The Effect of Aromatase Inhibition on the Cognitive Function of Older Patients with Breast Cancer

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Abstract

Purpose—To evaluate the association between aromatase inhibitor (AI) therapy and cognitive function (over a 6-month time period) in a cohort of patients age 60 compared with an age-matched healthy control group, and to evaluate changes in regional cerebral metabolism as measured by positron emission tomography (PET) scans of the brain done in a subset of the patient cohort.

Patients and Methods—Thirty-five patients (32 evaluable) and 35 healthy controls were recruited to this study. Patients with breast cancer completed a neuropsychological battery, self-reported memory questionnaire, and geriatric assessment prior to initiation of AI therapy and again 6 months later. Age-matched healthy control participants completed the same assessments at the same time points as the patient group.

Results—No significant decline in cognitive function was seen among individuals receiving an AI from pre-treatment to 6 months later compared with healthy controls. In the PET cohort over the same period, both standardized volume of interest (sVOI) and statistical parametric mapping (SPM) analyses detected specific changes in metabolic activity between baseline and follow-up uniquely in the AI patients, uniquely, most significantly in medial temporal lobes.

Disclosure of Potential Conflicts of Interest
AH has received research support from Celgene Corporation and GlaxoSmithKline, and consulting fees from Seattle Genetics and GTx, Inc., for work performed outside the scope of this manuscript. All remaining authors declare that they have no conflicts of interest.

Author Contributions
AH, SP, and DS were responsible for the conception, design, development of methodology, and supervision of the study. VK, RR, KH, and CG provided administrative, technical, or material support. All authors except TF and CC were involved in the acquisition of data, and all authors were involved in data analysis and interpretation. All authors except KH and RR participated in the writing, review, and revision of the manuscript.

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Conclusion—While patients undergoing AI treatment demonstrated few changes in neuropsychologic performance compared with healthy controls over a 6-month period during this interval, regionally specific changes in cerebral metabolic activity were identified in the patient group. Additional longitudinal follow-up is needed to understand the potential clinical implications of these findings.

Keywords

cognitive function; older adults; breast cancer; aromatase inhibitors; PET scan

Introduction

A growing body of literature has evaluated the potential effect of breast cancer therapy on cognitive function. There are limited data regarding the association between endocrine therapy and cognition, however, and despite the fact that breast cancer is a disease associated with aging, most studies have been performed with relatively young adults, so the impact of endocrine therapy for breast cancer on the cognition of older adults remains unknown.

Aromatase inhibitors – a mainstay of treatment for hormone receptor-positive, early-stage breast cancer in postmenopausal women – inhibit the enzyme aromatase, which leads to a reduction in estrogen levels throughout the body. Since estrogen receptors are spread throughout the brain, and studies have shown that estrogen promotes neuron growth and provides neuroprotective activity *in vitro*, there is a biologic reason to question whether aromatase inhibition might influence cognitive function.[1–3]

Conflicting data from randomized controlled studies exist concerning the impact of both estrogen replacement and estrogen deprivation on cognitive function in the clinical setting.[4–8] Likewise, clinical studies examining the effects of endocrine therapy on cognitive function of patients with breast cancer have produced inconsistent results, with some,[9–12] but not all,[13] suggesting a decline in cognitive function resulting from treatment.

The biologic basis of cognitive change as a result of cancer therapies is poorly understood. Previously, Silverman et al. demonstrated that treatment-related regional changes in brain metabolism are associated with changes in neuropsychological performance.[14] For example, diminished metabolism in the posterior inferior frontal gyrus in the vicinity of Broca's area was specifically associated with diminished performance on a neuropsychological test of short-term memory in patients with breast cancer who had received adjuvant therapy.

In this study, we sought to use neuropsychological testing to examine the association between aromatase inhibitor (AI) therapy and cognitive function in a cohort of patients age 60 compared with an age-matched healthy control group and to evaluate changes in regional cerebral metabolism as measured by positron emission tomography (PET) scans of the brain performed for a subset of the patient cohort. We hypothesized that there would not be short-term changes in cognitive function among patients taking an AI compared to an age-matched healthy control group; however, regional changes in brain metabolism on PET imaging may be seen.

Materials and Methods

Study Population

Thirty-five patients (32 evaluable) and 35 healthy controls were recruited to the study. Patients age 60 with hormone receptor-positive stage I-III breast cancer who were about to receive adjuvant AI therapy as systemic therapy for breast cancer were eligible for the study and were recruited from the outpatient practice at City of Hope National Medical Center. These patients had received surgical treatment for their breast cancer and chemotherapy (if indicated). An age-matched healthy control group, solicited through the services of Marketing Systems Group, was recruited to participate in the study to enable comparison with the patients receiving AI therapy. Three patients who missed follow-up assessments were excluded from analysis. The study was approved by the institutional review board, and all study participants provided written, informed consent.

Patients were deemed ineligible if they had received estrogen replacement therapy within the past year or previous radiation treatment of the central nervous system. Other eligibility criteria included literacy in English, since many of the study measures were not validated in other languages.

Study Procedure

Study participants with breast cancer completed a neuropsychological battery, a self-reported memory questionnaire, and a geriatric assessment prior to initiation of AI therapy as well as 6 months later. Age-matched study participants in the healthy control group completed the same assessments at the same time points as the patient group.

The neuropsychological battery consisted of 13 standardized tests of neuropsychological function across seven domains: attention; verbal memory; visual memory; verbal, spatial, psychomotor, and executive functions (Table 1). The tests were chosen for succinctness, reliability, validity, and past use to enable comparison with normative data. This battery was previously tested in a study of older patients with breast cancer.[15]

The patients' self-reported assessment of their cognitive function was collected through the Squire Memory Self-Rating Questionnaire.[16] The questionnaire contains 18 items of self-reported cognitive function rated on a scale from –4 to +4. Three of the questions were found to have ambiguous loadings and were excluded from analysis, consistent with methodology used in a previously reported study [16]. The participants also completed a geriatric assessment including validated measures of functional status, comorbid medical conditions, psychological state, social support, nutritional status, cognitive function, and medications.[17,18]

Ten patients and ten healthy controls completed a PET scan at both time points, to assess changes in regional cerebral metabolism. [F-18]-labeled fluorodeoxyglucose (FDG), was used as the tracer. At each time point, 5 millicuries of FDG were administered intravenously. After a 40-minute period of tracer uptake in a dimly-lit, quiet room, emission data were acquired for 30 minutes with an HR+ dedicated PET scanner (Siemens/CTI). Images were attenuation-corrected with emission data obtained from an external positron-

emitting source, and summed over the acquisition period to yield a three-dimensional representation of the regional distribution of resting metabolism.[19]

Statistical Analysis

Using independent samples t-tests and chi-squared tests, 32 patients receiving adjuvant AI therapy were compared with 35 healthy controls by baseline demographic characteristics as well as the functional domains that constitute the geriatric assessment battery. The longitudinal analysis evaluated the change in neuropsychological performance between baseline and 6-month follow-up using paired t-tests. Standard scoring of neuropsychological tasks was based on population norms and adjusted for age, sex, and, in some cases, education. Comparisons between patients and their healthy counterparts were performed at baseline using independent sample t-tests. In order to control for the practice effects associated with repeated cognitive testing and to assess the clinical significance of changes in neuropsychological function, the degree of longitudinal change observed in patients was compared to that observed in controls using a t-test.

Prior to analysis, PET images were reoriented into standardized space, spatially smoothed (FWHM 8 mm), and normalized to mean whole-brain metabolic activity. As previously described,[19,20] data were analyzed by (1) a standardized volume of interest (sVOI) approach using NeuroQ software (Syntermed Inc., Atlanta) and (2) a voxel-based statistical parametric mapping (spm) method using SPM8 software generously provided by the Wellcome Trust Centre for Neuroimaging (London). To statistically protect for multiple comparisons, regions identified by spm were noted only when containing voxels with significance $P < 0.0005$, and the sVOI approach was used for methodologically independent corroboration of location of changes in metabolism observed with spm. Furthermore, it was established *a priori* that only significant longitudinal changes in neuropsychological findings would be correlated with PET findings.

Results

Patient Characteristics

The healthy control group in this study did not significantly differ from our patient cohort with regard to age, race, education, employment and marital status, and previous hormone replacement therapy (Table 2). Fourteen study subjects had received prior hormone replacement therapy. Seven patients had received prior chemotherapy treatment and 12 patients had prior radiation therapy. Among the patient group that underwent PET imaging, only one had had prior chemotherapy and three had prior radiation therapy to the breast. Functional status, as evaluated by the geriatric assessment, statistically differed between the two groups on Instrumental Activities of Daily Living (IADLs) at both baseline and follow-up ($P < 0.01$), such that healthy controls reported a higher level of functioning than the patient group (Table 3).

Neuropsychological Assessment (Tables 3–5)

At baseline, the control group had significantly higher scores than the patient group on the Wechsler Adult Intelligence Scale (WAIS) Digit Symbol test ($P = 0.02$) and the Boston

Naming Test ($P = 0.01$); the latter difference persisted at 6 months, but not the former, as patient performance significantly improved from baseline to 6-month follow-up in WAIS Digit Symbol ($P = 0.02$). Patient performance also improved with respect to Block Design ($P = 0.01$), Boston Naming Test ($P = 0.003$), Stroop Color Page ($P = 0.04$), and Rey-Osterreith Complex Figure (ROCF) Immediate Recall ($P = 0.04$). Longitudinal change significantly differed between the two groups on Block Design ($P = 0.02$) and WRAT-4 reading test ($P = 0.0005$), the latter due to a significant decrease that was seen only in the control group. At follow-up, patients also reported significantly better memory function on the Squire Memory Self-Rating Questionnaire than the controls ($P = 0.02$; Table 3)

PET Imaging

sVOI analyses revealed change to four cortical regions between baseline and 6-month follow-up in patients with breast cancer who underwent AI therapy. Relative to baseline, anterior medial temporal activity tended to increase bilaterally (left, $P = 0.02$; right, $P = 0.06$), as did left posterior medial temporal activity ($P = 0.03$). In addition, a region in the vicinity of Broca's area showed decreased activity ($P = 0.02$) following AI therapy. These changes were not observed in the control group.

SPM analyses revealed increased metabolism in bilateral medial temporal and cerebellar regions in patients who underwent AI therapy, with the largest and most significant cluster of increased metabolism occurring in the right medial temporal lobe *($P < 0.0005$)*. Direct statistical comparison of longitudinal changes between the patient group and control group further demonstrated that the change observed in this region differed significantly between groups ($P < 0.0005$) (Figure 1). Finally, in cancer patients who had received AI, a positive correlation between Block z-scores (an index of visuospatial ability) and bilateral occipital region activity was observed ($P < 0.0005$). This relationship also appeared to be therapy-specific, in that it was only present at follow-up in patients who had received AI, and was not observed at baseline, or at either time point in controls.

Discussion

The literature regarding the association of endocrine treatment with cognitive function is conflicting. Several studies support the idea that treatment is associated with cognitive decline in patients with breast cancer. A study by Jenkins et al. indicated that patients taking anastrozole, tamoxifen, or the combination, experienced cognitive impairments compared with a healthy control group, specifically in processing speed and immediate verbal memory.[9] A study by Collins et al. found similar results, with patients taking anastrozole or tamoxifen experiencing a decline in cognitive function (from start of endocrine therapy to 6 months later) when compared with healthy controls.[11] Relative to healthy controls, patients receiving anastrozole demonstrated a nine-fold increase in risk for cognitive decline. Also, in the BIG 1-98 trial, Phillips et al. found that cognition significantly improved from end of endocrine therapy to one year after treatment stopped.[21]

Other studies, however, have demonstrated no association between AI treatment and cognitive function. A study by Jenkins et al. concluded that use of anastrozole had little or no association with impairment of cognitive performance compared with a placebo in

women at increased risk for developing breast cancer.[13] Also, a study by Schilder et al. examined tamoxifen and exemestane as adjuvant therapies in postmenopausal patients with breast cancer.[12] That study found that one year of exemestane treatment was not associated with significant negative effects on cognitive function, although patients receiving tamoxifen did show lower functioning in verbal memory and executive functioning compared with healthy controls. This study did suggest age-dependent effects of tamoxifen on cognition.

The PET scan findings showed an increase in bilateral anterior medial temporal activity, left posterior medial temporal activity, and cerebellar region activity, and a decrease in the Broca's area activity following AI therapy. These changes were not observed in the controls. In order to put these results into a clinical context, the medial temporal area is responsible for long-term memory. The cerebellar area is primarily responsible for motor control and coordination, with lesser roles in attention and language. Broca's area is responsible for speech production. Although the estrogen pathway plays a role in verbal memory and language, the significance of these PET findings is unclear in the relative absence of neuropsychological test findings. The PET scan did show a correlation between scores on the Block Design and occipital region activity. The Block Design test is a test of visuospatial ability and the occipital region of the brain, as well as the right temporal lobe, plays a key role in this function.

Most prior studies examining the effects of endocrine therapy on cognition have involved subjects treated with tamoxifen, or a mixture of subjects treated with either tamoxifen or aromatase inhibitors. This is the first study, to our knowledge, to utilize PET scans to understand cognitive function in patients with breast cancer who are receiving AI therapy. To date, only one other study has incorporated a PET scan component to investigate cerebral dysfunction through examination of brain metabolism in patients with breast cancer. That study, by Silverman and colleagues, showed that breast cancer survivors (5–10 years after completion of chemotherapy) had alterations in basal ganglia, frontocortical, and cerebellar activity. However, patients who received endocrine therapy received tamoxifen (not an AI).[14] In sum, the PET scan findings of this study are intriguing, and represent the first reported data regarding changes in regional cerebral metabolism among patients receiving AI therapy. Further follow-up is warranted.

Limitations to this study include its modest sample size, and the PET scans of the brain were only performed in a subset of our cohort. The sample was also heterogeneous, with administration of chemotherapy in 21% of the patients. Furthermore, although the study design did include a healthy control group, we did not accrue a cancer group who did not undergo endocrine therapy. A correction for multiple comparisons was performed for the PET scan findings; however, for the neuropsychological tests results we reported any results with $P < 0.05$, without doing a correction for multiple comparisons, in order to identify whether there were any signals from the neuropsychological testing to guide the selection of the neuropsychological tests to compare with brain metabolism.

Despite these limitations, this study has some notable strengths. We specifically sought to study older patients whose age would be representative of the majority of patients with

breast cancer, and compared these results with that of an age-matched healthy control group. We sought to further our understanding of the biology of aromatase inhibition and estrogen deprivation via PET scans of the brain, which confirmed changes in central nervous system (CNS) glucose metabolism. The clinical significance of these findings is unknown, and further long-term follow-up is warranted.

Conclusion

This study evaluated the impact of aromatase inhibition on cerebral function, as assessed by changes in neuropsychologic performance, and regional cerebral metabolism over six months. Overall, no dramatic effects of AI therapy on neuropsychologic performance were seen, and the few changes that were observed tended to be more favorable for the patient group than the control group. At the same time, both sVOI and SPM analyses detected specific changes in metabolic activity between baseline and follow-up in the patient group receiving AI, and not in the control group, with the largest and most significant change being an increase in medial temporal metabolism. In light of the similarity between the groups on neuropsychological testing, the PET findings may represent early detection of neuropsychological changes that had not yet manifested, or reflect a higher sensitivity for the detection of cerebral metabolic changes than changes in neuropsychologic performance. Alternatively, these findings could provide insight into compensatory mechanisms employed by patients to maintain neuropsychological performance.

Acknowledgments

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Clinical Practice Points

Aromatase inhibitors (AIs) are a mainstay of treatment for hormone receptor-positive, early-stage breast cancer in post-menopausal women. Conflicting data are available regarding the effects of endocrine therapy on cognitive function; some studies suggest a decline in cognitive function associated with treatment and others indicate no significant change. This study evaluated the short-term impact of aromatase inhibition on cognitive function of older patients via neuropsychological testing and sought to elucidate effects of aromatase inhibition on cerebral metabolic activity, using PET scans of the brain performed pre-initiation of aromatase inhibition and 6 months later. No worsening of cognitive function was seen among patients receiving an AI (from before treatment to 6 months later) and the few differences that were observed compared with healthy controls were actually in the direction of being more favorable for the patients. At the same time, there were localized increases in cerebral metabolic activity uniquely seen among patients receiving an AI. Additional long-term follow-up of this cohort is of interest.
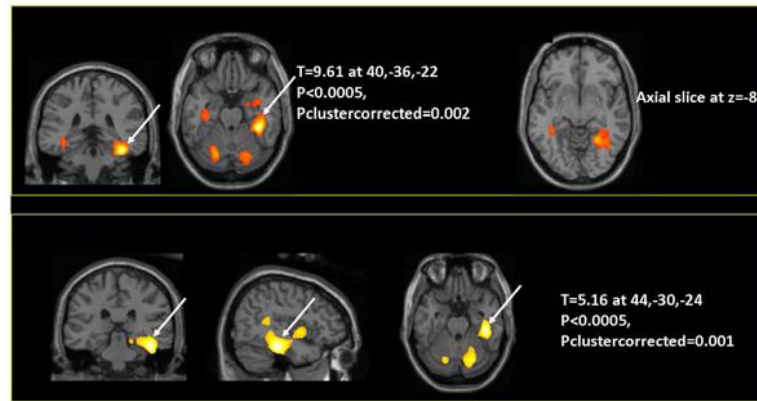
Fig 1.

The color scale in all images represents a statistical mapping of voxels in subjects' brain tissue, which are overlaid upon the structural images of the gray scale for anatomical reference. *Top panel:* regional increases in cerebral metabolic activity within the patient group from before initiation of AI therapy to six months after AI therapy was initiated, demonstrating increased metabolism in bilateral medial temporal ($P < 0.0005$) and bilateral cerebellar ($P < 0.0005$) areas, with the largest and most significant increase occurring in the right medial temporal region. *Bottom panel:* direct statistical comparison of longitudinal changes in the patient group relative to changes over the same time interval in the control group confirming that patients who received AI therapy experienced increases in metabolism that were greater than any increases occurring among control subjects, with the most significant inter-group difference also occurring in the right medial temporal area ($P < 0.0005$).

Table 1

Domains and Measures Assessed

Measures		Description	
Geriatric Assessment			
Functional Status			
1	Activities of Daily Living (Subscale of MOS Physical Health) [22]	1	Evaluates limitations in physical function by assessing activities ranging from bathing/dress to running.
2	Instrumental Activities of Daily Living (Subscale of the OARS) [23]	2	Assesses ability to complete daily activities (shopping, meal preparation, making phone calls, managing money) needed to maintain independence in the community.
Comorbidity			
	Physical Health Section (OARS Subscale) [23]		Evaluates the presence/absence of 13 comorbid illnesses and how much they interfere with daily activities.
Psychological			
	Hospital Anxiety and Depression Scale [24–28]		Assessment of depression and anxiety levels based on mood, feelings, and emotions in the past week.
Cognition			
	Squire Memory Self-Rating Questionnaire [16]		18 item self-assessment of cognitive function
Neuropsychological Battery			
Verbal Function			
1	WRAT-4 Reading Subtest [29]	1	Evaluates word recognition and pronunciation; Measure of pre-morbid intelligence.
2	Boston Naming Test [30]	2	Assesses the ability to name pictured objects.
3	Controlled Oral Word Association Test [31]	3	A verbal fluency task which measures the spontaneous production of words beginning with a specific letter with a limited period of time.
Verbal Learning and Memory			
	Hopkins Verbal Learning Test – Revised [32]		A brief verbal learning and memory test which includes delayed recall and recognition trials.
Visual Memory			
	Rey-Osterrieth Complex Figure Test [33] (copy, immediate, and delayed recall)		A measure of visuospatial construction and visual memory.
Spatial Function			
1	WAIS-III Block Design [34]	1	A measure of visuospatial ability. The examinee is asked to copy abstract designs using colored blocks.
2	Rey-Osterrieth Complex Figure Test [33] (copy, immediate, and delayed recall)	2	A measure visuospatial construction and visual memory.
Psychomotor Function			
1	WAIS-III Digit Symbol [34]	1	A task of psychomotor speed and provides a screening tool for neuropsychological impairment.
2	Trail Making Test – Part A and B [35]	2	A measure of divided attention and cognitive flexibility.
Attention			
	Trail Making Test – Part A [35]		A measure of divided attention and cognitive flexibility.
Executive Function			
1	Trail Making Test – Part B [35]	1	A measure of divided attention and cognitive flexibility.

Measures		Description	
2	Stroop Color and Word Test [36]	**2**	Measures selective attention and response inhibition.
3	Controlled Oral Word Association Test [31]	**3**	A verbal fluency task which measures the spontaneous production of words beginning with a specific letter with a limited period of time.

Abbreviations: WRAT-4, Wide Range Achievement Test, 4th Edition; WAIS-III, Wechsler Adult Intelligence Scale, 3rd Edition.

Table 2

Baseline Demographics

Variable	Control (n = 35)		Case (n = 32) [*]		P-value
	No.	%	No.	%	
Age, years					
Mean	71.1	NA	72.4	NA	
SD	7.37	NA	7.01	NA	0.48
Range	60–85	NA	62–89	NA	
Race					
White	28	82.4	28	87.5	
Asian	3	8.8	1	3.1	0.63
Other	3	8.8	3	9.4	
Marital Status					
Single	2	5.7	2	6.3	
Married	18	51.4	19	59.4	0.81
Widowed	9	25.7	8	25.0	
Separated/divorced	6	17.1	3	9.4	
Education					
High school or less	7	20.0	7	21.9	
Some college	13	37.1	12	37.5	
College degree	3	8.6	6	18.8	0.52
Advanced degree	12	34.3	7	21.9	
Employment					
Employed	7	20.0	3	9.4	
Homemaker	4	11.4	4	12.5	0.32
Retired	24	68.6	23	71.9	
Other	0	0.0	2	6.3	
Stage					
I	NA	NA	15	46.9	
II	NA	NA	13	40.6	NA
III	NA	NA	4	12.5	

Variable	Control (n = 35)		Case (n = 32)[*]		
	No.	%	No.	%	P-value
Prior treatment					
Chemotherapy	NA	NA	7	21.9	
Radiation	NA	NA	12	43.8	NA
Hormone replacement	14	40.0%	14	43.8	

[*] 3 patients were excluded from the analysis due to missing follow-up assessments.

Abbreviations: SD: standard deviation; NA: not applicable.

Table 3

Geriatric Assessment by Time Point

Variable	n	Control (n = 35) Mean	SD	Range	n	Case (n = 32)* Mean	SD	Range	P-value
Baseline									
IADL	35	13.9	0.43	12–14	31	13.3	0.65	12–14	0.0003
ADL	35	11.9	0.36	11–12	32	11.9	0.39	10–12	0.5914
Charlson	35	3.3	1.25	2–7	31	3.5	1.21	2–6	0.4505
Squire Memory Self-Rating Questionnaire	33	–1.5	17.02	–38–49	30	–4.8	18.78	–45–50	0.4779
HADS	35	5.8	3.80	0–14	32	6.4	3.98	1–15	0.5281
Follow-up									
IADL	34	13.8	0.54	12–14	32	13.1	1.32	8–14	0.0057
ADL	35	11.9	0.24	11–12	31	11.8	0.45	10–12	0.2576
Charlson	35	3.5	1.46	2–9	32	3.3	1.04	2–5	0.7176
Squire Memory Self-Rating Questionnaire	33	–8.7	12.29	–49–11	29	6.2	30.44	–28.5–96	0.0187
HADS	35	4.9	4.33	0–18	32	6.8	5.06	0–19	0.1088

*
3 patients were excluded from the analysis due to missing follow-up assessments.

Abbreviations: SD: standard deviation; IADL: Instrumental Activities of Daily Living; ADL: Activities of Daily Living; HADS: Hospital Anxiety and Depression Scale.

Table 4

Neuropsychological Assessment by Time Point

Variable	Control (n=35)			Case (n=32)*			P-value
	n	Mean	SD	n	Mean	SD	
Baseline							
WAIS Digit Symbol	35	12.4	2.93	32	10.8	2.52	0.0189
Block Design	35	11.4	3.03	32	10.9	2.79	0.5455
Trail Making Test A	35	10.1	2.66	32	9.6	2.88	0.4987
Trail Making Test B	35	10.5	2.86	32	9.3	3.44	0.1135
FAS	35	−0.3	0.76	32	−0.3	0.89	0.9288
WRAT-4 Naming list	35	105.6	16.84	32	103.1	13.65	0.5130
Boston Naming Test	35	0.2	1.18	32	−0.8	1.90	0.0141
STROOP							
-Word Page	35	43.1	14.07	32	45.4	9.79	0.4388
-Color Page	35	44.6	13.66	32	39.3	8.45	0.0582
-Color Word Page	35	47.6	10.72	32	47.3	8.49	0.8947
-Interference	35	45.7	8.70	32	46.2	7.57	0.7798
HVLT							
-Total	35	52.6	8.69	32	50.5	10.10	0.3572
-Delayed Recall	35	51.1	10.40	31	51.7	9.22	0.7894
-Retention	35	49.2	9.35	31	51.4	8.07	0.3296
-RDI	35	50.3	9.19	31	49.6	9.17	0.7878
ROCF							
-Copy	35	28.7	4.00	32	28.0	6.05	0.5837
-Immediate Recall	35	49.7	11.95	32	46.8	13.76	0.3444
-Delayed Recall	35	48.5	12.30	32	46.5	16.26	0.5558
Follow-up							
WAIS Digit Symbol	35	12.7	3.09	32	11.4	2.63	0.0812
Block Design	35	11.3	2.93	32	11.8	3.43	0.5768
Trail Making Test A	35	10.2	2.85	32	9.7	2.23	0.4751
Trail Making Test B	35	10.5	2.97	32	9.5	3.06	0.1737

Variable	Control (n=35)			Case (n=32)*			
	n	Mean	SD	n	Mean	SD	P-value
FAS	35	−0.1	0.85	32	−0.3	0.89	0.4259
WRAT-4 Naming list	35	98.8	9.68	32	104.8	11.29	0.0228
Boston Naming Test	33	0.6	0.76	32	−0.2	1.52	0.0135
STROOP							
-Word Page	35	42.6	13.12	32	43.5	9.98	0.7630
-Color Page	35	45.3	14.21	32	41.2	7.52	0.1386
-Color word Page	35	50.1	10.37	32	48.8	8.79	0.5831
-Interference	35	47.9	7.62	32	47.6	8.60	0.8833
HVLT							
-Total	35	51.3	10.50	32	48.5	11.35	0.2962
-Delayed recall	35	50.1	10.93	32	50.6	10.77	0.8580
-Retention	35	50.7	9.78	32	52.7	10.12	0.4275
-RDI	35	52.1	8.91	32	49.8	10.25	0.3359
ROCF							
-Copy	35	29.0	3.89	32	28.7	5.18	0.7681
-Immediate recall	35	54.2	11.86	32	50.5	12.89	0.2217
-Delayed recall	35	54.3	12.24	32	50.2	14.33	0.2019

*
3 patients were excluded from the analysis due to missing follow-up assessments.

Abbreviations: SD: standard deviation; WAIS: Wechsler Adult Intelligence Scale; WRAT: Wide Range Achievement Test, 4th edition; HVLT: Hopkins Verbal Learning Test; RDI: Recognition Discrimination Index; ROCF: Rey-Osterreith Complex Figure.

Table 5

Longitudinal Change in Neurocognitive Performance

Variable		Baseline (T_1)		6-month follow-up (T_2)		Difference (T_2-T_1)	p^a	p^b
		Mean	SD	Mean	SD			
WAIS Digit Symbol								
	Control	12.4	2.93	12.7	3.09	0.3	0.3419	0.3261
	Patient	10.8	2.52	11.4	2.63	0.6	0.0210	
Block Design								
	Control	11.4	3.03	11.3	2.93	−0.1	0.8005	0.0227
	Patient	10.9	2.79	11.8	3.43	0.9	0.0116	
Trail Making Test A								
	Control	10.1	2.66	10.2	2.85	0.1	0.8351	0.9885
	Patient	9.6	2.88	9.7	2.23	0.1	0.8037	
Trail Making Test B								
	Control	10.5	2.86	10.5	2.97	0.0	0.9478	0.6814
	Patient	9.3	3.44	9.5	3.06	0.2	0.4370	
FAS								
	Control	−0.3	0.76	−0.1	0.85	0.2	0.0735	0.2898
	Patient	−0.3	0.89	−0.3	0.89	0.0	0.4720	
WRAT-4 Reading Test								
	Control	105.6	16.84	98.8	9.68	−6.8	0.0004	0.0005
	Patient	103.1	13.65	104.8	11.29	1.7	0.2626	
Boston Naming Test								
	Control	0.3	0.93	0.6	0.76	0.3	0.0567	0.1075
	Patient	−0.8	1.90	−0.2	1.52	0.6	0.0030	
STROOP-word page								
	Control	43.1	14.07	42.6	13.12	−0.5	0.6616	0.3999
	Patient	45.4	9.79	43.5	9.98	−1.9	0.1192	
STROOP-color page								
	Control	44.6	13.66	45.3	14.21	0.7	0.3830	0.2939
	Patient	39.3	8.45	41.2	7.52	1.9	0.0368	

Variable	Baseline (T₁)		6-month follow-up (T₂)		Difference (T₂-T₁)	p^a	p^b
	Mean	SD	Mean	SD			
SRTOOP-color word page							
Control	47.6	10.72	50.1	10.37	2.5	0.0133	0.4902
Patient	47.3	8.49	48.8	8.79	1.5	0.1669	
STROOP-interference							
Control	45.7	8.70	47.9	7.62	2.2	0.0557	0.6020
Patient	46.2	7.57	47.6	8.60	1.4	0.2518	
HVLT-total							
Control	52.6	8.69	51.3	10.50	−1.3	0.3122	0.7509
Patient	50.5	10.10	48.5	11.35	−2.0	0.2754	
HVLT-delayed Recall							
Control	51.1	10.40	50.1	10.93	−1.0	0.4863	0.9008
Patient	51.7	9.22	51.0	10.65	−0.7	0.6577	
HVLT-retention							
Control	49.2	9.35	50.7	9.78	1.5	.4804	.7561
Patient	51.4	8.07	53.7	8.32	2.3	.2001	
HVLT-RDI							
Control	50.3	9.19	52.1	8.91	1.8	0.2440	0.4593
Patient	49.6	9.17	49.8	10.41	0.2	0.9407	
ROCF-copy							
Control	28.7	4.00	29.0	3.89	0.3	0.5222	0.5852
Patient	28.0	6.05	28.7	5.18	0.7	0.2648	
ROCF-immediate recall							
Control	49.7	11.95	54.2	11.86	4.5	0.0015	0.7285
Patient	46.8	13.76	50.5	12.89	3.7	0.0370	
ROCF-delayed recall							
Control	48.5	12.30	54.3	12.24	5.8	0.0018	0.4208
Patient	46.5	16.26	50.2	14.33	3.7	0.0723	

Abbreviations: SD: standard deviation; WAIS: Wechsler Adult Intelligence Scale; WRAT: Wide Range Achievement Test, 4th edition; HVLT: Hopkins Verbal Learning Test; RDI: Recognition Discrimination Index; ROCF: Rey-Osterreith Complex Figure.

[a] P-value for change between T₁ and T₂.

[b] *P*-value for difference in slope between cases and controls.