ORIGINAL ARTICLE

The effect of oral medications on fMRI brain activation: A randomized, double blind, controlled pilot trial of older women with overactive bladder

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Abstract

Introduction and aim Observational studies have associated oral anticholinergic medications for overactive bladder (OAB) with cognitive impairment. This is the first pilot trial to compare the effects of two classes of OAB medications on brain activity in women. We evaluated the effect of anticholinergic versus non-anticholinergic (Non-Ach) interventions on regional brain activation during a cognitive task.

Methods Twelve cognitively normal women seeking OAB therapy were recruited to a randomized, double-blind, parallel, controlled pilot trial. Whole-brain regional activity at baseline and 29 ± 1 days postintervention was assessed with functional magnetic resonance imaging during a working memory task. Average activation strength by region was compared after anticholinergic, beta-3 agonist, or placebo. Two-way ANOVA compared effects of group and time on average activation strength in anticholinergic versus Non-Ach (beta-3 agonists or placebo) groups.

Results The mean (SD) age and body mass index of 12 women were 61 (7) years and 36 (7) kg/m^2. Baseline depression and learning scores differed in the anticholinergic group ($n = 3$) versus the Non-Ach group ($n = 9$). Right mamillary body activation postintervention was higher after Non-Ach exposure (F 4.9, $p < 0.04$). In the full sample of participants at follow-up, there was less activation of the right middle frontal gyrus ($p = 0.02$), superior frontal gyrus ($p < 0.01$), and supramarginal ($p < 0.01$) gyrus.

Conclusion Activation strength in brain regions underlying working memory was lower over time, and recognition scores improved. A powered trial is needed to adequately evaluate for differential effects of OAB oral medications on regional brain activation.

Keywords Anticholinergic · Beta agonist · Cognition · Incontinence · Memory · Overactive bladder

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Introduction

Overactive bladder syndrome (OAB) is characterized by urinary urgency, usually with urinary frequency and nocturia, with or without urgency urinary incontinence [1]. OAB increases in prevalence with advanced age, and urgency urinary incontinence (UUI) is more prevalent in women [2, 3]. OAB symptoms have a negative effect on emotional well-being and activities of daily living such as work productivity and social and family relationships [2]. UUI is associated with numerous comorbid conditions and may be an early manifestation of declining cognitive function [4, 5].

Longitudinal studies have associated dementia with lower urinary tract symptoms such as urinary incontinence [5, 6]. In cross-sectional studies of community-dwelling older adults, those with OAB demonstrate inferior performance

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on tests of executive function [7, 8] compared to their peers with stress incontinence or no urinary complaints.

Conservative therapies including behavioral modifications, pelvic floor therapy, and oral medications are typical initial therapies for OAB. The widespread use of anticholinergic (Ach) oral medication for OAB has been challenged because of association with incident dementia in several longitudinal population-based studies [9–11]. Ach oral medications for bladder indications increased odds of dementia compared to those for other indications [9, 10]. Other than oxybutynin specifically, the association of OAB Ach with short-term cognitive effects has not been demonstrated consistently [11]. The newer β-3 adrenergic agonist (β3) medications are similar in efficacy without known short- or long-term cognitive effects [12, 13].

Biomarkers of OAB and UUI are present in functional neuroimaging studies of brain activity and functional connectivity [13]. Similarly, biomarkers of cognitive impairment have been identified with functional magnetic resonance imaging (fMRI) [14]. The effect of the Ach oral medications on brain activity has not been compared to β3 oral medications or placebo. This study aims to evaluate the effect of short-term exposure to Ach OAB medication on regional brain activity during a working memory task in older women. We hypothesized activation of regions involved in working memory will be lower after Ach exposure compared to placebo or β3.

Methods

Patient selection and enrollment

This registered clinical trial (NCT03817931, clinicaltrials. gov) was initiated in August 2019 with a randomized, parallel, controlled trial. The study was approved by the Baylor Scott and White (#160362), Houston Methodist Research Institute (#Pro00019252) institutional review boards. Recruitment took place from September 2019 through July 2020. The SARS COVID-19 pandemic presented persistent barriers to recruitment starting in March 2020; thus, subject recruitment was discontinued before meeting goals in the original published protocol [15]. English-speaking women ages 50 to 90 years of age seeking therapy from community urology and urogynecology clinics were recruited and screened for eligibility. Exclusion criteria were voiding dysfunction (post-void residual volume ≥ 250 ml), neurogenic bladder, or positive screen for bladder pain syndrome. Per protocol, any recruits screening positive for mild cognitive impairment, severe depression, or severe anxiety were excluded. These screening criteria were defined as Montreal Cognitive assessment (MoCA) score ≤ 26, Patient Health Questionnaire-9 (PHQ9) score ≥ 14, and Hamilton Anxiety Assessment (HAMA) score ≥ 20, respectively. Patients with presence of a self-reported history of central neurologic conditions, stroke, pregnancy, use of medications, or pelvic floor therapy for OAB in the past 6 months were excluded. Patients with contraindications to MRI (metal implants, claustrophobia) or study medications were excluded.

After full informed consent and eligibility were confirmed, all participants were provided an informational handout on behavioral modifications and treatment options for OAB. Baseline data collection included validated questionnaires on OAB symptoms: The Patient Perception of Bladder Condition (PPBC), Overactive Bladder Questionnaire-Short Form including the Symptom Bother Score (SBS), and health-related quality of life score (QOL) were completed. Higher PPBC and QOL scores are indicative of improvement while higher SBS indicates worsening of symptoms. Subjects were instructed on how to complete a 24-h bladder diary prior to their baseline imaging. A health history questionnaire and review of all current medications were performed. Subjects were instructed to avoid any changes to their current medications during the study period.

Study aims

The primary aim of this study was to compare regional brain activity after Ach oral medication versus placebo and β3 medication. The secondary aim was to compare cognitive scores after exposure to Ach oral medication versus placebo and β3 medication. Prior to unmasking the study team to allocations, the investigators met to reach consensus on how to proceed with the most clinically relevant analysis given the early closure of this study. To evaluate the primary and secondary study aims, the decision was made to combine the β3 and placebo groups into a group titled "Non-Anticholinergic (Non-Ach)" for comparison to the Ach cohort.

Interventions

Baseline and postintervention imaging and questionnaires were completed at the Houston Methodist Hospital Translational Imaging Center. The day of baseline testing, patients received 30 capsules in a vial from the Investigational Drug Service pharmacy. Blinding to allocation and randomization was managed by an investigational drug pharmacy. To blind subjects and investigators to allocation, the Ach tablets and the β3 tablets as manufactured are placed intact within methylcellulose in an opaque locking gelatin capsule.

Subjects were randomized 1:1:1 to receive 29 ± 1 days of intervention with Ach (solifenacin 5 mg), β3 (mirabegron 25 mg), or placebo. Participants received standardized counseling on lifestyle modifications and fluid management before randomization. Participants, investigators, and outcome assessors were blinded to allocation. Blinding was

maintained until after recruitment and all data collection was complete. Subjects initiated their intervention (1 capsule daily for 29 ± 1 days) following the baseline imaging and cognitive testing.

Outcome assessment

The Rey Auditory Verbal Learning test (RAVLT) is a neuropsychological test widely used to assess cognition in pre-dementia and dementia conditions. RAVLT is sensitive to verbal memory deficits caused by a variety of neurological diseases causing cognitive impairment [16]. During the RAVLT, lists of 15 words are used to assess recognition, learning, and immediate and delayed recall. These raw scores were used to calculate the following summary scores: short-term retention (STR), long-term retention (LTR), learning over trials (LOT), and recognition percentage correct (Recog).

On the dates of imaging, a modification of the RAVLT test was completed where the recognition component was visual rather than auditory. Tests for recall and recognition of RAVLT word lists were performed prior to entering the scanner. Anatomic scans and resting state imaging were followed by a video providing non-verbal instructions for the delayed recognition task. The sequence for the RAVLT testing and imaging protocol is given in Fig. 1. Subjects were instructed to push a button with their dominant hand when they recognized a word from the trial lists. Each single word was displayed on the screen for 5 s. After 29 ± 1 days of the intervention, the same imaging and cognitive testing procedure was performed using different word lists from the RAVLT handbook.

Data acquisition and image processing

Images were acquired in a 3.0-Tesla full-body scanner (Siemens MAGNETOM Vida) with a 20-channel head coil. The baseline and post-intervention sessions included the following scans: (1) three-dimensional T1-weighted MPRAGE structural scan ($0.86 \times 0.86 \times 1.00$ mm^3 spatial resolution); (2) T2*-weighted blood oxygen level-dependent (BOLD) fMRI scans in resting state (TR = 2000 ms, TE = 30 ms, isotropic spatial resolution 2.98 mm) and then during the recognition task. Analysis of Functional NeuroImages (AFNI) software was used for fMRI data processing [17]. The imaging protocol included slice time correction, motion correction, spatial normalization to the Montreal Neurological Institute (MNI) template, and spatial smoothing using a 5-mm full-width-at-half-maximum Gaussian kernel. The resting-state fMRI time series were then temporally band-pass-filtered between 0.01 and 0.1 Hz. After spatial smoothing, individual fMRI activation maps were created using a generalized linear model in MNI space. An averaged group fMRI activation map during the recognition task was then created in which significantly activated voxels were identified using a Student's t-test. The threshold for results was at an uncorrected p-value of 0.01, and statistical significance was assessed after correction for multiple comparisons at cluster level (corrected $p < 0.05$).

Statistical analysis

Baseline characteristics and questionnaire scores were described using mean [standard deviation (SD)], median [(interquartile range (IQR)], or number (%). Shapiro-Wilk test for normality was used to identify parametric and non-parametric characteristics and score data. Bivariate analysis compared characteristics with Fisher's exact test and two-sample t-test or Mann-Whitney test for parametric and nonparametric data. Bladder symptom scores (SBS, QOL, PPBC) and cognitive scores (LOT, STR, LTR, Recog) were compared by two-way ANOVA to assess differences by group, time, and group:time. Group by time interactions were not explored further due the sample size.

Regarding the fMRI results, the mean and standard deviation of the activation strength were calculated for

Fig. 1 Flow chart of the RAVLT and fMRI testing: After six recall trials, participants were positioned for fMRI. Anatomic and resting state images were acquired first. Next, the recognition trial was performed with a television screen displaying single words for 5 seconds each. Participants indicated word recognition by pushing a button. Intervening resting state periods were taken after every six words. This cycle was repeated five times for a total of thirty words
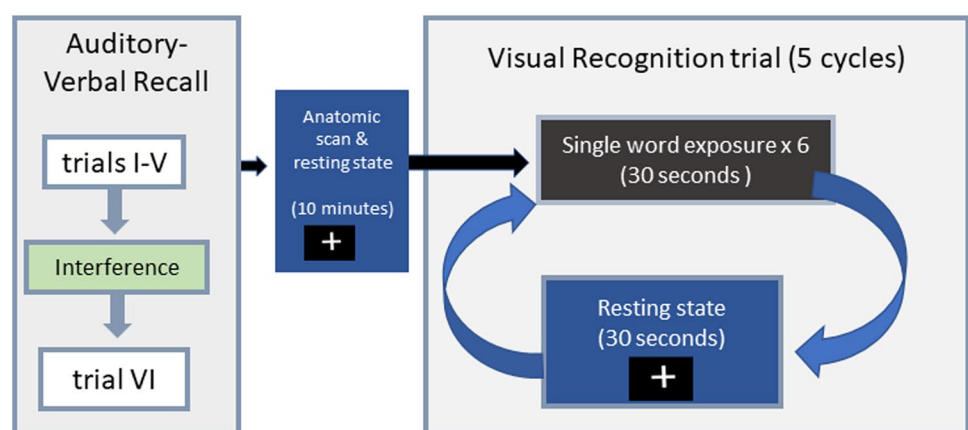
154 regions. The average activation strength (AveAS) in each region was quantified as the average of the t-statistic within that region. Baseline regional AveAS were evaluated with two-sample t-tests for differences by group. Two-way ANOVA was used to explore differences in regional AveAS by group and by time using baseline AveAS as a covariate. Due to small sample sizes, correction for multiple comparisons was not pursued. *P*-values were reported with $p < 0.05$ defining the significance threshold. For the primary outcome measured (regional AveAS), F-statistics and *p*-values are reported for regions with a significant *p*-value (< 0.05) for time, group, or group by time effect. Statistical analysis was completed using RStudio 2021.09.1 © 2009-2021 RStudio, PBC.

Results

Fourteen women were recruited and consented (Fig. 2). Two women dropped out prior to randomization because of scheduling issues (2/14, 14%). Twelve participants were randomized to Ach ($n = 3$), β3 ($n = 5$), and placebo ($n = 4$). There was no post-randomization attrition, and data collection was complete except one missing daily void (n) on a participant's bladder diary.

Participants were a mean (SD) age of 61.6 (7) years and mean (SD) BMI of 36 (7). The ACB score was higher in the Ach group at study end [4 (2,5) vs 8 (4,9), $p < 0.03$]. Depression score (PHQ-9) was higher in the Non-Ach group [7 (3) vs 2 (2), $p < 0.04$]. Baseline learning over trials score was higher in the Ach group [16 (8) vs 29 (7), $p < 0.04$]. Scores on the HAMA and Montreal cognitive assessment did not differ in Ach versus Non-Ach. Cognitive scores (LTR, STR, Recog) did not differ at baseline. Table 1 shows the full list of descriptive statistics for other variables which did not significantly differ.

Cognitive scores and overactive bladder assessment comparisons

Descriptions of data and comparison over time of the Ach and Non-Ach groups are given in Table 2.. By two-way ANOVA, these measures did not differ by group at postintervention. In the overall sample, PPBC decreased from baseline to postintervention (F 7.1, $p < 0.01$). The recognition percentage correct (Rec%) increased from baseline to postintervention (F 6.4, $p < 0.02$). Of note, the final sample was not adequately powered to detect differences by group for PPBC and R or other variables.
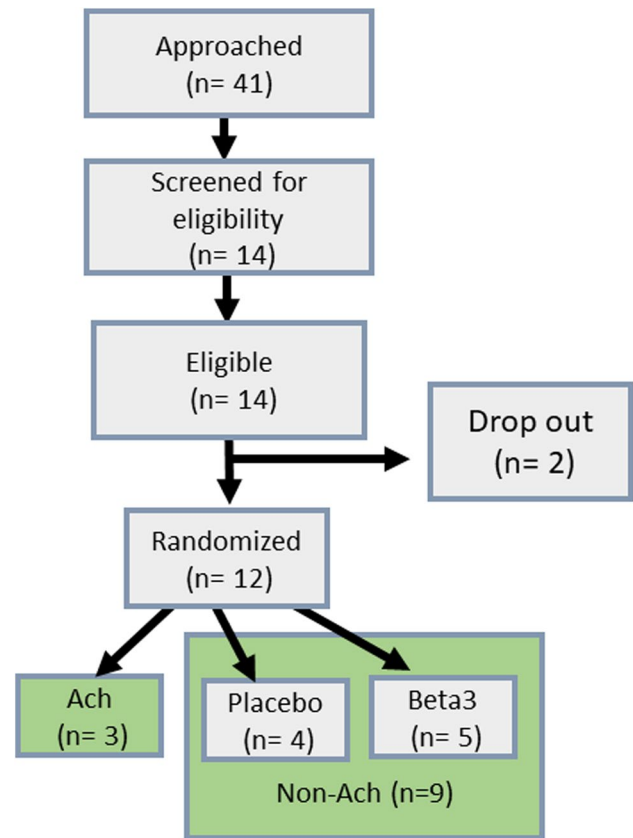
Fig. 2 Flow chart of recruitment: 41 potential subjects were approached; 14 were screened for eligibility. All 14 were eligible and consented to the study. Dropout occurred in two subjects because of scheduling conflicts before randomization. The final analytic sample included the Ach ($n = 3$) and Non-Ach cohorts ($n = 9$)

Recognition task activation maps

During the recognition task, there was activation of the middle cingulate gyrus, supplemental motor area, inferior frontal gyrus, inferior parietal lobules, and angular gyrus. The right middle frontal gyrus was activated during this task. There was bilateral deactivation of the precuneus, precentral gyrus, paracentral gyrus, and rectal gyrus. Excerpts from activation maps in the sagittal and axial planes are presented in Fig. 3.

Primary comparison: anticholinergic versus non-anticholinergic

Baseline AveAS by region did not differ in women who received Ach ($n = 3$) versus Non-Ach ($n = 9$). Seven regions with a significant difference in AveAS by group, time, or group by time interaction ($p < 0.05$) are presented in Table 3.. There were 147/154 (95%) regions which did not demonstrate differences in AveAS by group, time, or group by time interaction (all $p \geq 0.05$); thus, they are not listed in the table.

Table 1 Baseline characteristics of 12 subjects (Ach vs Non-Ach)

Variable	All (n = 12)	Non-Ach (n = 9)	Ach (n = 3)	p-value
Age, years, mean (SD)	62 (7)	62 (7)	59 (5)	0.47
Body mass index, kg/m^2, mean (SD)	36 (7)	35 (8)	40 (5)	0.39
Symptom bother score, mean (SD)	58 (20)	61 (21)	51 (14)	0.49
Quality of life score, mean (SD)	112 (37)	112 (43)	112 (4)	1.00
Patient perception of bladder condition, median (IQR)	4 (3, 5)	4 (3, 5)	3 (3, 4)	0.37
Voids/24 Hours, mean (SD)	11 (4)	11 (4)	12 (3)	0.87
Urgency episodes/24 Hours, mean (SD)	9 (4)	9 (4)	10 (1)	0.65
Incontinence episodes/24 Hours, mean (SD)	4 (3)	5 (3)	3 (3)	0.26
Baseline ACB, median (IQR)	4 (1, 5)	4 (2, 5)	5 (1, 6)	0.52
Postintervention ACB, median (IQR)	4 (4, 5)	4 (2, 5)	8 (4, 9)	**0.03**
Montreal cognitive assessment, mean (SD)	27 (1)	27 (2)	27 (2)	0.28
Depression score (PHQ9), mean (SD)	6 (3)	7 (3)	2 (2)	**0.04**
Anxiety score (HAMA), median (IQR)	4 (2, 11)	6 (2, 13)	3 (3, 4)	0.46
Learning over trials score, mean (SD)	19 (10)	16 (8)	29 (7)	**0.04**
Short-term retention score, mean (SD)	40 (13)	39 (14)	43 (15)	0.70
Long-term retention score, mean (SD)	107 (23)	109 (26)	103 (6)	0.74
Recognition score, median (IQR)	14 (14, 15)	13 (12, 14)	14 (11, 15)	0.28
Variable (yes)				
Postmenopausal, n (%)	10 (83)	7 (78)	3 (100)	1.00
Ethnicity, Hispanic, n (%)	1 (8)	0 (0)	1 (33)	0.55
Race, White, n (%)	12 (100)	9 (100)	3 (100)	1.00
Highest education level				0.51
Less than high school, n (%)	2 (17)	2 (22)	0	
High school, n (%)	5 (42)	3 (33)	2 (67)	
College or greater, n (%)	5 (42)	4 (44)	1 (33)	

p-value <0.05 are in bold

Table 2 Comparisons of OAB and cognitive scores by group & time

Two-way ANOVA^

Scores	Group effect: Non-Ach vs Ach			Time effect: baseline vs post		
	Mean Difference (95% CI)	F-value	p-value	Mean Difference (95% CI)	F-value	p-value
Symptom bother	27 (-8, 62)	2.9	0.10	19 (-0.2, 38)	4.4	0.05
Quality of life	34 (-31, 99)	0.7	0.42	28 (-7, 63)	2.5	0.13
PPBC	1 (-1, 2)	2.4	0.14	1 (0.2, 2)	7.1	**0.01**
Learning over trials	2 (-7, 11)	4.5	0.05	2 (-4, 9)	0.5	0.50
Short-term retention	7 (-26, 40)	0.4	0.55	14 (-1, 29)	3.3	0.85
Long-term retention	5 (-31, 41)	0.0	0.97	16 (-3, 35)	2.4	0.13
Recognition % correct	1 (-1, 2)	1.2	0.29	2 (-0.3, 2)	6.4	**0.02**

^There was no significant interaction effect (group: time)

p-values < 0.05 are in bold

AveAS was lower from baseline to post-intervention in three distinct regions. This decreased response during the working memory task was found in the right middle frontal gyrus (F 6.3, $p = 0.02$), right superior frontal gyrus (F 7.9, $p = 0.01$), and right supramarginal gyrus (F 8.5, $p = 0.008$). There was a difference in AveAS by group in one region. The right mamillary body AveAS was lower in the Ach group (F 4.9, $p < 0.04$) compared to the Non-Ach group. Significant group by time interactions were found in the left amygdala (F 4.9, $p = 0.04$), left cerebellar lingual (F 7.6, $p = 0.01$), and left mamillary body (F 7.0, $p = 0.02$).
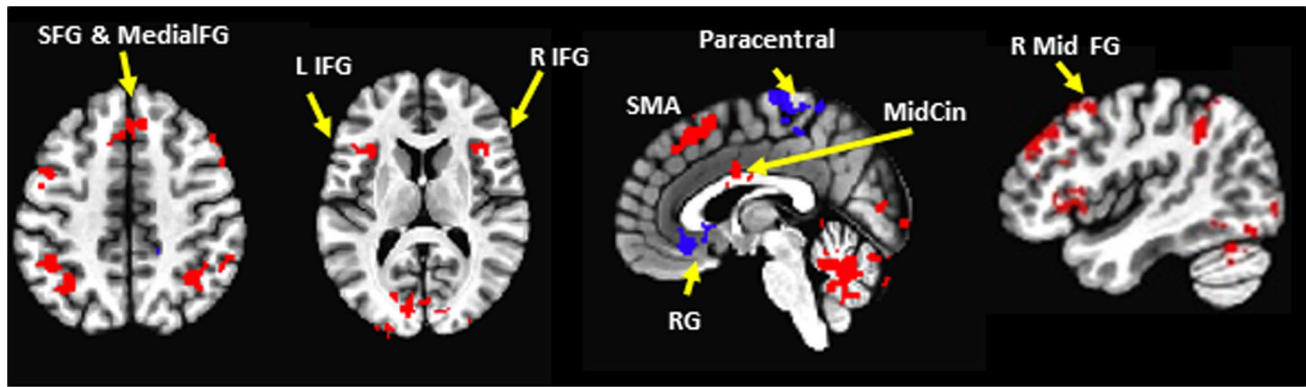
Fig. 3 Activation maps show regions of significant signal change during the memory task. **Activated**: Superior frontal gyrus (SFG) and medial frontal gyrus (MFG), bilateral inferior frontal gyrus (L&R IFG), middle cingulate gyrus (MidCin), supplemental motor area (SMA), right middle frontal gyrus (r MFG). **Deactivated**: paracentral gyrus (PCG) and rectal gyrus (RG)

Table 3 Two-way ANOVA comparison of average activation strength (AveAS)

Comparison	Group effect (Ach vs Non-Ach)			Time effect (baseline vs post)			Group: time interaction	
Association	AveAS mean difference (95% CI)	F-statistic	P-value	AveAS mean difference (95% CI)	F-statistic	P-value	F-statistic	P-value
Right mammillary body	-0.99 (-1.93, -0.05)	4.9	**0.039**	-0.36 (-1.18, 0.45)	0.9	0.366	0.4	0.540
Right middle frontal gyrus	0.22 (-0.33, 0.77)	0.7	0.418	-0.57 (-1.05, -0.10)	6.3	**0.021**	0.0	0.870
Right superior frontal gyrus	-0.08 (-0.48, 0.32)	0.0	0.916	-0.46 (-0.81. -0.12)	7.9	**0.011**	0.2	0.670
Right supramarginal gyrus	-0.17 (-0.76, 0.42)	0.4	0.548	-0.71 (-1.22, -0.20)	8.5	**0.008**	0.0	0.850
Left amygdala	0.08 (-0.41, 0.57)	0.1	0.750	-0.03 (-0.45, 0.40)	0.02	0.890	4.9	**0.040**
Left cerebellar lingual	0.05 (-0.69, 0.79)	0.0	0.890	-0.20 (-0.84, 0.44)	0.4	0.520	7.6	**0.010**
Left mammillary body	-0.16 (-0.83, 0.50)	0.3	0.610	-0.34 (-0.92, 0.22)	1.6	0.220	7.0	**0.020**

p-values <0.05 are in bold. Not displayed: 147 regions with non-significant relationships ($p \geq 0.05$) by group, time, or group:time interaction

Discussion

Regional brain activation differed in the right mamillary body after Ach versus Non-Ach interventions. The sample of participants exposed to Ach was small, and group differences should be interpreted with caution. Activation in the right middle frontal gyrus, right superior frontal gyrus, and right supramarginal gyrus was lower in participants at follow-up. Scores on the recognition task (Recog) improved at the follow-up assessment.

At baseline, groups were similar except for a higher depression score (PHQ-9) in the Non-Ach group. All study participants scored a minimal to mild depression risk, so this is not likely of meaningful clinical significance. Baseline LOT scores in the Ach group at baseline were higher; however, over time the LOT scores did not differ in either group. There was improvement of patient's perception of bladder condition in all participants at the follow-up visit without difference by groups.

The superior and middle frontal gyrus are implied in executive control and have roles in reorienting attention, impulse control, and language [18–20]. The supramarginal gyrus is in the inferior parietal lobule and has a role in visuospatial orientation and language processing [21]. Our findings of lower activation in these three regions with repetition of working memory tasks, further support existing literature. In a meta-analysis of 36 fMRI studies, working memory training (i.e., task repetition) was associated with decreased activity of the inferior parietal lobules, middle frontal gyri, and superior frontal gyri [22]. Our analysis of 12 participants showed less activation during a working memory task, specifically visual recognition, in the same three regions. Performance on most working memory domains (learning over trials, short- and long-term retention) did not change over time; however, recognition domain performance increased on repetition of memory testing. This study adds to the abundant literature on cognitive performance in the short term after solifenacin or mirabegron, which shows no negative effect [23, 24]. The task during imaging was a recognition

task specifically; the increase in domain performance may be related to a short interval practice effect.

Though this study sample was too small to adequately assess group effects, there were trends with possible effect of anticholinergics on mamillary body activation. The mamillary bodies are thalamic nuclei with connections with the hippocampus and anterior thalamic nuclei [25]. Mamillary bodies are a part of the theorized circuit for working memory and as part of this circuit their primary function is in recollective memory [25].

Effects of Ach exposure on functional connectivity have been demonstrated after 1 year of exposure. Functional connectivity was decreased in the Ach exposure group, with a greater effect noted in adults with mild cognitive impairment [26]. Functional connectivity and regional activation have been associated with differences in the hippocampus, parahippocampus, and medial temporal gyrus across healthy adults versus cognitively impaired in systematic reviews and meta-analyses [14, 27, 28]. Those functional neuroimaging biomarkers are reflective of degeneration over years or decades. In contrast, our study population of women was cognitively normal at baseline screening and measured memory outcomes in the short term.

Strengths and limitations

This is the first pilot study to include neural correlates to a working memory after exposure to anticholinergic medication in women with OAB. The working memory task activated frontal and parietal regions and the cingulate gyrus as expected in whole-brain activation studies with visual recognition tasks [22, 27]. In short-term (< 1 year) clinical assessments of cognitive performance after oral OAB Ach, only oxybutynin has consistently shown a consistent negative effect [29]. Functional neuroimaging has reflected working memory clinical performance and changes after Ach exposure in general populations [26–28]. This RCT pilot achieved good participant retention and compliance, no adverse events, and maintained blinding of the participants and all assessors and may inform future studies adequately powered to detect differences in women with OAB.

There are several limitations of this pilot study; most apparent is the inadequate sample size, which poses a high risk of type I and type II error. Improvement of OAB measures did not differ by group or time in most measures. Symptom improvement (and activation outcome measures) could be affected by the combination of the β3 and placebo groups. All participants were uniformly counseled on behavioral modifications for OAB (including placebo group) upon study initiation; differences in implementation and other unmeasured psychosocial factors could influence symptoms and activation over time. This population included non-responding participants who may differ from women who

are clinical responders; a longer exposure and flexible drug dosing may be beneficial in future investigations. The study duration of 1 month is brief but may reflect a common exposure period for many adults prescribed OAB medications. Prescription database literature indicates mean persistence of use of oral Ach is around 30–60 days [30]. Cognitive function is comprised of many domains: neuropsychiatric testing for attention, association, and processing speed was not assessed in this protocol. Future studies of cognitive effects may benefit from more extensive assessments and should be powered to detect differences across groups.

In conclusion, this pilot study presents a novel longitudinal evaluation of regional brain activation during a working memory task in OAB patients receiving oral medications. Cognitive changes are typically not detectable in short-term studies and may be difficult to detect in clinical settings. Detection of short-term effects, if present, may be detected through neural activity during a working memory task but larger studies are needed.

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