shared variance between transient and delay period regressors is effectively excluded from estimation of the individual effects within the general linear model and amounted to less than 8% and 16% across all initial delay and delay response pairings, respectively. Saccades and median eye position were monitored during each delay period (using an infrared eye tracker: ASL Model 540, Applied Science Group Co., Bedford, MA; refresh rate = 60 Hz); trials in which central fixation did not occur were discounted from the behavioral and imaging analysis.

Imaging and Image Processing

MRI data were acquired from a 2T VISION system (Siemens, Erlangen, Germany) equipped with a head coil. Functional images were acquired with a gradient echo-planar T2* sequence using BOLD (blood oxygenation level-dependent) contrast. The acquired image consisted of 33 × 3 mm thickness axial slices that covered the entire brain, with an effective repetition time of 2.51 s. The first six volumes were discarded to allow for T1 equilibration effects. Images were realigned to the first scan of the first session, time corrected, normalized to a standard echo-planar image template, and smoothed with a Gaussian kernel of 8 mm full-width half-maximum.

Statistical Analysis of Images

Data were analyzed with a general linear model for blocked, event-related designs (SPM99; Wellcome Department of Cognitive Neurology, London, UK; Friston et al., 1995) using a random-effects analysis. Data were globally scaled and high-passed filtered at 1/256 Hz. For each subject and session, the following events and epoch types were modeled separately: attention cue (R and L, separately), attention delay (R and L), attention target (R and L, and for each, valid and invalid), WM study (R and L), WM delay (R and L), WM probe, control cue, control delay, control target (all control trials were arbitrarily divided into two to allow for independence in a conjunction analysis of attention and WM versus control), false alarms, and saccades or eye deviation (R and L). In those attention trials in which the target was missed, the modeled delay period was extended until the end of the checkerboard presentation. All modeled events and epochs were convolved by a canonical hemodynamic response function; temporal derivatives of these functions were modeled separately (Friston et al., 1998). The six head movement parameters were included within the model as confounding covariates.

In order to control for sensorimotor differences between conditions and performance between treatments, only contrasts of delay period activity were made (except for testing of drug effects on WM encoding—see below). Differences in BOLD signal magnitude between conditions of interest (viz. delay period of all tasks versus baseline; attention delay versus control delay; WM delay versus control delay; attention right delay versus attention left delay and vice versa) were calculated for each subject and treatment before being submitted to one-sample t tests with generation of statistical parametric maps (SPMs) of the t statistic. Comparisons of these contrasts were then made between treatments (treatment × condition interactions). The interaction of treatment × condition, comparing specifically attention with WM, was restricted to within 12 mm (the estimated smoothness) of those coordinates also showing interactions of treatment × condition comparing either attention or WM with control. In order to test for regions showing both attention and working memory activity, contrasts of each condition versus its own set of control trials, under placebo, for each subject were submitted to repeated-measures ANOVA corrected for nonsphericity (Glaser et al., 2001). A conjunction analysis was then performed over contrasts from both conditions (Price and Friston, 1997). Similar analyses were performed to test the hypotheses that physostigmine modulates selective occipital activation with both spatial attention and spatial WM laterality, and that physostigmine modulates both attention (attention delay versus control delay) and WM encoding responses (study versus test phases) in the same regions. We report areas that achieve $p < 0.05$ significance after correction for whole brain or 12 mm radius spheres centered on MNI coordinates derived from equivalent contrasts in previous nonpharmacological studies (Hopfinger et al., 2000, for main effect of attention; Martinez et al., 1999, for attention laterality; Rowe and Passingham, 2001, for main effect of WM delay). We also list areas surviving a threshold of $p < 0.001$, uncorrected. Reported interactions (treatment × condition) are also significant for the simple effect of condition under the

strongest treatment effect ($p < 0.001$, uncorrected), except where indicated in the tables.

We emphasize that the drug effects reported here are task specific, as mean session effects are modeled separately. All regions that showed significant treatment-by-condition interactions were found to show insignificant between-treatment session effects ($p > 0.10$, uncorrected). Furthermore, the global session-mean activity did not differ between treatments ($p > 0.10$), suggesting that physostigmine did not engender significant general vascular effects.

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