
Decrements in vigilance and cognitive functioning associated with ragweed-induced allergic rhinitis

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Background and Objective: The adverse effects of untreated seasonal allergic rhinitis (AR) on performance in the workplace, school, and home are poorly understood. To delineate more clearly the impact and consequences of the disease on performance, the effect of symptomatic AR on vigilance and a wide range of cognitive functions was investigated.

Methods: A battery of automated neuropsychological tests was administered to asymptomatic adult subjects with histories of AR. Subjects were randomized to either a symptomatic or to an asymptomatic group. Subjects in the symptomatic group were exposed to ragweed pollen in a controlled exposure setting until they demonstrated predetermined severities of AR symptoms. Subjects in the asymptomatic group were not exposed to ragweed pollen in the environmental unit and retained a minimum symptom profile. The battery of cognitive measures was re-administered to both groups.

Results: AR had major adverse impacts on measures of vigilance. Further, AR adversely affected a broad range of cognitive functions. Specifically, subjects with AR symptoms demonstrated longer response times and decreased efficiency on measures of working memory, psychomotor speed, reasoning/computation, and divided attention as compared with asymptomatic subjects.

Conclusions: In addition to decreased vigilance, AR was associated with decrements in speed and efficiency across several cognitive domains. This is similar to findings in research on medications and medical conditions that cause sedation. Findings may represent a link between AR and poor productivity/personal safety among AR sufferers. This suggests that these results have implications with regard to public health.

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INTRODUCTION

A growing body of research has focused on the negative impact of allergic rhinitis (AR) on quality of life, personal safety, work performance, and performance in school.^{1–3} Studies have alluded to AR-associated cognitive impairment as one of the major factors underlying these adverse effects.¹ There has been much research on cognitive decrements associated with the sedating antihistamines used to treat AR.^{4–6} However, there has been little published research specifically addressing the treatment-independent cognitive correlates of AR and findings have been equivocal. Some of this research indicates that AR causes decreased vigilance,⁷ but other studies have suggested either no association between AR and cognitive functioning⁸ or limited cognitive decrements associated with AR.^{9,10} Unfortunately, the number of subjects in several of these studies was small and procedures did not allow for controlled allergen exposure. Further, the test batteries have been circumscribed or comprised primarily of

traditional (ie, paper-and-pencil) measures less sensitive to small, yet clinically important, cognitive changes.

The main objective of the present investigation was to conduct a controlled, large-scale investigation of the cognitive effects of unmedicated AR. The primary variable of interest in the research was vigilance. Research indicates that vigilance is consistently impacted by sedation related to illness and/or medication side effects.^{4,7,8} Further, sedation-related decrements in vigilance are strongly linked to decreased safety (including driving fatalities) and lost productivity in the real world.^{11,12}

To evaluate potentially subtle cognitive changes that may not have been detected in previous research, the battery used in the present investigation included measures tapping a broad range of cognitive functions. The study used reproducible, computer-based tests that are sensitive to clinically meaningful changes in response times, accuracy, and cognitive efficiency.^{13–16}

METHODS

Study Design

A randomized, parallel-group, single-center study was conducted during off-season for AR symptoms. Because of the number of subjects needed for adequate power, it was necessary to enroll subjects during two distinct time periods (summer and late fall 2000). The requirement that all subjects be asymptomatic as a prerequisite for enrollment ensured equivalence of allergy status regardless of the time period. An

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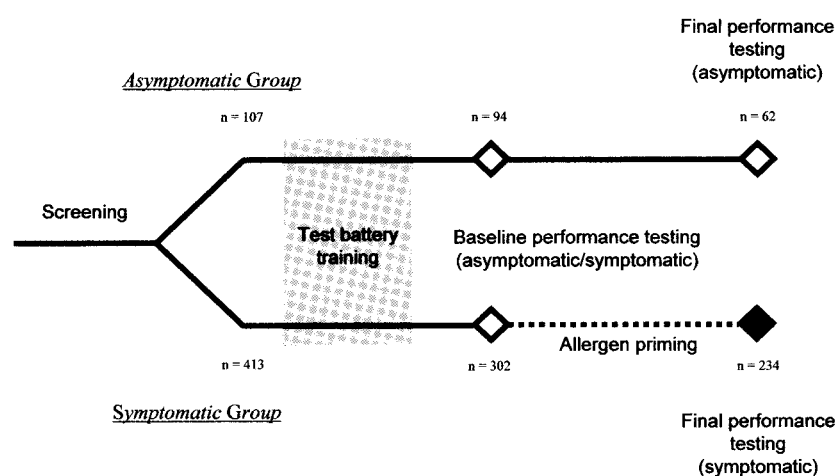


Figure 1. Study design.

allergen exposure unit (AEU) was used to minimize uncontrolled allergen exposure and maximize the development of symptomatic AR of acceptable severity. After screening, subjects with histories of AR to ragweed were assigned randomly to either the symptomatic or asymptomatic testing group. All subjects attended five training sessions to familiarize themselves with the computerized battery of cognitive tests (Fig 1 for study design). The training sessions were included to minimize the potential for practice effects during the active portion of the study.¹³ The appropriate number of training trials was determined via a review of the literature on practice effects and a pilot study conducted before this trial.

After confirming their asymptomatic status (through self-report of signs and symptoms), all subjects underwent performance testing to establish baseline levels of cognitive functioning. Subsequently, subjects in the symptomatic group were exposed to ragweed pollen in an AEU until symptomatic (as per subject report and predetermined criteria) and the cognitive battery was re-administered. Their counterparts in the asymptomatic group received no allergen exposure (and did not meet symptomatic criteria) before the re-administration of the battery. Study subjects and investigators were blinded to study group assignments until the completion of baseline performance testing. To control for potential effects of diurnal variables, all subjects received alternate forms of the performance battery at the same time of day each testing day. An investigational review board approved the study protocol, and research was conducted in accordance with the 1996 World Medical Association Declaration of Helsinki. Written informed consent was obtained at enrollment.

Subjects

Potential subjects with a minimum 2-year history of ragweed-associated AR were screened. Unless performed within the previous 12 months, skin prick or intradermal testing was performed to confirm hypersensitivity to ragweed. Subjects were eligible if the resulting wheal was at least 3 mm (skin prick) or 7 mm (intradermal) in diameter greater than the

wheal for saline control. Subjects were also required to be in good general physical health and not pregnant, and have a negative urine screen for drugs or abuse. The exclusionary criteria included: history or current presentation of frequent, clinically significant sinusitis or chronic purulent postnasal drip; rhinitis medicamentosa; upper respiratory tract or sinus infection requiring antibiotic therapy within 14 days of baseline performance testing or a viral upper respiratory tract infection within 7 days of baseline performance testing; nasal structural abnormalities that significantly interfere with nasal air flow; presence of asthma, unless adequately controlled by as-needed inhaled β_2 -agonists (= 2 days per week); and use of allergen immunotherapy, unless on a stable maintenance schedule. Subjects were not permitted to use corticosteroids, mast cell stabilizers, antihistamines, leukotriene inhibitors, central nervous system (CNS) depressants, theophylline, nasal decongestants, tri- or tetracyclic antidepressants, or anorexic agents/cerebral stimulants during the study; appropriate washout periods were established. Subjects were not permitted to ingest caffeine after breakfast on performance testing days. Subjects were asked to maintain a regular sleep schedule throughout the study.

Symptom Evaluation and Allergen Exposure

Immediately before baseline performance testing, subjects individually rated the eight traditional nasal and nonnasal AR

Table 1. Evaluated Signs and Symptoms* of Seasonal AR

Nasal	Nonnasal
Rhinorrhea	Itching/burning eyes
Nasal stuffiness/congestion	Tearing/watering eyes
Nasal itching	Redness of eyes
Sneezing	Itching of ears or palate

* Severity graded as 0 = none, 1 = mild (clearly present but minimal awareness, easily tolerated), 2 = moderate (definite awareness, bothersome but tolerable), or 3 = severe (hard to tolerate, may have interfered with activities of daily living and/or sleeping).

Table 2. Tests Used, Task Requirements, and Parameters Analyzed

Test Name	Task Requirement	Parameters Analyzed
Primary measure (Vigilance)		
Key Continuous Performance Test (KCPT) ⁴	Series of different symbols presented consecutively on screen over 10 minutes. Subject required to tap key only when specified symbol is presented.	Accuracy, omission errors, commission errors, response time
Secondary measures		
ANAM* Running Memory CPT ¹⁵	Series of numbers presented rapidly and consecutively on screen over 10 minutes. Subject required to determine whether current number is same or different from previous number	Accuracy, throughput,† response time‡
ANAM Logical Reasoning ¹⁵	Subject required to determine whether order of symbols (i.e., #, &, \$) is accurately described by an accompanying statement	Accuracy, throughput,† response time‡
ANAM Math Processing ¹⁵	Subject required to determine whether math problems (each including both addition and subtraction) sum to greater or less than 5	Accuracy, throughput,† response time‡
ANAM Digit Sequence Comparison Test ¹⁵	Subject required to determine whether a sequence of digits matches a sequence presented on the prior screen	Accuracy, throughput,† response time‡
ANAM Matching-to-Sample with Delay ¹⁵	Visual grid with specified pattern appears on screen. After 5 second delay, subject required to choose grid with matching pattern to first from two similar grids	Accuracy, throughput,† response time‡
CogScreen Digit Symbol Coding ¹⁴	Subject required to match a series of symbols to a series of numbers as instructed by an on-screen key	Accuracy, throughput†
CogScreen Digit Symbol Coding Delay ¹⁴	After 20 minutes, subjects required to accurately match numbers with symbols as per the original Digit Symbol Coding key	Accuracy
CogScreen Visual Sequence Comparison Test ¹⁴	Subjects required to quickly judge whether two numeric sequences presented on screen simultaneously are identical	Accuracy, throughput,† response time‡
CogScreen Pathfinder ¹⁴	Subject required to sequence series of numbers presented out of order on screen, then a series of letters. Finally, subject required to alternate sequence between numbers and letters (combined condition)	Accuracy, throughput,† response time,‡ coordination (deviation from center of number or letter)
CogScreen Shifting Attention Test ¹⁴	Subject required to choose correct response from multiple choices based on specified rule (arrow color, arrow direction, border color)	Accuracy, throughput,† response time‡
CogScreen Dual Task Test ¹⁴	Subject required to perform visual tracking task simultaneously with a working memory task (determining whether current number matches previous number)	Accuracy, throughput,† speed (previous # task); tracking errors, tracking boundary hits (tracking task)

* Automated Neuropsychological Assessment Metrics

† Throughput score is a function of response time and accuracy.

‡ Response time measured in milliseconds.

signs/symptoms on a 0 to 3-point scale (Table 1). To qualify, subjects were required to be essentially asymptomatic as defined by a total symptom score (TSS) of 4 or less (maximum score, 24). After establishing an asymptomatic baseline, subjects in the symptomatic group were exposed to ragweed pollen in an AEU, where a consistent pollen count ranging

from 3,046 to 4,539 grains/m³ was maintained until the subject was judged to be symptomatic (defined by a TSS >10, a total nasal symptom score of >6, and a total nonnasal symptom score of >4). Subjects in the symptomatic group could attend as many as six 90-minute allergen priming sessions over a 7-day period until they achieved these scores.

Table 3. Cognitive Domains, Definitions, and Associated Tests

Cognitive Domain	Definition	Associated Test(s)*
Primary domain		
Vigilance	Sustained attention over time. It is the ability to maintain a certain level of arousal or attention while engaged in a monotonous or repetitive task. An example would be driving on a boring road for several hours while maintaining alertness or maintaining accurate performance on an assembly line	KCPT, all parameters
Secondary domains		
Working memory	The ability to solve problems in one's head. Requires one to acquire information, perform some type of mental operation on the information, and produce a correct response. The "memory" part of this definition is the ability to hold in one's head all elements of the problem (and various subsolutions of the problem) while performing the mental operation. A good example is keeping a running tally of a cumulative sequence of numbers	ANAM Running Memory CPT ANAM Digit Set Comparison ANAM Matching-to-sample CogScreen Shifting Attention Test
Psychomotor speed	The speed and accuracy with which one can complete tasks that rely on hand-eye coordination. It does not just entail speed of mental processing or speed of motor functioning. Rather, it is a combination of the two. It looks at how well a person can perform a task that involves both motor processing and efficient thinking. A good example is typing	CogScreen Symbol Digit Coding CogScreen Visual Sequence Comparison CogScreen Pathfinder (Number and Letter conditions)
Reasoning/computation	This domain can be thought of as including tasks that require higher cognitive functioning. This is defined as the ability to reason, problem solve, or perform complex mental calculations	ANAM Logical Reasoning ANAM Math
Divided attention	The ability to divide one's attention between two simultaneous tasks or to alternate attention back and forth between two tasks. A good example is talking on the phone while cooking dinner	CogScreen Dual Task Test CogScreen Pathfinder (Combined Condition)

* Because of a computer malfunction, CogScreen Symbol Digit Coding Delay was not administered properly (i.e., two-thirds of the items were not administered). Therefore, this test was not included in data analysis or interpretation.

Symptom status was verified immediately before the final performance testing session, which was conducted 6 to 8 days after the baseline session. Subjects in the symptomatic group with a TSS <10, a total nasal symptom score (TNSS) of <6, and a total nonnasal symptom score (TNNSS) of <4 were excluded from the final round of testing, as were asymptomatic group subjects with a TSS >4.

Vigilance and Cognitive Performance Testing

A panel of experts on sedation, AR, and ability measurement assembled a comprehensive battery of computerized cognitive performance tests for use in this study (Table 2). Because the current paradigm was part of a larger research program focusing on the effects of sedating antihistamines on cognitive functioning, the battery was constructed to tap both burden of disease and burden of treatment. Given the major role that vigilance appears to play with regard to safety and

productivity,¹² a measure of vigilance (Kay Continuous Performance Test, or KCPT) was designated as the primary endpoint. The expert panel constructed the remainder of the battery in the context of previous research, revealing broad cognitive decrements associated with the use of sedating medications.^{4–6} Thus, in addition to vigilance, the final battery tapped a wide range of cognitive abilities, including working memory, reasoning, calculations, and psychomotor functioning. Given previous research indicating slowed processing speed in patients with symptomatic AR,¹⁰ each measure included parameters sensitive to decrements in response time. All measures had multiple alternate forms and were computer administered, making them suitable for a repeated measures design. All tests used have adequate validity and reliability, as well as real-world significance and sensitivity to mild degrees of brain dysfunction.^{4,14–16}

Table 4. Demographic and Baseline Characteristics (All Randomized Subjects)

Characteristic	*Symptomatic group at screening (n = 413) †Per protocol symptomatic group at final testing (n = 234)	*Asymptomatic group at screening (n = 107) †Per protocol asymptomatic group at final testing (n = 62)
Age, years		
Mean (SD)	*36.4 (9.8) †36.7 (9.5)	*37.7 (9.2) †37.2 (7.6)
Male, n (%)	*117 (28.3) †66 (28.2)	*23 (21.5) †13 (21)
Race, n (%)		
Caucasian	*189 (45.8) †101 (43.2)	*41 (38.3) †25 (40.3)
Black	*215 (52.1) †128 (54.7)	*66 (61.7) †37 (59.7)
Asian	*7 (1.7) †5 (2.1)	*0 †0
Hispanic	*2 (0.5) †0	*0 †0
AR duration, years		
Mean	*16.2 †15.9	*16.4 †16.1
Range	*2–51 †3–48	*3–47 †2–47

Note: None of the differences between screening and per protocol totals were significant at the 0.05 level.

Cognitive Domains/Grouping of Tests

Given the large number of tests and parameters to be analyzed, tests were grouped a priori based on cognitive function for purpose of interpretation. The factor analytic structure derived from previous antihistamine research using some of the same performance measures⁴ served as the initial template for collapsing the data into clinically meaningful groups. Information on construct validity from the CogScreen and Automated Neuropsychological Assessment Metrics (ANAM) test manuals^{14,15} and factor analytic studies of Automated Neuropsychological Assessment Metrics and traditional neuropsychologic measures^{17,18} were used to determine the final test groupings. Finally, to confirm the appropriateness and goodness-of-fit of the test groupings, a correlation matrix of all test parameters was created and analyzed.

As noted, previous research has indicated that one of the main sequelae of AR is decreased vigilance,⁷ and that medications causing sedation affect performance on measures of vigilance.⁴ Although this domain was designated as the primary area of interest, four cognitive domains (working memory, psychomotor speed, reasoning/computation, and divided attention) were also evaluated. The five domains, with definitions and associated tests, can be found in Table 3.

Randomization and Statistical Analyses

This experiment was part of a larger research program evaluating the cognitive effects of both AR symptoms and antihistamines in patients with symptomatic AR. Randomization to the symptomatic and asymptomatic groups was conducted in a 4:1 ratio to ensure an adequate number of subjects in the symptomatic group in the next phase of the research (reported separately). All cognitive performance test parameters and AR symptom data were analyzed as continuous variables. Power analysis was used to determine the minimum number of subjects required per group to detect between group differences. Subjects in the two groups were compared with regard to change from the asymptomatic baseline to the final testing session. Difference score comparisons between the symptomatic and asymptomatic groups were based on an analysis of covariance model with the baseline evaluation as the covariate. All statistical tests were two-sided and performed at the 0.05 level of significance. To help determine whether cognitive decrements associated with AR were related more to physical symptoms (eg, poor vision from eyes tearing) or actual changes in CNS functioning (eg, sedation, mental slowing), the change scores for all cognitive measures

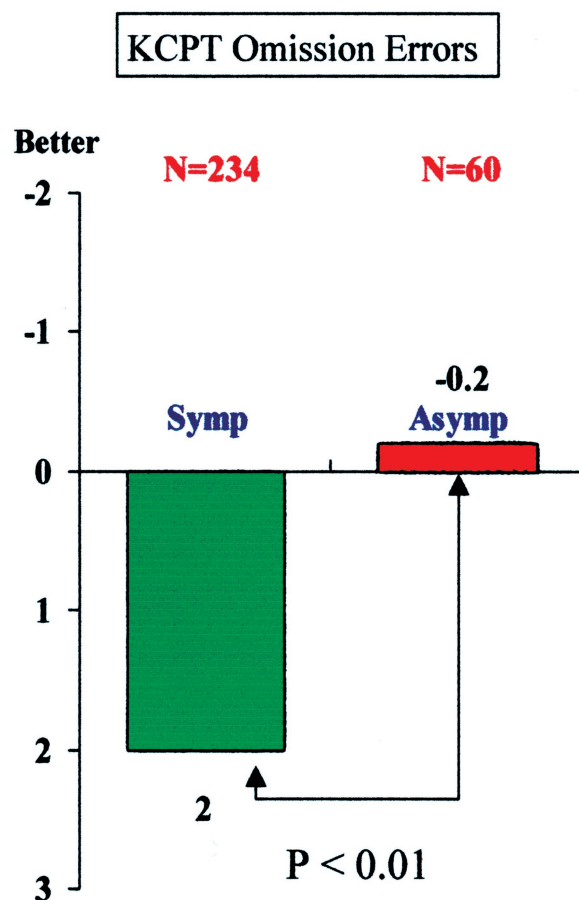


Figure 2. Change from baseline in number of KCPT omission errors.

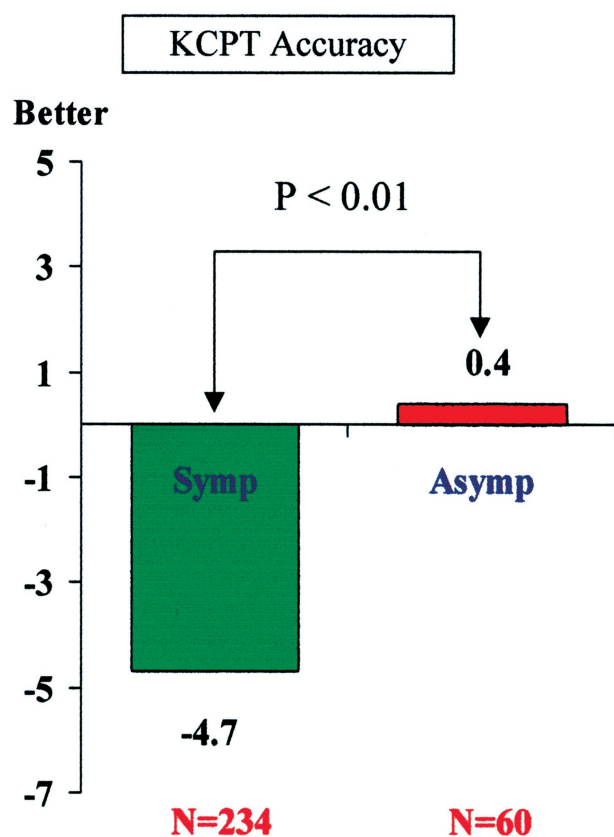


Figure 3. Change from baseline in accuracy percentage.

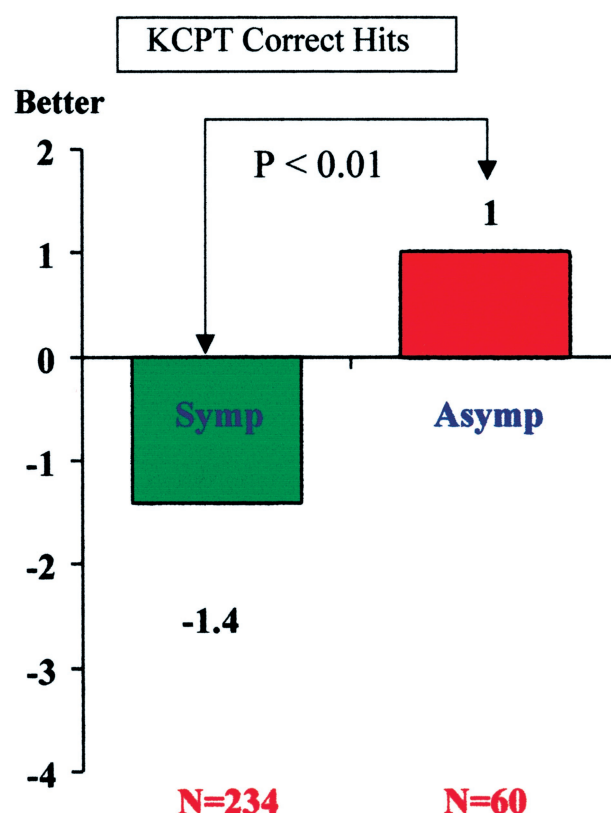


Figure 4. Change from baseline in number of correct hits.

(between the baseline and final testing sessions for subjects in the symptomatic group) were correlated with AR composite symptom scores (TNSS, TNNSS, and TSS).

RESULTS

Demographics

In all, 520 subjects tested positive for ragweed and met all other screening criteria: 413 and 107 subjects were assigned randomly to the symptomatic and asymptomatic groups, respectively (intent-to-treat population). Per the study protocol, subjects were excluded for being too symptomatic (ie, TSS >5) on the day of the baseline evaluation and for being too symptomatic (asymptomatic group) or not symptomatic enough (symptomatic group) at followup testing. Some subjects failed to complete all required visits and/or withdrew for personal reasons. Thus, a total of 234 subjects in the symptomatic group and 62 subjects in the asymptomatic group completed all evaluations (per-protocol population). The number of subjects completing each evaluation is noted on Figure 1. Demographic data for the original 520 subjects are presented in Table 4; the groups were balanced at randomization in both the intent-to-treat and per-protocol populations. The demographic characteristics of the subjects at the baseline visit and the followup visit were similar to those of the original screened sample.

At the baseline testing session, significant differences ($P < 0.05$) were found between groups for only five of the test parameters, including: KCPT, response time; CogScreen Digit Symbol Coding, throughput; CogScreen Dual Task Test, tracking errors alone; CogScreen Dual Task Test, tracking errors-dual; CogScreen Dual Task Test, boundary hits-dual. In each case, subjects in the symptomatic group (who were not symptomatic at the baseline test) performed better than subjects in the asymptomatic group. Adjustments for these baseline differences were made using an analysis of covariance model with the baseline evaluation as the covariate.

Signs and Symptoms: Efficacy of Allergy Induction

After allergen priming, subjects in the symptomatic group experienced a significant increase in TNSS, TNNSS, and TSS ($P < 0.001$ for all comparisons) as compared with subjects in the control group. Subjects in the symptomatic group also reported significantly increased sedation on the Stanford Sleepiness Scale ($P < 0.001$), increased drowsiness and lethargy ($P < 0.001$), and decreased clear-headedness, quick-wittedness, attentiveness, coordination, and proficiency ($P < 0.001$ for all comparisons).

Effects of AR on Vigilance

Symptomatic subjects performed significantly worse than asymptomatic subjects on all parameters of the KCPT (Figs

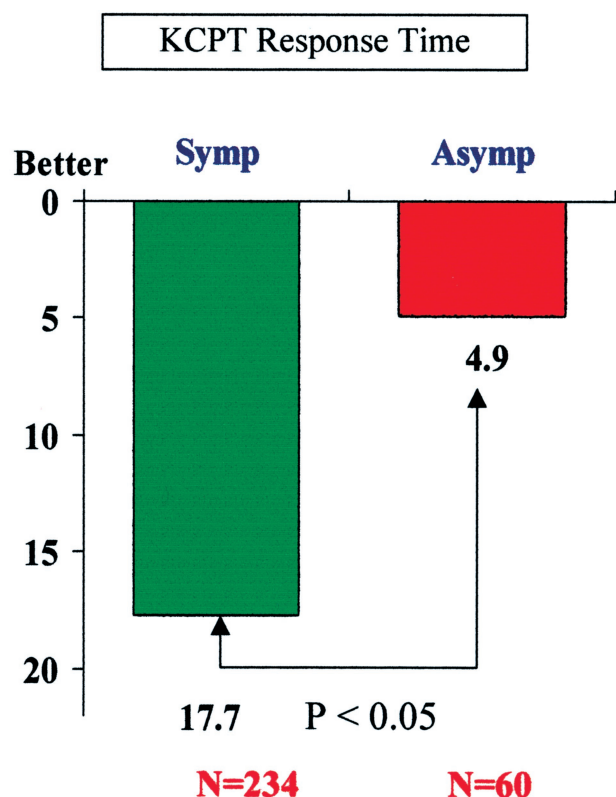


Figure 5. Change from baseline in response time in milliseconds.

2, 3, 4, and 5). Difference score effect sizes between asymptomatic and symptomatic subjects (in standard deviation units) for the KCPT parameters were in the moderate range (omission errors 0.41, accuracy 0.40, correct hits 0.41, and response time 0.34).

Effects of AR on Performance on Broad Cognitive Battery

As summarized in Table 5, symptomatic subjects performed significantly worse than asymptomatic subjects on measures across the cognitive functions evaluated (working memory, psychomotor speed, reasoning/computation, divided attention). The range of effect sizes for mean differences between groups was between 0.21 and 0.68, with the majority between 0.4 and 0.6 (moderate to high). The greatest effect sizes were for tests tapping working memory and psychomotor speed.

Correlations Between Cognitive Performance and AR Symptoms

There was no statistically significant correlation between any of the composite AR symptom severity scores and decrements in cognitive performance. Correlations between composite AR symptom scores and performance parameters never rose above 0.15 or fell below -0.11 .

DISCUSSION

In the present study, untreated AR was found to have a significant detrimental impact on vigilance. Analysis of the

cognitive battery revealed that AR also has a negative impact on a broad range of cognitive functions. Effects sizes were greatest with regard to working memory and psychomotor speed, but modest effect sizes were noted on measures tapping reasoning/computation and divided attention as well.

Across most cognitive domains, symptomatic subjects were slower than asymptomatic subjects, even when they remained accurate (eg, they completed simple math calculations accurately but were much slower). These findings suggest a cognitive profile consisting of reduced speed and efficiency across a broad array of performance domains for AR sufferers. This profile has implications with regard to public health and productivity. Specifically, symptomatic AR sufferers may experience dangerous lapses in attention or decreased reaction times when driving motor vehicles or operating heavy machinery. In the workplace, people with untreated AR will be slower in the completion of tasks requiring calculations, working memory/sequencing (eg, writing computer code), or verbal reasoning (eg, word processing). This finding appears to offer at least a partial explanation for the school and workplace impairments commonly reported by AR sufferers.

It is important to note that what might seem to be relatively small decrements in performance on measures of vigilance or the efficiency of mental processing often have meaningful real-world consequences. For example, on the KCPT, the decrement of 0.41 standard deviation (SD) observed in this study indicates the omission of an additional two of the target symbols. Because vigilance is necessary to complete even the most basic work,¹⁹ this finding can be extrapolated over an entire day. This 0.41-SD change then represents an increase of 96 omission errors throughout an 8-hour workday. Real-life consequences of such omissions could include missing alarms on security systems, missing warning lights or sudden changes in road conditions while driving, or missing errors while proofreading or typing documents. Hence, although an increase of omission errors of this magnitude on a 9-minute test may at first appear small, this apparently small increase could affect everything from simple worker productivity at a clerical job to worker safety to personal security.

The lack of correlation between the traditional AR signs/symptoms and cognitive decrements helps with the interpretation of current findings. Specifically, it does not appear that changes in cognitive function seen in symptomatic AR patients have a simple mechanical explanation (ie, poor performance because of eyes tearing and inability to see the screen). Rather, cognitive decrements appear to be attributable to sedation or downregulation of the CNS. This is consistent with research on other CNS conditions in which the cause of cognitive deterioration is a diffuse process affecting the whole brain. For instance, mild diffuse cognitive impairment has been observed in studies on severe asthma,¹⁹ mild hypoxia,²⁰ and mild brain injury.^{20–22} In these conditions, as in AR, there seems to be a mild downregulation of cognition such that people are performing slightly below their normal level.

Table 5. Secondary Endpoints: Means and Effect Sizes for Significant ANOVA Results

Cognitive domain	Neuropsychological test	Asymptomatic group change score* mean (SD)	Symptomatic group change score* mean (SD)	P value†	Effect size‡
Working memory	ANAM Running Memory CPT				
	Accuracy	0.5 (4.7)	−2.3 (12.4)	$P = 0.035$	0.28
	Throughput§	3.6 (12.5)	−7.4 (17.2)	$P < 0.001$	0.68
	Response Time	−12.4 (42.7)	24.2 (53.3)	$P < 0.001$	0.63
	ANAM Matching-to-Sample				
	Throughput	−0.1 (9.2)	−1.8 (7.5)	$P = 0.029$	0.21
	CogScreen Shifting Attention Test				
	Border Color Condition (Throughput)	2.9 (10.1)	−1.7 (8.7)	$P < 0.001$	0.51
	Border Color Condition (Response Time)	−24.0 (80.0)	18.0 (81.0)	$P < 0.001$	0.52
Psychomotor speed	Instruction Condition (Response Time)	3.0 (170.0)	73.0 (176.0)	$P = 0.004$	0.40
	CogScreen Number Pathfinder				
	Throughput	3.0 (11.8)	−2.2 (11.6)	$P = 0.005$	0.45
	Response Time	−20.0 (89.0)	23.0 (93.0)	$P = 0.002$	0.47
	CogScreen Letter Pathfinder				
	Throughput	−1.7 (14.2)	−6.3 (12.2)	$P = 0.014$	0.37
	Response Time	3.0 (109.0)	62.0 (115.0)	$P < 0.001$	0.52
Reasoning/computation	ANAM Logical Reasoning				
	Throughput	0.8 (4.9)	−0.9 (6.8)	$P = 0.008$	0.27
	ANAM Math				
	Throughput	0.1 (4.5)	−1.2 (4.9)	$P = 0.028$	0.27
Divided attention	Response Time	−103.1 (332.8)	53.2 (678.4)	$P = 0.009$	0.25
	CogScreen Dual Task Test				
	Dual Condition (Tracking Errors)	−7.5 (24)	−1.6 (16.7)	$P = 0.049$	0.32

* Mean change scores from baseline to followup testing.

† P values for the comparisons between symptomatic and asymptomatic subjects was based on an ANCOVA model with the baseline measurement as the covariate.

‡ Effect sizes represent difference in change scores between symptomatic and asymptomatic subjects. Pooled Standard deviations for mean changes in both groups used to calculate effect sizes.

§ Throughput is a composite measure of efficiency (correct responses/minute); higher scores indicate improved performance.

|| In milliseconds; higher scores indicate worse performance.

Present findings indicate that the cognitive effects of AR are more diffuse and widespread than suggested in previous studies. The initial report by Marshall and Colon¹⁰ suggested that AR may lead only to slower decision-making and psychomotor speed on simple and choice reaction time tasks, but the treatment group in their study was small and consisted solely of AR subjects with comorbid depression. Burns et al⁸ found that AR did not lead to decrements in cognition, but this study also had a small sample size and liberal criteria for a diagnosis of AR. This raises the possibility that the subjects were not significantly symptomatic when tested. In addition, the focus of their experiment was attention and working memory, possibly excluding other cognitive domains sensitive to the effects of AR.

Marshall et al⁹ recently conducted a more comprehensive evaluation but found only one main difference between controls and symptomatic AR subjects: decreased speed of men-

tal processing. A number of factors likely accounted for the greater number of statistically significant cognitive findings in the current investigation. First, because of the large number of enrolled subjects, the statistical power of the current study was likely greater than that of the previous investigation. Second, allergen exposure was carefully controlled, thus decreasing a major source of subject variance. Third, the battery of computerized tests was highly sensitive to clinically meaningful changes in response time and cognitive efficiency. The previous investigation used a number of traditional cognitive tests, which are more susceptible to imprecision (ie, decreased reliability because of use of a stopwatch) and administrator variability. Finally, the focus of the battery in the current experiment was broader than that used by Marshall et al,⁹ thus making it well suited to detect a more diffuse array of cognitive changes.

Future research should be conducted with a focus on establishing more formally the link between cognitive performance, productivity, and economic consequences of AR. One line of research to meet this end might entail having the same subjects complete the cognitive performance measures and productivity tasks. This would allow for the determination of which AR-associated cognitive decrements are responsible for decreased productivity on real-world tasks. Another important direction for future research is the economic modeling of these decrements in cognitive functioning.

CONCLUSION

The present study is an evaluation of the cognitive effects of AR. The reported findings help clarify the association between AR and vigilance and between AR and cognitive decrements. Thus, they have significant relevance with regard to issues of public health and productivity for sufferers of AR.

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REFERENCES

1. Settipane RA. Complications of allergic rhinitis. *Allergy Asthma Proc* 1999;20:209–213.
2. Canonica GW, Geal HS. The impact of allergic rhinitis on quality of life and other airway diseases. Summary of a European conference. *Allergy* 1998;53(Suppl):1–31.
3. Meltzer EO, Nathan RA, Selner JC, Storms W. Quality of life and rhinitis symptoms: results of a nationwide survey with the SF-36 and RQLQ questionnaires. *J Allergy Clin Immunol* 1997;99:S815–S819.
4. Kay GG, Berman B, Mockoviak SH, et al. Initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood, and psychomotor performance. *Arch Intern Med* 1997;157:2350–2356.
5. Simons FE, Fraser TG, Reggin JD, et al. Adverse central nervous system effects of older antihistamines in children. *Pediatr Allergy Immunol* 1996;7:22–27.
6. Meador KJ, Loring DW, Thompson EE, Thompson WO. Differential cognitive effects of terfenadine and chlorpheniramine. *J Allergy Clin Immunol* 1989;84:322–325.
7. Spaeth J, Klimek L, Mosges R. Sedation in allergic rhinitis is caused by the condition and not by antihistamine treatment. *Allergy* 1996;51:893–906.
8. Burns M, Shanaman JE, Shellenberger CH. A laboratory study of patients with chronic allergic rhinitis: antihistamine effects on skilled performance. *J Allergy Clin Immunol* 1994;93:716–724.
9. Marshall PS, O'Hara C, Steinberg P. Effects of seasonal allergic rhinitis on selected cognitive abilities. *Ann Allergy Asthma Immunol* 2000;84:403–410.
10. Marshall PS, Colon EA. Effects of allergy season on mood and cognitive function. *Ann Allergy* 1993;71:251–258.
11. O'Hanlon JF, Ramaekers JG. Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989–94. *Allergy* 1995;50:234–242.
12. Nolen TM. Sedative effects of antihistamines: safety, performance, learning, and quality of life. *Clin Ther* 1997;19:39–55.
13. Feinstein A, Brown R, Ron M. Effects of practice of serial tests of attention in healthy subjects. *J Clin Exp Neuropsychol* 1994;16:436–447.
14. Kay GG. CogScreen-Aeromedical Edition: Professional Manual. Odessa, FL: Psychological Assessment Resources, Inc, 1995.
15. Reeves DL, Winter KP, LaCour S, et al. Automated Neuropsychological Assessment Metrics Documentation, Volume I: Test Administration Guide. Silver Spring, MD: Office of Military Performance Assessment Technology, Walter Reed Army Institute of Research, 1992.
16. Kane RL, Kay GG. Computerized assessment in neuropsychology: a review of tests and test batteries. *Neuropsychol Rev* 1992;3:1–117.
17. Bleiberg J, Kane RL, Reeves DL, et al. Factor analysis of computerized and traditional tests used in mild brain injury research. *Clin Neuropsychol* 2000;14:287–294.
18. Kabat MH, Kane RL, Jefferson AL, DiPino RK. Construct validity of selected Automated Neuropsychological Assessment Metrics (ANAM) battery measures. *Clin Neuropsychol* 2001;15:498–507.
19. Dunleavy RA, Baade LE. Neuropsychological correlates of severe asthma in children 9–14 years old. *J Consult Clin Psychol* 1980;48:214–219.
20. Grant I, Adams KM. Neuropsychological assessment of neuropsychiatric disorders, 2nd ed. Chapters 16, 21. New York: Oxford University Press, 1996.
21. Lezak MD. Neuropsychological assessment, 3rd ed. New York: Oxford University Press, 1995.
22. Capruso DX, Levin HS. Cognitive impairment following closed head injury. *Neurol Clin* 1992;10:879–893.

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