Cognitive Development in Adults With Attention-Deficit/Hyperactivity Disorder: A Controlled Study in Medication-Naive Adults Across the Adult Life Cycle

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Objective: This study evaluated the association between attention-deficit/hyperactivity disorder (ADHD) and psychometrically defined cognitive variables across the adult life span, using data from a large controlled study of adults with and without ADHD.

Method: Comparisons were made between 2 groups of adults: participants with *DSM-IV*–diagnosed ADHD who had never received pharmacotherapy for their ADHD (n = 116) and 146 control participants. Subjects received a battery assessing IQ, neuropsychological measures, and academic testing. We modeled cognitive measures as a function of age and group status using linear regression. The study was conducted at Massachusetts General Hospital, Boston, between 1998 and 2003.

Results: ADHD and control subjects maintained similar, statistically significant differences in all psychometrically assessed measures of cognition within each decade that was represented (all P values < .01).

Conclusion: The negative impact of ADHD on multiple, nonoverlapping, psychometrically assessed measures of cognition remained constant across the life cycle, suggesting that the association between ADHD and cognition neither improves nor deteriorates across the life cycle.

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A spate of literature documents that individuals with attention-deficit/hyperactivity disorder (ADHD) display lower levels of intellectual performance than control subjects.[1–4] A meta-analysis by Frazier et al[5] showed that the mean difference in full-scale IQ across numerous studies was 9 points for standardized IQ tests. Similarly, that same meta-analysis found significant deficiencies in academic functions in numerous studies comparing the academic achievement scores of children with ADHD with healthy controls. Additionally, recent studies have shown the same deficits to be present in adults with ADHD.[6,7]

Because adult ADHD spans several decades, and because cognition can decline over time, questions have arisen as to the effect that ADHD may have on cognition over the adult life cycle, considering that many aspects of cognitive functioning decline with age.[8–10] Verhaeghen and Salthouse[11] conducted a meta-analysis of 91 studies to derive a correlation matrix for adult age, speed of processing, primary-working memory, episodic memory, reasoning, and spatial ability. Their results revealed that negative age-cognition relations were significant for the 18- to 50-year-old sample and that age-related declines accelerated significantly over the adult life span for variables assessing speed, reasoning, and episodic memory. Given that many of the cognitive domains presumed to be responsible for cognitive decline in aging are also areas found to be deficient in neuropsychological profiles of individuals with ADHD,[1,4,12,13] it can be hypothesized that individuals with ADHD may display lower levels of cognition in many areas as they age when compared to controls. Despite the contributions of these studies to the literature on cognitive deficits in ADHD, important questions remain unanswered: (1) Does ADHD moderate cognitive functioning in individuals with ADHD across the adult life span? (2) Are patterns of cognitive functioning in individuals with ADHD different from those of controls?

The main aim of this study was to evaluate patterns of cognitive functions across the adult life cycle. To this end we used data on multiple psychometrically assessed domains of cognition from a large sample of medication-naive adults with and without ADHD from ages 19 to 55 years. We hypothesized that cognitive deficits in ADHD would be observed across the adult life cycle. To the best of our knowledge, this is the first evaluation of these issues in ADHD.

METHOD

Subjects

Detailed study methodology has been previously reported.[14] Briefly, men and women between the ages of 18 and 55 were eligible for this study. We excluded potential participants if they had major sensorimotor handicaps (eg, deafness, blindness), psychosis, autism, inadequate command of the English language, or a full-scale IQ less than 75. No ethnic or racial group was excluded. Participants with ADHD (n = 224) were ascertained from referrals to a psychiatric clinic at Massachusetts General Hospital (MGH),

Boston, and through media advertisements in the greater Boston area. Non-ADHD control participants (n = 146) were recruited through e-mail broadcasts to employees at MGH and through media advertisements in the same media outlets as those used to recruit participants with ADHD. A 3-stage ascertainment procedure was used to select all participants. The first stage was the participant's referral (for participants with ADHD only) or response to media advertisements. The second stage confirmed (for participants with ADHD) or ruled out (for controls) the diagnosis of ADHD by using a telephone questionnaire that asked about symptoms of ADHD, as well as study inclusion and exclusion criteria. The third stage confirmed (for participants with ADHD) or ruled out (for controls) the diagnosis of ADHD with face-to-face structured interviews with these individuals. To be given a full diagnosis of adult ADHD, the participant had to have endorsed full *DSM-IV* criteria and described a chronic course of ADHD symptomatology from childhood to adulthood. Only participants who received a positive (participants with ADHD) or a negative (controls) diagnosis at all 3 stages were accepted into the study. For the purposes of this analysis, we used participants with ADHD who had never received pharmacotherapy for ADHD (n = 118). The MGH institutional review board approved this study, and all participants completed a written informed consent before inclusion in the study. The study was conducted between 1998 and 2003.

Psychiatric Assessments

All participants were assessed with the Structured Clinical Interview for *DSM-IV*[15] to assess psychopathology, supplemented with modules from the Schedule for Affective Disorder and Schizophrenia for School-Age Children; Epidemiologic Version, Fifth Edition, adapted for *DSM-IV*,[16] to assess ADHD and other childhood disorders. The interviewers had undergraduate degrees in psychology, and they were trained to high levels of interrater reliability for the assessment of psychiatric diagnoses. We computed κ coefficients of agreement by having experienced, board-certified child and adult psychiatrists and licensed clinical psychologists diagnose participants from audiotaped interviews made by the assessment staff. κ coefficient for ADHD was 0.88.

A committee of board-certified child and adult psychiatrists and psychologists resolved all diagnostic uncertainties. The committee members were blind to the participants' ascertainment group, ascertainment source, and all nondiagnostic data. Diagnoses were considered positive if, based on the interview results, *DSM-IV* criteria were unequivocally met to a clinically meaningful degree. We estimated the reliability of the diagnostic review process by computing κ coefficients of agreement between clinician reviewers. κ coefficient for ADHD was 1.0.

Socioeconomic status (SES) was measured using the 5-point Hollingshead scale (Hollingshead AB, 1975, unpublished), which evaluates a combination of educational and occupational levels. Higher scores on the scale reflect lower SES.

Cognitive Assessment

Using the methods of Sattler,[17] we estimated full-scale IQ from the vocabulary and block design subtests of the Wechsler Adult Intelligence Scales-III (WAIS-III).[10] Academic achievement was assessed using the Wide Range Achievement Test, Third Edition (WRAT3) reading and arithmetic subtests.[18] Neurocognitive measures were administered to all subjects by psychometricians who were blind to the diagnostic status of the subjects and who received ongoing supervision by a licensed clinical neuropsychologist. These psychometricians participated in an extensive training course in which they were introduced to principles of neuropsychological assessment and taught to administer measures. Prior to administering tests themselves, they observed senior raters until they reached high levels of reliability for scoring. Initial test administrations were then observed and double-coded by a senior rater to insure proficiency and reliability in test administration and scoring.

The neuropsychological battery assessed domains of cognitive functioning known to be relevant in ADHD, including tests of executive functioning, learning, and memory. Tests were selected to measure domains of functioning thought to be indirect indices of fronto-striatal systems, which have been found to be impaired in youth and adults with ADHD.[19–22] These functions include sustained attention, working memory, interference control, abstract problem solving/set shifting, planning/visuospatial organization, processing speed, and verbal learning.[23–25] The tests included in this study were consistent with those used in our previous work.[26–28] As in previous studies,[26,27] tests were administered in a fixed order: (1) the Rey-Osterrieth Complex Figure Copy[29]; (2) the WAIS-III,[10] Vocabulary, Digit Span, and Symbol Search; (3) the Rey-Osterrieth Recall; (4) the WAIS-III (Wechsler Intelligence Scale for Children, 3rd Edition, for individuals under 17) block design, arithmetic and coding/digit symbol subtests; (5) the auditory continuous performance test[30]; (6) the total words learned on the California Verbal Learning Test[31]; (7) the computerized Wisconsin Card Sorting Test[32]; and (8) the Stroop Test.[33] The test battery usually took approximately 2 hours on 1 day to administer. Rest periods were given during the testing sessions as needed.

Statistical Analysis

The interaction of ADHD status and age was tested using linear regression. If the interaction effect was significant, the effect of age was interpreted separately for each group. If the interaction effect was not significant, the independent effects of age and group were reported after removing the interaction term. All tests were 2-tailed. We used an α level of .05 to assert statistical significance.

RESULTS

Demographics

Of the 118 adults with ADHD who had never received pharmacotherapy for ADHD, 2 subjects did not complete

cognitive assessments. Thus, the final sample consisted of 116 adults with ADHD and 146 healthy comparisons without ADHD. Subjects were assessed from 19 to 29 years of age (n = 114), 30 to 39 years of age (n = 70), 40 to 49 years of age (n = 58), and 50 to 55 years of age (n = 20). The ADHD group was somewhat older than the controls ($P < .001$; Table 1). However, age was included in all analyses as part of our a priori statistical models. Sex and ethnicity did not vary by group. Subjects in the ADHD group had a lower SES compared to the controls. Socioeconomic status was controlled for only as a secondary analysis, because the independent variable ADHD may have had an effect on SES and therefore was not a true covariate.

Table 1. Demographic Characteristics of Subjects With ADHD Who Had Never Received Pharmacotherapy for Their ADHD and Control Participants

Characteristic	Controls (n = 146)	ADHD Nonmedicated (n = 116)	Test Statistic	*P* Value
Age, mean ± SD, y	30.3 ± 8.7	37.8 ± 9.8	$t_{260} = -6.59$	< .001
Sex, male, n (%)	66 (45)	57 (49)	$\chi^2_1 = 0.40$	.53
Race, white, n (%)	114 (78)	99 (85)	$\chi^2_1 = 2.24$	.13
Socioeconomic status,[a] mean ± SD	1.8 ± 0.6	2.4 ± 1.1	$z = -4.94$	< .001

[a]Socioeconomic status (SES) was measured using the 5-point Hollingshead scale. Higher scores on the scale reflect lower SES.

Associations Between ADHD, Age, and Neurocognition

Figure 1 shows the linear fit for regression analyses modeling each cognitive outcome measure as a function of age. Separate regressions were fit for ADHD and control subjects. There were no significant interaction effects of ADHD and age on any neurocognitive outcomes (all *P* values > .10). There were also no significant interaction effects when analyzed separately for men and women (all *P* values > .10). Independent of age, ADHD was associated with significantly lower scores on all 6 measures: 6.9 full-scale IQ points ($t = -3.99$, $P < .001$), 5.1 performance IQ points ($t = -2.81$, $P = .005$), 7.2 verbal IQ points ($t = -3.91$, $P < .001$), 8.5 WRAT arithmetic points ($t = -4.97$, $P < .001$), 3.6 WRAT reading points ($t = -2.81$, $P = .005$), and a 0.26 lower neuropsychological aggregate score ($t = -5.07$, $P < .001$). Independent of ADHD status, every year of age was associated with 0.20 points lower full-scale IQ ($t = -2.36$, $P = .02$), 0.21 points lower verbal IQ ($t = -2.34$, $P = .02$), and 0.28 points lower WRAT arithmetic score ($t = -3.24$, $P = .001$). Age was not significantly associated with performance IQ, WRAT reading, or the neuropsychological aggregate variable (all *P* values > .05). After SES was controlled for, ADHD was no longer associated with a significantly lower WRAT reading score ($P = .15$), but all other findings remained significant. After full-scale IQ was controlled for, ADHD was still significantly associated with poorer WRAT arithmetic ($P = .002$) and neuropsychological aggregate ($P = .002$) scores, but not WRAT reading scores ($P = .71$).

DISCUSSION

This analysis evaluated the impact of ADHD on multiple psychometrically assessed domains of neurocognition in medication-naive adults. Findings revealed that ADHD was associated with lower scores on all cognitive measures assessed across the adult life cycle when compared to non-ADHD controls. These findings suggest that cognitive deficits in subjects with ADHD are consistent across the adult life cycle. Because we studied a medication-naive sample of adults with ADHD, these results reflect the natural course of adult cognitive development in this population. To our knowledge, this is the first study to assess the association between cognition and ADHD over the adult life span.

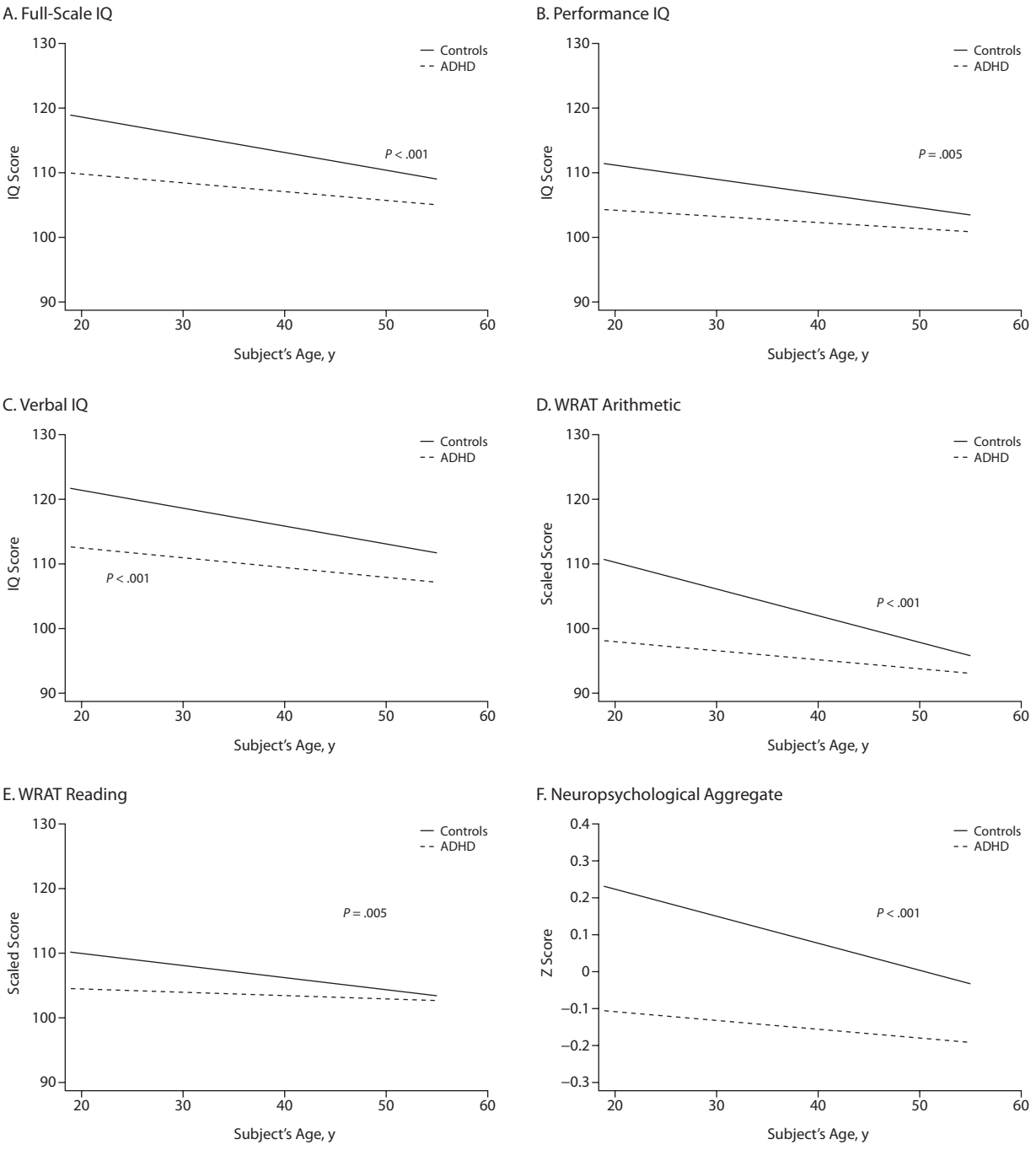
Our results showing that medication-naive adults with ADHD had lower scores on all 3 measurements of IQ scores assessed (performance, verbal, and full-scale IQ) across the adult life cycle are consistent with previously reported findings in ADHD adult populations. Barkley[12] reported findings that individuals with ADHD were significantly impaired on measures of IQ. Likewise, the findings of Frazier et al[5] indicated that overall cognitive ability was significantly lower in persons with ADHD in comparison to control participants. Similar findings were reported by Faraone et al,[34] who found that adults with ADHD have significantly lower IQ than controls. Taken together, these findings indicate that lower IQ is part of ADHD, and they call into question the practice of statistically controlling for IQ in studies of ADHD.

Moreover, our findings showing that ADHD and control subjects maintained a similar, statistically significant difference in cognition within each decade of age from the 20s through the 50s expand the current literature and document that the differential between cognitive scores of nonmedicated individuals with ADHD and controls extends over the adult life span. Considering that cognitive functioning is a major determinant of academic and occupational success, the lower cognitive scores of unmedicated adults with ADHD across the life cycle suggest that individuals with ADHD may continue to follow a pathway of functional impairments across their life span when untreated.

Our finding showing that the IQ scores of both groups (medication-naive adults with ADHD and controls) had a downward slope with increasing age is puzzling considering that the literature purports that IQ remains stable over time and, if anything, vocabulary raw scores of individuals increase over time.[35] Although the reasons for this finding remain uncertain, as suggested by Verhaeghen and Salthouse,[11] it could be due to the fact that raw scores of psychometric measures tend to be higher in those individuals born closest to the age of publication of the test.[36] Since the version of the WAIS (III) in this study was published in 1997, and the subjects were tested from 1998 to 2003, younger subjects may have been exposed to the updated vocabulary list. More work is needed to replicate these results and help elucidate them.

Our results also showed that adults with ADHD had significantly lower WRAT arithmetic, WRAT reading, and neuropsychological aggregate scores compared to the controls. This finding is consistent with the literature, including

Figure 1. IQ, Achievement, and Neuropsychological Aggregate by Age and ADHD Status[a]



[a]No significant interactions of age and ADHD. *P* values reflect differences between ADHD and control groups.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, WRAT = Wide Range Achievement Test.

our previous work.[6] In the meta-analytic study by Frazier et al[5] a moderate-to-large discrepancy in academic achievement between individuals with ADHD and typical controls was documented. This outcome substantiates the significant impact of ADHD symptoms on academic performance, and it revealed a pattern of impairments beyond the achievement test decrements identified previously by the same author.[5]

Our results are consistent with the literature, which indicates the presence of neuropsychological deficits in subjects with ADHD. In a review of the literature pertaining to the neuropsychological dysfunctions that are found in children and adults with ADHD, Seidman et al[37] reported that the neuropsychological deficits found in adults with ADHD (in subjects up to approximately age 40) appear to be qualitatively similar to those seen in children with the disorder. Biederman et al[6] also found that significantly more adults with ADHD had deficits of executive functioning

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than comparison subjects and, further, that these deficits significantly impaired academic and occupational functioning. In a meta-analysis, Hervey et al[38] reported that neuropsychological deficits are expressed in adults with ADHD across multiple domains of functioning, with notable impairments in attention, behavioral inhibition, and memory.

These data raise interesting questions about the relationship between aging and ADHD. A review of the literature came up empty in terms of empirical studies. Clinically, there are numerous concerns raised by individuals around the issue of memory loss and decline in cognitive abilities, yet this issue has not yet been studied. These results will add to the literature from a public health and clinical perspective. More work is needed on this topic.

Results of this study should be tempered by some methodological limitations. Because our sample was referred for ADHD, our results cannot be generalized to nonreferred samples. Our sample was skewed toward white participants (85% of participants with ADHD), and thus results may not generalize to other ethnic groups. The ADHD and control groups were not matched on possible confounding factors such as education or parental SES. However, the differences in IQ observed here are consistent with studies comparing hyperactive children and their matched nonhyperactive siblings,[39] as well as a meta-analysis of ADHD and IQ.[40] Although we used the terms *life cycle* and *life span*, this is a cross-sectional study of adults 19 to 55 years of age. Longitudinal studies should seek to replicate our findings.

Despite these considerations, the findings show that the negative impact of ADHD on cognition is constant across the life cycle in the unmedicated state. These results suggest that the association between ADHD and cognition remains unchanged across the adult life cycle. Further work should be done to clarify the effect of medication on the cognition of individuals with ADHD over the adult life span.

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