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Anticholinergic Exposure During Rehabilitation: Cognitive and Physical Function Outcomes in Patients With Delirium Superimposed On Dementia

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Abstract

Objectives—We examined the association between anticholinergic medication exposure and subsequent cognitive and physical function in patients with delirium superimposed on dementia during rehabilitation. We also examined length of stay and discharge disposition by anticholinergic medication exposure.

Design—In this secondary analysis we used control group data from an ongoing randomized clinical trial.

Setting/Participants—Participants with delirium and dementia were enrolled at admission to post-acute care. These 99 participants had a mean age of 86.11 (± 6.83) years; 67.6% were female; 98% were Caucasian; and 33% were positive for at least one APOE e4 allele.

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Measures—We obtained daily measures of cognitive and physical function using: Digit Span; memory, orientation and attention items from the Montreal Cognitive Assessment; CLOX; Confusion Assessment Method; and Barthel Index. Anticholinergic medication exposure was measured weekly using the Anticholinergic Cognitive Burden Scale.

Results—Using multilevel models for time we found that greater use of clinically relevant anticholinergic medications in the previous week reduced cognitive and physical function, as measured by Digit Span Backwards and the Barthel Index, in the current week. There was no effect of anticholinergic medication use on delirium severity, and APOE status did not moderate any outcomes. Greater use of clinically relevant anticholinergic medications was related to longer length of stay but not discharge disposition.

Conclusion—For vulnerable older adults, anticholinergic exposure represents a potentially modifiable risk factor for poor attention, working memory, physical function and greater length of stay during rehabilitation.

Keywords

Anticholinergic exposure; Cognition; Physical function; Post-acute care; Dementia

Objective

Medications with anticholinergic effects are prescribed for many clinical problems common to older adults. It is estimated that between 20 and 50% of older adults take at least one medication with anticholinergic effects to manage a variety of medical and psychiatric symptoms such as urine incontinence, depression, or insomnia [1]. In addition to their beneficial effects these medications have clinically relevant adverse effects that impact the central nervous system [1]. A recent systematic review of 46 studies evaluated these effects in 60,944 participants and found strong evidence for an association between increased anticholinergic exposure and deteriorating cognition, and consistent evidence for an association with a decline in physical function [2]. The association with delirium and mortality was inconclusive. Despite appreciable risks, the proportion of older adults prescribed anticholinergic medications has actually increased between 1995 and 2010 [3].

Older adults with dementia have lower cholinergic activity than those with normal cognition making them potentially more sensitive to anticholinergic medications [4]. They are also more likely to be carriers of the APOE e 4 allele than the general population. In some studies [5] but not others [6] APOE e 4 allele carriers were found to have a greater sensitivity to anticholinergic medications.

The adverse effects of anticholinergic medications on community-dwelling [7, 8], hospitalized [9], and institutionalized [10, 4] older adults with dementia have been described. We did not find any studies that examined the effects of anticholinergic medication exposure on cognitive and physical function in older adults with dementia in post-acute care settings. This was surprising given the growing number of people with dementia who require rehabilitation following hospitalization and the strong emphasis on functional outcomes in these settings. Data indicate that patients with dementia benefit from

post-acute care and can experience significant functional improvements over their admission status. [11]

Patients with dementia who receive rehabilitation following an acute medical event have complex medical and psychiatric comorbidity that may interfere with their recovery such as urine incontinence, depression, insomnia, pain and gastrointestinal symptoms. The management of this comorbidity may include prescribing medications with anticholinergic activities such as oxybutynin for urine incontinence, paroxetine for major depression, or diphenhydramine for insomnia. In the case of depression, the use of antidepressants may be life saving. In the case of delirium, however, the evidence for use of antipsychotic medications outside of intensive care settings is weak. [12]

The purpose of this study was to examine the association between anticholinergic medication exposure and subsequent cognitive (attention, memory, orientation, executive function and delirium) and physical function in patients with delirium superimposed on dementia who receive rehabilitation in post-acute care settings. We explore the moderating effect of APOE status on the association of anticholinergic medication exposure to functional outcomes because the evidence is not consistent in the literature. Delirium superimposed on dementia is common on admission to post-acute care settings and may compromise rehabilitation goals [12]. Thus we examine length of stay and discharge disposition by anticholinergic medication exposure.

Methods

Data from an ongoing randomized clinical trial were used to address the aim of the study (ClinicalTrials.gov identifier: NCTO1267682). The efficacy of cognitively stimulating activities for resolving delirium in patients with dementia during rehabilitation is being tested in that trial. The protocol received Institutional Review Board approval and was published [13].

Setting and Sample

Participants were recruited and enrolled at the time of admission to one of eight skilled nursing facilities located in central and northeast Pennsylvania that provide post-acute care. All admissions to the facility followed an inpatient hospitalization.

Eligible participants were those 65 years of age or older, community-dwelling prior to hospitalization, having a knowledgeable informant and both dementia and delirium on admission to the post-acute care facility. The diagnosis of dementia was based on a Modified Blessed Dementia Rating Scale [14] score of three or greater and a Clinical Dementia Rating [15] score ranging from 0.5 to 2.0, indicating mild to moderate stage dementia. The presence of delirium was established by screening potential participants using two instruments: 1) the Mini-Mental State Exam [16], a 30-item cognitive screen, and 2) the Confusion Assessment Method [17], a standardized diagnostic algorithm for delirium. All dementia and delirium diagnoses were adjudicated by a panel of three experts in dementia: a neuropsychologist, a neurologist, and a geriatrician. Exclusion criteria included having: any neurological or neurosurgical disease associated with cognitive impairment other than

dementia, including Parkinson's disease with Lewy bodies, Huntington's disease, normal pressure hydrocephalus, seizure disorder, subdural hematoma, head trauma, or known structural brain abnormalities; a life expectancy of less than six months; acute major depression or psychosis; severe hearing and vision impairment; and being nonverbal.

Following written consent, participants were randomly assigned to one of two conditions: cognitive stimulation (intervention) or usual care (control). For this study only participants assigned to usual care were included.

Procedure

Participants were assessed by trained and blinded research staff using the instruments described below. Demographic variables and APOE genotype were obtained at baseline. Observational measures of cognition (attention, memory, orientation, executive function and delirium) and physical function were taken daily for 30 days or until discharge. A weekly medical chart audit was conducted during which data on medications with anticholinergic effects and their administration over the past week were extracted. Three months following admission to the facility a phone interview was conducted with the participant's responsible party to determine discharge disposition (community, nursing home, death).

Measures

Anticholinergic medication exposure was defined as used vs. not used, and was measured weekly using the Anticholinergic Cognitive Burden (ACB) Scale [18, 1]. The ACB is an expert based practical index that ranks the severity of a medication's anticholinergic activity on cognition using a scale of: 1 (mild, with no known clinically relevant cognitive effects); 2 (moderate) or 3 (severe), both with clinically relevant effects.

APOE genotype was determined by extracting DNA from buccal swabs using a protocol optimized by the Institute of Psychiatry in London [19]. To identify the six APOE genotypes comprising the APOE e2, e3 and e4 alleles, two single nucleotide polymorphisms (SNPs) were assayed using the TaqMan Allele Discrimination method.

Physical function was measured using the Barthel Index [20], a commonly used ordinal scale for assessing activities of daily living in patients receiving inpatient rehabilitation. The Index has ten items (seven for self-care and three for mobility) that are scored in steps of five points with a total score range of 0 (totally dependent) to 100 (fully independent). The Barthel Index is a reliable indicator of functional ability in older adults when administered by face-to-face interview (ICC 0.89) and on testing by different observers (ICC 0.95–0.97).

Attention was measured using Digit Span Forward and Digit Span Backward [21]. Participants are given increasingly longer sequences of digits to repeat initially forwards then backwards and receive a point for each correct sequence. The assessment ends when the participant misses two sequences in a row. The maximum possible score is 16 (forward) and 14 (backward). Higher scores indicate better attention and working memory. Median reliabilities reach .97 and .96 for forward and backward spans respectively.

Memory and orientation were measured using the memory and orientation items from the Montreal Cognitive Assessment, a valid assessment of cognition that shows good agreement with existing screening tools and global measures (convergent validity) [22].

Executive function was measured using the CLOX [23]. This instrument has two parts: CLOX 1, a free drawing of a specified time, and CLOX 2, a simple copying task. Both steps are rated on 14 items with scores ranging from 0 to 15, higher scores indicate better executive function. The CLOX has an internal consistency of .82, interrater reliability of .94 (CLOX 1) and .93 (CLOX 2) and correlates strongly with other measures of cognitive function in healthy and cognitively impaired older adults.

Delirium severity was measured using two instruments: 1) Montreal Cognitive Assessment and 2) the Confusion Assessment Method. The severity score was calculated using a method developed by Inouye and colleagues [24]. Using both instruments, the responses to the following items were summed: Confusion Assessment Method fluctuating course item (0–1); Montreal Cognitive Assessment attention item (0–5); and Confusion Assessment Method level of consciousness item (0–2). Total scores can range from one to eight with higher scores indicating greater delirium severity.

Analytic strategy

Data in the current study were treated as nested with three levels of nesting: days nested in weeks, weeks nested in persons. Multilevel models (SAS proc mixed) allowed individuals to have different intercepts at baseline and at the beginning of each week to account for learning and recovery over the course of the study. Using the chi-square likelihood ratio test, initial models testing whether including nesting by facility improved model fit indicated that there was not sufficient variability at this level. At level 1 (day), day in study was included to control for changes due to treatment. Anticholinergic medication usage, the primary predictor, was included at level 2 (week) as well as previous week's cognitive and physical function performance and the number of days in the facility that week. The latter was included because some individuals were discharged earlier in the week compared with others. This variable allowed us to control for differences in the number of days in the facility across weeks. We were interested in anticholinergic medications with a clinically relevant effect. Therefore weekly moderate and severe anticholinergic medication use was summarized as a binary variable: weeks with any moderate or severe anticholinergic medication administration(ACB score of 2 or 3) were coded as 1; and weeks without any moderate or severe anticholinergic medication administration (ACB score of 1) were coded as 0. This was also supported by the data; most individuals received just one type of moderate or severe anticholinergic medication each week. Because medication administration was collected at weekly intervals, we chose the prior week exposure rather than the current week as exposure to some medications may occur on an as-needed basis and could have occurred after outcome measures were performed. For significant effects, pseudo-R^2 was calculated as a measure of the variance accounted for in the outcome variable by anticholinergic use [25].

At level three, age, gender, education level, ethnicity, clinical dementia rating score, APOE status, and comorbidity scores were entered as person-level covariates. Models included a

cross-level interaction between APOE status and anticholinergic medication usage to test for moderation of the usage effect.

Results

The sample had a mean age of 86.11 (± 6.83) years, a Charlson Co-morbidity Index score [26] of 2.97 (± 1.96), and a Clinical Dementia Rating score of 1.20 (± 0.59); 67.6% were female; 98% were Caucasian; and 33% were positive for at least one APOE e4 allele. These 99 participants provided 474 weeks of data for analysis.

Eighty one participants (81.8%) were taking a medication with mild anticholinergic effects and 25 (25.2%) were taking one with a moderate or severe effect. Only 15 participants (15.1%) received no medication with anticholinergic properties throughout the study. Medications with mild anticholinergic effects were administered on 78.3% of weeks (n_{weeks} = 371). Medications with moderate or severe anticholinergic effects were administered on 22.2% of weeks (n_{weeks} = 105). More than one medication with moderate or severe anticholinergic effects was administered on only 7.6% of weeks (n_{weeks} = 8). Those individuals who were given medications with moderate or severe anticholinergic effects received those drugs consistently across weeks (i.e. 77% of weeks). Quetiapine, Dicycloverine, Carbamazepine, Paroxetine and Amitriptyline were the most frequently administered level 2/3 anticholinergic medications. Table 1 lists the anticholinergic medications administered by frequency and severity of anticholinergic activity.

Descriptive statistics for the outcome measures appear in Table 2. Tables 3 and 4 include the estimates for the models predicting the outcomes of interest. As expected, previous week's performance on the cognitive tasks (attention, memory, orientation, and executive function) was significantly related to current performance with higher previous performance predicting higher current performance. Greater dementia severity predicted lower performance on all of the cognitive measures. Previous week use of a medication with moderate or severe anticholinergic effects predicted poorer performance on the Digit Span Backwards task (b = −.575, SE = .259, df = 948, t = −2.22, p = .03, pseudo-R^2 = .129). None of the other effects for anticholinergic medication use were significant. There was no evidence of moderation by APOE status.

Delirium severity was significantly and positively associated across weeks. Higher dementia severity scores were related to greater delirium severity scores. Younger age, lower comorbidities, and presence of the APOE 4 allele were related to higher delirium severity scores. Use of a medication with moderate or severe anticholinergic effects was not related to delirium severity.

Similar to the cognitive performance measures, physical function scores from the previous week were positively related to current scores. Older individuals had lower physical function scores compared to younger individuals. Individuals with higher comorbidity scores also had higher physical function scores compared to those with lower comorbidity scores. Use of a medication with moderate or severe anticholinergic effects in the previous week predicted a lower physical function score in the next week (b = −5.761, SE = 1.994, df =

1081, t=−2.89, p = .004, pseudo-R^2 = .052). APOE status did not moderate the effect of anticholinergic medication use on physical function scores.

Supplemental analysis

To determine whether use of anticholinergic medications increased length of stay, nonlinear models (SAS proc genmod using a negative binomial distribution and log link) examined number of days in facility predicted by anticholinergic medication use and the level 3 covariates from previous models. Results of these models also appear in Tables 3 and 4. Use of a moderate or severe anticholinergic medication increased the number of days spent in a rehabilitation facility ($M_{no\ ACB}$ = 16.77 days vs. M_{ACB} = 21.04 days). We found no difference in discharge disposition (community, nursing home, or death) by anticholinergic medication use.

Conclusions

This is one of the first studies to examine the effects of anticholinergic medication exposure on rehabilitation outcomes in patients with delirium superimposed on dementia, a group at high risk for poor outcomes following hospitalization. We controlled for socio-demographic and health related factors (age, gender, education, ethnicity, comorbidity, dementia severity) allowing us to see the independent effect of anticholinergic medications on cognition, physical function, and length of stay. We found an independent and significant negative effect of clinically relevant anticholinergic medication use in the previous week on performance in two areas: Digit Span Backwards, a measure of attention and working memory, and the Barthel Index, a measure of physical function. There was no effect of anticholinergic medication use on delirium severity, and APOE status did not moderate any outcomes. We also found an association between use of these medications and longer length of stay but not discharge disposition.

The cognitive outcomes we measured included several domain-specific cognitive functions as opposed to a single measure of global cognition such as the MMSE, the outcome most often reported in prior research [2]. Our measurement approach likely improved specificity, and our findings point to the possibility that anticholinergic medications may not affect all cognitive domains equally. There are several other possible reasons for our cognitive findings. First, all participants were recovering from an acute illness and for the vast majority their delirium was resolving. The lack of effect on most cognitive domains may have been due to this general improvement in neurocognition. Second, the cognitive effects of anticholinergic medications might be difficult to detect in people with dementia as we found in an earlier study [10] and as reported by Fox and colleagues [27]. Nonetheless, we did see an effect of these medications on Digit Span Backwards, a measure of attention and working memory [28]. These cognitive functions are critical for performance of everyday tasks [29], and their impairment has been associated with reduced ability to carry out activities of daily living [30]. Our finding is important when considered in light of the results we report on physical function, and could adversely impact transitions from post-acute care to home, as we found and as discussed below.

In addition to their cognitive effects, recent evidence indicates that medications with anticholinergic effects impact "global parameters" such as physical function in older adults [31]. Our findings are similar, and extend those of Koshoedo and colleagues who found a negative effect of these medications on physical function in older adults who undergo orthopedic rehabilitation [32]. In that study less than 2% of the sample had a history of dementia while in this study all participants had an adjudicated diagnosis of dementia. Worsening functional status during rehabilitation is an important risk factor for 30-day unplanned re-hospitalizations [33], the rate of which is over 23% in post-acute care facilities [34]. For people with dementia, the loss of physical function is a major risk factor for permanent institutionalization, and contributes heavily to the national burden of healthcare costs [35].

Medicare expenditures for post-acute care are second only to inpatient hospital care, and length of stay drives much of this cost. A recent Office of the Inspector General (OIG) report indicated that outcomes in post-acute care settings are often suboptimal and costly due to poor-quality treatment.[36] Problems with medication management were among the most prevalent reasons for the incurrence of harms that involved re-hospitalization or prolonged the length of stay. Our findings indicate that patients who received anticholinergic medications with significant clinical effects had a length of stay that was on average 4 days longer than patients not receiving these medications. These findings are similar to those of Lowery and colleagues [31] who also found a negative impact of anticholinergic medications on hospital length of stay in their unadjusted analyses.

The results of this study have important clinical implications for maximizing functional potential and reducing the costs of care for a growing number of people with dementia in need of rehabilitation. Many co-morbid conditions have alternative therapeutic options with less negative impact on recovery. The detrimental effects of anticholinergic medications during post-acute care might be addressed by stopping unnecessary medications,[37] switching to an alternative medication with a lower anticholinergic effect or using non-pharmacological interventions to address clinical problems that respond to them.[38] For example: in place of using antipsychotic medications, reversible contributions to delirium such as infection should be identified and appropriately treated[12]; in place of using diphenhydramine, sleep hygiene behaviors or a trial of melatonin can be attempted to reduce sleep problems[39]; and in place of using oxybutynin, a non-anticholinergic medication or prompted voiding might be instituted to address incontinence.[40] Although general de-prescribing trials have shown improvements in quality of life without significant adverse withdrawal effects,[41] de-prescribing studies of anticholinergics have shown anticholinergic reduction is possible but little is known about the effects on clinical outcomes, particularly among older adults with dementia.[42]

Our findings and that of others also have implications across settings of care. Many medications with strong anticholinergic activity, such as diphenhydramine, are readily available over the counter and consumed by older adults in the community as an over the counter sleep aide. It is not known if anticholinergic-induced cognitive impairment is reversible, but recent evidence suggests that higher cumulative use of anticholinergic medications is associated with an increased risk for dementia [43]. The potential for these

medications to impair cognition and function is an important public health message and a needed targeted area for education of both consumers and healthcare professionals.

We acknowledge several limitations of this study. Our observational study used data from an ongoing clinical trial; unmeasured confounding variables could have biased our estimates. We did, however, control for a number of socio-demographic and health related factors that have shown an association to our outcomes. Our sample size was not large and we conducted several tests relative to our outcomes increasing the potential for obtaining statistical significance by chance. We did, however, make use of multiple observations over time in our within person analyses. These within-person analyses improve the precision of measurement so that even small effects could potentially be detected; and we acknowledge that some of our effects were small.

We did not have data to establish the duration of anticholinergic medication use prior to post-acute care admission. We did, however, find that the vast majority of participants who received strong anticholinergic medications did so consistently across the study duration. We also did not have data on the dosage of medications administered. Lack of data on duration and dosage may have underestimated the true effect of strong anticholinergics in our analyses, as seen in recent work by Gray and colleagues [43].

There are also several strengths of the study. The sample was composed of individuals with delirium superimposed on dementia who were receiving rehabilitation, a growing population that has not been systematically studied to any extent. We used data on actual medication administration, not just prescription order data. Rather than using global measures of cognition to assess anticholinergic effects, we used measures of specific cognitive domains. Lastly, our study data were taken from an ongoing clinical trial that used reliable and valid measures.

The goal of post-acute care is to optimize function. For people with dementia, appropriate anticholinergic medication management may help achieve rehabilitation goals and reduce the cost of care.

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Table 1

Most commonly used anticholinergic medications

Mild Anticholinergic Medications		**Moderate/Severe Anticholinergic Medications**	
Drug	Number of administrations	Drug	Number of administrations
Metoprolol	3403	Quetiapine	584
Furosemide	1312	Dicycloverine	161
Warfarin	918	Carbamazepine	126
Hydralazine	729	Paroxetine	124
Risperidone	624	Amitriptyline	124
Isosorbide	579	Methocarbamol	119
Alprazolam	418	Olanzapine	63
Digoxin	362	Diphenhydramine	49
Atenolol	348	Hydroxyzine	43
Prednisone	301	Meclizine	38

Table 2

Descriptive statistics for outcome measures

Outcome	Mean	SD	Min	Max
Clox 1	3.989	3.597	0	14
Barthel	39.323	25.232	0	100
Orientation	3.097	1.945	0	7
Digits forward	8.022	2.897	0	15
Digits backward	2.719	2.205	0	10
Memory	0.352	0.736	0	3
Delirium severity	0.955	1.546	0	7
Length of stay†	21.758	8.442	0	30

Note.

†Calculated as the total number of days in the study. All other values represent performance at baseline.

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Table 3

Results of multilevel models using weekly mild anticholinergic medication use to predict outcomes

	Clox 1		Barthel		Orientation		Digit forward		Digit Backward		Memory		Length of stay	
Predictor	**b**	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**
Any mild AC	0.024	0.536	−3.411	2.145	−0.178	0.213	0.327	0.473	−0.406	0.287	−0.212	0.161	0.105	0.124
Gender	−1.689	0.936	0.816	4.939	−0.043	0.468	0.132	0.748	−0.096	0.548	−0.353	0.248	0.103	0.103
Ethnicity	−1.755	2.767	**29.590**	15.268	1.471	1.433	1.286	2.239	−0.795	1.616	1.253	0.735	0.166	0.339
Charlson	0.122	0.211	**2.433**	1.146	0.060	0.108	0.007	0.168	0.020	0.122	0.009	0.055	0.016	0.024
CDR	**−3.126**	0.748	−4.255	3.781	**−1.260**	0.363	**−1.251**	0.573	**−1.330**	0.419	**−0.653**	0.190	0.031	0.082
Age	−0.028	0.076	**−0.960**	0.360	−0.030	0.035	**0.133**	0.059	0.065	0.045	−0.040	0.020	0.012	0.008
APOE	−1.165	1.340	−3.410	6.121	−0.124	0.592	−1.606	1.111	−1.314	0.734	0.164	0.372	0.065	0.108
APOE*mild AC	1.698	1.077	5.710	4.283	0.192	0.425	0.165	0.949	0.885	0.574	0.126	0.321	--	--
Repetition	0.002	0.010	**0.109**	0.035	0.006	0.004	0.004	0.008	0.009	0.005	**0.008**	0.003	--	--
Education	1.508	1.548	**21.840**	8.358	0.821	0.786	−1.508	1.229	−0.829	0.888	0.395	0.403	0.003	0.182
Previous week's performance	**0.356**	0.081	**0.304**	0.063	**0.122**	0.058	**0.275**	0.062	**0.148**	0.064	**0.419**	0.061	--	--
Days WP	−0.193	0.162	−0.185	0.536	0.041	0.060	−0.092	0.130	0.016	0.078	0.027	0.044	--	--

Note. AC = anticholinergic; Bold values $p < .05$; b = unstandardized regression weight; t-test ($df_{between} = 90$, $df_{within} = 1099$)

Table 4

Results of multilevel models using weekly moderate/severe anticholinergic medication use to predict outcomes

	Clox 1		Barthel		Orientation		Digit Forward		Digit Backward		Memory		Delirium severity		Length of stay	
Predictor	**b**	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**	**b**	**SE**
Any AC	0.502	0.508	**−5.761**	1.994	−0.195	0.203	0.235	0.426	**−0.575**	0.259	−0.008	0.144	0.160	0.170	**0.227**	0.109
Gender (ref = female)	−1.853	0.961	2.037	4.983	−0.006	0.463	0.092	0.753	0.001	0.548	−0.360	0.247	**−0.274**	0.134	−0.139	0.102
Ethnicity (ref = Caucasian)	−1.771	2.835	**31.554**	15.404	1.479	1.418	1.385	2.251	−0.656	1.613	1.149	0.733	−0.586	0.451	−0.277	0.337
Charlson	0.122	0.215	**2.334**	1.152	0.053	0.106	0.019	0.168	−0.001	0.121	0.001	0.055	**−0.070**	0.031	0.020	0.024
CDR	**−3.086**	0.755	−3.655	3.798	**−1.225**	0.357	**−1.309**	0.567	**−1.207**	0.414	**−0.617**	0.187	**0.600**	0.108	0.021	0.079
Age	−0.036	0.077	**−1.051**	0.363	−0.035	0.034	**0.136**	0.059	0.050	0.045	−0.041	0.020	**−0.025**	0.011	0.016	0.008
APOE (ref = present)	0.270	1.018	1.194	5.043	−0.003	0.472	−1.389	0.761	−0.656	0.545	0.233	0.248	−0.322	0.332	0.090	0.105
APOE*AC	−0.238	0.998	2.235	3.942	0.298	0.400	−0.643	0.836	0.762	0.507	0.333	0.282	−0.050	0.345	--	--
Repetition	−0.001	0.010	**0.113**	0.035	0.006	0.004	0.004	0.008	0.009	0.005	**0.007**	0.003	0.000	0.006	--	--
Education	1.706	1.571	22.438	8.405	0.842	0.773	−1.493	1.225	−0.728	0.880	0.391	0.398	−0.013	0.231	−0.001	0.176
Previous week's performance	**0.353**	0.080	0.318	0.063	**0.123**	0.058	**0.270**	0.062	**0.168**	0.064	**0.427**	0.061	**1.155**	0.079	--	--
Days WP	−0.220	0.161	−0.121	0.530	0.045	0.060	−0.102	0.130	0.026	0.078	0.027	0.044	**0.299**	0.089	--	--

Note. AC = anticholinergic; Bold values $p < .05$; b = unstandardized regression weight; t-test ($df_{between} = 90$, $df_{within} = 1099$)