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Background

Combination antiretroviral therapy (cART) is effective in preventing or reverting HIV-associated cognitive disorders (HAND) only in a subset of HIV-infected individuals; complementary treatments, as well as cognitive rehabilitation training, are needed. Previous studies have demonstrated the improvement of specific cognitive functions thanks to cognitive rehabilitation, although without obtaining a complete resolution of HAND¹.

We aimed to investigate the efficacy of a new computer-based cognitive rehabilitation protocol (restorative approach) in improving the cognitive performance of patients affected by HAND.

¹Livelli et al, 2015;Towe et al, 2017

Methods

Pilot, unblinded, randomized controlled trial (parallel allocation 1:1) enrolling HIV-infected patients on cART or at first HIV diagnosis (San Paolo Infectious Diseases, SPID Cohort, Milan, Italy). At screening, patients underwent a neuropsychological battery (11 tests, 7 cognitive domains plus assessment of mental health and quality of life by Beck Anxiety Inventory, Beck Depression Inventory and Medical Outcome Study HIV Health Survey) to diagnose HAND (Frascati criteria).

Exclusion criteria: AIDS-defining illnesses, not adequately managed depression, neurological/psychiatric comorbidities, active alcohol/substance abuse, cirrhosis/severe comorbidities requiring hospitalization, not comprehension of Italian language, detectable HIV-RNA for cART-treated patients.

Patients diagnosed with HAND were randomly allocated to continue cART (control group) or to the cognitive rehabilitation training in association with their ongoing cART regimen (intervention group: ERICA software, 12 weekly sessions of 9 computer-based exercises lasting 1 hour under the supervision of a physician aimed at improving 5 cognitive domains). After completion of the protocol (t12), patients were reassessed by the same neuropsychological battery. In the intervention and control group, repeated measures ANOVA was used to compare pre- and post-rehabilitation mean T scores on each cognitive domain; the two groups were compared by Student's t test.

Results

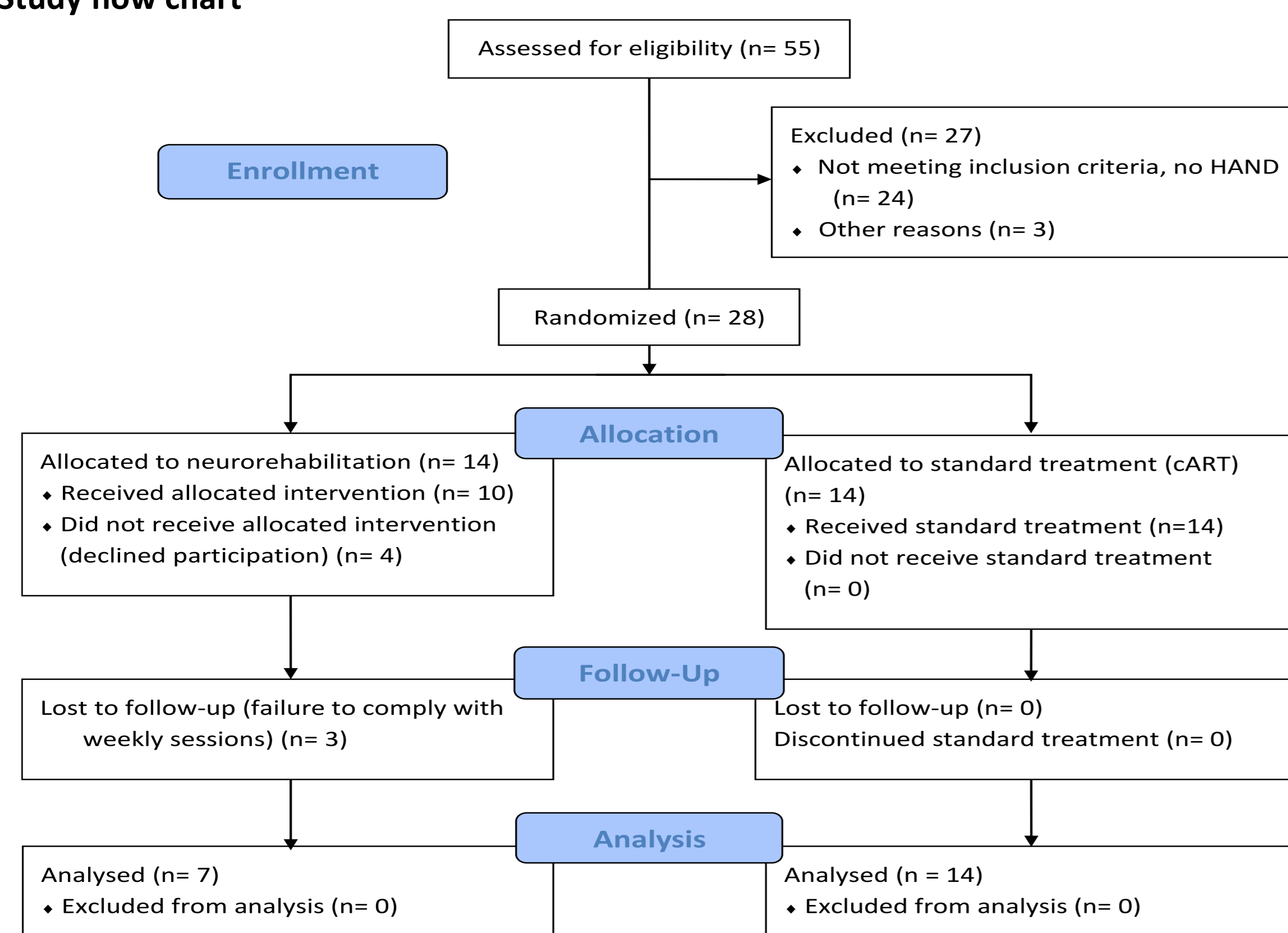
We screened 55 patients; 28 patients with HAND were randomized (14 intervention group, 14 control group) (Figure 1). The two groups were balanced at randomization (Table 1).

Table 1: Baseline demographic, clinical and immunovirologic characteristics of the enrolled subjects (N 28)

Characteristics	Population (N 28)	Intervention group (N 14)	Control group (N 14)	p values
Age [years], median (IQR)*	46,5 (38,2-54,5)	43,5 (35,8-49,2)	51 (39,8-61,2)	0,069
Males, n (%) ^a	24 (85,7)	12 (85,7)	12 (85,7)	1
Time since HIV diagnosis [months], median (IQR)*	83,5 (42-164)	108,5 (43,5-284,8)	78,5 (32,5-116)	0,164
Mode of HIV transmission, n (%) ^a :				0,187
Homosexual contact	15 (53,6)	10 (71,4)	5 (35,7)	
Heterosexual contact	8 (28,6)	4 (28,6)	4 (28,6)	
IDU/Unknown	5 (17,8)	0	5 (35,7)	
HCV-Ab, n (%) ^a	4 (14,3)	0	4 (28,6)	0,098
AIDS-defining conditions, n (%) ^a	7 (25)	4 (28,6)	3 (21,4)	1
cART regimen, n (%) ^a :				0,246
PI-based	3 (10,7)	0	3 (21,4)	
NNRTI-based	7 (25)	3 (21,4)	4 (28,6)	
INSTI-based	16 (57,1)	10 (71,4)	6 (42,9)	
Other	2 (7,1)	1 (7,1)	1 (7,1)	
cART CPE score, median (IQR)*	6 (6-8,5)	6 (6-10)	6 (6-7)	0,769
Time since ART initiation [months], median (IQR)*	49,5 (28,2-76,5)	57,5 (29,8-159)	44 (4,5-72,2)	0,265
Nadir CD4+ T cell count [cells/mm ³], median (IQR)*	226 (68,8-420)	150 (46,5-406,5)	258 (92,5-434)	0,448
Current CD4+ T cells [cells/mm ³], median(IQR)*	486,5 (414,8-836,5)	562 (391,2-761)	469,5 (393,2-888,2)	0,91
Plasma HIV-RNA <40 cp/mL, n (%) ^a	25 (89,3)	12 (85,7)	13 (92,8)	1
ANI ^a	27 (96,4)	14/14 (100)	13/14 (92,9)	-
MND ^a	1 (3,6)	0	1/14 (7,1)	
HAD ^a	0	0	0	
Years of education ^a	13 (8-13)	13 (11,8-13)	10,5 (7,2-14)	0,482
Attention and working memory	13,28 (7,6)	14,1 (7)	13,4 (8,5)	0,454
Speed of information processing	3,4 (5,5)	1,5 (2,7)	5,2 (7)	0,285
Learning and memory	6,2 (6,1)	5,5 (6,8)	6,8 (5,5)	0,804
Abstraction and executive functions	13 (5,3)	12,7 (4,5)	13,3 (6,2)	0,946
Verbal fluency	0,7 (9,1)	2,5 (10,2)	-1,1 (7,8)	0,482
Motor skills	3,6 (7,3)	3,3 (8,2)	3,9 (6,6)	1

LEGEND: The raw scores obtained at the neuropsychological tests are corrected for age, educational level and gender and then converted to normative T scores. T scores for each cognitive domains are presented as mean, standard deviation (SD). ANI, Asymptomatic Neurocognitive Impairment; MND, Mild Neurocognitive Disorder; HAD, HIV-Associated Dementia.

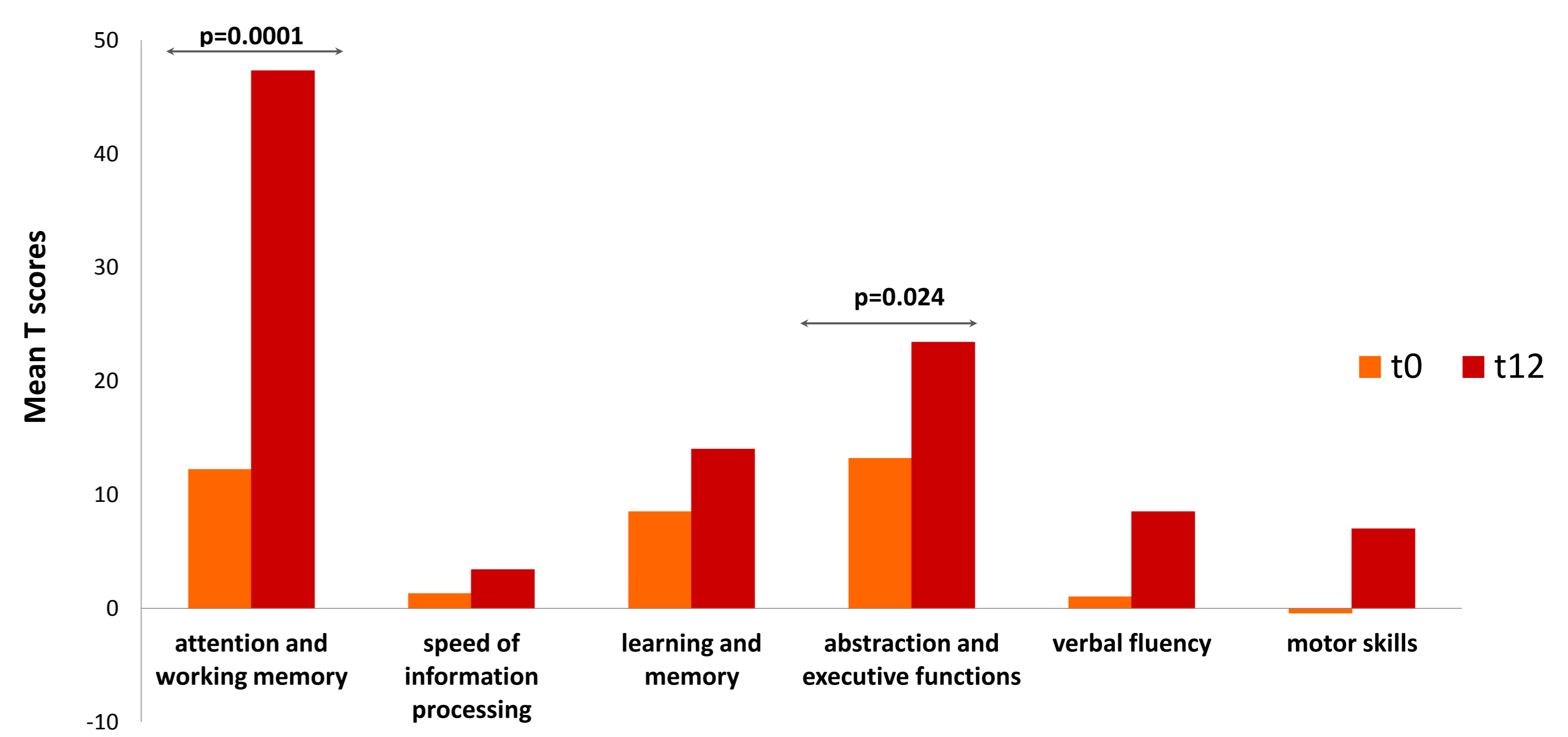
Figure 1: Study flow chart



At t12, in the intervention group the proportion of HAND has declined with no cognitive impairment in 2/7, 28% patients; 14/14 (100%) patients in the control group maintained HAND at t12 (p<0,0001).

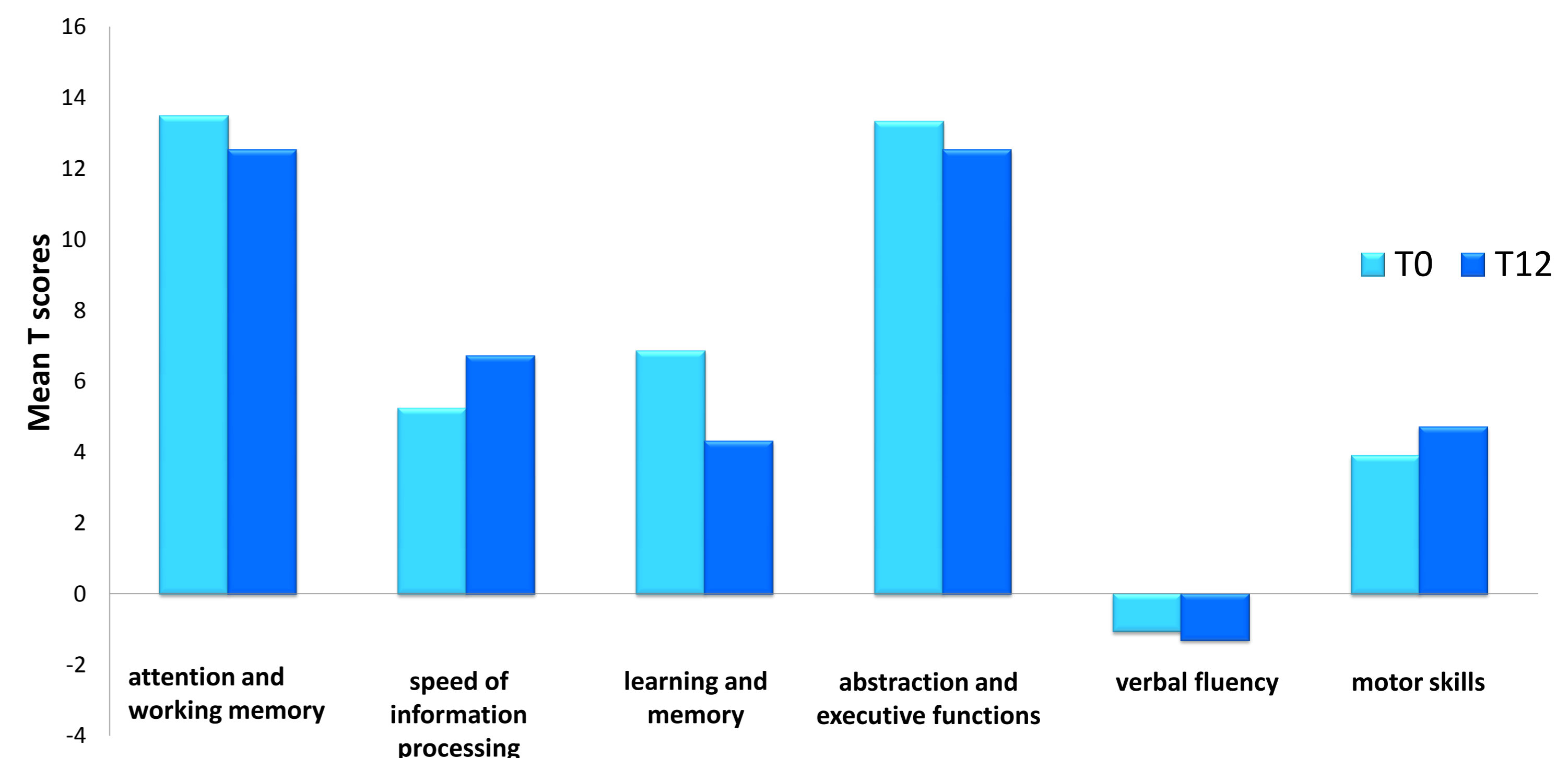
The mean T scores in two cognitive domains, (attention/working memory and abstraction/executive functions), and five neuropsychological tests (Digit Span Test-Backward, Rey Auditory Verbal Learning Test-Delayed Recall, Rey-Osterrieth Complex Figure test-Delayed Recall, Stroop Color and Word Test-Errors and Phonemic Fluency Task), significantly improved from baseline to t12 in the intervention group (Figure 2 a).

Figure 2 a Change in cognitive domains' mean T scores after the rehabilitation protocol (intervention group)



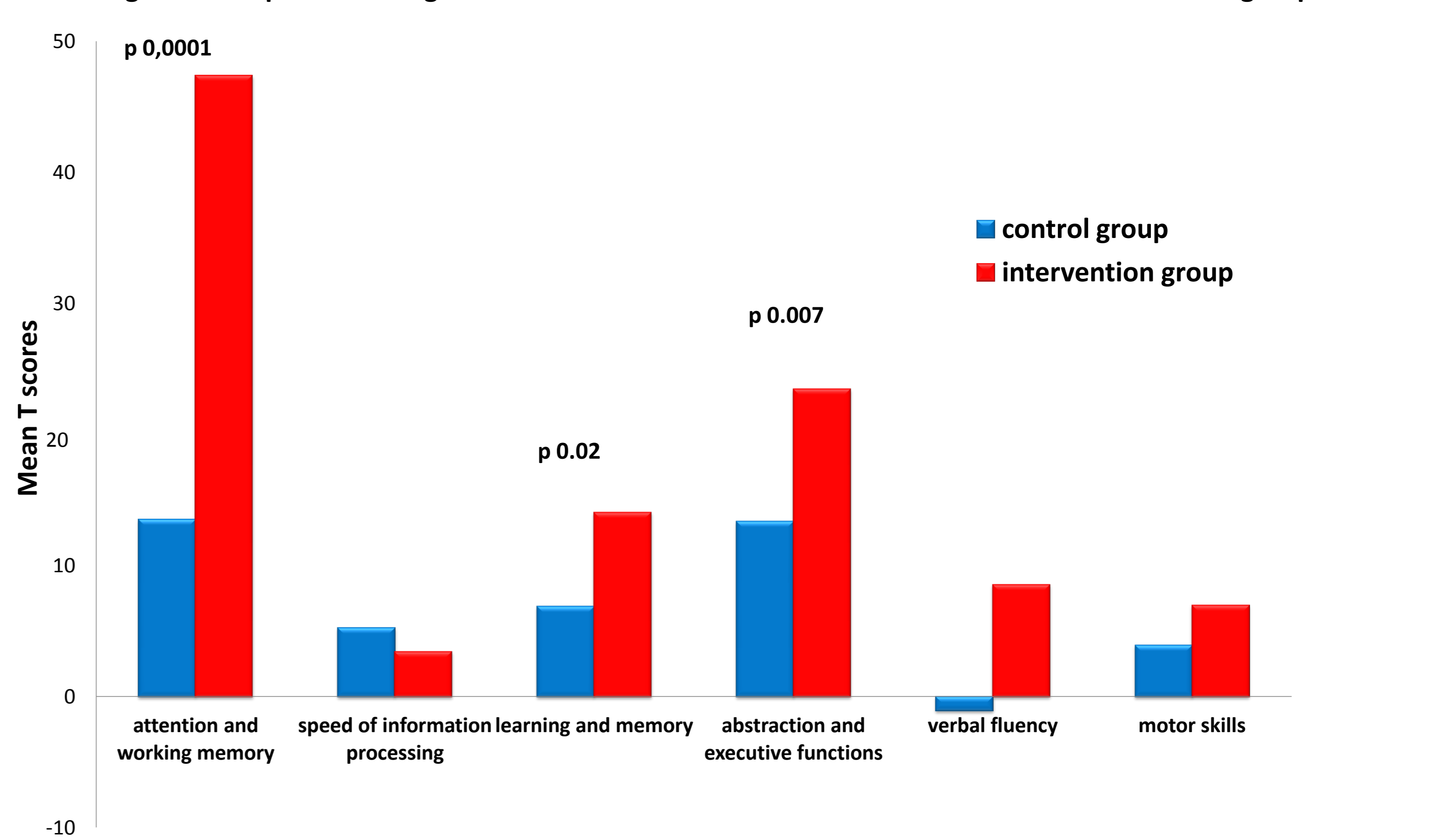
No difference in cognitive function between T0 and T12 was observed in the control group.

Figure 2 b Change in cognitive domains' mean T scores between T0 and T12 (control group)



The mean T scores in three cognitive domains, (attention/working memory, learning/memory and abstraction/executive functions) significantly improved in the intervention group compared to the control group (Figure 3).

Figure 3 Comparison of cognitive domains' mean T scores between control and intervention group at t12



No differences in symptoms of anxiety/depression (the Beck Anxiety Inventory/Beck Depression Inventory) and in health-related quality of life (MOS-HIV questionnaire) were found between the two groups at screening and T12. Similarly, at t12, the study participants did not show any significant change from baseline in the anxiety, depression and quality of life scores.

Conclusions

Cognitive rehabilitation training with ERICA software showed an overall positive effect on cognitive performance, with a greater efficacy in the two domains of attention/working memory and abstraction/executive functions. However, the rehabilitation protocol was not able to fully restore HAND.

In conclusion, the study shows promising results but its methodological limitations, first of all the small sample size, warrant further studies to better investigate the efficacy of ERICA cognitive rehabilitation.