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Cognitive slowing associated with elevated serum anticholinergic activity in older individuals is decreased by caffeine use

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Abstract

Objectives—The present study examined whether some of the age-associated decrements in basic cognitive resources (information-processing speed and working memory) result from anticholinergic medication use (as measured by serum anticholinergic activity) and whether such decrements are lessened by caffeine.

Design—Cross-sectional observational study

Setting—University medical center

Participants—152 normal-elderly community volunteers

Measurements—Two tests each of information-processing speed and of working memory were administered and blood samples were drawn before and after cognitive testing to determine serum levels of anticholinergic activity and of paraxanthine - a caffeine metabolite.

Results—Elevated serum anticholinergic activity was associated with a significant but modest slowing in information-processing time, but only in those individuals who had low levels of serum paraxanthine. Serum anticholinergic activity did not correlate with performance on tests of working-memory.

Conclusions—These results suggest that anticholinergic medications are a relatively minor contributor to the decrements in basic processing resources commonly found in studies of normal aging.

Keywords

aging; anticholinergic activity; caffeine; cognitive slowing

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OBJECTIVE

Research into physiological factors contributing to the decline in cognitive performance with normal aging has focused on changes with increasing age in brain structure such as cortical atrophy and white matter pathology (1,2) or in hormonal function (3). Another potential factor is medication use by older individuals. Many of the drugs commonly prescribed to the elderly inhibit acetylcholine (4,5), a neurotransmitter essential for normal cognitive function. The potential for a cumulative anticholinergic burden is considerable, since many older individuals not only take multiple prescribed anticholinergic medications, but also use over-the-counter (OTC) drugs with anticholinergic effects such as antihistamines (e.g., diphenhydramine). A study (6) of community-dwelling elderly found varying degrees of serum anticholinergic activity in 90% of the sample. Elderly individuals are also hypersensitive to the detrimental effects of anticholinergic drugs (7), perhaps due to the reduction in muscarinic receptor density that occurs with increasing age (8). Thus, anticholinergic medications could be responsible for some of cognitive decrements commonly attributed to normal aging.

Studies of the cognitive effects of anticholinergic medications usually involve acute administration of a potent anticholinergic such as scopolamine, which produces widespread cognitive deficits. The source of these deficits has been attributed to a drug-induced reduction in information-processing capacity (9), similar to that postulated to underlie the cognitive decline found with normal aging. Anticholinergic medications have been shown to slow the speed of cognitive operations (7,10,11,12) as well as possibly reducing working-memory capacity (9). While the decrements associated with acute scopolamine administration are well established, there is limited evidence that similar effects occur with the lower anticholinergic burden associated with chronic anticholinergic drug use by the elderly. Even though anticholinergic drug use by community-dwelling elderly (determined from medical records) has been shown to be associated with poorer performance on neuropsychological tests (13), this study did not actually measure serum levels of anticholinergic medications nor did it investigate the basic processing resources (information processing speed and working memory) thought to underlie the cognitive decline present in normal aging.

Assessing the cognitive effects of anticholinergics is complicated by another commonly consumed drug, caffeine, which can counteract even the deleterious effects of scopolamine (14). Caffeine use in humans is associated with improved performance in many of the same cognitive domains in which anticholinergic drugs produce impairment, such as information-processing speed (15,16). The elderly also show increased sensitivity to caffeine (16). Thus, caffeine has the potential to obscure any detrimental cognitive effects associated with anticholinergic drug use by older individuals.

In the present study, normal-older individuals were given tasks commonly used to assess the basic processing resources of information-processing speed and working memory (17,18). Blood was drawn to measure serum levels of anticholinergic medications and of a caffeine metabolite (paraxanthine) at the time of cognitive testing. The major question is whether elevated serum anticholinergic activity in normal older individuals is associated with impaired cognitive performance and whether any such deficits are mitigated by caffeine intake.

METHOD

Participants

One hundred fifty-two individuals aged 65 to 80 were recruited from the community. During initial screening, a nurse practitioner obtained a complete medical history, performed a physical and neurological exam and reviewed participants' medications, both prescription and OTC. Individuals with major neurological or medical disease were excluded as was anyone taking psychoactive medications (antidepressants, prescription sleeping pills, antipsychotics, anxiolytics, cognitive enhancers or narcotic analgesics). Individuals scoring 15 or more on the Geriatric Depression Scale (19) or performing more than two standard deviations below the mean for their age group on the Repeatable Battery for the Assessment of Neuropsychological Status (20) were also excluded. The testing session occurred in the morning with no restriction being placed on participants' use of medications or on their caffeine intake prior to starting the session. Blood samples to measure serum anticholinergic activity (SAA) and the caffeine metabolite were drawn immediately before and after testing.

Information Processing Speed—The time participants took to make two types of decisions was measured. In the Perceptual Comparison task they had to determine whether two shapes ("Wingdings") presented side by side on a computer screen were physically identical. They pressed a button with their dominant hand if the two shapes were the same and with their nondominant hand if they were different. In the Conceptual Comparison task, they saw two stimuli (single letters and digits) and had to decide whether they were from the same conceptual category (i.e., both letters or both digits) or whether they were from different categories (e.g., L 5). Mean response time (RT) in milliseconds for correct "same" responses were used in the analyses. As a control for sensorimotor speed, participants were given a simple RT task in which they pressed a button with their dominant hand when a large dot appeared in the center of the computer screen. Here, the inter-trial interval varied randomly between 1.5 and 3 seconds to reduce anticipatory responses.

Working memory—In the N-Back test (21) participants heard a string of random digits presented one digit every two seconds. After they heard each digit, they were to say the digit that had occurred "N" back in the string, where N ranged between 0 and 5. For example, if $N=2$, they were to say the digit that had been presented two items prior to the digit they just heard. If they heard "5, 2, 7, 4" they would say nothing after the first two digits; after hearing "7" they would say "5"; after hearing "4", they would say "2", etc. The participants were given two digit strings at each N , with each string requiring ten responses. Their score on a string was the number of correct responses given before making an error, for a maximum correct on each string of 10. The data used in the analyses was the sum of the participant's highest scoring string in each of the six conditions.

The second working-memory task was a modified version of the Letter-Number Sequencing subtest of the Wechsler Adult Intelligence Scale III (22). Participants were shown on a computer screen a string of digits and letters (e.g., **6, M, 3, K, 5**), with each digit or letter appearing for 750 msec with a 500 msec interval between items. After all items were presented, the participant responded by first recalling the digits in ascending order and then the letters in alphabetic order (i.e., 3, 5, 6, K, M). The number of items in a string started at two and increased up to a maximum of eight, with three strings at each level. The participant's score was the number of strings recalled totally correct.

Determination of Serum Anticholinergic Activity (SAA) and Caffeine use—

Blood from the pre- and post-cognitive testing samples were analyzed separately and the results averaged. SAA was determined using a radioreceptor binding assay which quantifies

the competitive displacement of tritiated quinuclidinyl benzilate (3H-QNB) from rat brain muscarinic receptors (4,5,6). This assay measures the cumulative concentration of serum anticholinergic activity, including parent compounds and active metabolites. Drugs that block muscarinic receptors, regardless of structure, competitively inhibit binding of 3H-QNB to muscarinic receptors and thus, specific binding of QNB to muscarinic receptors is reduced in proportion to the concentration and potency of drugs with anticholinergic effects in the serum. Results are reported in picomoles of atropine equivalents per milliliter (mL) of serum. The marker for caffeine consumption was paraxanthine, the principal metabolite of caffeine, whose serum concentration is highly correlated with measured caffeine intake (23). Paraxanthine level was determined using reverse phase HPLC and is reported as nanograms per milliliter.

Statistical analysis—Pearson correlation coefficients were determined between participants' mean SAA and their performance on the cognitive measures. Since the response times in the two processing-speed tasks were skewed, the RT data were log transformed prior to analysis. Studies examining the cognitive effects of caffeine have typically acutely administered known quantities of caffeine (e.g., 14). The present study, however, had information only on paraxanthine in the participants' system at the time of cognitive testing. While paraxanthine is a valid marker for the amount of caffeine that an individual has recently consumed, we know of no results demonstrating the nature of the relation between serum paraxanthine concentration and cognitive performance (i.e., is the effect linear or is there a behaviorally-relevant threshold). Therefore, to determine how the relation between SAA and cognitive performance varied as a function of the participants' caffeine load, we divided the sample at the median paraxanthine concentration (534 ng/ml) into high- and low-paraxanthine groups (28 males / 48 females - high paraxanthine group; 27 males / 49 females - low paraxanthine group). If caffeine does counteract the deleterious cognitive effects of anticholinergic medications, then the relation between SAA and performance should be stronger in the low- than in the high-paraxanthine group (see Table for subject characteristics in the two groups). A generalized linear model (GLM) was constructed to compare the differential relationship of performance on SAA across the paraxanthine groups by examining the interaction term. Given the major effect that increasing age has on cognition and the fact that older individuals may be taking more medications, all correlations and the GLM partialled out the effect of participant age. For all correlations with SAA, the $df = 73$ (except for the two processing-speed tasks in the low-paraxanthine group where it was 72 due to missing data on one subject).

RESULTS

The mean SAA in this sample was 1.54 pmole/mL ($SD = 1.7$), with a median SAA of 1.1 pmole/mL. These values are quite close to those in a sample of 201 persons randomly selected from participants in an epidemiological study of older individuals in western Pennsylvania (6) where the mean SAA was 1.45 pmole/mL ($SD = 1.1$) with a median of 1.2 pmole/mL. Thus, the anticholinergic burden in the present sample appears representative of older individuals in the local area. The mean paraxanthine level was 725 ng/mL ($SD = 696$) with a median of 534 ng/mL (23 individuals had 0 ng/mL). The SAA and paraxanthine levels were not significantly correlated ($r = -.06$). Thus, there was no evidence that individuals with higher SAA were consuming more caffeine to offset any sedating effects of their anticholinergic medications.

On the day of testing subjects had brought in containers from all medications they had taken in the last 24 hours. This information was compared to a recent rating of the anticholinergic properties of prescription and OTC medications (24). The most common anticholinergic medications used by our participants were antihistamines (e.g., diphenhydramine,

chlorpheniramine), medications for acid reflux or excess stomach acid (metoclopramine, ranitidine) and for incontinence (toleterodine, oxybutynin). It should be remembered, however, that persons taking psychoactive medications (e.g., nortriptyline, olanzapine) were specifically excluded from this study.

To verify that the present cognitive tasks yielded the typical age-related difference in performance we compared the scores of the total elderly sample to those from a sample of 37 young (age 18-30; 13 males / 24 females) on the same measures. The young performed significantly better than the old on all the measures (individual t tests were all > 5.45 , $df = 187$, $p < .0001$) as would be expected from the aging literature. The sole exception was the N back comparison which just reached significance ($t = 2.04$, $df = 187$, $p < .05$).

Looking just at the effect of caffeine use on processing-speed and working-memory, there were no significant differences in cognitive performance between the high and low paraxanthine groups (see Table) and thus, no evidence for a major effect of caffeine on the cognitive performance of these elderly.

There were significant correlations between SAA and mean RT for both Perceptual Comparison and Conceptual Comparison, but only in those older participants whose paraxanthine levels were in the lower half of the distribution (RT results were missing for one participant in the low-paraxanthine group). In the low-paraxanthine group, SAA correlated $r = .30$ ($df = 72$, $p < .009$) with mean Perceptual Comparison response time and $r = .28$ ($df = 72$, $p < .017$) with mean Conceptual Comparison response time. Thus, the higher the participants' anticholinergic load, the slower their decision time. In the high-paraxanthine group these correlations were not significant ($r = -.18$, $p = .12$ and $-.02$, $p = .84$, $df = 73$). The relation of SAA with Perceptual Comparison was different between low and high paraxanthine groups as demonstrated by a significant group by SAA interaction in the GLM ($F = 7.90$, $df = 1,145$, $p = .006$). This interaction in the GLM for Conceptual Comparison was not quite significant ($p < .08$). Both GLMs were covaried for age and for sensorimotor speed.

The relation between SAA and response time on the two decision-time tasks was not due simply to a reduction in sensorimotor speed, since the correlation between SAA and simple response time was not significant in either paraxanthine group ($r = .10$ and $.12$) and, as noted above, covarying for sensorimotor speed did not eliminate the effect of SAA in the GLM.

In contrast to the processing speed results, there was no evidence for an association between SAA and working memory in either group. The correlation of SAA with Letter-Number Sequencing performance was $r = -.07$ in the low-paraxanthine group and $r = .01$ in the high-paraxanthine group. The correlations of SAA with N back scores were $r = .01$ for both groups.

There are a number of possible confounds that could contribute to the differential effect that SAA had on processing speed in the two paraxanthine groups. Cerebrovascular disease is widespread after age 70, as shown by white matter hyperintensities (WMH) on structural MR scans and WMH are associated with cognitive decrements. WMH severity and SAA may even have a synergistic effect on information-processing speed (25). Thus, if the low-paraxanthine individuals had more severe cerebrovascular disease, this could explain their greater sensitivity to SAA. Severity of cerebrovascular disease was determined for each participant by entering data from the physical exam and from the participant's primary care physician into an algorithm (Framingham Stroke Risk Profile) that estimates an individual's percent risk for having a stroke within the next ten years (26). This score served as a composite measure of the cerebrovascular risk factors (e.g., hypertension, diabetes, smoking) present in that person. There was no group difference in stroke risk (Table) and

thus, it is unlikely that severity of cerebrovascular disease was responsible for the differential effect of SAA in the two paraxanthine groups.

Another possible factor is the arousal level of our subjects. Anticholinergics have a sedating effect which could reduce subjects' performance, whereas caffeine increases arousal. We had administered a Visual Analogue Scale (27) on the day of testing which has a subscale (Global Vigor) composed of subjects' self-ratings of how weary, sleepy, and alert they felt and how much of an effort it was to do anything. SAA did not correlate significantly with this subscale in either the low- ($r = .04$) or high-paraxanthine groups ($r = -.05$), nor was there a significant difference between the high and low paraxanthine groups, with both groups rating their vigor as fairly high (79 on a 0 – 100 scale - see Table), suggesting that differences in alertness / sleepiness were not responsible for the pattern of cognitive results.

CONCLUSIONS

In the present study, elevated serum anticholinergic activity (SAA) was associated with an increase in the time older participants took to make decisions about perceptual and conceptual information. The higher the SAA, the longer participants took to make their decision. That is, an elevated SAA was associated with a slowing in information-processing speed in normal-elderly individuals. However, this was true only for persons whose recent caffeine intake (indexed by the caffeine metabolite paraxanthine) was low. In persons with a higher amount of serum paraxanthine, decision time did not correlate with SAA. Thus, caffeine intake appeared to counteract the deleterious effects of anticholinergic medications on processing speed. The relation of SAA to cognitive performance was evident only for the two measures of processing speed and did not extend to the two measures of working memory even in individuals with low levels of paraxanthine.

Why was increased SAA associated with a slowing in cognitive speed, but not with a decrement in the other major cognitive resource - working memory? The evidence that anticholinergic drugs such as scopolamine reduce information-processing speed, is strong and consistent (7,10,11,12). However, while it has been claimed that scopolamine reduces working-memory capacity (9), tasks that require simultaneous manipulation and storage of information (often viewed as the defining characteristic of working memory) have not shown an effect of acute scopolamine administration, including variants of the N back task administered here (10,28). Thus, even acute administration of a potent anticholinergic such as scopolamine, does not consistently impair working-memory performance.

We have assumed that the demonstrated relation between processing speed and SAA reflects anticholinergic medication use by our participants. However, there are several limitations to SAA. First, SAA is a peripheral measure reflecting anticholinergic activity in the serum not the brain. Not all medications pass the blood-brain barrier and thus SAA may overestimate anticholinergic activity in the central nervous system. However, with advancing age the blood-brain barrier does show increased permeability (29) which may allow anticholinergic medications easier access to the brains of older persons. Second, there is evidence that endogenous compounds with anticholinergic activity contribute to measured SAA (30), thus complicating attempts to link SAA to cognitive performance. Finally, the present study examined the cross-sectional relation between SAA and performance which may underestimate the deleterious effects of anticholinergic drugs. Bottiggi et al. (12) found anticholinergic use at baseline had little effect on neuropsychological tests in older individuals, whereas long-term use of anticholinergic medications was strongly related to a longitudinal decline in their performance.

In any study of aging there are numerous medical conditions difficult to detect without specialized methodologies that could have contributed to the cognitive decrements found. For example, abnormal levels of serum glucose, sodium, thyroid hormone are potential sources of unaccounted variance in these results since we did not measure these variables. Similarly, slow-developing neurological conditions such as Alzheimer's disease could be present in some individuals at a preclinical level that, while not severe enough to be detected, could still contribute to performance impairments (31).

The extensive literature demonstrating cognitive decrements in the elderly following acute administration of potent anticholinergics (7,9,11), could suggest that anticholinergic medications (both prescription and OTC) contribute to the cognitive decrements found in studies of normal aging because of the high likelihood that participants in such studies will be taking anticholinergic drugs. While the present results do show the anticholinergic burden present in participants' serum to be significantly related to their cognitive performance, the magnitude and breadth of this relationship was smaller than that seen with experimental administration of scopolamine. The adverse cognitive effects associated with higher SAA in this sample were restricted to speed of information processing and then, only in individuals whose co-existing paraxanthine level was low. SAA accounted for a relatively small amount of the total variance in the choice response time (9%) even in the low paraxanthine group. Since the present sample consisted of community volunteers recruited in a manner similar to that used by most normal-aging studies, it is likely that the relation of SAA to cognitive performance in the present sample reflects the magnitude of effect that anticholinergic medication use by older participants would have in such studies. However, it should be noted that our sample had a mean age of only 72 and results might have been different with an older sample since increasing age is associated with an enhanced sensitivity to anticholinergic medications (7).

Based on examination of the anticholinergic medications found in our sample of elderly, researchers wishing to avoid even the modest effects of anticholinergic medications on information processing speed should consider excluding persons taking antihistamines such as diphenhydramine (also found in over-the-counter "PM" versions of many pain relievers), or stomach acid reducers or incontinence medications.

Overall, these results suggest that the chronic anticholinergic load carried by the community-dwelling elderly makes a relatively minor contribution to the cognitive slowing that is such a prominent finding in cognitive studies of normal aging. These results also suggest that the cognitive decrements associated with typical anticholinergic medication intake by the elderly can be counteracted by caffeine intake, as has previously been found with acute scopolamine administration (14). While this might suggest that increased consumption of caffeine would be a useful approach to offset any deleterious cognitive effects of anticholinergic medications, caffeine has been associated with significant medical problems (32), making it potentially hazardous for some older individuals.

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Personal characteristics and cognitive performance for older participants in the high paraxanthine (≥ 534 ng/mL) and low paraxanthine (< 534 ng/mL) groups and for a young comparison group.

Table

	Low-Paraxanthine Elderly N = 76		High-Paraxanthine Elderly N = 76		Young N = 37	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age	72.1	(4.1)	72.0	(4.0)	22.6	(3.3)
Education in years	13.3	(1.7)	13.6	(2.2)	14.1	(2.0)
SAA (pmole/mL)	1.72	(2.03)	1.35	(1.37)	-----	-----
Paraxanthine (ng/mL)	177	(178)	1273	(580)	-----	-----
Percent Stroke Risk	13.0	(10.0)	11.2	(6.6)	-----	-----
VAS ² – Global Vigor (/100)	78.6	(17.3)	79.1 ¹	(14.9)	-----	-----
Perceptual Comparison (ms)	781.4 ¹	(158.9)	755.2	(133.5)	527.1	(74.1)
Conceptual Comparison (ms)	799.5 ¹	(147.3)	795.6	(134.1)	623.8	(66.4)
Sensorimotor Time (ms)	276.4	(62.1)	262.1	(44.6)	230.7	(58.6)
N Back (/ 60)	32.6	(13.5)	34.1	(12.6)	38.2	(12.8)
Letter – Number (/ 21)	9.5	(2.9)	10.0	(2.6)	12.6	(3.0)

¹ N = 75

² VAS = Visual Analogue Scale