ORIGINAL RESEARCH ARTICLE

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Improvement in Cognitive Function as Measured by NeuroTrax in Patients with Relapsing Multiple Sclerosis Treated with Natalizumab: A 2-Year Retrospective Analysis

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Abstract

Background Cognitive impairment affects many patients with multiple sclerosis (MS). NeuroTrax, a computerized cognitive screen that can be administered during routine clinical care, provides a consistent, validated, objective cognitive profile measure with a global cognitive score (GCS) and seven individual domain scores. Natalizumab is an efficacious therapy for relapsing MS, demonstrating reductions in disability worsening and MS disease activity measured by magnetic resonance imaging.

Objective The aim of this study was to assess cognitive function as measured by NeuroTrax in MS patients treated with natalizumab for ≥ 2 years.

Methods This retrospective observational study included adult MS patients in the United States who received 300 mg intravenous natalizumab every 4 weeks for ≥ 2 years. NeuroTrax data were evaluated at baseline and yearly thereafter. Changes in GCS and the seven individual cognitive domain scores from baseline to after 24 infusions of natalizumab were analyzed.

Results In the study population at baseline ($N = 52$), 22 patients (42.3%) had disease duration of 0–5 years; 12 patients (23.1%) were treatment naive. GCS score improved significantly from baseline [mean 95.5, standard deviation (SD) 12.9] to year 2 (mean 98.9, SD 13.2; change from baseline 3.4; $p = 0.003$). After 2 years on natalizumab, 17 patients (32.7%) demonstrated clinically significant improvement (increase from baseline > 1 SD) in GCS. Results were similar regardless of whether patients had previously received MS therapy.

Conclusions Patients treated with natalizumab demonstrated significant improvement in cognitive function, measured by NeuroTrax GCS, over 2 years of treatment.

Key Points

Natalizumab significantly improved NeuroTrax global cognitive score over 2 years of treatment, regardless of whether patients were treatment-naive or were previously treated with other disease-modifying therapies.

Numerical improvements were observed for all seven individual cognitive domains from baseline to 2 years.

These results indicate that some aspects of cognitive impairment can be reduced in patients with multiple sclerosis treated with natalizumab.

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1 Introduction

Cognitive impairment affects approximately 40−65% of patients with multiple sclerosis (MS) [1, 2], but may be insufficiently recognized or monitored [3]. Nonetheless, cognitive impairment has a significant adverse impact on the quality of life and functional ability of MS patients; patients with MS and cognitive impairment experience greater difficulties with activities of daily living than patients who remain cognitively intact [3, 4]. Cognitive impairment has adverse effects on outcomes such as mobility and fall risk, driving safety, and employment status [4–8]. Although cognitive function is an important consideration when treating patients with MS, screening for deficits using traditional neuropsychological testing can be time-consuming and therefore difficult to complete in clinical practice [9], limiting its use in the management of MS.

NeuroTrax™ (NeuroTrax Ltd, Modiin, Israel; also referred to as the Mindstreams Computerized Cognitive

Battery or the Mindstreams Global Assessment Battery) is a computerized cognitive screening test that can be administered in an office setting in approximately 45 min [10–12]. It provides an objective cognitive function profile with a global cognitive score (GCS) and seven individual domain scores (memory, executive function, visual-spatial processing, verbal function, attention, information processing speed, and motor function). Learning effects associated with NeuroTrax appear to be minimal [10, 13, 14]. The test has been validated for screening patients with MS for cognitive impairment and for monitoring them for cognitive change over time [10, 11]. Additionally, the GCS has demonstrated a strong correlation with cognitive impairment as assessed by the Symbol Digit Modalities Test [15].

A recent study using NeuroTrax showed that patients with MS ($N = 1500$) exhibited poorer cognitive performance than healthy subjects [10]. Cognitive impairment in these patients was most common in the information processing speed and executive function domains.

In addition to a need for cognitive screening to determine the cognitive effect of MS at diagnosis and to monitor disease worsening, there is also a need for screening to evaluate the effects of treatment on cognitive function in MS. Natalizumab has demonstrated efficacy in the treatment of patients with relapsing MS (RMS) [16]. In the 2-year AFFIRM trial, natalizumab significantly reduced disease activity, as reflected by brain magnetic resonance imaging, clinical relapse rate, and rate of confirmed disability worsening, and significantly improved health-related quality of life relative to placebo [16–18]. Some patients with RMS treated with natalizumab also exhibit sustained improvement in disability [19, 20]. Improvement or stabilization of cognition has also been reported in patients treated with natalizumab for 1–3 years [21–24].

In this retrospective study, we evaluated longitudinal changes in cognitive function, as measured by NeuroTrax, in patients with MS who initiated and received continuous treatment with natalizumab for ≥ 2 years.

2 Methods

2.1 Study Design

The study sample consisted of patients with MS who initiated natalizumab between May 2007 and August 2012 at one study center (Patchogue, NY, USA). Electronic health records from the study center were retrospectively reviewed for this observational study. Patients had two or more cognitive test dates > 10 and ≤ 30 months apart in the course of routine clinical care while receiving 300 mg intravenous natalizumab every 4 weeks for ≥ 2 years.

To be included in the study, patients had to have available NeuroTrax tests at baseline (prior to initiating natalizumab) and after 1 and 2 years of treatment, and were required to have met the McDonald criteria for relapsing–remitting MS diagnosis [25] and be 18–70 years of age at each cognitive testing date. Patients were excluded if they had an interruption in natalizumab treatment (missed more than one dose during the course of the 28-day dosing cycle), were not compliant with study timelines, or had comorbid neurological or psychiatric disease or other documented cognitive impairment. Included patients did not have any relapses or exacerbations recognized or treated with steroids during the study period.

A waiver of informed consent was obtained from the Institutional Review Board on the basis of non–personally-identifiable retrospective data collection and minimal risk.

2.2 Assessments

All cognitive assessments were performed using NeuroTrax; the specific methodology for conducting the NeuroTrax test has been previously reported [10]. Three different forms of the test were used to minimize learning effects. Chart information was retrospectively reviewed to assess eligibility criteria and to extract NeuroTrax data at baseline (prior to natalizumab initiation) and annually thereafter. Index scores were normalized and fit to an IQ-like scale [mean 100, standard deviation (SD) 15] stratified by age and education [10, 26], with lower scores indicating greater cognitive impairment. The study measured change from baseline in GCS and the seven individual domain scores after 24 infusions of natalizumab. The proportion of patients achieving a clinically significant change in cognition from baseline and the proportion of patients exhibiting cognitive impairment at each time point were also evaluated. Previously used definitions of clinically significant change (an increase in score > 1 SD from baseline) and cognitive impairment [a score > 1 SD below the mean for cognitively healthy individuals (i.e. score < 85)] [10] were employed for this analysis.

This was a non-interventional, post-authorization study based on secondary use of data. Therefore, adverse event reporting in the form of individual case safety reports was not required.

2.3 Statistical Analyses

Demographics and baseline characteristics were analyzed using summary statistics [i.e. mean (SD), median, minimum, and maximum values for continuous variables, and frequency tables for categorical variables]. Change from baseline in global and individual domain scores at 1 and 2 years was analyzed using a generalized estimating equation model adjusted for baseline Expanded Disability Status Scale score and age. Data within 30 days of a relapse were censored.

3 Results

3.1 Patients

The study population included 52 patients. At baseline, 22 patients (42.3%) had a disease duration of 0–5 years, and 30 patients (57.7%) had a disease duration ≥ 6 years (Table 1). Before initiating natalizumab, most patients ($n = 40$; 76.9%) had prior treatment with another disease-modifying therapy (DMT), whereas 12 patients (23.1%) were treatment-naive.

Prior to natalizumab initiation, mean scores in this population for visual-spatial processing (99.4) and motor function (99.1) were near the population-normalized mean for a healthy sample (100) (Fig. 1). Mean scores for GCS and all other domains were lower than the population-normalized mean, with the lowest mean scores observed in information processing speed (91.5).

3.2 Overall Improvement in Global Cognitive Score and Cognitive Domains

In the overall study population, GCS improved numerically from baseline to 1 year (mean change from baseline 2.06; $p = 0.064$), and improved significantly from baseline to 2 years (mean change from baseline 3.43; $p = 0.003$) (Fig. 1a; Table 2). From baseline to 1 year, verbal functioning score improved significantly (mean change from baseline 6.36; $p = 0.007$), while other cognitive domains exhibited numerical improvements, with mean changes from baseline ranging from 0.94 (memory) to 2.54 (information processing speed) (Table 2). All seven cognitive domains demonstrated improvement from baseline to 2 years, and significant changes from baseline were identified for memory, visual-spatial processing, attention, and information processing speed (Fig. 1b; Table 2).

3.3 Clinically Significant Cognitive Improvement

The proportions of patients achieving a clinically significant improvement in cognition scores (i.e. > 1 SD [10]) from baseline to 1 and 2 years are shown in Fig. 2. The percentage of patients experiencing a significant change in GCS increased from 21.6% at 1 year to 32.7% at 2 years. When looking at individual domain scores, the percentage of patients experiencing a clinically significant improvement increased in all domains from baseline to year 1, and in all but one domain (visual-spatial processing) from year 1 to year 2.

Both treatment-naive patients and those with prior DMT use experienced clinically significant improvement (Fig. 3), and no statistically significant differences were observed between patients with or without prior DMT use.

Table 1 Patient characteristics at baseline

Baseline characteristic	Natalizumab-treated patients ($N = 52$)
Age, years (mean [SD])	45.9 (8.80)
Female	39 (75.0)
Time from diagnosis of MS, years	
0–5	22 (42.3)
6–10	14 (26.9)
11–15	13 (25.0)
≥ 16	3 (5.8)
EDSS score	
Mean (SD)	2.2 (1.74)
Median (range)	2.0 (0.0–8.0)
Prior DMT treatment	40 (76.9)

Data are expressed as *n* (%) unless otherwise specified

DMT disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *MS* multiple sclerosis, *SD* standard deviation

3.4 Reduction in Cognitive Impairment

Prior to natalizumab initiation, 21.2% of patients (11/52) exhibited cognitive impairment (score < 85) as measured by GCS (Fig. 4). For the individual domains, percentages of patients with impairment ranged from 19.2% (verbal function) to 39.2% (information processing speed). Compared with baseline, the percentages of patients who had cognitive impairment assessed by GCS or any of the seven domains were lower at years 1 and 2 (Fig. 4). At 2 years, 13.5% of patients (7/52) exhibited cognitive impairment as shown by the GCS. The greatest relative reductions in the percentage of patients with impairment were observed for the attention [26.9% (14/52) to 11.5% (6/52)] and information processing speed [39.2% (20/51) to 22.4% (11/49)] domains.

4 Discussion

Patients with MS who were treated with natalizumab exhibited significant improvements in cognitive function as measured by NeuroTrax. After 2 years of treatment, global scores were significantly improved from baseline, and approximately one-third of patients exhibited global score improvement that was clinically significant. Numerical score improvements and clinically significant improvements from baseline to 1 and 2 years were observed for all seven individual cognitive domains. Scores did not differ significantly at 2 years, based on whether or not patients had received prior DMT, although the patient numbers in each group were small. Both treatment-naive patients and those previously
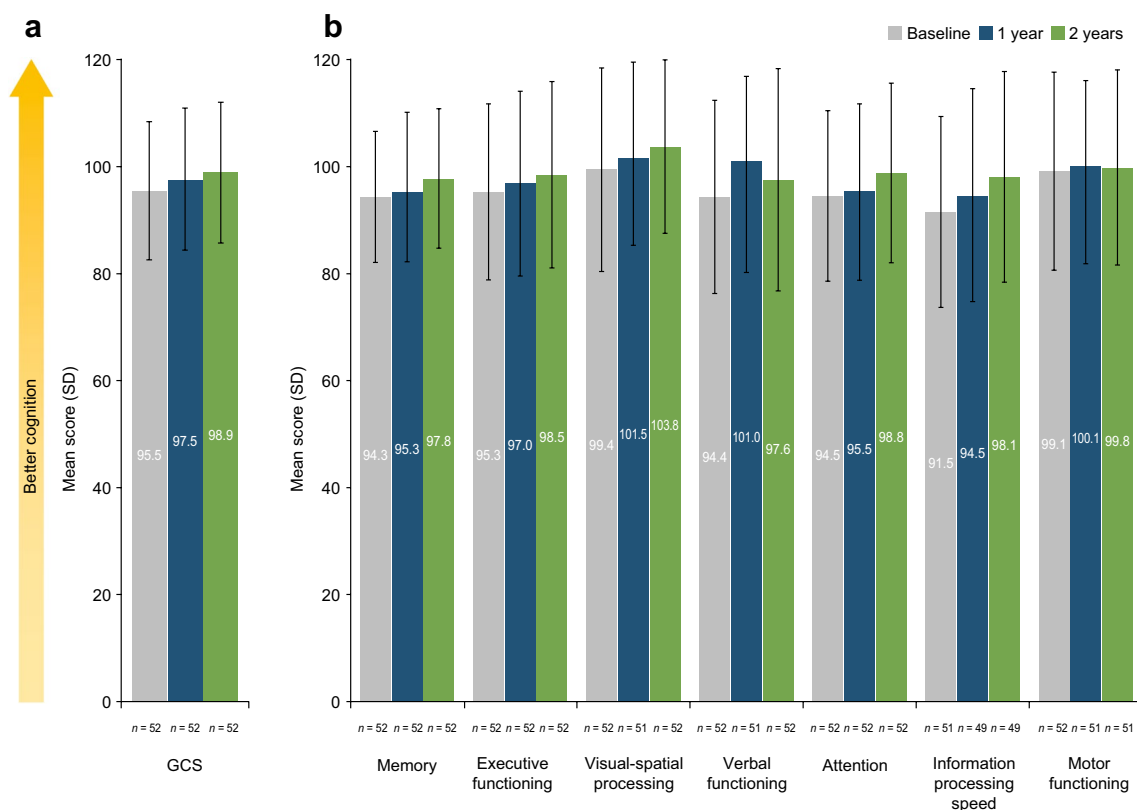
Fig. 1 Mean **a** GCS and **b** cognitive domain scores at baseline and after 1 and 2 years of natalizumab treatment (*N*=52). *SD* standard deviation, *GCS* global cognitive score

Table 2 Change from baseline for GCS and the seven cognitive domains at 1 and 2 years of natalizumab treatment (*N*=52)

	1 year			2 years		
	Mean	95% CI	*p* value[a]	Mean	95% CI	*p* value[a]
GCS	2.06	−0.12, 4.24	0.064	3.43	1.18, 5.69	0.003
Memory	0.94	−2.30, 4.18	0.570	3.44	0.97, 5.92	0.006
Executive function	1.68	−1.75, 5.11	0.337	3.21	−0.24, 6.66	0.068
Visual-spatial processing	1.39[a]	−2.39, 5.16	0.471	4.31	0.54, 8.08	0.025
Verbal functioning	6.36	1.75, 10.97	0.007	3.19	−2.28, 8.66	0.253
Attention	1.00	−2.11, 4.11	0.529	4.27	0.76, 7.79	0.017
Information processing speed	2.54[b]	−0.59, 5.68	0.112	5.15[b]	1.96, 8.34	0.002
Motor function	1.02[a]	−1.87, 3.92	0.487	0.05[a]	−3.38, 3.48	0.976

p Value for change based on generalized estimating equation model of change with treatment group, visit, and their interaction as effects, adjusted for baseline Expanded Disability Status Scale score and baseline age

GCS global cognitive score, *CI* confidence interval

[a]*n*=51

[b]*n*=49

treated with other DMTs experienced clinically significant improvements over 2 years of treatment. In addition, the percentages of patients with cognitive impairment decreased over 1 and 2 years of natalizumab treatment.

The findings of the current analysis are consistent with previous studies demonstrating that natalizumab therapy is associated with stable or improved cognitive performance after 1−3 years of treatment [21–23, 27]. While the current study was not designed to assess the mechanism underlying this improvement in cognitive function, previous work has suggested that these effects may be due to natalizumab's strong anti-inflammatory effect [28, 29]. Research in animal
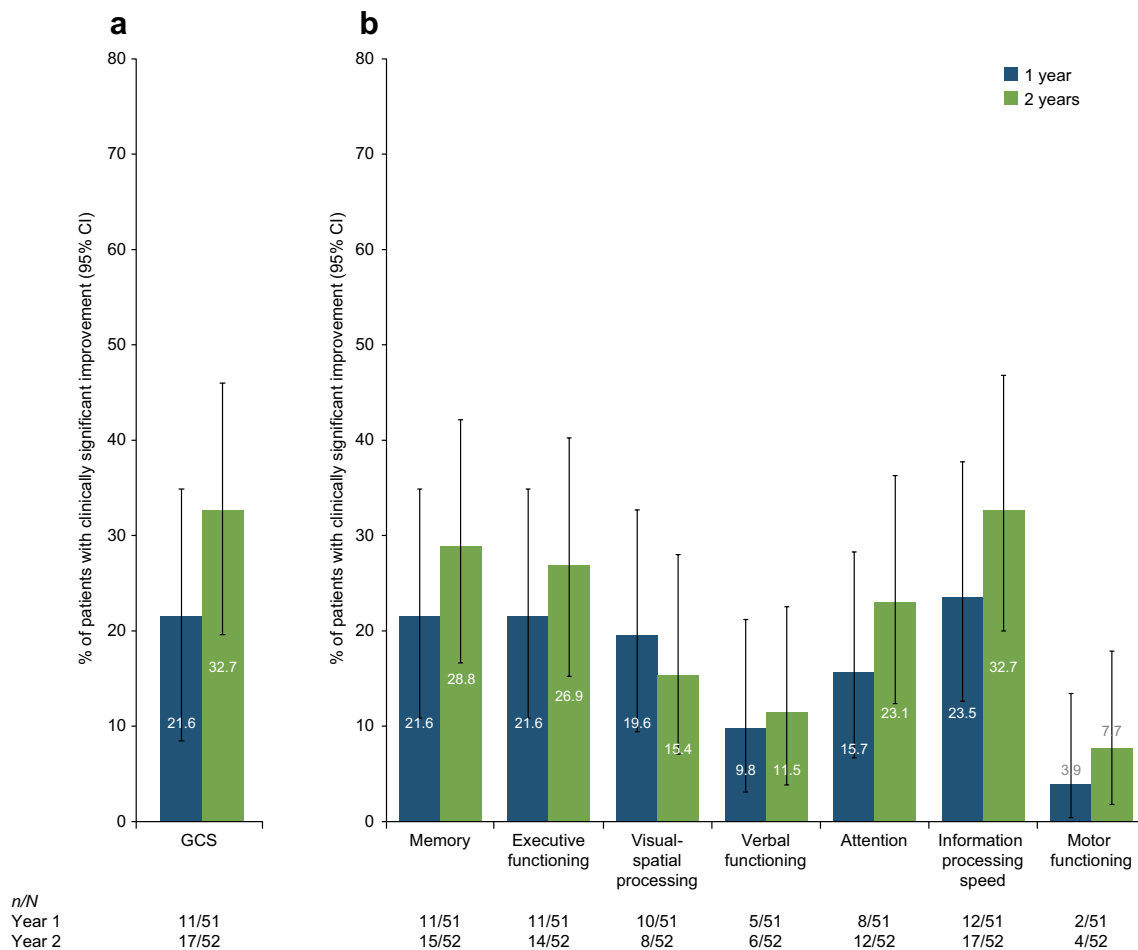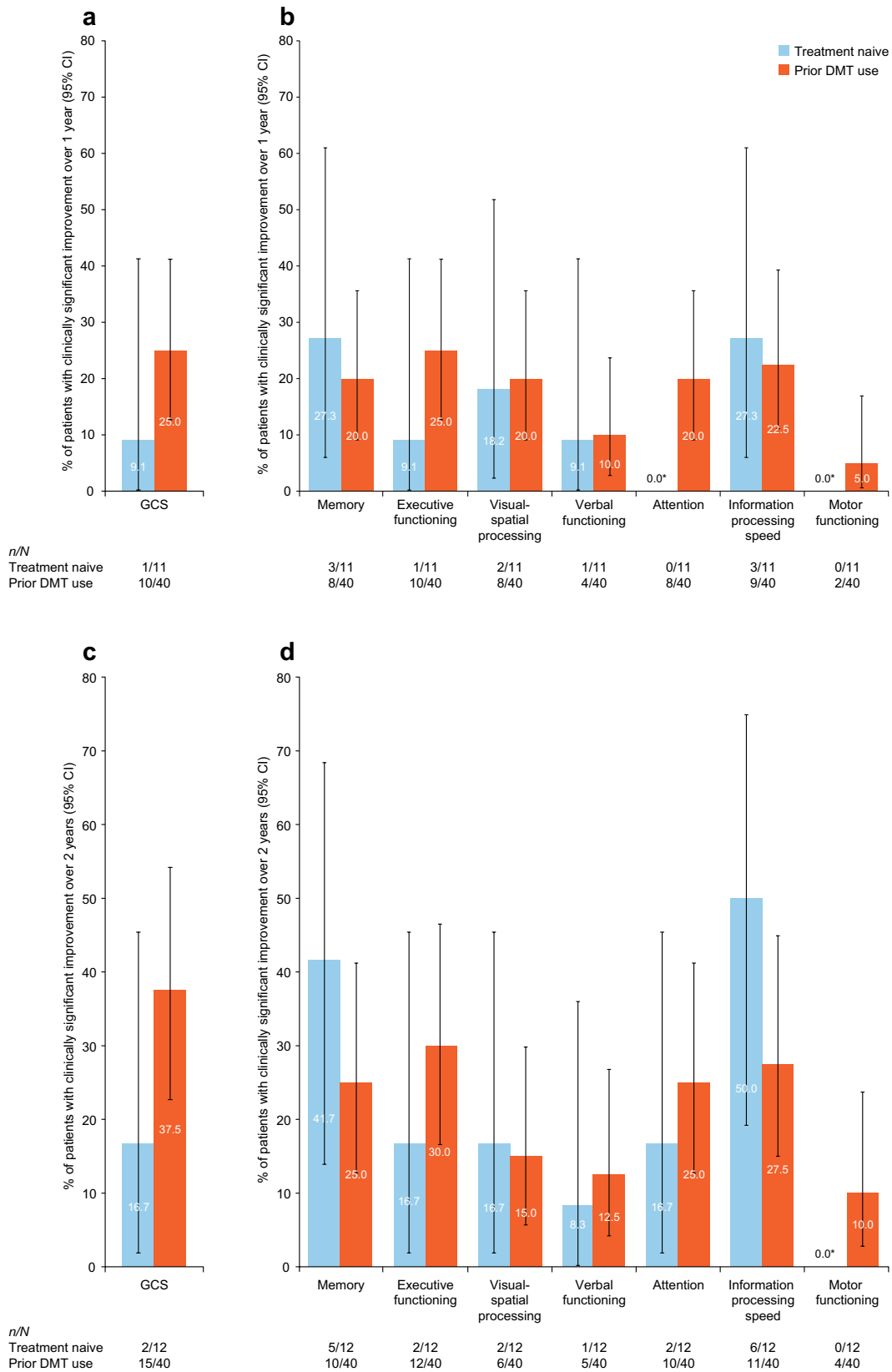
Fig. 2 Percentage of patients exhibiting a clinically significant change from baseline to 1 and 2 years of natalizumab treatment in **a** GCS and **b** cognitive domains. 95% CI is based on exact binomial. *CI* confidence interval, *GCS* global cognitive score

models has further suggested that inflammation may cause synaptic degeneration and, subsequently, the cognitive dysfunction observed in patients with MS [30, 31]. Natalizumab reduces levels of proinflammatory cytokines in the cerebrospinal fluid [32] and plasma [23, 33], and these reductions have been associated with improvement in cognitive function [23]. Natalizumab's neuroprotection of cortical brain regions, potentially as a result of reduced inflammation, has also been suggested as an explanation for its effect on preserving cognitive function [21].

The prevalence of cognitive impairment in MS may be high, but varies depending on the study setting [3], and increases with disease duration [10]. One study using NeuroTrax to screen for cognitive function showed that 20.9% of patients with a disease duration of 5 years exhibited cognitive impairment (using the > 1 SD cut-off also applied in this analysis); that percentage of patients increased to 29.3% at a disease duration of 10 years. More severe cognitive impairment was found in 6.0% of patients at 5 years and 9.0% at 10 years [10].

Cognitive impairment is one of the most disabling symptoms of MS [11]. It negatively impacts a number of aspects of everyday life, including social and familial interactions, competence in legal and financial matters, adjustment to disability, driving skills, behavior, treatment adherence, and the ability to benefit from rehabilitation [3–8]. For a substantial number of patients, the cognitive effects of MS lead to the loss of employment and financial hardship [3, 4].

Given the considerable toll that cognitive impairment exacts from patients, and the likelihood that patients with such impairment will be inadequately identified, therapy that could mitigate this adverse effect of the disease would be highly beneficial. It has been suggested that prolonged response times on certain cognitive tasks in MS indicates abnormal conduction within demyelinated tracts [11]. Supporting this contention, MS patients have prolonged response time but intact accuracy relative to healthy individuals [11]. This indicates that early therapeutic intervention with a high-efficacy therapy to reduce the nerve damage caused by the inflammation associated with MS may

Fig. 3 Proportions of patients with and without prior DMT use achieving a clinically significant change in cognition score from baseline to 1 year (**a**, **b**) and to 2 years (**c**, **d**) of natalizumab treatment. All *p* values for between-group comparisons were ≥ 0.05. *CI is not shown. *GCS* global cognitive score, *DMT* disease-modifying therapy, *CI* confidence interval
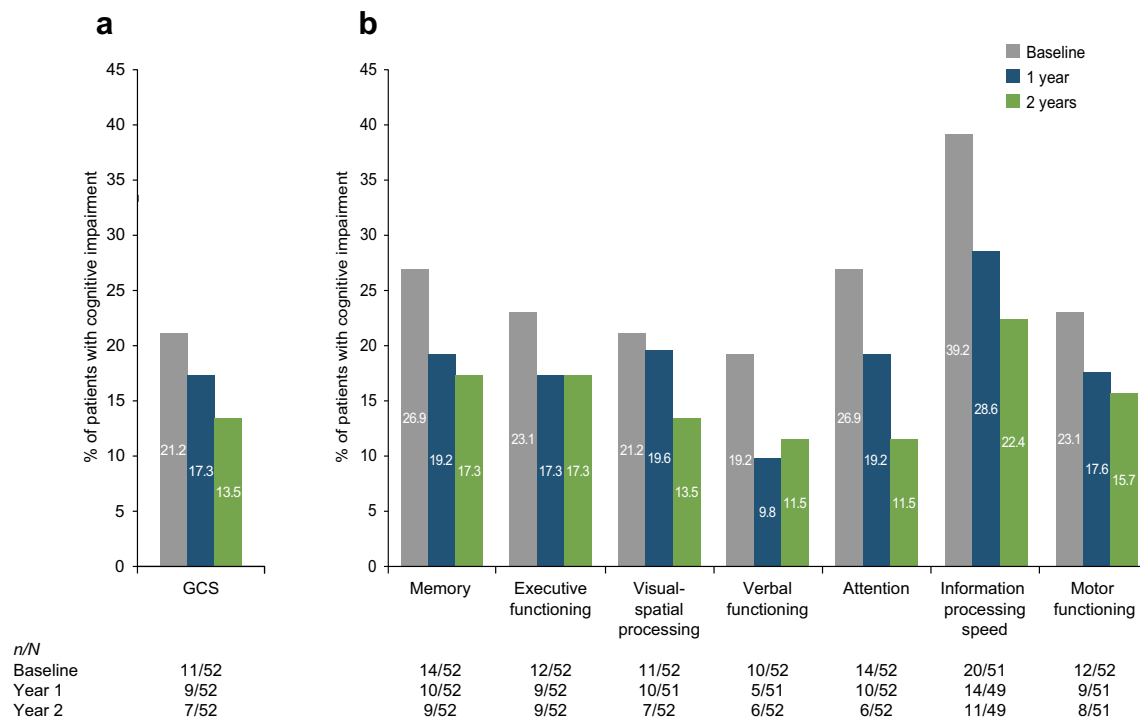
Fig. 4 Proportion of patients with cognitive impairment (score < 85) at baseline and after 1 and 2 years of natalizumab treatment in **a** GCS and **b** cognitive domains. *GCS* global cognitive score

help prevent or delay these adverse cognitive effects. In the current study population, information processing speed showed the greatest deficit of any of the cognitive domains at baseline. The greatest on-treatment improvements were also observed in this domain as the proportion of patients with clinically significant improvement in information processing speed was higher than that for any other domain at both years 1 and 2.

The limitations of the study include the lack of a control group for comparison; however, this was dictated by the retrospective study design and was partially compensated for by the repeated-measures study design. The influence of learning effects is a common concern for longitudinal studies of cognitive function; however, NeuroTrax has good test–retest reliability and has been found to be reliable for longitudinal studies [10, 13, 14]. Moreover, in this study, three different forms of the test were used and patients completed the test only once a year, both of which should have minimized learning effects. As an additional limitation, this was a single-center study conducted in the US, and the sample size was small. Further studies in additional locations and larger and more diverse patient populations are needed to establish more generalizable results. In particular, as many patients in this cohort were relatively early in their disease course (42.3% with ≤5 years since MS diagnosis) and displayed minimal disability at baseline, further investigation is needed for patients with higher levels of

disability. Longer-term analysis is also needed to confirm that the cognitive changes measured by NeuroTrax will be sustained over longer durations of natalizumab treatment. Continued follow-up is also needed to evaluate cognition in patients who discontinue natalizumab, as previous work has suggested that natalizumab's cognitive benefits may not be maintained post-discontinuation [34].

5 Conclusions

Overall, the results of this study support previous findings [21, 22, 27] indicating that cognitive function can be improved in patients with RMS treated with natalizumab. Prospective studies may consider incorporation of cognitive measures as important outcomes for assessing treatment efficacy.

Compliance with Ethical Standards

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