Neurophysiologie Clinique/Clinical Neurophysiology (2017) 47, 47—53

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ORIGINAL ARTICLE/ARTICLE ORIGINAL

Repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease

Stimulation magnétique transcrânienne répétitive associée à l'entraînement cognitif pour le traitement de la maladie d'Alzheimer

Jean-Paul Nguyen[a,b], Alcira Suarez[a], Gilles Kemoun[c], Michel Meignier[a], Estelle Le Saout[a], Philippe Damier[d], Julien Nizard[b,*], Jean-Pascal Lefaucheur[e]

[a] *Multidisciplinary Pain Center, clinique Bretéché, groupe Elsan, 44000 Nantes, France*
[b] *UIC22 and EA2826, Multidisciplinary Pain, Palliative and Support Care Center, University Hospital, 44093 Nantes cedex 1, France*
[c] *EA6314, Laboratory MOVE, Faculty of Sports Sciences, University Hospital, groupe Elsan, 86000 Poitiers, France*
[d] *Inserm U913, Neurology Department, University Hospital, 44093 Nantes cedex, France*
[e] *EA4391, Clinical Neurophysiology Department, Henri Mondor University Hospital, University Paris-Est Créteil, 94010 Créteil cedex, France*

Received 2 December 2016; accepted 3 January 2017
Available online 1 February 2017

KEYWORDS
Alzheimer's disease;
Cognitive training;
Repetitive transcranial magnetic stimulation;
rTMS;
Treatment

Summary
Objective. — To assess the efficacy of a combination of cognitive training (COG) and repetitive transcranial magnetic stimulation (rTMS), on cognitive performance, locomotor activity, apathy, caregiver burden and dependence of patients with Alzheimer's disease (AD).
Methods. — A combination of COG and rTMS was performed in 10 patients with AD (NeuroAD procedure) for a period of 5 weeks (one session per day, 5 days a week), without maintenance sessions. Patients were evaluated at the end of the treatment (D45) and 6 months later (M6) by the Mini Mental State Examination (MMSE), the Alzheimer disease assessment scale — cognitive

* Corresponding author.
E-mail address: julien.nizard@univ-nantes.fr (J. Nizard).

http://dx.doi.org/10.1016/j.neucli.2017.01.001

subscale (ADAS-Cog), various neuropsychological tests and clinical scores specific for locomotor activity, apathy, caregiver burden, and dependence, recorded before the study (baseline).
Results. — The primary endpoint was the improvement of the ADAS-Cog score at D45, which was reached. Six months after the end of the treatment, the ADAS-Cog score returned to baseline value, except for the best responders who remained significantly improved. The other main result was the improvement of apathy and dependence scores at both D45 and M6 for the entire series of patients. No serious adverse events occurred and all patients completed the study.
Conclusions. — The results of this open-label study confirm the feasibility of the rTMS-COG procedure in AD patients, and suggest that these patients can benefit from the procedure, in terms of cognitive performances, apathy and dependence, even in the long term. These promising results remain to be confirmed in controlled studies based on a larger population size, which could also help identify the prognostic factors associated with good outcome, in order to optimize patient selection.

MOTS CLÉS
Entraînement cognitif ;
Maladie d'Alzheimer ;
RTMS ;
Stimulation magnétique transcrânienne répétitive ;
Traitement

Résumé
Objectif. — Évaluer l'efficacité de la combinaison de l'entraînement cognitif (COG) et de la stimulation magnétique transcrânienne répétitive (rTMS) sur les performances cognitives, l'activité locomotrice, l'apathie, le fardeau de l'aidant et la dépendance des patients atteints de la maladie d'Alzheimer.
Méthodes. — Un traitement combiné par COG et rTMS a été réalisé chez 10 patients atteints de la maladie d'Alzheimer (procédure NeuroAD) pendant une période de 5 semaines (une séance par jour, 5 jours par semaine), sans séances d'entretien. Les patients ont été évalués à la fin du traitement (j45) et 6 mois plus tard (M6) par le Mini Mental State Examination (MMSE), l'échelle d'évaluation de la maladie d'Alzheimer — sous-échelle cognitive (ADAS-Cog), divers tests neuropsychologiques et des scores cliniques spécifiques pour l'activité locomotrice, l'apathie, le fardeau de l'aidant et la dépendance.
Résultats. — Le critère d'évaluation principal était l'amélioration du score ADAS-Cog à j45, qui a été atteint. Six mois après la fin du traitement, le score ADAS-Cog est retourné à la valeur de base, sauf pour les meilleurs répondeurs qui sont restés sensiblement améliorés. L'autre résultat principal observé a été l'amélioration des scores d'apathie et de dépendance aussi bien à j45 qu'à M6 pour l'ensemble de la série de patients. Aucun événement indésirable grave n'est survenu et tous les patients ont terminé l'étude.
Conclusions. — Les résultats de cette étude ouverte confirment la faisabilité de la procédure combinée de rTMS-COG chez les patients atteints de la maladie d'Alzheimer, et suggèrent que ces patients peuvent bénéficier de la procédure, en termes de performances cognitives, d'apathie et de dépendance, même à long terme. Il reste à confirmer ces résultats prometteurs par des études contrôlées basées sur une plus grande population et à identifier des facteurs pronostiques potentiels de bon résultat, afin de sélectionner les meilleurs candidats.

Introduction

The neuropathological background of Alzheimer's disease (AD) is characterized by progressive neuronal loss associated with accumulation of amyloid β-protein (Aβ) in brain areas involved in learning and memory [26]. Disease development could be explained by an alteration of neural plasticity, affecting dendritic ramifications, synaptic remodelling, long-term synaptic potentiation (LTP), axonal sprouting, neurite extension, synaptogenesis and neurogenesis [4,5]. Since the potential for brain plasticity decreases with aging, concomitantly with reduced learning and memory capacities [23], age is a major risk factor for the development of AD [18]. High levels of Aβ accumulation could also enhance long-term synaptic depression (LTD), responsible for abnormal patterns of neural network activity [27,35]. In turn, this could also trigger trans-synaptic mechanisms of neurodegeneration and lead to episodic and working memory impairment [19,29].

Cognitive training (COG) and non-invasive transcranial brain stimulation (NIBS) could promote neural plasticity, which is a therapeutic objective in AD. COG training has been used in patients with mild-to-moderate AD on the basis of person-to-person or computer-based training [14,37]. It has been suggested that COG could modulate the excitability of neurons inducing plastic changes (intrinsic plasticity), further supporting synaptic plasticity and learning capacities [34]. A meta-analysis [36] showed promising evidence for the efficacy of COG training in the treatment of AD, but with only medium effect sizes for learning, memory, executive functioning, activities of daily living, and general cognitive performance. One limitation is the adherence of AD patients

to the intensive and time-consuming COG training exercises [6]. Another limitation is the short-lasting benefit of COG training, with an observed improvement only for the trained task, with little or no change in other cognitive features [14]. This obviously limits the value of including COG training in rehabilitation programs, since the goal of such programs is to improve the long-term global quality of everyday life of AD patients.

NIBS techniques include repetitive transcranial magnetic stimulation (rTMS), which is able to selectively activate neural circuits in the cortex, and transcranial direct current stimulation (tDCS), which is a purely neuromodulatory intervention. Both NIBS techniques are safe and have therapeutic potential in patients with AD, especially by promoting synaptic plasticity, including LTP [1,22]. It has been suggested that NIBS can also probe homeostatic plasticity, which is thought to stabilize neural activity and facilitate learning [21]. A meta-analysis of publications dealing with the cognitive effects of rTMS found convincing data supporting rTMS-induced improvement only in a subset of cognitive functions [15]. Most of these studies assessed the effects of NIBS delivered over the dorsolateral prefrontal cortex (DLPFC), but multiple-target stimulation protocols have been suggested to be more effective [7].

A combination of adapted COG training and NIBS targeted to different brain areas involved in the cognitive decline of AD patients showed promising therapeutic results in this context [2,24,30]. In these studies, rTMS was delivered over 6 brain areas (right and left DLPFC, right and left posterior parietal cortex associative areas, and Broca and Wernicke language areas) in combination with COG training (rTMS-COG) (NeuroAD, Neuronix Ltd, Yoqnea'm, Israel). The reported benefits were thought to result from modulation of intrinsic, homeostatic and synaptic plasticity, leading to normalization of neural network activity. Another study using tDCS delivered to the right prefrontal and parietal cortices combined with verbal and visual working memory training tasks recently showed long-term benefits in cognitive performance, with extension to untrained tasks [20]. However, the follow-up remained less than 6 months. The goal of the present study was to assess the effect of the rTMS-COG protocol on trained and untrained cognitive performance and working memory up to 6 months after the end of treatment.

Methods

Ten patients (5 men and 5 women aged 61 to 84 years (mean $\pm$ SEM: 73.0 $\pm$ 7.2) diagnosed with probable AD were included in this study between February and September 2015. MRI findings were compatible with the diagnosis of AD in all patients [9]. Cognitive disorder had been present from 2 to 15 years (5 $\pm$ 2.3) at the time of inclusion. All patients had sufficient autonomy to be maintained at home.

These 10 patients were treated by the NeuroAD procedure, which has been described in detail elsewhere [2]. Before initiating this protocol, a pilot trial with the NeuroAD procedure had been conducted in our center on 2 AD patients, who were not included in this study. The NeuroAD procedure combines NIBS using rTMS and cognitive training. Briefly, rTMS was targeted over 6 brain areas thought to be dysfunctional in AD: right and left prefrontal cortex, right and left parietal cortex, and Broca's and Wernicke's areas. These various cortical targets were identified by the Neuronix neuronavigation system based on the individual patient's MRI. rTMS was delivered by a figure-of-eight coil connected to a generator delivering a maximum power of 140 Joules per shock (Neuronix). For each region, stimulation consisted of delivering series of 20 trains of 20 pulses at 10 Hz (20 trains of 2 s for a total of 400 pulses over a period of about 10 minutes). The intensity of stimulation was set at 100% of the resting motor threshold. Three different regions were treated each day (for example, Broca's area, Wernicke's area and right parietal cortex) and three other regions (for example, left and right prefrontal cortex and left parietal cortex) were treated on the following day. Since one of the main goals of the procedure was to promote short-term memory improvement, which was supposed to be related to a ''word recall'' training associated with DLPFC stimulation, an additional shorter session of 5 trains of 20 pulses at 10 Hz (5 trains of 2 sec for a total of 100 pulses over a period of about 2 minutes and a half) was delivered every day over either the left or the right DLPFC. Because we did not want to deliver more than 1300 pulses per day (400 $\times$ 3 plus 100) for safety purposes [33], during a treatment session that should last less than one hour to avoid concentration problems for the patient, we limited the number of pulses allocated to this specific DLPFC paradigm added to the other three paradigms performed every day. Each cortical region was stimulated by rTMS and simultaneously activated by a specific cognitive task. There were 12 paradigms of cognitive tasks for the three different cortical regions:

- naming of actions and objects, word recall and spatial memory tasks (localization and colors) for the prefrontal cortex (5 tasks);
- spatial attention tasks (shape and letter recognition and localization) for the parietal cortex (3 tasks);
- syntax and grammar tasks for language areas (4 tasks).

For each treated region, about 40 s of cognitive tasks were performed between each 2-sec train of 10 Hz-rTMS. As mentioned above, a series of 20 trains per session was done for each treated region and the patients received 3 sessions (corresponding to three different cortical regions and thereby different cognitive tasks), plus a shorter session of 5 trains over the DLPFC, per treatment day. Only one of the cognitive tasks associated with each of the stimulated cortical regions was performed in each session, except for the ''word recall'' training, which was systematically performed with the additional DLPFC session. For each task, the cognitive training test included six levels of increasing difficulty, from level 1 (''very easy'') to level 6 (''advanced pro''). The percentage of correct responses provided by the patient was scored. When the percentage of correct responses was higher than 80% at a given level, the patient was allowed to progress to the next level of difficulty. For each task, the performance corresponded to the total percentage of correct responses at the last level of difficulty performed, with a maximal score of 600% (100% of correct response at level 6). Regarding the three major functions (memory, visuospatial skills, and language) potentially affected by AD and assessed by the test, a function was considered deficient when the performance of the patient on at least one of

the task corresponding to this function was not good (score equal or less than 90% at baseline). For the first session, all patients started on the same lowest level of difficulty. At end of each week, the software determined the patient's level of achievement and adjusted the level of difficulty for the following week, based on the patient's performance. The performance on the cognitive training test was then scored at baseline and at the end of the treatment (D45).

In addition, the patients underwent a neuropsychological and clinical assessment based on various scales, questionnaires and interviews, including the AD assessment scale — cognitive subscale (ADAS-Cog) [32], the Mental Mini State Examination (MMSE) [12], the Dubois score [11], the Frontal Assessment Battery (FAB) [10], the Stroop color test [38], the locomotor (Tinetti) score [39], the apathy score [31], the caregiver burden (Zarit) interview [3,17], and the dependence score [13]. In addition, the MMSE language score and the ADAS-Cog word recognition and word recall scores were evaluated separately. This neuropsychological assessment was performed at baseline, at the end of the treatment (D45), and also 6 months (M6) after the end of the treatment (i.e. 7.5 months after treatment onset).

The primary endpoint of this study was to determine whether the NeuroAD procedure can significantly improve the ADAS-Cog score, at least in the short term (D45). Secondary endpoints were to determine whether NeuroAD could also provide long-term (M6) improvement of general functions (apathy, dependence, locomotor activity). We also determined whether this procedure could induce transfer of improvement from trained tasks to untrained tasks, which could be interpreted as improvement of the neuronal networks involved in cognition. To evaluate the learning transfer capacity, we considered that a significant improvement of word recall score (ADAS-Cog) reflected transfer of learning to related tasks and that a significant improvement of language score (MMSE), word recognition score (ADAS-Cog), Dubois score, FAB score and Stroop score reflected transfer of learning to unrelated tasks.

In order to identify prognostic factors for a response to this type of treatment, we analyzed the correlation between the percentage of improvement of the ADAS-Cog score at D45 (primary endpoint) and the various clinical scores at baseline. Conversely, to determine the influence of cognitive decline at baseline on treatment outcomes, we analyzed the correlation between the ADAS-Cog score at baseline and the percentage of change of the various clinical scores at D45 and M6.

Since not all data were normally distributed, as revealed by Kolmogorov-Smirnov tests, we used the following non-parametric tests:

- the Wilcoxon signed-rank test to compare the results between baseline and D45 for the performance on each task of the cognitive training test; due to multiple pairwise comparisons, a Bonferroni correction was applied and the significance level of P value was set at 0.0038;
- the Friedman test (ANOVAs with repeated measures) to compare the results between the three time points (baseline, D45, M6) for the neuropsychological scores; in case of significant P value of ANOVA (less than 0.05), Bonferroni post-hoc tests were used to compare D45 and M6 results to baseline;
- the Mann-Whitney test for unpaired comparisons;
- the Spearman test for correlation studies.

Results

Regarding the performance on cognitive training task at baseline, patients 1 to 5 presented cognitive dysfunction for only one function (memory), compatible with mild cognitive impairment. Patient 9 presented cognitive dysfunction for 2 functions (memory and language), corresponding to an early stage of AD, while patients 6, 7, 8, and 10 presented cognitive dysfunction for the 3 functions evaluated (memory, visuospatial skills, and language), evoking moderate-to-severe AD, based on our clinical experience.

At the end of the treatment, there was a clear improvement of the performance on all the tasks. This result was mainly due to a test—retest effect and an effective learning, although we took the opportunity to use a different subset to assess each item of the ADAS-Cog test at each evaluation time, for example. However, after correction for multiple comparisons, cognitive improvement was found to be especially significant for the tasks corresponding to both parietal and language areas (Table 1).

Regarding the neuropsychological assessment, at baseline, patients had an ADAS-Cog score ranging from 6.5 to 36 (20.1 ± 8.3) and a MMSE score ranging from 12 to 26 (18.8 ± 5).

Following the NeuroAD procedure, four clinical scores changed over time, showing a significant improvement (Table 2): ADAS-Cog score ($P = 0.0165$, Friedman test), locomotor (Tinetti) score ($P = 0.0478$), apathy score ($P = 0.0125$), and dependence score ($P = 0.085$). None of the other clinical scores showed significant variation. Improvements were observed for the tasks specifically related to the cognitive training. On the other hand, we did not find any significant transfer of learning to unrelated tasks.

As showed by Bonferroni post-hoc tests, the ADAS-Cog score significantly improved from baseline to the end of treatment (D45) (mean $\pm$ SEM: 20.1 ± 3.1 to 17.2 ± 2.5, $P < 0.05$). About this primary efficacy endpoint, mean improvement was 13%. At M6, the ADAS-Cog score returned to baseline value (20.1 ± 3.4 vs. 20.1 ± 3.1, $P < 0.05$). However, if we compare the 5 best responders who were improved on the ADAS-Cog at D45 by more than 13% (patients 1, 4, 5, 7, and 10) with the worst responders at D45 (patients 2, 3, 6, 8, and 9), the ADAS-Cog score still was improved at M6 in the former group, but not in the latter (16.5 ± 5.2 vs. 23.8 ± 4.3, i.e. a mean difference of 7.3, corresponding to a percentage of change of $-16.5\% \pm 4.2$ vs. $+14.6 \pm 6.1$, $P = 0.016$, Mann-Whitney test).

Regarding the apathy and dependence scores, both significantly improved from baseline to D45 (17.4 ± 2.2 to 10.8 ± 2.0 and 48.4 ± 5.5 to 36.8 ± 5.0, $P < 0.05$) in the entire series of patients. For these parameters, the improvement remained stable at M6 (9.4 ± 1.8 and 34.7 ± 4.4, $P < 0.05$ compared to baseline).

Correlation analyses remained negative. We did not identify any clinical parameter at baseline correlated to the percentage of improvement of the ADAS-Cog score at D45

Table 1 Results of the cognitive training test (13 tasks designed to activate 6 cortical areas).

	Baseline	D45	Wilcoxon test (*P*)
Tasks for the right prefrontal cortex			
Action naming	84.0 (2.8)	326.2 (63)	0.0039
Subject naming	77.5 (5.1)	270.0 (54.9)	0.0137
Word recall	87.0 (7.2)	283.0 (46.2)	0.0078
Tasks for the left prefrontal cortex			
Word recall	82.9 (6.7)	261.0 (37.5)	0.0039
Color recognition	78.0 (3.8)	200.2 (28.7)	0.0098
Localization of objects	72.0 (5.5)	186.7 (32.1)	0.0098
Tasks for the right parietal cortex			
Red rectangle recognition	75.5 (7.6)	383.5 (61.6)	0.002
Blue rectangle recognition	85.3 (6.7)	387.3 (60.5)	0.002
Task for the left parietal cortex			
Letter recognition	79.4 (7.3)	422.7 (67.8)	0.002
Tasks for Broca's area			
Sentence similarity	70.5 (5.9)	348.7 (71.5)	0.0039
Right/wrong words	80.8 (5.8)	401.4 (61.5)	0.002
Tasks for Wernicke's area			
Words/pseudowords	79.5 (6.7)	451.9 (58.8)	0.002
Categories	93.8 (1.9)	461.9 (46.5)	0.002

Mean (SEM) are presented from the data recorded in the series of 10 patients. Significant *P* values are underlined.

Table 2 Results of the neuropsychological and clinical assessment.

	Baseline	D45	M6	Friedman test (*P*)
ADAS-Cog score	20.1 (3.1)	17.2 (2.5)	20.1 (3.4)	0.0165
ADAS-Cog word recognition score	17.8 (1.4)	18.5 (1.7)	19.0 (1.3)	0.1738
ADAS-Cog word recall score	2.7 (0.5)	2.8 (0.5)	2.7 (0.5)	0.9592
MMSE score	18.8 (1.9)	19.7 (1.4)	17.8 (1.5)	0.1168
MMSE language score	6.4 (0.4)	6.6 (0.3)	6.6 (0.4)	0.5945
Dubois score	5.0 (0.8)	4.3 (0.8)	4.5 (1.1)	0.2466
FAB score	11.5 (1.3)	11.7 (1.4)	11.4 (1.5)	0.9155
Stroop color test score	39.3 (7.3)	36.3 (6.1)	40.6 (8.2)	0.8357
Locomotor (Tinetti) score	26.2 (0.6)	27.0 (0.4)	27.0 (0.5)	0.0478
Apathy score	17.4 (2.7)	10.8 (2)	9.4 (1.8)	0.0125
Caregiver burden (Zarit) score	4.1 (0.4)	3.6 (0.5)	3.7 (0.4)	0.2385
Dependence score	48.4 (5.5)	36.8 (5)	34.7 (4.4)	0.0085

Mean (SEM) are presented from the data recorded in the series of 10 patients. Significant *P* values are underlined.

and any clinical change at D45 or M6 correlated to the ADAS-Cog score at baseline.

Finally, the 10 included patients completed the study. The only adverse effect resulting from the NeuroAD procedure was transient fatigue observed during the third week of treatment in patients 7 and 8, which did not require interruption of treatment.

Discussion

To our knowledge, only 3 publications [2,24,30] have previously reported results obtained with the NeuroAD protocol in patients with AD. As for the study reported by Bentwich et al. [2], our prospective open-label study suffers from the weaknesses inherent to a non-randomized study. Due to the absence of a control group, a placebo effect cannot be excluded. Despite this absence of a control group and in addition to a possible test—retest effect due to the procedure, it also cannot be ruled out that the demonstrated improvements would just be consecutive to cognitive training, without any added value of rTMS. However, at least two previous studies [24,30], using the same rTMS device and the same protocol as in the present study, demonstrated an additional effect of active rTMS procedure to cognitive training, as compared to a sham rTMS procedure.

Beyond its methodological limitations, our study had the advantage of being a ''real life'' study, demonstrating the potential clinical impact of this type of procedure in the routine management of AD patients in the long term. The follow-up was longer in our study than in the previous studies, in which the longest reported follow-up was 4.5 months. Our study also confirms the safety and medium-term efficacy of a NIBS technique combined with cognitive training

in patients with AD. As in previously published series [1], we did not observe any serious adverse event related to the procedure.

The primary endpoint was reached, i.e. a significant decrease in the ADAS-Cog score at the end of treatment (D45), with an average improvement of 13% compared to baseline. The ADAS-Cog score returned to baseline at M6 on average in the entire series of patients. However, the best responders at D45 remained significantly improved at M6, whereas the worst responders worsened, leading to a mean difference of 7.3 on the ADAS-Cog scale between these two groups. This observation suggests that the best responders to this procedure could benefit from a single NeuroAD procedure for a prolonged time beyond the time of stimulation. This is all the more interesting given that, like some others (Lee et al. [24]), we limited the treatment period to 45 days, whereas previously reported results were obtained with a period of a three-month maintenance protocol [2,30].

We more especially studied the effect of the NeuroAD protocol on general functions, reflecting the impact of AD on various aspects of everyday life, such as locomotor activity, apathy, caregiver burden and dependence. All the corresponding scores were significantly improved after the procedure, except for the caregiver burden. Moreover, the beneficial effects of the NeuroAD protocol on apathy and dependence was still significant six months after the end of the treatment. In particular, the improvement of apathy is a very interesting result, since this symptom is considered to be one of the most disabling symptoms for the patients and their families. In the study by Rabey et al. [30], the Neuropsychiatric Inventory (NPI) score [8], which includes assessment of apathy, was also improved but not significantly following NeuroAD treatment. The improvement of the locomotor (Tinetti) score confirms the links between motor functions and cognitive capacity, as clearly demonstrated by several studies [16,28]. In addition, this suggests that this type of therapeutic protocol could be useful in degenerative diseases associating dementia and motor disorders, such as advanced Parkinson's disease.

The transfer of learning of trained tasks to untrained tasks could be one objective of such therapeutic protocols combining COG and NIBS [19,20]. However, this study fails to show improvement of tasks such as word recall and recognition or the Stroop test, which could have indicated a beneficial effect of the procedure on working memory and attention, essential for the performance of episodic memory [25]. However, this study was based on only a small sample size (10 patients), which likely reduced the chance of detecting any effect. This is also the case for the prognostic factors. Previous studies suggested that the results of the NeuroAD protocol were better in patients with an MMSE score situated between 21 and 26 [24]. Although the two patients with the highest MMSE scores at baseline (26 and 28) were among the best responders (defined on the percentage of improvement of the ADAS-Cog score at D45), we did not find any significant correlation between the MMSE or ADAS-Cog score at baseline and the clinical outcome measured on the ADAS-Cog score. This study did not allow identification of the best candidates for this type of treatment. Studies based on larger populations will be necessary to address this issue. Similarly, it would be interesting to identify criteria to exclude candidates who are unable to perform cognitive training, which is an essential component of the protocol. For example, major language disorders, preventing patients from understanding the test instructions, appear as a contraindication. A language score (MMSE) less than 5 would appear to be a cut-off for the selection of candidates.

This study showed promising results. Cognitive performance assessed on ADAS-Cog score (primary endpoint) significantly improved at the end of the treatment. Six months later, this score returned to baseline values, when the entire series of patients was considered. However, good responders, constituting half of the series, remained significantly improved at M6 on this cognitive score. To identify these good responders will be a challenge for future studies. In addition, the NeuroAD protocol appeared especially beneficial for apathy and dependence in the long term. The duration of the benefit suggests that the repetition of a full course of NeuroAD protocol every six months might be sufficient to produce a sustained clinical effect. The possibility of an additional impact of a shorter protocol performed as maintenance sessions should be investigated. All these issues should be addressed in controlled studies based on a larger population size.

Disclosure of interest

The authors declare that they have no competing interest.

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