Nicotinic Versus Muscarinic Blockade Alters Verbal Working Memory-Related Brain Activity in Older Women

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Objectives: An important aspect of furthering our understanding of the central nervous system function after menopause is to examine the cerebral circuitry that appears to be influenced by cholinergic antagonist drugs in the presence and absence of estrogen. This pilot study investigated the effects of two anticholinergic drugs on brain activation and working memory performance in postmenopausal women not taking estrogen. This approach simulates the effects of age- or disease-related neuroreceptor or neuronal loss by temporarily blocking pre- and postsynaptic muscarinic and nicotinic cholinergic receptors. Design: Six healthy postmenopausal women took part in three drug challenges using the antinicotinic drug mecamylamine (MECA, 20 mg, oral), the antimuscarinic drug scopolamine (SCOP, 2.5 µg/kg, IV), and placebo during functional magnetic resonance imaging. The cognitive measure was a visually presented verbal N-back test of working memory. Results: Neither MECA nor SCOP significantly impaired performance on the verbal N-back. Functional magnetic resonance imaging results showed greater increases in frontal lobe activation in the placebo condition relative to each drug condition with different specific regional activation for MECA and SCOP. Conclusions: These preliminary results suggest that brain activation patterns are sensitive to cholinergic modulation in postmenopausal women and that differential effects may be observed following nicotinic versus muscarinic blockade. This approach offers a potentially valuable method for modeling age-related changes in brain function, and the findings may have implications for cholinergic contributions to normal and pathologic aging. (Am J Geriatr Psychiatry 2008; 16:272–282)

Key Words: Working memory, postmenopausal women, fMRI, cholinergic system
Converging evidence from psychopharmacological, neuroimaging, and psychological studies shows that the cholinergic system has a specific modulatory role in cognitive processing. In humans, the cholinergic system has been implicated in many aspects of cognition including the partitioning of attentional resources, working memory, inhibition of irrelevant information, and improved performance on effortful tasks. Prior research has shown that older adults perform more poorly than younger adults in a variety of cognitive domains including working memory. Cholinergic deficits due to degeneration of basal forebrain cholinergic nuclei appear to be intimately tied to the cognitive deficits in attention, learning, and memory in patients with neurodegenerative disorders such as Alzheimer disease and Lewy body dementia.

Further, the activity of the central nervous system cholinergic system may be a primary determinant of the effectiveness of attentional, learning, and memory mechanisms. Intriguingly, cognitive symptoms reported by women at menopause also include difficulties in memory, attention, and word finding, and some studies have shown an acceleration of cognitive problems of aging after menopause. Women also have a higher risk than men of developing cholinergic-related dementing disorders such as Alzheimer disease.

What has not yet been fully elucidated is how the effect of aging on neurotransmitter systems affects the cognitive processes these systems support. This study examined the effects of cholinergic antagonists on working memory performance and related brain activation in cognitively normal postmenopausal women without hormone therapy. Specifically, the effects of nicotinic and muscarinic blockade on working memory performance and brain activation patterns were examined in older women.

In the working memory models of Baddeley and Norman and Shallice, the central executive or supervisory attention system is a limited capacity processing resource that coordinates necessary operations for a task. Warburton and Rusted proposed that the cholinergic system modulates processes that are supported by a limited capacity central executive and influences information processing during tasks that engage the control processes for the allocation of cognitive resources. Additionally, age-related changes in cognition may occur as a result of impairments in allocating necessary resources to a task, thereby implicating negative alterations in the cholinergic system as one of the main factors in cognitive aging. Thus, there is a link between cholinergic dysfunction and age-related cognitive dysfunction.

Prior research by Sunderland and Newhouse using scopolamine (SCOP), a muscarinic antagonist, and mecamylamine (MECA), a nicotinic antagonist, have shown that these agents can be used to simulate age- and disease-related cognitive impairments. These studies have shown that muscarinic and nicotinic blockade impairs performance on initial sensory processing, attention, and psychomotor function, thereby implicating a role for the cholinergic system in the initial processing and encoding of information into memory. Thus age- and disease-related differences in cholinergic system integrity may influence sensitivity to anticholinergic challenge on cognitive performance.

Actions of the cholinergic system in cognitive processing have also been revealed by neuroimaging studies (see Ref. 15 for a review). Increased cortical activity after physostigmine, a cholinesterase inhibitor, compared with placebo has been shown during a working memory task in extrastriate and intraparietal areas during encoding, but not during retrieval. Physostigmine administration also facilitated visual attention by increasing activity in the extrastriate cortex during a repetition priming task. A number of studies have examined the effect of SCOP on brain activation during cognitive task performance in younger adults and in older adults. In general, when SCOP impaired performance, there was also a decrease in brain activity relative to placebo in regions required for task performance. The tasks utilized in these studies were auditory conditioning, repetition priming, associative encoding, delayed-matching-to-sample, recognition memory, and object location learning.

Nicotinic blockade with MECA has not been examined in humans using functional magnetic resonance imaging (fMRI), nor have the effects of nicotinic or muscarinic blockade on working memory. The current study examined the brain activity associated with working memory and interaction with the cholinergic system after menopause. A prior study by Green et al. showed that high-dose muscarinic and combined muscarinic and nicotinic cholinergic blockade can impair performance on the N-back test of working memory in younger adults. The current study examined the effects of nicotinic and
muscarinic cholinergic blockade separately on N-back performance and associated brain activation in cognitively normal older postmenopausal women utilizing fMRI. Given the proposed role of the cholinergic system in central executive function and the known age-related changes in working memory, we utilized an anticholinergic challenge paradigm to examine the effects of MECA and SCOP on working memory performance and brain activation in older postmenopausal women. We hypothesized that anticholinergic drugs would result in decreases in frontal cortical activation relative to placebo during a working memory task.

**METHODS**

**Subjects**

Subjects were six cognitively normal women, aged 51–72, $M = 58.8$ (SD = 9.1) who were postmenopausal for an average of 9.9 years since their last menses (SD = 11.0). Subjects had an average of 16.6 years of education (SD = 1.4). Subjects were required to be postmenopausal, without menses for 1 year, have follicle-stimulating hormone (FSH) levels $>30$ mIU/mL, without surgically induced menopause, and without the use of hormone therapy for at least 1 year. These requirements for participation were utilized to ensure a homogeneous sample with regard to hormone status, which has been shown to affect brain activation (i.e., Ref. 25). Exclusion criteria included history of breast cancer, smoking, heavy alcohol or coffee use, significant cardiovascular disease, asthma, active peptic ulcer, hyperthyroidism, pyloric stenosis, narrow angle glaucoma, epilepsy, or current or past Axis I psychiatric disorder.

Initial screening and study procedures took place at the University of Vermont General Clinical Research Center. After signing informed consent documents, subjects gave a medical history and underwent a physical and laboratory tests assessing hematopoietic, renal, hepatic, and hormonal function. Subjects were cognitively evaluated using the Mini-Mental State Exam (MMSE),$^{26}$ Brief Cognitive Rating Scale,$^{27}$ and the Mattis Dementia Rating Scale (DRS)$^{28}$ to establish a Global Deterioration Scale (GDS) score rating the degree of cognitive impairment.$^{27}$ Subjects were required to have an MMSE score greater than or equal to 27, a Mattis DRS score of 123 or greater, and a GDS score of 1 or 2.

Behavioral screening consisted of a partial Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)-Text Revision$^{29}$ to establish the presence or absence of Axis I psychiatric disorders. In addition, subjects completed the Beck Depression Inventory (BDI).$^{30}$ A cutoff score of 10 was used for the Beck Depression Inventory, and subjects scoring over this criterion were discontinued from further participation. All subjects met required criteria for the cognitive and behavioral screening.

**Cholinergic Challenge Procedure**

After screening at University of Vermont, subjects took part in three cholinergic challenges and fMRI testing sessions at Dartmouth-Hitchcock Medical Center. At each visit, subjects performed a baseline motor skill sobriety test to have as a comparison with a second test before discharge in the afternoon. An intravenous line (IV) was inserted and baseline vitals were assessed. A double-blind, double placebo method of administration of the challenge drugs was followed. Subjects received one of the following medications: 2.5 g/kg SCOP (calculated as the base), 20 mg MECA (calculated as the salt), or placebo. SCOP was administered intravenously and MECA was administered orally. At time 0, a capsule was administered containing MECA or placebo. Thirty minutes later, an injection of SCOP or saline placebo was administered through the IV. On each day, only one of the drugs was active or both were placebo. The order of the drug administration across the 3 days was counterbalanced. Ninety minutes after the injection and 2 hours after oral pill administration, the fMRI session began at a running time of 120 minutes. Structural and functional MRI studies took approximately 70 minutes, after which subjects and the experimenter completed behavioral assessment measures. Subjects completed the Profile of Mood States (POMS),$^{31}$ Stanford Sleepiness Scale,$^{32}$ Subjective Visual Analogue Scale (SVAS),$^{14}$ and a Physical Symptom Checklist (PSCL). The experimenter completed the Brief Psychiatric Rating Scale (BPRS)$^{33}$ and Objective Visual Analogue Scale (OVAS)$^{14}$.
Vital signs and pupil diameter were assessed at six time points throughout the session at running times of 0, 30, 60, 120, 210, and 240 minutes. At the end of the study day, after passing the sobriety test to the satisfaction of the research nurse and covering physician, subjects were discharged.

**fMRI Working Memory Task**

We used a visually presented verbal N-back task to probe working memory circuitry, wherein subjects saw a string of consonant letters (except L, W, and Y), presented in upper or lower case to control for pattern recognition, one every 3 seconds. Four conditions were presented: 0-back, 1-back, 2-back, and 3-back. The 0-back control condition had a minimal working memory load; subjects were asked to decide if the current letter matched a single target letter that was specified before the epoch began. In the 1-back condition, they were asked to decide if the current letter matched the previous one. During the 2-back condition, the task was to decide whether the letter currently presented matched the letter that had been presented two back in the sequence; the more difficult 3-back condition followed the same pattern. Subjects responded to all items by button press through an MRI compatible fiber optic button response system (LUMItouch, Lightwave Medical Industries Ltd., Vancouver, British Columbia, Canada) to indicate whether the item matched the target condition. Stimuli were delivered through an MR-safe goggle and headphone system (Resonance Technology, Inc., Northridge, CA). Experimental tasks were presented by computer interface and were programmed using the Presentation software package; the computer recorded subject responses and reaction times. This task is highly robust in producing bilateral frontal and parietal activation in healthy young and elderly controls and is sensitive to differences in patient groups.34–38

**fMRI Scan Procedure and Preprocessing**

All scans were acquired using the same GE Signa 1.5 T Horizon LX scanner with echo speed gradients using a standard head radio frequency (RF) coil. fMRI parameters were repetition time (TR) 2,500 milliseconds, echo time (TE) 40 milliseconds, field of view (FOV) 24 cm, NEX 1, yielding 29 contiguous 5 mm sagittal slices in a 64 × 64 matrix with 3.75 mm² in-plane resolution. Initial volumes before spin saturation were discarded. Spatial realignment was performed on all raw scan data before further analysis to remove any minor (subvoxel) motion-related signal change. All volumes for each subject were normalized into standardized Montreal Neurological Institute (MNI) atlas space using SPM2 (Wellcome Department of Cognitive Neurology, University College, London). During spatial normalization all scans were resampled to 2 mm³ isotropic voxels. Spatial smoothing to a full width half maximum of 10 mm was performed before statistical analysis.

**fMRI Analyses**

fMRI analysis included statistical parametric mapping on a voxel-by-voxel basis using the general linear model approach39 as implemented in SPM2. This procedure involves deriving one mean image per individual for each relevant contrast in the activation task (e.g., 3 > 0 back) after accounting for the hemodynamic response function. These contrast images were then used for the second level multisubject or between-group random effects analyses.40 These contrast images were further analyzed using standard paired t test and analysis of variance procedures in SPM2. Given the preliminary nature of this study and small sample size, the critical significance level for group level analyses was based on clusters of activated voxels with the probability threshold set at p_{corr} < 0.05 and a minimum cluster extent (k) of three contiguous voxels. We chose to use p values corrected for searching the whole brain volume to attempt to minimize Type I error, given the small sample size. Interpretation of imaging data focused on differences in targeted brain regions known to be involved in working memory processing based on prior functional imaging and lesion studies, including the prefrontal and parietal cortices and interconnected components of the attentional network shown to be activated in positron emission tomography (PET) and fMRI studies.41,42 Focusing on differences only in regions which constitute the brain network activated by this task and targeting our hypotheses to these areas also provides an additional means of minimizing Type I error.
RESULTS

Performance Data

N-back scores were adjusted for false alarms with the following formula: adjusted score = proportion (hits) – proportion (false alarms). This formula corrects for subjects adopting a strategy where they endorse all items as targets. Data were analyzed with a 2 (drug versus placebo) × 4 (working memory load) analysis of variance for SCOP and MECA separately. The expected effects of working memory load were found in both the SCOP \(F_{[3,15]} = 4.19\), \(p < 0.05\) and MECA \(F_{[3,15]} = 24.0, p < 0.001\) analyses. No interactions of drug and working memory load were found for SCOP \(F_{[3,15]} = 0.44, p > 0.70\) or MECA \(F_{[3,15]} = 0.33, p > 0.80\). Neither SCOP nor MECA impaired performance relative to placebo on the N-back task \(F_{[1,15]} = 0.14, p > 0.7, F_{[1,15]} = 0.95, p > 0.3\), respectively.

Neuroimaging Data

Performance was examined on the most difficult condition of the N-back task, the 3-back condition, compared with the 0-back control condition, as the more difficult working memory load conditions have proved most sensitive to group differences in our prior studies. Activation related to SCOP and MECA challenges was examined separately as was done for the performance data. Across drug conditions (SCOP, MECA, placebo), the expected pattern of bifrontal, biparietal, and bicerebellar activation was seen for activation during 3-back relative to 0-back, consistent with our prior work.34–38To determine the effects of anticholinergic challenge on working memory circuitry, we examined brain activation patterns for each drug relative to placebo in three different ways. First, we examined the drug-induced reduction in brain activation by comparing placebo relative to each drug condition. We hypothesized that regions with decreased activation on drug relative to placebo represent those areas where anticholinergic challenge results in diminished working memory-related brain activation. Second, we examined whether regions existed with increased activation under each drug relative to placebo suggesting compensatory activation of neural circuitry recruited to maintain task performance during anticholinergic challenge. Third, we directly compared MECA with SCOP to examine the differences in antinicotinic and antimuscarinic drug challenges on working memory-related brain activation. These contrasts are described below, with results from paired t test comparisons between drug conditions (MNI coordinates, cluster extent, and region descriptions) presented in Table 1. As noted above, results discussed below and in Table 1 include only those regions with \(p_{corr} < 0.05\). Although other clusters of activation can be observed in the figures, these did not survive statistical correction for the whole brain search volume.

The potential impairing effect of the drugs was assessed by examining brain regions with less activation during each drug challenge relative to placebo. Diminished activation during MECA challenge relative to placebo was seen in the right medial frontal gyrus and right superior frontal gyrus (Figure 1). A similar effect was found for SCOP challenge in which there was less activation for SCOP relative to placebo in the right middle frontal gyrus and the left precuneus (Figure 2). Overall, the distribution of regions with diminished activation on drug (SCOP or MECA) relative to placebo was similar, though more pronounced for SCOP than for MECA.

The potential for compensation during anticholinergic drug challenge was assessed by examining re-

### Table 1

<table>
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<tr>
<th>Contrast</th>
<th>MNI Coordinates X Y Z</th>
<th>Cluster Extent</th>
<th>Region Description</th>
<th>(p_{corr})</th>
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<tr>
<td>PLC &gt; MECA</td>
<td>4  -22  60</td>
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<td>8  62  38</td>
<td>562</td>
<td>Right superior frontal gyrus (BA 9)</td>
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<td></td>
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<td>4,220</td>
<td>Left precuneus (BA 31)</td>
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<tr>
<td>MECA &gt; PLC</td>
<td>10 -40 -4</td>
<td>502</td>
<td>Right parahippocampal gyrus (BA 30)</td>
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<td></td>
<td>-6 -44 42</td>
<td>640</td>
<td>Left cingulate gyrus (BA 31)</td>
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regions with greater activation during drug challenge relative to placebo. Significantly greater activation was found in the right parahippocampal gyrus during the MECA challenge relative to placebo. No other regions showed significantly greater activation on drug (either MECA or SCOP) than placebo.

The differential effects of nicotinic versus muscarinic challenge on working memory-related brain activation during the 3-back were examined using a paired t test in which two images per subject were entered into the model. Comparing the 3 > 0 back contrast image for the MECA and SCOP challenges allowed direct comparison of brain areas activated after nicotinic versus muscarinic blockade. In these analyses, greater activation on MECA relative to SCOP was found in the left middle frontal gyrus, whereas greater activation on SCOP relative to MECA was found in the right superior parietal lobule and in the left cingulate gyrus (Figures 3A, B). Thus, both muscarinic and nicotinic blockade resulted in specific alterations in brain activation in working memory circuitry relative to placebo, and the effects of these anticholinergic drugs appeared to be dissociable.

Behavioral Measures

Questionnaires were completed by the participants and experimenter after returning from the MRI suite to assess whether there were any negative effects of the anticholinergic drugs or fMRI session on mood and physical symptoms. Similar to the performance data analysis, the behavioral data were analyzed separately for SCOP and MECA relative to placebo challenge. Overall, there were no effects of either SCOP or MECA relative to placebo on the subjective measures: the POMS, the Stanford Sleepiness Scale, the SVAS, and the PSCL. On the experimenter-completed OVAS the expected effects of SCOP were observed with subjects being rated as more drowsy ($t_{[5]} = 3.79, p < 0.05$), more fatigued ($t_{[5]} = 2.61, p < 0.05$), and less alert ($t_{[5]} = 2.60, p < 0.05$) relative to placebo. There were no effects of MECA relative to placebo observed on the OVAS.

Vital Signs

Blood pressure, pulse, and pupil diameter were monitored at six time points throughout the challenge.
day. Analyses were conducted on the maximum change score from the baseline measurement for each variable. Only two significant changes were observed, both of which were expected. SCOP was associated with a higher pulse rate relative to the placebo condition ($t_{[5]} = 4.05, p < 0.01$). MECA was associated with a significantly greater decline in systolic blood pressure relative to the placebo condition ($t_{[5]} = 3.21, p < 0.05$).

**DISCUSSION**

This study is the first to directly compare the effects of anticholinergic blockade of nicotinic and muscarinic systems during a working memory task using fMRI. A pattern of diminished activation on drug relative to placebo was found for both MECA and SCOP with differing specific frontal regions affected by each of the drugs. Overall, this may demonstrate that the activity of brain regions involved in performance of the N-back task was impaired by anticholinergic blockade. Performance on the N-back task was not significantly impaired by the cholinergic antagonists. It is possible that the lack of a significant effect of the drugs on performance may be secondary to the dose of SCOP particularly and the relatively small sample size. Our performance findings are somewhat different from that of Green et al., who saw significant effects of SCOP and combined SCOP-MECA on N-back performance in younger adults. However, Green et al. used a dose of SCOP that was on average 2.5 times larger than that used here and their sample size was twice as large. Thus, taken together with prior studies, these data lend support to a model that impairment of the cholinergic system leads to reduced ability to activate frontal regions typically involved in working memory processing.

We propose that in our postmenopausal sample the recruitment of additional frontal brain areas may be a result of activity of the cholinergic system. Our data showed that when the cholinergic receptors are partially blocked, frontal regions are less active relative to placebo. We are unable to differentiate whether the frontal deficits seen in this study are a result of age- or menopause-related effects on brain
FIGURE 3. Statistical Parametric Maps Showing Areas with Greater Activity on MECA Relative to SCOP [A] and SCOP Relative to MECA [B] (p < 0.05) Displayed Over the MNI Template Surface Rendering. See Text for Results of Statistical Analyses. R: Right, L: Left
activity. If menopause has similar or additive effects to aging on cholinergic system activity and subsequent influences on task-related brain activity, then similar deficits may be produced.

The data in the current study can be compared with data from Saykin et al., who examined the effects of donepezil, a cholinesterase inhibitor that increases both nicotinic and muscarinic signaling, on N-back performance in subjects with mild cognitive impairment (MCI). They found increases in frontal activation in MCI subjects after donepezil treatment. In these patients with MCI, frontal regions were recruited during this task with the aid of the procholinergic drug, suggesting that pharmacological manipulation counteracted dysfunction of the cholinergic system to allow successful performance of the working memory task. Taken together, data from the current study and Saykin et al. support the idea that the cholinergic system is important for successful working memory performance and illustrate that cholinergic influences on task-related effortful processing can be examined with fMRI.

In addition, we found a dissociation for these activation patterns for nicotinic versus muscarinic challenges. Studies comparing nicotinic and muscarinic effects on the same cognitive process have been few. In a series of studies, Nathan and colleagues and Little et al. have shown that muscarinic blockade consistently produces larger effects than nicotinic blockade on working memory performance, but combined antagonism showed a greater magnitude of impairment than either drug alone, suggesting interaction of muscarinic and nicotinic mechanisms for optimal working memory performance. The potential mechanism(s) for these effects and interaction have been suggested by two prior neuroimaging studies. In a xenon inhalation study, Gitelman and Prohovnik showed that SCOP produced frontal cortex flow reduction that correlated with SCOP-induced memory deficits and MECA produced a perfusion deficit in parietotemporal cortex. In a PET study of visual processing, Mentis et al. were able to demonstrate that muscarinic activities predominated in primary and secondary visual processing areas (striate cortex, lateral visual association areas), whereas nicotinic stimulation appeared to affect areas consistent with attention to the visual stimulus (thalamus and inferior parietal regions).

Prior functional imaging studies of nicotinic stimulation have strongly suggested nicotinic modulation of attentional processing. Thiel et al. and Lawrence et al. showed a stimulus-specific modification of neural activity in parietal cortex consistent with improved signal-driven attentional performance on a visual spatial orienting task and visual processing tasks following nicotine. Interestingly, Kumari et al. found that administration of nicotine during the performance of a verbal N-back task also showed parietal activity modulation and, as with our results with MECA, found alterations in a distributed neural network which the authors proposed is related to online task monitoring and attention. Increased activation in the superior parietal region seen in the placebo versus MECA contrast from this study (Figure 1) is consistent with this interpretation. A hypothesis suggested by prior neuroimaging studies suggests that nicotinic and muscarinic systems may be responsible for different aspects of task performance; e.g., nicotinic stimulation may affect attentional modulation, rather than simply acting as a general signal gain enhancing system, whereas muscarinic effects may be more tied to stimulus processing or encoding.

The results of the present study tend to support this hypothesis, as the patterns of cortical activity shift were different between muscarinic and nicotinic antagonisms compared with placebo rather than simply an alteration in the intensity of task-related activation. These results are also consistent with the proposal of Sarter et al. that the cholinergic system optimizes signal-driven detection (bottom-up) processes as well as top-down knowledge-based detection and filtering of irrelevant information. Nicotinic and muscarinic mechanisms may influence separate components of these processes and attentional changes in normal and pathologic aging.

Finally, working memory has been shown to be affected by the loss of circulating estrogen after menopause. The loss of estrogen during menopause and associated alterations in cognitive functioning may be a result of the effect of estrogen loss on cholinergic system functioning. We have shown that 3 months of estrogen treatment attenuated the effects of anticholinergic-induced impairment on cognitive task performance. Thus, future studies should directly examine the effects of the estrogen-cholinergic interaction on brain activation in postmenopausal women.
Some caveats should be considered with the interpretation of the current results. Although the design of this study was an intensive within-subjects design, this study had a small sample size, thus limiting the power to detect some effects of anticholinergic drugs on performance and related brain activity. Additional brain areas, particularly in the drug versus placebo comparison, may have survived correction with a larger sample size. In addition, we did not use a range of doses of the anticholinergic drugs. A larger range of doses would allow for differentiation of brain and performance effects of the different antagonists. Further studies will benefit from using a range of doses to better establish correlates between performance and brain activity. Also, we were not able to separate effects of menopause from aging in this study. To do so would require studying women on and off hormone therapy. Additionally, as our subjects were a small sample of healthy, highly educated postmenopausal women not on hormone therapy, these results do not generalize to the population of all older women. Finally, the N-back task is a complex working memory task that does not allow for the dissociation of attentional, storage, and manipulation components of the processes necessary to perform the task. Tasks that allow for these dissociations will need to be examined to differentiate the involvement of nicotinic and muscarinic systems on attention and memory processes.

In summary, this preliminary study of the effects of anticholinergic drug challenge on brain activity in postmenopausal women showed areas of decreased activation in the frontal lobe under cholinergic blockade which were different for muscarinic versus nicotinic blockade. We interpret these data to suggest that both nicotinic and muscarinic systems are important for the performance on working memory tasks and contribute differentially to task performance. Our subjects were postmenopausal women who were not taking hormone therapy and thus had low levels of circulating estradiol. We have previously shown that estrogen treatment attenuates the effects of anticholinergic challenge on tests of attention and thus estradiol status may be important in influencing the activity of the cholinergic system. A recent study by Smith et al. demonstrated the influence of estrogen and progesterone treatment in postmenopausal women on brain activation during a working memory task. This study found differences in brain activation between the hormone and placebo condition in frontal regions typically involved in working memory tasks. Thus, estrogen effects on brain activation patterns are important to examine in postmenopausal women, and future studies should examine effect of the estrogen-cholinergic system interaction on specific cognitive operations using fMRI.

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fMRI in Older Women During Anticholinergic Challenge

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