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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

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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

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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