Effect of Hormone Levels and Aging on Cognitive Function of Patients with Pituitary Adenomas Prior to Medical Treatment

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■ BACKGROUND: **Cognitive impairments have been reported in patients with pituitary adenomas (PAs). The aim of this research was to demonstrate the effects of hormones and age on cognitive decline in patients with PAs.**

■ METHODS: **A total of 64 patients with PA and 69 healthy control subjects (HCs) were recruited for this study. Both PAs and HCs were divided into a younger group (<50 years of age) and an older group (≥50 years of age). Neurocognitive domains were assessed using the Wechsler Adult Intelligence Scale-Chinese Revision (WAIS-RC) and Wechsler Memory Scale-Chinese Revision (WMS-RC) tests. Furthermore, we also investigated the relationship between cognitive domains and tumor volume, and the hormone levels and age of patients with PA.**

■ RESULTS: **Several of the cognitive impairments found on the WAIS-RC and WMS-RC tests were more frequently observed in untreated patients with PA. Importantly, no significant correlations were found between cognitive domains and tumor volume after controlling age, sex, and educational levels. Furthermore, several significant correlations were found between cognitive domains and hormone levels, such as free thyroxine and adrenocorticotropic hormone, after controlling age, sex, and educational levels. Finally, the age of the patients was found to correlate with a decrease in memory after controlling sex and educational levels.**

■ CONCLUSIONS: **Our findings demonstrate a significant decline in the cognitive performance of patients with PA prior to medical treatment, especially in older patients, which suggests that hormones and age have the ability to interact and aggravate cognitive decline in patients with PA.**

INTRODUCTION

Pituitary adenomas (PAs) are benign, slow-growing, expansive, and monoclonal tumors that present either because of hormonal hypersecretion of pituitary and/or local mass effects and hyposecretion of some or all of the pituitary hormones, which consist of adenohypophysial cells.[1,2] Currently, PAs are the third most common masses of intracranial tumors, representing approximately 10%–15% of all intracranial tumors based on pathologic immunohistochemical confirmation.[1] With the increased use of imaging techniques and better diagnostic modalities, Agustsson et al.[3] demonstrated that the total PAs prevalence of 115.57 per 100,000 was higher than that of any previous study in their nationwide study spanning 6 decades. Standardized incidence rates have significantly increased and are currently estimated to be 5.8 per 100,000 per year.[3] PAs are often associated with complex health problems, such as cognitive impairments. Cognitive impairment was observed in patients with PA and was mainly present in memory and

Key words
- Cognitive function
- Hormone levels
- Pituitary adenomas
- Tumor volume

Abbreviations and Acronyms
ACTH: Adrenocorticotropic hormone
FSH: Follicle stimulating hormone
GH: Growth hormone
HC: Healthy control subject
LH: Luteinizing hormone
MRI: Magnetic resonance imaging
PA: Pituitary adenoma
T3: Triiodothyronine
T4: Thyroxine
WAIS-RC: Wechsler Adult Intelligence Scale-Chinese Revision
WMS-RC: Wechsler Memory Scale-Chinese Revision

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executive function.[4,5] However, the underlying mechanisms of action responsible for cognitive impairment in patients with PA are not well known.

Therefore, cognitive impairment is a clinical syndrome that may be caused by pathologic changes, aging, or consciousness dysfunction, and might negatively affect a patient's health-related quality of life.[6-8] In addition, there are too many neuropsychologic tests available to assess the patients' general and specific cognitive domains.[9] Before testing, it will need to be considered if a patients' physical condition is suitable for assessing cognition by currently existing methods.

Recently, several studies have documented cognitive dysfunction in patients who were diagnosed with PA. Indeed, Grattan et al.[5] demonstrated that patients with PA showed impairment of memory and executive function, which did not appear to be related to the size or type of tumor or the effects of therapeutic modalities, such as radiotherapy or surgery. Furthermore, in several studies, it has been reported that neurocognitive deficits commonly seen in patients with PA affected memory and executive function because of hormone levels, and this effect may be long lasting or have an irreversible effect on the nervous system.[10] However, many studies focus on cognitive dysfunction in patients with PA after treatment.[11-13] However, studies that focus on the factor of cognitive impairment in patients with PA prior to treatment are limited. Currently, the incidence rate of PAs per year is increasing[3]; therefore, there is an unmet need to monitor patient cognitive function prior to medical treatment. Therefore, having a clear understanding of cognition impairment and mental state in patients with PA prior to medical treatment could offer a new therapeutic strategy for the treatment of patients with PA.

Here, we investigated the extent of tumor and age on impacting cognition in patients with PA. In addition, we tested our hypothesis that these factors were implicated in cognitive decline. We hypothesized that the cognitive decline seen in patients with PAs was related to the level of hormones in blood and patient age, and was not related to tumor volume or tumor type (nonfunctioning and functioning). In our study, we evaluated 64 patients diagnosed with PA to understand the factors responsible for cognitive decline prior to the start of treatment, and provided a reference for clinical treatment.

METHODS

Patients

In this cross-sectional study, a total of 64 patients were recruited for participation at the neurosurgery inpatient clinic of the Brain Hospital affiliated with Nanjing Medical University, in the Jiangsu Province of China, from January 2017 to May 2018. The patients evaluated were diagnosed with PA by pathologic evidence, and met the inclusion criteria. For healthy control subjects (HCs), one family member of the recruited patient, staff of the hospital, or volunteer, with matched sex and education background, was also recruited with written informed consent. This study was approved by the ethics committee of the Brain Hospital affiliated with Nanjing Medical University.

Patient inclusion criteria were as follows: 1) first time for medical visit; 2) PA confirmed by pathologic diagnosis after surgery; 3) basic ability of motor and verbal communication to complete neurocognitive testing; 4) no previous radiotherapy, hormone replacement therapy, or surgery; and 5) no history of neurologic or psychiatric disorders. HC inclusion criteria were as follow: 1) no history of neurologic or psychiatric disorders, and 2) no previous medical treatments that could possibly influence intelligence within 1 week of the evaluation.

Patient exclusion criteria were as follows: 1) cerebrovascular diseases, including intracerebral hemorrhage and cerebral infarction, or other complications that could affect cognitive functions; 2) the patient had not received education; 3) recurrence of PA; 4) hearing loss or aphasia; 5) visual impairment where the participant could not see the text in books clearly; and 6) inability to write.

After admission, patient characteristics and attributes were collected, including age, sex, educational background, course of disease, tumor volume (in centimeters, based on magnetic resonance imaging [MRI]), and hormone levels. On the second morning after admission, blood samples were collected from patients for hormonal tests, including thyroxine (T4), triiodothyronine (T3), free T3, free thyroxine T4, thyrotropin, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, growth hormone (GH), and adrenocorticotropic hormone (ACTH). On the same day, cognition evaluation and MRI scans were conducted to obtain cognitive scores and tumor volume before surgery. We then divided the tumor group and the control group into 4 groups (group 1: younger patients <50 years of age; group 2: older patients ≥ 50 years of age; group 3: younger HCs <50 years of age; group 4: older HCs ≥ 50 years of age) based on the age of 50 years to explore the influence of aging and tumor on cognition. According to the 2017 World Health Organization classification[14] of tumors of the pituitary gland, we divided the 64 PAs into null cell adenoma (n = 28), lactotroph adenoma (n = 12), somatotroph adenoma (n = 9), gonadotroph adenoma (n = 12), thyrotroph adenoma (n = 1), corticotroph adenoma (n = 1), and plurihormonal adenoma (n = 1). In total, there were 28 patients with nonfunctioning PAs and 36 with functioning PAs. Then, we divided the tumor groups into 2 groups according to functional and nonfunctional tumor types to explore the different types of tumors cognition.

Tumor Volume Assessment

Preoperative MRI was performed with a 3.0-T Siemens Verio scanner (Berlin, Germany), and was reviewed using a centricity picture archiving and communication system workstation to ascertain the ellipsoid volumes of the tumor. The ellipsoid volume was calculated using the formula $4/3\Pi[A, B, C]$, where A, B, and C are the maximal orthogonal diameters in each dimension (**Figure 1**).[15]

Cognitive Test

The cognitive tests used in our study were administered during quiet and comfortable circumstances. With written consents from patients, their family members, and the hospital staff, cognitive testing was conducted in the same room by the same professionally trained doctor each time. The Wechsler Adult Intelligence Scale-Chinese Revision (WAIS-RC) and the Wechsler Memory Scale-Chinese Revision (WMS-RC) tests were used to assess different cognitive domains or tasks associated with cognitive

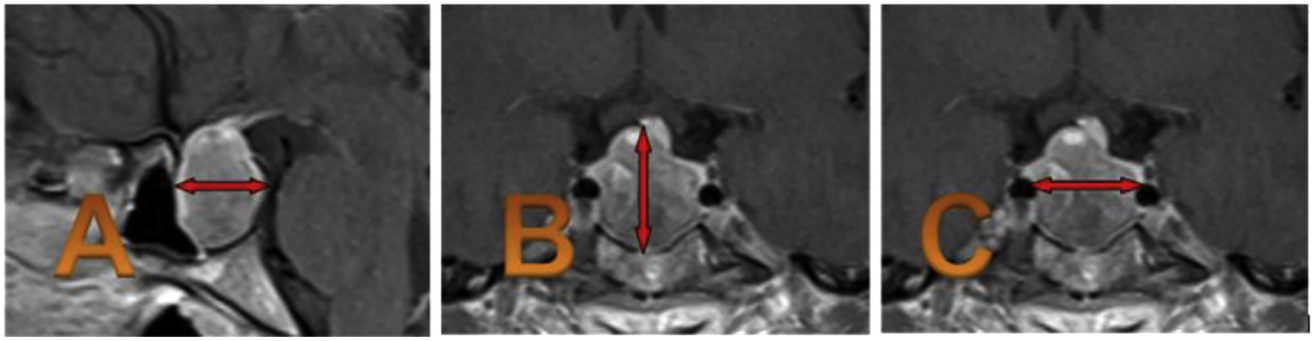

Figure 1. Pituitary adenoma volume estimation. **A**, **B**, and **C** maximal diameters (should bisect the midpoint) in each dimension (x, y, and z) are shown.[15]

skills, respectively. Attention and working memory were evaluated using the digit span of the WAIS-RC test.[16] The visuospatial function assessment was assessed using the block design of the WAIS-RC test, whereas the similarity task was used for executive function.[9] The picture completion task was assessed for visual perception and semantics.[17] In addition, the arithmetic and digit symbol tasks were chosen to evaluate attention and processing speed.[16,18] Meanwhile, the picture recall task of the WMS-RC test was used for assessing memory function.

Data Analysis

All data analyses were carried out using SPSS 20.0 (IBM, Armonk, New York, USA). All results were presented as mean ± SD. The significant level of statistical tests was set at a P value of 0.05. Independent sample t test was used to assess group differences in age, education, and tumor volume, and χ^2 test was used to assess sex differences. To investigate possible interactions between the effects of tumor and aging on cognitive test performances, participants were grouped by tumor (PAs vs. HCs) and age (<50 vs. ≥50 years of age), for a total of 4 groups (groups 1–4). The 2-way analysis of variance and Bonferroni correction post hoc tests were used to test the hypothesis that tumor and aging interact and aggravate cognitive decline in patients with PA. Then cognitive function comparison of functioning, nonfunctioning, and control groups was done using 1-way analysis of variance. Post hoc analyses were then carried out for corrected multiple comparisons using the Bonferroni test. The Pearson correlation coefficient test was used to find the correlation between cognitive function and tumor volume, and hormonal levels after controlling the covariates of age, sex, and educational level. We also did the Pearson correlation coefficient test between cognitive scores and patient age after controlling the covariates of sex and educational levels.

RESULTS

The attributes and characteristics of patients with PA compared with HCs are shown in Table 1. Similarly, attributes and characteristics of patients with functioning PA and nonfunctioning PA are shown in Table 2. There were no significant differences observed between the sex or educational levels between PAs and HCs. In addition, there were no significant differences observed in age, sex, and tumor volume between the nonfunctioning PA group and the functioning PA group.

Cognition Changes in Patients with PAs

Table 3 shows group performances for each cognitive test. The 2-way analysis of variance was performed to evaluate group differences. Our results showed that the main effect of tumor was significant in digit span ($F = 152.778$, $P < 0.001$), picture recall ($F = 62.222$, $P < 0.001$), block design ($F = 58.9$, $P < 0.001$), digit symbol ($F = 105.902$, $P < 0.001$), arithmetic ($F = 109.482$, $P < 0.001$), picture completion ($F = 25.349$, $P < 0.001$), and similarity ($F = 48.284$, $P < 0.001$). The results also showed the main effect of age was significant in digit span ($F = 68.749$, $P < 0.001$), picture recall ($F = 37.352$, $P < 0.001$), digit symbol ($F = 8.453$, $P = 0.004$), arithmetic ($F = 46.814$, $P < 0.001$), and picture completion ($F = 14.051$, $P < 0.001$). However, the main effect of age was not significant in block design ($F = 3.176$, $P = 0.077$) or similarity ($F = 0.481$, $P = 0.489$). Moreover, the interaction effect was significant in digit span ($F = 33.243$, $P < 0.001$), arithmetic ($F = 22.723$, $P < 0.001$), picture completion ($F = 8.022$, $P = 0.005$), and similarity ($F = 14.106$, $P < 0.001$), but it was not significant in picture recall ($F = 1.112$, $P = 0.294$), block design ($F = 0.626$, $P = 0.43$), or digit symbol ($F = 0.284$, $P = 0.595$).

Table 1. Clinical Characteristics of Patients With Pituitary Adenoma and Healthy Control Subjects

Characteristic	Patients with Pituitary Adenoma (n = 64)	Healthy Control Subjects (n = 69)	*P* Value
Age (years)	49.13 ± 14.137	33.58 ± 15.264	<0.001
Sex, M/F	26/38	34/35	0.384
Educational level (years)	10.11 ± 3.626	10.87 ± 2.572	0.163
Tumor volume (cm^3)	53.55 ± 88.47	-	-
Duration disease (months)	29.57 ± 56.11	-	-

Data are expressed as mean ± SD, number of patients, or as otherwise indicated. M, male; F, female.

Table 2. Clinical Characteristics of Patients With Nonfunctioning and Functioning Pituitary Adenomas

Characteristic	Nonfunctioning PA Group (n = 28)	Functioning PA Group (n = 36)	*P* Value
Age	52.89 ± 11.77	46.19 ± 15.25	0.059
Sex, M/F	15/13	11/25	0.077
Tumor volume (cm^3)	48.91 ± 49.26	57.15 ± 111.39	0.717
Duration of disease (months)	10.04 ± 16.36	44.75 ± 70.77	0.014
Education levels (years)	9.07 ± 3.288	10.92 ± 3.714	0.042
Headache	15	11	-
Visual impairment	11	10	-

Data are expressed as mean ± SD, number of patients, or as otherwise indicated.
PA, pituitary adenoma; M, male; F, female.

Figure 2 shows significant differences in post hoc comparisons after performing 2-way analysis of variance. Nonetheless, there were no significant differences found in tested cognitive domains between patients (groups 1 and 2) during post hoc comparisons, except for the picture recall. Post hoc comparisons showed that groups 1 and 2 have significant decline in digit span, picture recall, block design, arithmetic, and digit symbol when compared with group 3. In addition, there is a significant difference in the similarity task between groups 2 and 3. Meanwhile, post hoc comparisons showed that group 1 presented significant differences in block design, digit symbol, picture completion, and similarity compared with group 4. Post hoc comparisons indicated that group 2 had a significant decline in all tested cognitive domains when compared with group 4. Moreover, there were significant differences in tested cognitive domains between HCs (groups 3 and 4) during post hoc comparisons, except for block design and digit symbol.

Correlation Between Cognitive Function and Tumor Volume, Hormone Levels, and Aging

To understand the potential factors affecting the cognitive function of patients with PA, we performed Pearson correlation coefficient test between cognitive scores and tumor volume and hormone levels after controlling the covariates of age, sex, and educational levels. We also did Pearson correlation coefficient test between cognitive scores and patient age after controlling covariates of sex and educational levels. However, no correlations were found between the tested cognitive domains and tumor volume. Figure 3 shows the relationships between cognitive function and hormones of patients with PA. Markedly, logged T3, T4, free T3, free T4, GH, FSH, LH, and prolactin were found unrelated to any of the cognitive domains assessed after controlling covariates of age, sex, and educational levels. However, logged free T4 was found to be positively associated with the picture recall task score ($r = 0.287$, $P = 0.031$). Moreover, logged ACTH was found to be negatively associated with the arithmetic score ($r = -0.299$, $P = 0.025$). Importantly, the age of patients was also found to be correlated with some of the cognitive functions assessed (Figure 4). The age of patients was negatively associated with the picture recall ($r = -0.3$, $P = 0.018$) task scores after controlling covariates of sex and educational levels.

Cognitive Function in Patients with Nonfunctioning and Functioning PAs

In our evaluation, we found that both the functioning PA group and nonfunctioning PA group demonstrated significantly impaired cognitive functions compared with the HCs ($P \leq 0.001$) (Table 4) after completing the cognitive function tests. Figure 5 shows the results of post hoc comparisons after 1-way analysis of variance. Post hoc comparisons showed that the functioning PA group and nonfunctioning PA group presented no significant differences in the cognitive domains tested when compared with each other ($P > 0.05$), except for picture recall ($P = 0.007$).

Table 3. Cognitive Testing Scores of Studied Groups Prior to Medical Treatment and Post Hoc Analysis Results

Cognitive Assessment	Total	Group 1	Group 2	Group 3	Group 4
Digit span	13.04 ± 4.236	10.45 ± 3.315	9.43 ± 2.615	17.77 ± 0.937*†	12.09 ± 2.18†‡
Picture recall	10.62 ± 3.829	9.59 ± 3.5	7.11 ± 3.644*	13.96 ± 0.806*†	10.45 ± 2.444†‡
Block design	10.76 ± 3.349	8.97 ± 3.19	8.49 ± 2.994	13.06 ± 0.673*†	11.82 ± 3.911*†
Arithmetic	10.74 ± 4.278	8.24 ± 3.71	7.29 ± 2.761	15.26 ± 1.113*†	9.91 ± 2.599†‡
Digit symbol	12.97 ± 4.119	11 ± 3.295	9.2 ± 4.384	16.11 ± 1.127*†	14.86 ± 1.859*†
Picture completion	9.32 ± 2.551	8.31 ± 2.565	8.69 ± 2.867	9.21 ± 1.122	11.91 ± 2.635*†‡
Similarity	10.26 ± 3.927	9.31 ± 2.817	7.49 ± 3.921	11.21 ± 1.573†	13.86 ± 5.13*†‡

Data are shown as mean ± SE. The 2-way analysis of variance was applied to investigate possible influences of tumor and aging on cognitive performance in the 4 groups.
*Bonferroni post hoc test: significant differences when comparing group 1 with group 2, group 3, and group 4.
†Bonferroni post hoc test: significant differences when comparing group 2 with group 3 and group 4.
‡Bonferroni post hoc test: significant differences between group 3 and group 4.

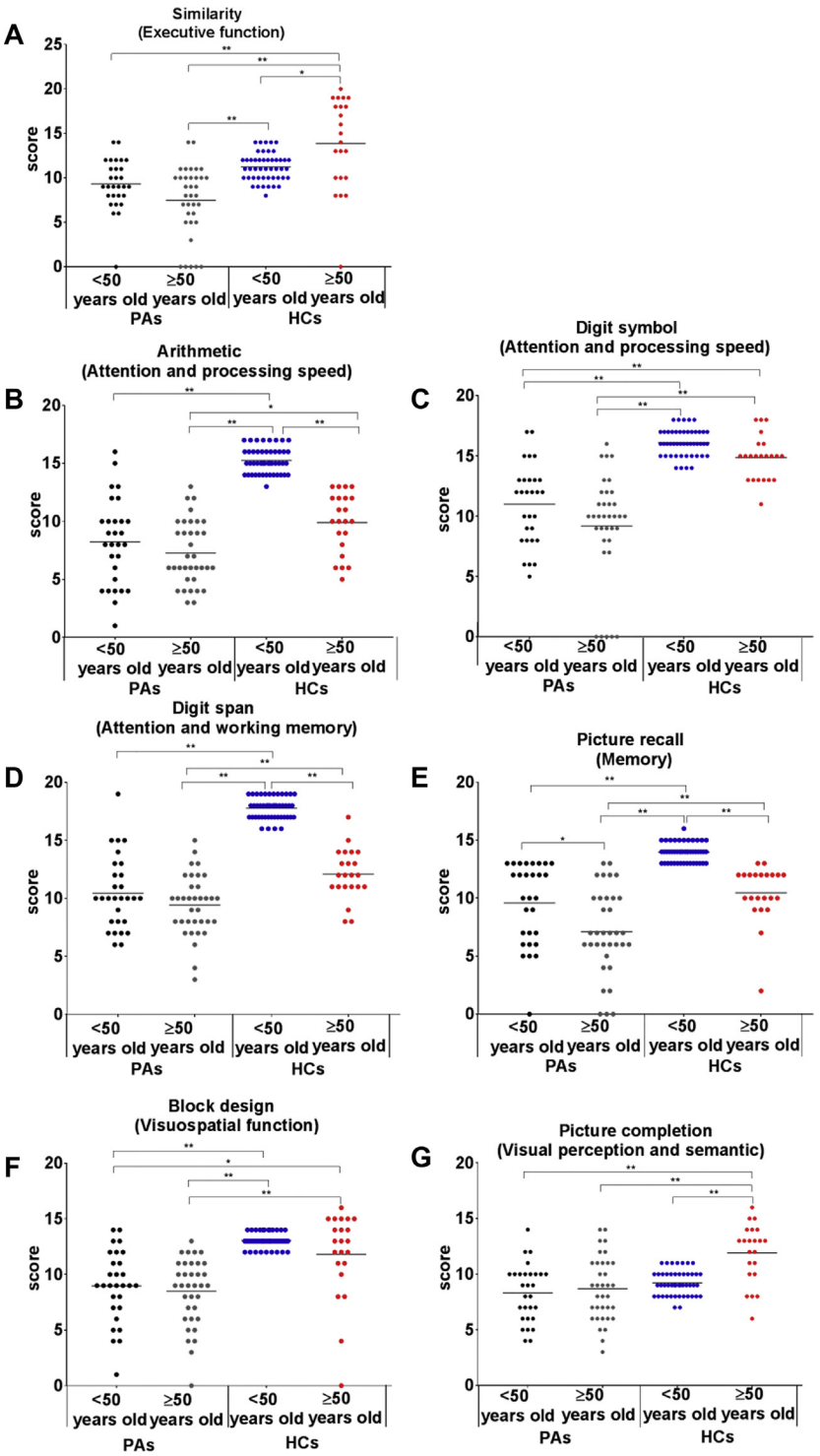

Figure 2. Representation of cognitive performance between groups. Results showing the distribution of cognitive test scores in group 1 (*black dots*), group 2 (*gray dots*), group 3 (*blue dots*), and group 4 (*red dots*). *Black bars* represent the mean of the cognitive scores. (**A**) Executive function between the 4 groups. (**B** and **C**) Attention and processing speed between the 4 groups. (**D**) Attention and working memory between the 4 groups. (**E**) Memory between the 4 groups. (**F**) Visuospatial function between the 4 groups. (**G**) Visual perception and semantics between the 4 groups. $*P < 0.05$ and $P \geq 0.001$; $**P < 0.001$. HC, healthy control subjects; PA, pituitary adenoma.

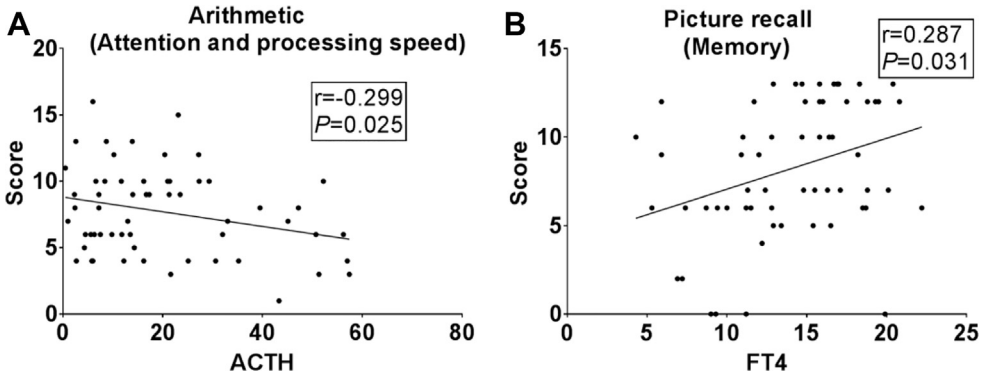

Figure 3. Scattergrams representing the significant correlations between cognition and hormone levels in patients with pituitary adenom. (**A**) Significant negative correlation between adrenocorticotropic hormone and arithmetic (attention and processing speed) after controlling the covariates of age, sex, and educational levels is shown. (**B**) Significant positive correlation between the levels of free T4 and picture recall (memory) after controlling covariates of age, sex, and educational levels is shown. Correlation coefficients (*r*) and *P* values are reported in each correlation graph. ACTH, adrenocorticotropic hormone; FT4, free thyroxine.

DISCUSSION

In this study, we revealed cognitive decline and the factors for cognitive impairment in patients with PA prior to medical treatment. When compared with HCs, all patients with PA exhibited significantly worse performance regarding attention, working memory, visuospatial function, processing speed, visual perception, semantics, executive function, and memory. Our results were consistent with the findings presented in several previous studies demonstrating that patients with PA have apparent impairment in cognitive function, particularly in memory, executive function,[5,19] and attention.[7] In addition, our results suggested that the main effects of both tumor and age result in significant differences in the assessed cognitive domains. However, the main effect of age did not significantly result in differences in visuospatial function or executive function. Moreover, the interaction of tumor and age was significant in areas of attention, working memory, processing speed, visual perception, semantics, and executive function, but was not significant in other tested cognitive domains.

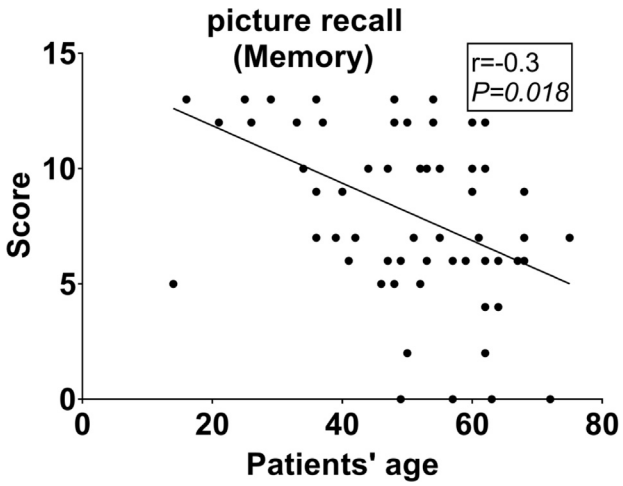

Figure 4. Scattergram representing the correlation between cognition and age of patients. The significant negative correlation between patient age and picture recall (memory) after controlling the covariates of sex and educational levels is shown. Correlation coefficients (*r*) and *P* values are reported.

In our study, we demonstrated that older HCs displayed significantly impaired cognitive function in areas of attention, working memory, processing speed, and memory when compared with younger HCs. Our results are generally consistent with previous studies demonstrating that attention,[20,21] memory,[8] processing speed,[22] and working memory[22,23] performance were lower in older adults compared with younger adults. Notably, we have also observed that older HCs have significantly higher scores in visual perception and semantics compared with younger HCs. In a previously published review article, it was reported that semantics knowledge and vocabulary remained relatively stable until late in life,[24,25] thereby indicating that life experience might breed knowledge and exhibit wisdom seen in older adults.[26] Unfortunately, the results for executive function, however, contradicted the previous studies that healthy older adults demonstrated worse executive function when compared with healthy younger adults.[27] However, Ferreira et al.[28] reported subtle executive dysfunction before the age of 50 years in healthy participants. Besides the results previously mentioned, we found that, before any treatment, younger patients with PA presented with higher scores in all tested cognitive domains when compared with older patients with PA. Significant differences were only observed in 1 domain (memory). Moreover, a significant negative correlation was found between patient age and memory after controlling for covariates of sex and educational levels.

Regarding factors of cognitive impairment, we analyzed the relationships between cognitive scores and tumor volume, and hormone levels. Few statistically significant correlations were observed between tumor volume and cognitive functions after controlling for

Table 4. Cognitive Function Scores of the Nonfunctioning Pituitary Adenoma Group, Functioning Pituitary Adenoma Group, and Healthy Control Subjects Prior to Medical Treatment

Cognitive Assessment	Total	Nonfunctioning PA Group	Functioning PA Group	HC Group	*P* Value
Digit span	13.04 ± 4.236	9.46 ± 3.383	10.22 ± 2.427	15.96 ± 3.027*†	<0.001
Picture recall	10.62 ± 3.829	6.93 ± 3.819	9.25 ± 3.434‡	12.84 ± 2.234*†	<0.001
Block design	10.76 ± 3.349	8.79 ± 2.515	8.64±3.474	12.67 ± 2.318*†	<0.001
Arithmetic	10.74 ± 4.278	7.46 ± 3.469	7.92 ± 3.074	13.55 ± 3.037*†	<0.001
Digit symbol	13.07 ± 3.975	9.26 ± 4.101	10.86 ± 3.506	15.71 ± 1.506*†	<0.001
Picture completion	9.32 ± 2.551	8.32 ± 2.374	8.67 ± 2.986	10.07 ± 2.144*†	0.001
Similarity	10.26 ± 3.927	8 ± 3.464	8.56 ± 3.66	12.06 ± 3.369*†	<0.001

Data are shown as mean ± SE or as otherwise indicated.
PA, pituitary adenoma; HC, healthy control subject.
*Bonferroni post hoc test: significant differences between the nonfunctioning PA group and HC group.
†Bonferroni post hoc test: significant differences between the functioning PA group and HC group.
‡Bonferroni post hoc test: significant differences between the nonfunctioning PA group and the functioning PA group.

covariates of age, sex, and educational levels, implying that compression from the tumor might not affect cognitive impairment. These results are in agreement with the findings presented in previous studies,[5,7] and strengthens the hypothesis that tumor volume did not affect cognition impairment.

Because tumor volume was not a major factor for declined cognition, we focused on the other potential cause of impairment, hormone levels. We found that the relationships of logged ACTH and free T4 to certain cognitive domains were significant after controlling for covariates of age, sex, and educational level. In our study, we found that in general, logged ACTH data were consistent with the findings presented in previous studies, demonstrating that ACTH has a negative effect on attention and processing speed.[29,30] Furthermore, in a chronic mild stress animal model, Li et al.[31] reported that cognitive impairment was associated with an increase in circulating hormone plasma levels, including ACTH levels. Notably, our findings suggest that the levels of free T4 significantly correlate with an increase in cognitive performance on memory, which is in line with the results obtained by Bojar et al.,[32] who demonstrated that higher levels of free T4 positively correlate with the abilities of memory and psychomotor speed in women. Therefore, logged ACTH initially predicted lower levels of cognitive functioning in attention and processing speed, whereas logged free T4 predicted higher levels of cognition in memory.

In several previous studies, it was suggested that other pituitary hormones impaired cognition in patients with PA, such as GH,[33] LH,[34] and FSH.[29] However, these studies did not consistently isolate the possible cognitive effects of hormones from the confounding effects of aging, sex, and educational level. Therefore, in the future, we need to further investigate the relationships between other pituitary hormones and cognition after controlling for confounding effects, to unravel the underlying mechanism of action for cognitive impairment in animal models.

Our study suggested that patients in the nonfunctioning PA group had significant impairment in memory when compared with patients in the functioning PA group. In contrast, Grattan et al.[5] demonstrated that patients with PA have memory impairment, which did not appear to be related to tumor type. Moreover, in another previous study, it was suggested that patients in the nonfunctioning PA group exhibited significantly better performance on memory when compared with patients in the functioning PA group.[7] The findings between patients in the nonfunctioning PA group and functioning PA group, however, contradicted the hypothesis that cognitive impairment was not related to tumor type, and motivates additional studies to evaluate the cognition between patients in the nonfunctioning PA group and functioning PA group.

Study Limitations

Our study has several limitations that need to be addressed. First, the sample size used was small (N = 64). Second, it might be very hard to exclude the confounding effects that impaired cognition. Third, preoperative stress and anxiety experienced by the patient could affect the pattern and magnitude of observed neurocognitive impairment. Fourth, we did not have objective evidence to prove the cognitive impairment in patients with PA. Currently, functional MRI is an advanced technology used for the study of cognitive function in diseases of the brain.[6,35,36] In our future studies, we will evaluate the relationship between cognitive decline and abnormal functional networks in patients with PA using advanced functional MRI techniques.

CONCLUSIONS

The data presented in this study showed that patients with PA do suffer from cognitive decline before given any treatment, which may be the result of hormones and aging, and are not associated with tumor volume. Hormone levels and aging might be the main causes of cognitive dysfunction after controlling for covariates, and may predict cognitive impairment. Moreover, for patients with PA, factors including tumor volume and age could interact and aggravate impairment in several cognitive domains. In addition, our data showed that patients in the nonfunctioning PA group had significant impairment in memory when compared with patients in the functioning PA group.

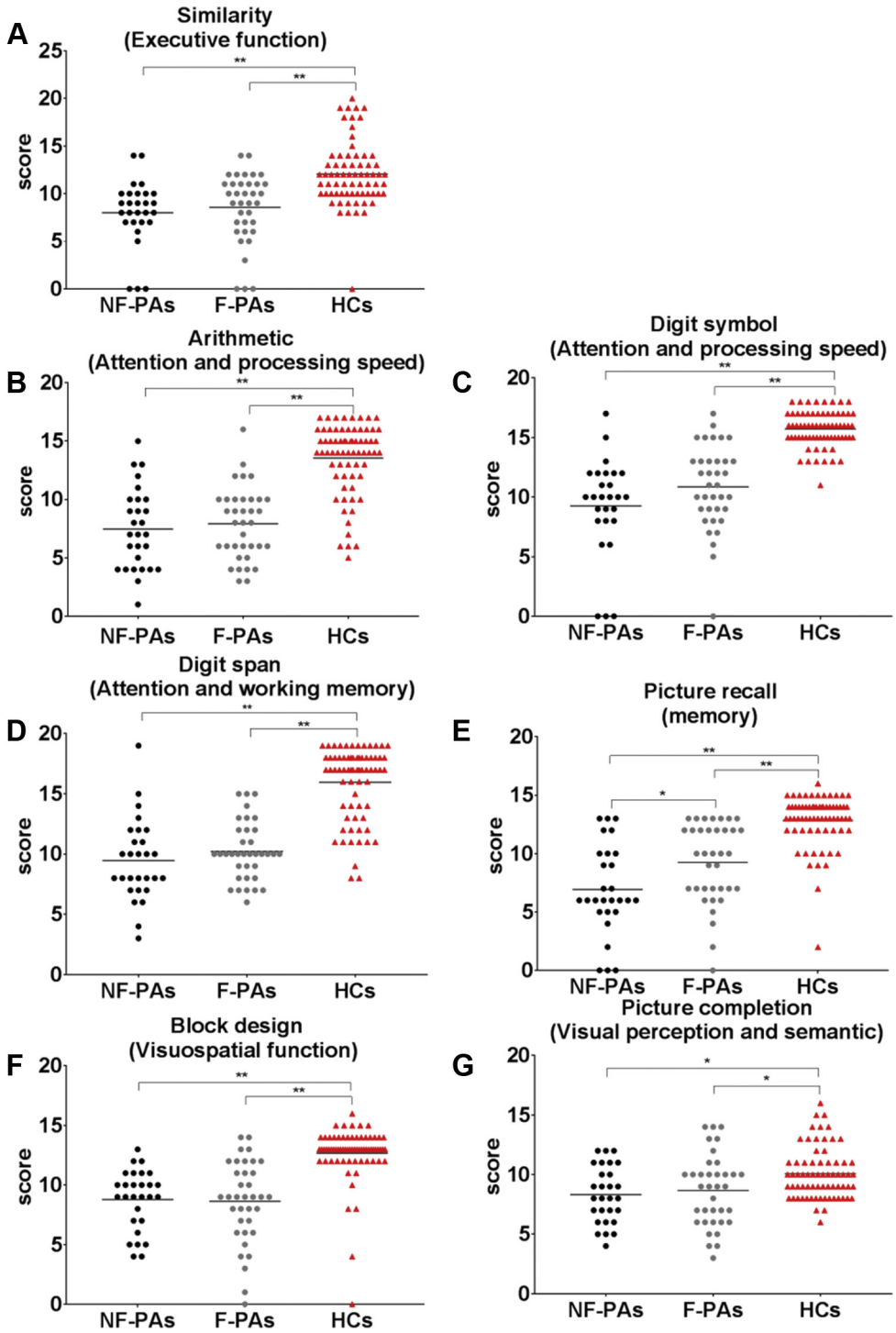

Figure 5. Comparison of cognitive function between the nonfunctioning pituitary adenoma (NF-PA) group, the functioning pituitary adenoma (F-PA) group, and the healthy control subject (HC) group, with post hoc comparison results. Graphs show the dispersal distribution of the different cognitive test scores in the NF-PA group (*black dots*), the F-PA group (*gray dots*), and the HC group (*red dots*). *Black bars* represent the mean of all the cognitive scores. (**A**) Executive function between the 3 groups is shown. (**B** and **C**) Attention and processing speed between the 3 groups is shown. (**D**) Attention and working memory between the 3 groups is shown. (**E**) Memory between the 3 groups is shown. (**F**) Visuospatial function between the 3 groups is shown. (**G**) Visual perception and semantics between the 3 groups is shown. $*P < 0.05$ and $P \geq 0.001$; $**P < 0.001$.

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