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Cholinergic modulation of visual working memory during aging: A parametric PET study

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Abstract

Age-related differences in the regional recruitment of prefrontal cortex (PFC) during cognitive tasks suggests that aging is associated with functional reorganization. Cholinergic enhancement with physostigmine reduces activity in the PFC regions selectively recruited during working memory (WM) and increases activity in visual processing areas, suggesting that augmenting cholinergic function reduces task effort by improving the visual representation of WM stimuli. Here, we investigated how cholinergic enhancement influenced PFC and visual cortical activity in young and older subjects as WM difficulty was altered. Regional cerebral blood flow (rCBF) was measured using H₂¹⁵O-PET in 10 young and 10 older volunteers during a parametrically varied face WM task, following an i.v. infusion of saline and physostigmine. Reaction time decreased during physostigmine relative to placebo in both groups. Prefrontal brain regions selectively recruited in each age group that responded differentially to task demands during placebo, had no significant activity during physostigmine. Medial visual processing areas showed task-selective increases in activity during drug in both groups, while lateral regions showed decreased activity in young and increased activity in older participants at longer task delays. These results are consistent with our previous findings, showing that the modulatory role of the cholinergic system persists during aging, and that the effects of cholinergic enhancement are functionally specific rather than anatomically specific. Moreover, the use of the parametric design allowed us to uncover group specific effects in lateral visual processing areas where increasing cholinergic function produced opposite effects on neural activity in the two age groups.

Keywords

Cholinergic modulation; Working memory; Aging; PET; Physostigmine; Visual cortex

1. Introduction

Working memory (WM) refers to a cognitive process that temporarily stores and manipulates an active representation of information for further processing or recall [2,3]. The role of the cholinergic neurotransmitter system in cognitive functions including WM is well established in both humans and animals, with cholinergic enhancement improving performance on WM and attention tasks [19–23,26,41,46,55] and cholinergic blockers impairing performance [12,22,46,48]. In previous studies, we found that pharmacological enhancement of the brain cholinergic system improved behavioral performance during a visual WM for faces task, and modulated neural activity throughout the brain [19–21]. Specifically, the administration of an anticholinesterase, physostigmine, reduced neural activity in prefrontal cortical areas known to be critical for WM function, and increased the response to task relevant stimuli in ventral visual cortical regions [21]. We hypothesized that cholinergic enhancement improved the efficiency of perceptual processing, producing an enhanced visual percept of the WM task stimuli, thus reducing the effort required to perform the task and indirectly diminishing the need to recruit the prefrontal cortex.

Regions in prefrontal cortex that are known to be central to WM are modulated systematically with variations in task difficulty [4,6,28]. Parametric paradigms have been utilized to gain more specific information regarding the role of brain regions in specific task components, in that the manipulation of task difficulty will uncover regions whose response varies systematically with task difficulty. Previously we found that inferior frontal and anterior middle frontal cortices showed systematic increases in neural response as the retention interval in a WM task was increased [23]. These prefrontal brain regions that increased activity as a function of task demands during placebo showed less activity during cholinergic enhancement. Moreover, visual processing areas in occipitotemporal cortex showed increased activity during enhanced cholinergic function, and these visual areas are the only brain region to show augmented function during boosted cholinergic activity [23].

Anatomical, chemical and functional changes occur in the brain during healthy aging [10,42,43,45], including changes in the cholinergic system, such as a reduced number of cholinergic cells in the nucleus basalis and a reduction in the number of cholinergic receptors throughout the cortex [1,25,37,38,41]. These age-associated changes have led to the cholinergic hypothesis of aging which suggests cholinergic alterations contribute to age-associated deficits in WM, attention, and other cognitive functions [1,5,10,17,25], although some recently have challenged this hypothesis [11,14].

Results from functional imaging studies have suggested that during aging the brain undergoes functional reorganization, perhaps to compensate for age-associated regional dysfunction [8,27,30,44,49,50]. A visual WM task administered to young and older individuals elicited different patterns of neural responses [29], including reduced neural activity in dorsolateral prefrontal cortex, a critical WM region, and increased activity in other PFC areas in older as compared to younger individuals. Older individuals recruited a greater extent of occipitotemporal areas as compared to younger individuals, which also may reflect functional reorganization as a compensatory mechanisms [29,32]. Moreover, behavioral studies indicate an age-associated decline in cognitive functions including WM, and show that as task difficulty or complexity increases, the age-associated deficits are enhanced (reviewed in [32]).

During cholinergic enhancement, activity decreased in the prefrontal regions that had been selectively recruited during WM in each age group during placebo, thus cholinergic enhancement modulated neural activity in functionally defined regions that were selectively and distinctively recruited in the two age groups. Visual cortical areas, the only brain

regions to show increases in activity during cholinergic enhancement and WM, increased in both age groups but to a larger extent in older participants [18].

The present study was designed to examine how neural response to a visual WM task with parametrically varied difficulty is modulated by cholinergic enhancement in older healthy individuals. As our hypothesis suggests that cholinergic enhancement reduces task difficulty in a functionally defined (rather than anatomically defined) way, we expected that prefrontal brain regions that respond linearly to increases in task difficulty that were uniquely recruited in older individuals would show cholinergically mediated decreases in activity during WM. We also expect to see differential involvement in visual processing areas between the two age groups, regarding both recruitment during placebo and the response to cholinergic augmentation. Previously we observed larger recruitment of visual cortical areas in older individuals during a similar WM task without manipulation of task difficulty, perhaps as an age-related compensatory response [18]. In addition, we observed increased neural activity in lateral visual processing areas in older individuals during enhanced cholinergic activity that was not seen in younger individuals [18]. If the activity in lateral visual areas is related directly to variations in visual input as task difficulty is modulated, we expect to see increased activity during augmented cholinergic function in older but not younger individuals.

2. Methods

Ten young (mean age $\pm$ S.D. = 26.2 ± 1.4 years; gender: 5 M/5F; as reported in [23]) and 10 older (mean age $\pm$ S.D. = 68.4 ± 4.0 years; gender: 5 M/5F) healthy volunteers were studied. All participants were normotensive, had no abnormalities on laboratory studies (including routine blood and urine tests, liver, renal, and thyroid function serum tests, audiological and visual assessments, EEG, EKG, brain MRI, chest X-rays) and no history of relevant medical, neurological or psychiatric disorders. Clinical examination included the administration of the Mini-Mental State Examination: subjects had a score of ≥ 27 out of 30 to be included in the healthy control group (as detailed in [43,44]). All subjects were medication-free for 4 weeks prior to the study, including over the counter medications. Written informed consent was obtained from all subjects prior to participation in the study (according to protocol 93-AG-193 of the National Institute on Aging institutional review board).

rCBF was measured using H_2^{15}O and positron emission tomography (PET) (Scanditronix PC2048-15B PET Scanner, Uppsala, Sweden—FWHM: 6.5 mm) during a parametrically varied visual WM task [23]. The task included a sensorimotor control task and a delayed match-to-sample task with faces as stimuli, using 4 delay conditions (1, 6, 11 and 16 s) with all conditions presented in random order and counterbalanced across subjects (Fig. 1). The stimulus array consisted of three squares, one on the top and two on the bottom arranged side-by-side. For each trial, an unfamiliar face was presented in the upper square of the stimulus array, followed by one of the delay conditions, and then followed by the presentation of two faces in each of the bottom squares. One of the two choice faces matched the face shown previously and the other was a distracter. The delay between sample and choice faces was filled with 0–3 blank stimulus arrays, in which all three squares contained smaller grey squares. All stimulus arrays were presented for 4 s, separated by a 1 s interval. Pictures were black and white images of male and female faces. Target and distracter stimuli were always of the same sex. For the sensorimotor control task, nonsense pictures were presented in the same spatial and temporal manner, but there was no memory component to the task. Subjects were instructed to press both response buttons following the presentation of side-by-side nonsense pictures. The five task conditions were presented in randomized order across subjects, first during an i.v. placebo infusion of saline and

subsequently during i.v. infusion of physostigmine (1.93 mg/h for 10 min, followed by 0.82 mg/h to completion of the study). Prior to the infusion of physostigmine, 0.2 mg of the peripheral cholinergic antagonist, glycopyrrolate, was administered i.v. to reduce the potential of side effects [40]. Heart rate and blood pressure were monitored throughout each study. Subjects were unaware of when they would receive physostigmine.

Accuracy and reaction time data were analyzed using within and between group repeated measures ANOVA (repeated reaction time by delay length by infusion condition by group). Main effects and *t*-tests were used to characterize significant repeated measures ANOVA results. Drug effects on reaction time were assessed using 1-tailed tests based on previously reported findings [18–23].

Using Statistical Parametric Mapping 99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College, London (<http://www.fil.ion.ucl.ac.uk/spm>), images were coregistered, spatially normalized to the Talairach-Tournoux brain atlas [54], and smoothed using a 12 mm × 12 mm × 12 mm Gaussian filter.

Brain regions showing statistically significant rCBF increases during the WM task were identified by contrasting all task scans combined (1, 6, 11 and 16 s delays) to the sensorimotor control condition (individual voxel level of $p < 0.05$, with a minimum of 50 contiguous significant voxels) separately for the saline and physostigmine infusion conditions and for each of the two age groups. These results were used to create masks that restricted the search volume in subsequent analyses.

Linear trends analysis was used to identify brain regions with increases or decreases in rCBF that changed linearly with task delay. Linear trends were assessed under placebo and physostigmine conditions separately for each age group, and these analyses were masked with activation maps. Age group results also were compared directly to identify significant differences between groups. Statistical significance was assumed at an individual voxel level of $p < 0.05$, and required 50 contiguous significant voxels.

Brain regions showing significant group × task interactions were determined for both placebo and physostigmine conditions by contrasting task-specific rCBF responses during the WM task obtained from each of the two groups. To identify regions that responded more (voxel level $p < 0.05$, with a minimum of 50 contiguous significant voxels) in the young group, the interaction contrasts were masked by the activation maps of the young group. Similarly, to identify regions that responded more in the older group, the interaction contrasts were masked by the activation maps of the older group.

3. Results

3.1. Behavioral findings

Reaction time increased with increasing delay during placebo infusions over all subjects ($F = 31.0, p < 0.0001$). Younger individuals were faster than older participants ($F = 3.2, p < 0.05$), and this did not differ under placebo and physostigmine ($F = 0.51, p > 0.20$). Physostigmine reduced reaction time during the WM task ($F = 11.8, p = 0.006$), but the magnitude of this reduction did not differ over task delays ($F = 1.5, p > 0.20$) or between the two age groups ($F = 0.51, p > 0.20$). Physostigmine did not reduce reaction time associated with the control condition ($t = 1.6, p = 0.14$), and the two age groups did not differ from each other ($F = 1.05, p > 0.20$). Performance accuracy was at ceiling level in both groups (>90% correct) during placebo and during physostigmine (Fig. 2).

3.2. Imaging results

Linear trends analyses—The results of the linear trends analyses are displayed in Fig. 3 and reported in Table 1. In young subjects during placebo, positive linear trends (i.e. rCBF increased as task delay increased) were observed in right anterior middle and inferior frontal areas and negative linear trends (i.e. rCBF decreased as task delay increased) were observed bilaterally in occipitotemporal visual extrastriate regions (Fig. 3A and Table 1). Similarly, in the older group positive linear trends were observed in anterior middle and ventral medial frontal cortex, and negative linear trends were seen in occipitotemporal extrastriate cortex.

During physostigmine, negative linear trends were seen in occipitotemporal visual regions in the young group and in more medial and dorsal extrastriate areas in older individuals. No significant positive linear trend was observed in prefrontal cortex during physostigmine infusion in either group (Fig. 3B and Table 1).

The drug $\times$ task interaction of the linear model indicates that the absence of linear trends in prefrontal regions during physostigmine in the young group differs significantly from the placebo condition (Fig. 3C and Table 1), and the linear trends observed in visual extrastriate regions were unaffected by drug. In the older group, although the trend observed in prefrontal cortex under placebo was absent during physostigmine, this difference is not significant when compared directly. However, the negative trend observed in ventral visual area during placebo was significantly reduced by drug in the older group. No region differed significantly when the two groups were compared directly.

rCBF response to the working memory task—For completeness, Tables 2 and 3 provide results of the within group, between group, and drug interactions for but the majority of those results will not be discussed. Only results observed in visual processing areas will be conferred.

Within group rCBF responses during task—During placebo and physostigmine, increases in task-related rCBF were observed bilaterally in occipital and temporal visual extrastriate regions within the young and older participants. The within group drug $\times$ task interaction identified significantly lower task-specific rCBF during physostigmine lateral occipital and ventral temporal visual regions in both groups and significantly greater task-specific rCBF was observed in medial occipital visual cortex (Figs. 4A and 5; Table 3).

Age group differences during task—During placebo, the older group had significantly larger task-specific rCBF responses than the younger group bilaterally in occipital and temporal visual extrastriate regions. During physostigmine, older participants showed less activity during task in the medial visual cortex than the younger individuals, but greater activity bilaterally in lateral occipitotemporal cortices (Fig. 4B and Table 2).

Age group $\times$ drug interaction—A significant age group $\times$ drug interaction was observed bilaterally in lateral ventral occipital visual cortical areas, where physostigmine increased the magnitude of task-related activity in ventral lateral occipital visual cortices in older subjects, and decreased neural activity in the same regions in younger individuals (Fig. 4C and 5; Table 3).

Regional mean rCBF responses to working memory—Mean rCBF values were obtained from the previously reported medial visual area that showed significant increases in rCBF during physostigmine in young subjects [23]. This locus also overlaps with the medial visual area showing significant increases in rCBF in older subjects (Fig. 4A). Young subjects did not recruit this region under placebo as no significant increase in rCBF occurred

to any task delay condition. During physostigmine, significant (trend level at the 11 s delay) increases in rCBF relative to the control task were seen to the three longest task delay conditions, indicating that this region was recruited to perform the task during drug. In contrast in older subjects, this region was recruited to perform the task during placebo to the short delays (1 and 6 s) but not during the long delays (there was a trend level increase during the 16 s delay condition). During physostigmine, significant rCBF increases were seen to the longer delays, with trend level increases during the short delay (1 s) (Fig. 5B).

The lateral visual cortical region showed a significant group $\times$ drug interaction (Fig. 4 and Table 2). Region mean rCBF also was obtained from this region and is plotted in Fig. 5A. In the young group during placebo, significant responses to task were observed during the 1, 6 and 11 s delay conditions, with trend level responses observed during the 16 s delay, consistent with the negative trend observed in this region prior to drug (Fig. 3). Reductions in response magnitude were observed across delay conditions during physostigmine (except to the 1 s delay), reducing the contribution of this visual region. In the older subjects, this lateral visual area showed a significant increase in rCBF as compared to the control task to the short delays during placebo as seen in the younger group. In contrast to the young group, during physostigmine the older group had significantly higher rCBF in lateral visual cortex to the 6, 11 and 16 s delay conditions. Moreover, the response magnitude to the 1 s delay condition was significantly reduced. Thus, the overall effect in this region in the older group is that the response magnitude generally increased and did not differ across delay conditions during drug, and in this way explains the significant reduction in the linear trends analysis in lateral visual cortex. Finally, the interactions shown as deltas in Fig. 5 reflect the differences between the two age groups in the change in rCBF response to the 6, 11 and 16 s delay conditions, where the young group showed rCBF reductions and the older group showed rCBF increases.

4. Discussion

The potentiation of cholinergic function following the administration of the anticholinesterase physostigmine improved WM task performance and modulated activity throughout the WM system in both young and older individuals across levels of task difficulty. Different prefrontal regions that respond in a linear manner to task demands were observed in the two age groups under placebo. Enhancement of cholinergic function reduced task-related neural activity in the prefrontal regions that were distinctly recruited by each age group under placebo, suggesting both that cholinergic potentiation modulates task difficulty and that these effects are functionally specific rather than anatomically specific. Thus in prefrontal areas, the specific regions showing decreases in the two age groups were anatomically distinct while functionally similar. Medial visual regions showed similar drug-related increases in activity during task in both groups as seen before, but lateral visual processing regions showed opposite responses to increased cholinergic function, with the younger group having reduced activity and the older group having increased task-specific neural activity. Importantly, the same neuropharmacological modulation of cholinergic function in young and older individuals produced opposing neurophysiological effects.

An important finding inherent in these results is that the modulatory effects of the cholinergic system continue during aging, as indicated by selective effects on perceptual processing in visual areas and reduced contributions from prefrontal WM regions. The results also imply that the modulatory effects of the cholinergic system accommodate age-associated compensatory changes. Specifically, compensatory mechanisms that result in the recruitment of novel brain regions in elderly, both in prefrontal and visual processing areas, also show task associated changes in neural response following cholinergic enhancement. Moreover, cholinergic modulation produced opposite effects in the two age groups on neural

activity in lateral visual processing areas, demonstrating at another level that the effects are functionally specific and accommodate age-associated compensatory changes.

The linear trends analyses identified prefrontal regions in young and older individuals that showed systematic increases in neural response as task delay increased, suggesting that these regions specifically respond to changes in task demands [15,16]. While the regions that responded in this manner overlapped between the groups (i.e. anterior middle frontal cortex), unique loci that showed differential responses based on task demands also were identified in each of the two age groups (i.e. inferior frontal cortex in young and ventromedial PFC in older). All prefrontal regions in both groups that differentially responded to task demands during placebo showed no task-specific response during cholinergic enhancement, consistent with the hypothesis that cholinergic potentiation reduces task difficulty. Thus, regions responding differentially to task demands are modulated by cholinergic activity, despite the fact that age-associated differences in those prefrontal regions are evident, highlighting the functionally specific effects of cholinergic enhancement.

Medial visual cortex did not show differential task-specific activity during WM in the young group during placebo, but rather showed similar levels of activity to the control condition as well as to each task delay condition. In lateral visual areas, task-specific activity was observed, with a negative linear trend reflecting larger responses at short delays and progressively smaller responses to longer delays. This pattern of activity is consistent with the reduction in overall visual input that accompanies increases in task delay as the window during which rCBF is measured using O-15 water is unchanging from task condition to task condition. In the older group, task-specific activity was observed during placebo with greater activity during the shorter task delays in both medial and lateral visual processing areas. Moreover, there was a more extensive recruitment of occipitotemporal visual processing areas in the older group under placebo, which may reflect a compensatory process in the older participants [31,33,47].

Complex effects of cholinergic enhancement were observed in visual processing areas. In medial visual cortex, similar effects were observed in the young and old groups with task-selective increases in activity (i.e. no increase in activity was observed during the control condition), particularly at longer task delays. Thus, we do not observe a generalized increase in neural activity in response to visual input, but rather a selective increase during performance of the WM task. This increased neural activity may produce an enhanced visual representation of the information retained in WM, particularly when the task demands are greater. However, opposite effects of cholinergic modulation were observed in lateral visual areas in the two groups. In the younger group we observed a task-selective reduction in neural activity, primarily to longer delays, while in older participants we observed a task-selective increase in activity.

This pattern depicting opposite effects of cholinergic modulation in the two age groups is unique to the lateral visual area. Both groups also showed similar responses to cholinergic manipulation in medial visual processing areas, with both age groups showing task-specific increases in activity. Lateral visual cortex is the only area that is modulated by cholinergic enhancement in a task-selective manner in both age groups, but shows task-specific increases in one group and task-specific decreases in the other.

We can only speculate as to how the same drug manipulation in the context of the same cognitive task can produce opposite effects on neural processing based on age group. Evidence indicates that age-associated changes in brain function include the recruitment of additional brain regions in older individuals to perform the same tasks as in younger

[7,8,27,31,35]. Our data are consistent with this observation in that we observed the recruitment of some prefrontal areas and extensive occipitotemporal regions in older individuals that were not recruited in the younger group. Such changes are thought to reflect a task-related reorganization of brain function in the elderly [13,24,31,36]. Such a functional reorganization in visual processing areas may explain the difference observed in the neural response to cholinergic modulation, an interpretation that would be consistent with others [39], who have suggested that actions of acetylcholine become function-specific and are determined by the local architecture of brain circuits.

A possible alternative explanation for the reductions in neural activity seen in prefrontal WM regions may be related to an enhancement in neural efficiency correlated to increased cholinergic function. Evidence exists suggesting that increased neural efficiency may be associated with a reduction in overall neural activity, resulting in an increase in the focality of neural response [51–53]. However, this alternative explanation would argue overall improved efficiency would require less neural activity in entire WM network. While this interpretation cannot be ruled out, the increase in neural activity observed in medial visual areas in both age groups together with the complex, age dependant effects observed in lateral visual areas during cholinergic enhancement would be difficult to explain. Instead, we are arguing that the WM system is working more efficiently requiring less input from prefrontal brain regions as a result of an enhanced representation of the visual information in visual processing areas.

The cholinergic system plays an important role in mechanisms of stimulus processing and cognition, and has widespread projections throughout cortex, including prefrontal cortex and visual processing areas of the occipital and temporal cortices. Cholinergic changes are well documented in the literature on aging [5,9,30,34,37], and such changes are thought to contribute to aspects of cognitive aging. The extent to which we are able to evaluate the role of acetylcholine in age-associated changes in WM function in the context of this study is limited, primarily because the effects of cholinergic potentiation are similar in young and older individuals. Our results clearly suggest that the modulatory capacities of acetylcholine persist during aging.

One might question our experimental design where the drug infusion always followed the placebo infusion. Previously, we showed that the magnitude of the rCBF response in task-specific prefrontal brain regions was unchanging across repetitions of a working memory task, during both placebo and physostigmine [19,20]. We designed the study with the knowledge that task repetition per se would not alter the rCBF measurement. The alternative in a within-subjects experimental design would be to randomize the infusion conditions over two separate occasions, but the invasiveness of the arterial line makes this option undesirable.

In summary, our findings indicate that age-associated compensatory neural responses in prefrontal cortex and visual processing cortical areas occur in older individuals during WM while increasing task demands, and that these compensatory responses are modulated by cholinergic enhancement. While the effect of cholinergic enhancement in prefrontal activity is functionally similar in the two age groups, the effects observed in lateral visual cortex is opposite. This finding in visual cortex together with the effects observed in prefrontal cortex, may highlight the role of cholinergic modulation as having functionally specific rather than regionally specific effects that accommodate age-related compensatory changes.

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Fig. 1.

Task paradigm. Subjects performed a parametrically varied visual WM for faces task and a sensorimotor control task. For both conditions the stimulus array comprised of 3 equal-sized squares, one centered above two positioned side-by-side. For the control task, a nonsense image was presented in the top square followed by two identical images in the bottom two squares. Participants were asked press either button when the two nonsense images were presented in the bottom squares. For the WM task condition, each trial began with the presentation of a picture of a face in the top square, followed by delay interval that varied between 1, 6, 11 and 16 s, followed by two faces shown in the bottom two squares. Participants were asked to indicate which of the two faces matched the face previously presented in the top square.

Fig. 2. Performance results. The effect of physostigmine on mean reaction time ($\pm$ S.E.) is shown for the control task and for each of the WM delay conditions for young (light gray square) and older (dark gray circles) participants under placebo (continuous line) and physostigmine (dotted lines). *Indicates significant reduction in reaction time within the age groups ($p < 0.001$). No difference in the magnitude of response to drug was observed between age groups.

Fig. 3.

Brain areas showing linear trends between rCBF response and task difficulty in young and older subjects. Regions showing significant positive (red) and negative (blue) linear trends between rCBF and task delay conditions as measured during placebo (A) and physostigmine (B) are superimposed on the right hemisphere of a brain template for the two age groups. The task $\times$ drug interactions for each group also are shown (C). Scatter plots with fitted regression lines are shown for selected peak effects in anterior middle frontal cortex (26, 45 and 13) and in lateral visual cortex (31, -79 and -11) for young (yellow range) and older (green range) groups for placebo (dark shades) and physostigmine (light shades) conditions.

Fig. 4. Effect of physostigmine on regional cerebral blood flow (rCBF) during working memory in young and older adults. Brain regions showing significant increases in rCBF during a parametrically varied visual WM task as compared to a sensorimotor control condition during physostigmine (A—top row) infusions are projected onto the right and left hemispheres of a brain template and displayed for the two age groups. The age group $\times$ task interactions (yellow = greater rCBF response in young; green = greater rCBF response in old) are shown for the placebo and physostigmine conditions (B). The age group $\times$ task $\times$ drug interaction (C shows regions of greater rCBF in older participants than in young during task performance and physostigmine (green).

Fig. 5.

The effect of physostigmine on mean rCBF across task delays in visual processing areas in young and older adults. Volumes of 20 mm were averaged around a medial visual cortical locus (A) identified in a previously published paper [23], as well as a lateral visual cortical region (B) identified in the task $\times$ drug $\times$ group interaction. Mean rCBF ($\pm$ S.E.) values are plotted for the control task and each WM delay as obtained in young (yellow graphs) and old (green graphs) under placebo (dark shades) and physostigmine (light shades). The * identifies differences between the control task and the specified WM task delays within the same drug/placebo condition; *trend level ($p < 0.10$) and **($p < 0.05$). The # identifies significant differences between placebo and drug within the specified task delay.

Table 1

Cortical regions showing significant positive and negative linear trend between rCBF changes and maintenance delays of a parametrically varied working memory task in young and older individuals ($p < 0.05$ voxel-level, 50 contiguous voxels, local maxim 8-mm apart). For each brain region showing significant responses are indicated hemisphere, Brodmann areas, Talairach and Tournoux brain atlas coordinates [54], and Z-scores for each comparison.

Brain Areas	BA	Hem	Placebo			Drug			Drug × task interaction					
			Z score	x	y	z	Z score	x	y	z	Z score	x	y	z
Young individuals														
Positive trends														
Anterior middle frontal	9/46	R	2.97	26	45	13					3.45	26	45	13
Inferior frontal	45	R	2.89	33	28	5								
Cingulate	32	R	2.83	19	37	2					2.17	20	32	-2
Basal ganglia		R	2.59	8	1	3					2.90	13	-3	3
		R	2.13	6	10	4					2.10	19	4	-11
		R	2.05	8	16	-3								
		R					3.19	20	-4	8				
		R					2.87	20	4	0				
Negative trends														
Occipital	18	R	4.65	31	-79	-11	3.77	36	-82	-12				
	18	R	2.93	13	-87	-22	3.87	34	-80	-24				
	19	R	4.01	41	-63	-18	4.59	36	-68	-20				
	18	L	2.87	-34	-85	-19								
	18	L	2.58	-25	-67	-14	3.32	-30	-70	-20				
	18	L					2.68	-28	-82	4				
	18	L					2.43	-2	-82	-20				
19	L	2.18	-29	-91	-16	2.8	-44	-70	-16					
Older individuals														
Positive trends														
Anterior middle frontal	9/46	R	2.31	22	45	9								
			2.29	20	47	13								
Inferior frontal	45	R												
Cingulate	32	R	2.15	13	28	-6								
Ventral medial F			2.45	17	20	-10								

Brain Areas	BA	Hem	Placebo			Drug			Drug × task interaction					
			Z score	x	y	z	Z score	x	y	z	Z score	x	y	z
Basal ganglia		R												
		R												
		R												
Negative trends														
	18	R	4.59	31	-69	-21					3.73	34	-79	-22
	18	R	3.77	31	-83	-15					3.23	31	-89	-8
Occipital	18	R	3.74	26	-85	-22								
	18	R					3.04	20	-75	10				
	17/18	R					3.2	13	-62	0				
	19	R					3.14	17	-57	7				
	18	L	2.93	-27	-71	-18								
	18	L	2.8	-40	-71	-18								
	19	L	2.63	-25	-85	2					3.21	-36	-71	-18

Brain regions showing significant task × drug interactions were identified by contrasting rCBF during WM (all delays) between the placebo and drug conditions. To identify brain regions showing higher rCBF during task and physostigmine (relative to placebo), the interaction contrasts were masked by the activation map from the physostigmine condition for each of the two age groups separately. Similarly, to identify regions showing lower rCBF during task and physostigmine (relative to placebo), the interaction contrasts were masked by the activation map from the placebo conditions for each age group. Age group × drug interactions were identified by contrasting the physostigmine-induced changes in task-specific rCBF between the two age groups. Statistical significance was assumed at a voxel level of $p < 0.005$ and an uncorrected cluster level of $p \leq 0.05$.

We used a previously reported locus in medial visual cortex that showed task-related increases in rCBF during physostigmine in young individuals. A twenty-mm sphere was placed on this locus of the medial visual cortex as well as on the locus of the lateral visual cortex identified in the task × drug × group interaction, and volume mean rCBF values were obtained for the two age groups.

Cortical regions with significant rCBF increases during a parametrically varied working memory task before and during physostigmine infusion in young and older individuals ($p < 0.05$ voxel-level, 50 contiguous voxels, local maxim 8-mm apart). For each brain region showing significant responses are indicated hemisphere, Brodmann areas, Talairach and Tournoux brain atlas coordinates [54], and Z-scores for each comparison. Interactions where older subjects showed significantly larger effects than young subjects are shown in bold.

Table 2

Placebo														
Brain areas	BA	Hem	Young group			Old group			Age × task interaction					
			Z score	x	y	z	Z score	x	y	z	Z score	x	y	z
Superior frontal	8/9	R	2.63	19	37	33								
	9	R	2.3	24	41	27								
Anterior middle frontal	9	R	2.78	22	39	30								
	9/46	R	3.26	22	43	13								
	10/46	R	3.46	24	47	16								
	10/46	L	2.36	-24	41	16								
Inferior frontal	45	R	3.01	20	37	9								
	8/6	R	2.59	26	3	25	2.71	26	3	25				
	8/6	R	2.33	26	-3	24								
	8/6	R	1.97	36	3	32								
Inferior frontal/insula	46	R	2.26	38	30	15								
	45	R	2.58	33	28	5					3.15	33	28	5
	13	R	3.36	31	14	18					2.03	-41	14	15
	45	L	2.28	-40	12	14					2.00	-43	12	21
	45	L												
	45/13	L	2.35	-43	16	1								
Anterior cingulate	45/13	L					2.27	-27	16	4				
	47/13	L	2.64	-36	16	1	2.32	-24	16	-6	2.41	-38	18	-3
	32	R	2.96	10	18	36					3.42	12	18	36
	32	R	2.16	15	32	-6	2.95	15	30	-6				
	24/32	R	2.03	12	30	-2	2.62	20	30	-6				
	32	R					2.33	17	34	-2				
	32	R	2.86	19	35	2	2.86	19	26	-6				
	32	R	2.35	6	28	1								

Placebo															
Brain areas		BA	Hem	Young group			Old group			Age × task interaction					
				Z score	x	y	z	Z score	x	y	z	Z score	x	y	z
Hippocampus	11/25	L						3.18	-15	30	-13	3.41	-17	35	-5
	32	L		1.98	-1	34	1								
		R		2.15	27	-36	5								
		L										2.00	-18	-21	-5
		L		2.01	-22	-13	-15	2.84	-29	-30	-9	2.13	-24	-27	-9
Ventral temporal	35	R		2.6	17	-36	1								
	37	R		2.09	17	-46	-10								
	37											2.81	-48	-58	-14
Occipital	37											2.76	-41	-60	-21
	18	R		5.41	36	-71	-18	4.27	33	-79	-18	2.63	15	-71	-18
	18	R										2.05	8	-77	-18
	18	R		2.48	1	-71	-4								
	19	R		3.91	22	-71	17	4.19	19	-65	21	2.08	13	-69	14
	19	R		3	17	-85	-1								
	17	L										2.36	-15	-100	-16
	18	L		3.29	-32	-71	-18	4.35	-31	-77	-11	2.54	-40	-79	-1
	18	L		3.23	-34	-83	-15	4.31	-25	-83	-8	2.07	-41	-71	-7
	19	L										2.31	-20	-79	-8
Basal ganglia	19	L		3.64	-29	-89	2					2.12	-20	-93	-2
		R		3.36	10	-21	2	2.85	-15	-9	-1	3.16	12	4	-7
		R		3.28	12	1	-7	2.47	-8	-3	-7	2.09	19	-5	-15
		R		3.17	12	8	-3								
		L		2.45	-31	-15	-8								
	L						2.95	-24	1	14					

Physostigmine infusion														
Brain areas	BA	Hem	Young group			Old Group			Age × task interaction					
			Z score	x	y	z	Z score	x	y	z	Z score	x	y	z
Inferior frontal	8/6	R					2.57	36	18	22				
	45/46	R					2.32	34	32	15				

Physostigmine infusion													
Brain areas	BA	Hem	Young group			Old Group			Age × task interaction			z	z
			Z score	x	y	Z score	x	y	Z score	x	y		
Inferior prefrontal/insula	47/13	L				2.60	-40	26	19	2.09	-41	35	16
	45/13	L				2.27	-41	24	12				
Cingulate	32	R	2.78	3	39	5							
	32					2.36	10	30	-6				
	11/25					2.79	12	12	-14				
	11/25					2.58	12	22	-10				
	32	L				2.7	-25	16	15	2.24	-41	24	12
	45	L								2.14	-34	20	18
	11/25	L				2.57	-17	28	-13				
Hippocampus		R				2.81	29	-17	-15	2.67	27	-21	-15
Temporal	27	R	2.06	15	-30	-5	17	-7	-11	2.08	36	-23	-12
	27/35	R	2.04	12	-29	-12	36	-25	-16				
	19/37	R				4.22	22	-56	-10	2.96	20	-56	-7
	37	R				4.12	33	-56	-17	2.51	33	-56	-17
	36	L								2.88	-43	-36	-16
	36/20	L								2.66	-29	-32	-16
	39/19	L	2.59	20	-42	-20				2.74	-24	-48	-10
Occipital	18	R	3.21	38	-71	-18							
	18	R	1.84	26	-65	-18							
	19	R	4.26	20	-79	-1							
	19	R	4.13	13	-67	0							
	19	R				4.11	20	-67	17	2.26	34	-79	-1
	19	R								2.26	29	-81	10
	18	L	4.45	-20	-79	10				2.94	-18	-77	10
	18	L				3.85	-27	-75	-18	2.45	-32	-77	-15
	18	L				4.45	-32	-87	2	2.84	-34	-87	-1
	18	L				3.98	-27	-93	-2	2.93	-25	-93	-2
	18	L								2.23	-3	-91	-8
	18	L								2.13	-10	-77	-18
	19	L								2.92	-15	-71	3

Physostigmine infusion															
Brain areas	BA	Hem	Young group			Old Group			Age × task interaction						
			Z score	x	y	z	Z score	x	y	z	Z score	x	y	z	
Basal ganglia			1.83	3	-30	-2									
							3.36	-18	10	-14	2.96	-18	8	-14	
											2.49	-4	8	0	
							2.46	-10	3	-7	2.20	-13	6	-7	

Table 3

Cortical regions with significant rCBF drug-induced changes during a parametrically varied working memory task in young and older individuals ($p < 0.005$ voxel-level, uncorrected $p < 0.05$ cluster-level, local maxim 4-mm apart). For each brain region showing significant responses are indicated hemisphere, Brodmann areas, Talairach and Tournoux brain atlas coordinates [54], and Z-scores for each comparison. Interactions where older subjects showed significantly larger effects than young subjects are shown in bold.

Brain Areas	BA	Hem	Young group			Old group			Age $\times$ task interaction					
			Z score	x	y	z	Z score	x	y	z	Z score	x	y	z
Drug-induced rCBF decreases														
Superior frontal	9	R	5.23	22	32	33	2.68	31	26	22				
	8/9	R					2.74	19	41	30				
	8/9	R					3.96	26	41	16				
	8						5.42	27	8	28				
Ant mid frontal	10/46	R	3.99	20	39	19	4.26	20	43	16				
Middle frontal	6	R					2.82	29	-3	35				
Inferior frontal	8/6	R	4.07	33	3	25	3.51	27	-3	24				
	8/6	R	3.87	29	-5	38	3.03	31	-5	38				
	8/6	R					5.05	27	8	25				
Inf frontal/insula	45	R	4.88	22	45	2	4.66	27	12	21				
	45	R	3.41	31	22	4	4.42	29	10	18				
	45	R	3.58	38	24	19								
	47	R					3.75	27	-1	21				
Temporal	13/45	R	3.60	31	18	11								
	23/31	R	4.48	22	-50	25								
	31	R	3.71	24	-60	21								
	39/19	R	3.59	29	-65	21								
	37	R	4.14	34	-56	0								
	37	R	3.90	45	-58	-21								
Occipital	18	R	4.21	34	-83	-8								
	18	L	4.25	-31	-91	-12								
	18	L	3.65	-34	-87	-5								
	18	L	3.37	-38	-75	-18								
	19	L	4.25	-31	-91	-12								

Brain Areas	BA	Hem	Young group			Old group			Age × task interaction						
			Z score	x	y	z	Z score	x	y	z	Z score	x	y	z	
Drug-induced rCBF increases															
Occipital	19	R									3.7	40	-73	-15	
	19	R									3.43	33	-87	-15	
	19	L						4.17	-18	-71	-22				
	19	L													
	19	L	4.01	-15	-67	-7	3.25	-24	-69	-7	4.59	-38	-71	-18	
	19	L						3.22	-25	-60	-21	3.61	-27	-71	-22