

Radio electric asymmetric brain stimulation in the treatment of behavioral and psychiatric symptoms in Alzheimer disease

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Purpose: Behavioral and psychiatric symptoms of dementia (BPSD) are common in Alzheimer's disease (AD) and disrupt the effective management of AD patients. The present study explores the use of radio electric asymmetric brain stimulation (REAC) in patients who have had a poor response to pharmacological treatment.

Patients and methods: Eight patients (five females and three males; mean [\pm standard deviation] age at study baseline: 69.9 ± 3.0 years) diagnosed with AD according to the DSM-IV-TR criteria (mean onset age of AD: 65.4 ± 3.5 years) were cognitively and psychometrically assessed with the Mini-Mental State Examination (MMSE), the Activity of Daily Living (ADL), the Instrumental Activity of Daily Living (IADL), and the Neuropsychiatric Inventory (NPI), prior to and after each of 2 REAC treatment cycles.

Results: Scores on the MMSE and all subscales of the NPI (frequency, severity, and distress), the ADL, and the IADL were significantly improved following the initial REAC treatment. There was further significant improvement in all measurements (with a tendency for improvement in the IADL) after the second REAC treatment cycle.

Conclusion: The improvement of cognitive and behavioral/psychiatric functioning following REAC treatment suggests that this innovative approach may be an effective, safe, and tolerable alternative to pharmacological treatment of AD patients, especially in the area of BPSD. Elderly patients suffering from other types of dementia may also benefit from REAC treatment.

Keywords: anxiety, depression, insomnia, behavioral and psychiatric symptoms of dementia (BPSD)

Introduction

The progressively increasing number of the elderly in the general population and, consequently, the growing prevalence of Alzheimer disease^{1,2} (AD) highlight the need for new specifically targeted therapeutic options.³⁻⁶ The currently available psychological⁷⁻¹⁰ and psychopharmacological¹¹⁻¹⁵ treatments¹⁶ for AD provide relatively poor results. The inadequate and/or insufficient safety and tolerability profile of 'typical' AD therapies produce familiar social and economic difficulties.^{17,18} According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR), AD includes a disruption in attention,^{19,20} concentration, memory,^{21,22} and cognition.²³ While the DSM-IV-TR instructs diagnosing clinicians to specify whether cognitive symptoms of AD are accompanied by behavioral abnormalities (eg, delusions, depression, anxiety, agitation, wandering, sexual behavior alterations, sleep dysfunctions, disorientation), behavioral symptoms of AD are not included in the working definition.

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Table 1 Total score variation before and after first REAC treatment cycle

Test	TSV before REAC	TSV after 1 REAC cycle	ANOVA F	df	P
MMSE	18.5 ± 2.4	23.4 ± 2.3	64.0588	14	<0.01
NPI for "frequency"	32.2 ± 2.5	26.4 ± 2.4	309.8421	14	0.000
NPI for "severity"	28.6 ± 3.4	22.1 ± 3.4	529.000	14	0.000
NPI for "distress"	49.5 ± 3.6	41.0 ± 2.1	583.1538	14	0.000
ADL	3.8 ± 1.0	4.9 ± 0.5	33.8507	14	NS
IADL	10.0 ± 2.4	13.0 ± 1.1	134.8667	14	0.000

Abbreviations: REAC, radio electric asymmetric brain stimulation; TSV, total score variation; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric inventory; ADL, Activity of Daily Living; IADL, Instrumental Activity of Daily Living; NS, not statistically significant.

The relationship between AD and the behavioral and psychiatric symptoms of dementia²⁴ (BPSD) is becoming more prevalent. Symptoms of dementia accompany AD in about 90% of cases,²⁵ typically arising early in the course of the disease and persisting. Unlike the steady loss of "global" cognition, throughout the course of AD, behavioral symptoms are more variable, with different types of BPSD seen among patients.²⁶ Despite the observed inter-patient variability in number and type of behavioral symptoms encountered in AD, patients with advanced illness tend to have more behavioral symptoms than those in earlier phases of the disorder. Several long-term studies indicate that once a specific symptom occurs in a given patient, it is likely to persist or recur thereafter.

Radio electric asymmetric brain stimulation^{27,28} (REAC) treatment has proven efficacy in ameliorating several stress-related disorders, depression, and anxiety,^{29–35} and our unpublished data have shown promising results for some forms of dementias. REAC treatments are painless, noninvasive, and have a high safety and tolerability profile. On the basis these we can hypothesize that the treatments with REAC technology may be helpful in AD and, in general, in several forms of cognitive-impairment disorders.

Aim of the present study

REAC has demonstrated efficacy in improving certain psychiatric disorders such as anxiety, depression and bipolar disorder. The main goal of the present study was to investigate the efficacy of REAC in the treatment of behavioral symptoms in AD patients. In addition, effects on cognitive functioning were also investigated.

Materials and methods

The data for the current study were collected during routine therapy sessions at the Rinaldi Fontani Institute, Behavioral Disorder Department in Florence, Italy. Most patients referred

to the clinic were nonresponders to typical pharmacological strategies. Eight patients (five females and three males; mean [±SD] age at study baseline: 69.9 ± 3.0 years) diagnosed with AD according to the DSM-IV-TR criteria (mean onset age of AD: 65.4 ± 3.5 years), presenting with behavioral and/or psychiatric disturbances were psychometrically assessed using the Mini-Mental State Examination³⁶ (MMSE), the Activity of Daily Living³⁷ (ADL), the Instrumental Activity of Daily Living³⁸ (IADL), and the Neuropsychiatric Inventory³⁹ (NPI), before and after 2 treatment cycles of REAC.

REAC is applied by a medical device that is based on an innovative biostimulation technology.^{27,28} REAC works within a typical frequency range of 2.4, 5.8, or 10.5 GHz, selected by the operator for each specific protocol. For the current study, a frequency of 10.5 GHz, with a specific absorption rate (SAR) of 7 µW/kg, was used. The neuro postural optimization (NPO) protocol consisting of a single radiofrequency burst of 500 milliseconds (ms) applied by touching the metallic tip of the REAC probe (Convogliatore di Radianza Modulante – CRM; ASMED, Italy) to the ear pavilion was performed as an initial treatment. NPO was followed by another treatment protocol, named neuro psycho physical optimization (NPPO). This protocol consisting of seven REAC radiofrequency bursts of 500 ms applied by touching the metallic tip of

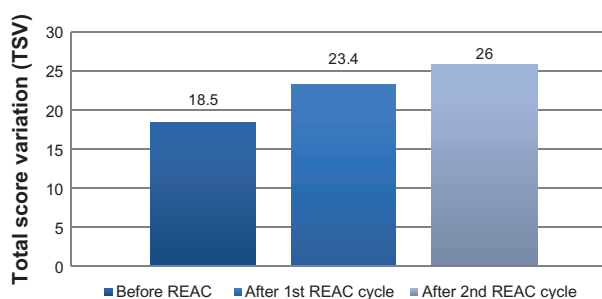


Figure 1 Mini-Mental State Examination (MMSE) before, after the first and second REAC treatment cycle.

Abbreviations: REAC, radio electric asymmetric brain stimulation; TSV, total score variation.

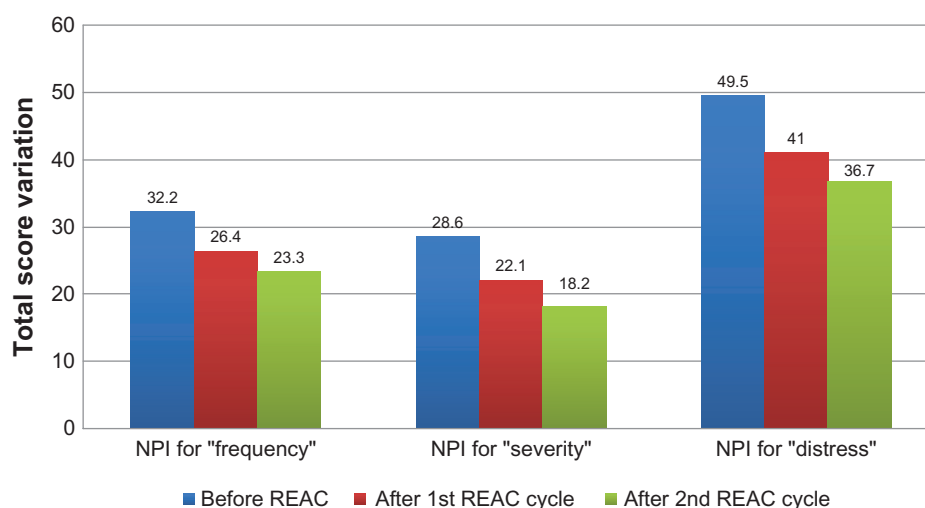


Figure 2 Neuro Psychiatric Inventory (NPI) before after first and second REAC treatment cycle.

Abbreviation: REAC, radio electric asymmetric brain stimulation.

the REAC probe at precise points of the ear. Each therapy session lasts about 5 seconds. An NPPO treatment cycle consists of 18 therapy sessions, administered on alternate days. The mean interval between the first and the second NPPO treatment cycle is about 6 months.

ANOVA for repeated measures was performed for statistical analysis of differences in MMSE, ADL, IADL, and NPI scores prior to and following REAC treatments. P values < 0.05 were considered significant.

Results

After the first REAC treatment cycle, patients showed great improvement in cognitive performance as demonstrated by a significant increase in average MMSE total score from $18.5 (\pm 2.4)$ to $23.4 (\pm 2.3)$ (ANOVA $P < 0.01$) (Table 1 and Figure 1). In addition, BPSD was improved as demonstrated by a decrease in average NPI frequency score (Table 1 and Figure 2) from $32.2 (\pm 2.5)$ to $26.4 (\pm 2.4)$ (ANOVA $P = 0.000$), NPI severity score (Table 1 and Figure 2) from

$28.6 (\pm 3.4)$ to $22.1 (\pm 3.4)$ (ANOVA $P = 0.000$), and NPI distress score from (Table 1 and Figure 2) $49.5 (\pm 3.6)$ to $41 (\pm 2.1)$ (ANOVA $P = 0.000$). In addition, average ADL score (Table 1 and Figure 3) increased from $3.8 (\pm 1.0)$ to $4.9 (\pm 0.5)$ (ANOVA $P = \text{NS}$) and average IADL score (Table 1 and Figure 4) increased from $10.0 (\pm 2.4)$ to $13.0 (\pm 1.1)$ (ANOVA $P = 0.000$).

After the second REAC treatment cycle, there were further significant ameliorations in both cognitive and behavioral performance (Table 2). There was a significant increase in average MMSE total score (Table 2 and Figure 1) to $26.0 (\pm 3.4)$ (ANOVA $P < 0.001$), and a significant decrease in NPI frequency score (Table 2 and Figure 2) to $23.3 (\pm 2.3)$ (ANOVA $P < 0.001$), NPI severity score (Table 2 and Figure 2) to $18.2 (\pm 3.7)$ (ANOVA $P = 0.000$), and NPI distress score (Table 2 and Figure 2) to $36.7 (\pm 4.3)$ (ANOVA $P = 0.000$). IADL total score was significantly increased after the second REAC treatment to $14.4 (\pm 0.7)$ (ANOVA $P = \text{NS}$) (Table 2 and Figure 4). The increase in

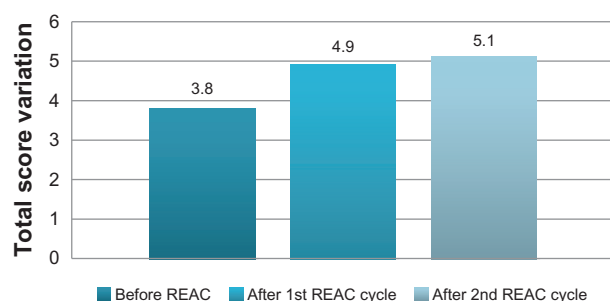


Figure 3 Activity of Daily Living (ADL), before, after first and second REAC treatment cycle.

Abbreviation: REAC, radio electric asymmetric brain stimulation.

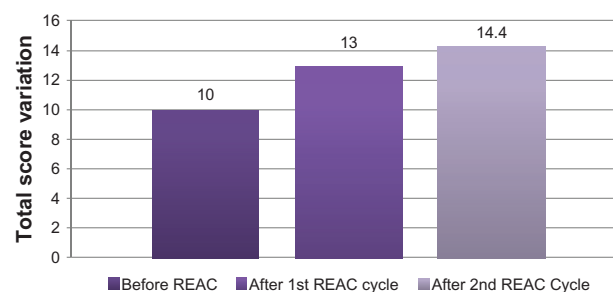


Figure 4 Instrumental Activity of Daily Living (IADL), before, after first and second REAC treatment cycle.

Abbreviation: REAC, radio electric asymmetric brain stimulation.

Table 2 Total score value of first versus second REAC treatment cycle

Test	TSV after 1 REAC cycle	TSV after 2 REAC cycle	ANOVA F	df	P
MMSE	23.4 ± 2.3	26.0 ± 3.4	44.800	14	<0.001
NPI for "frequency"	26.4 ± 2.4	23.3 ± 2.3	79.5455	14	<0.001
NPI for "severity"	22.1 ± 3.4	18.2 ± 3.7	203.8936	14	0.000
NPI for "distress"	41.0 ± 2.1	36.7 ± 4.3	191.6526	14	<0.05
ADL	4.9 ± 0.5	5.1 ± 0.4	0.4430	14	NS
IADL	13.0 ± 1.1	14.4 ± 0.7	0.7238	14	NS

Abbreviations: REAC, radio electric asymmetric brain stimulation; TSV, total score variation; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric inventory; ADL, Activity of Daily Living; IADL, Instrumental Activity of Daily Living; NS, not statistically significant.

ADL total score to 5.1 ± 0.4 (Table 2 and Figure 3) was not statistically significant (ANOVA $P = NS$).

Discussion

REAC treatment enhanced cognitive and behavioral functioning in patients with AD. All measures of cognitive functioning were significantly improved after the initial REAC treatment and continued to improve after the second REAC cycle. Similarly, all behavioral measurements were positively affected after the first REAC treatment and most continued to improve after the second cycle.

It is likely that the effects on cognition and behavior are due to a process of synchronization of brain function caused by the microelectric stimulation of the REAC.²⁹

While cognitive functioning benefitted from REAC treatment, the positive effects on BPSD may be of more importance in the management of AD patients. The improvement in these clinical parameters is reflected in functional terms by an increase in the quality of life of patients as reported by relatives, physicians, and caregivers and is psychometrically demonstrated by the ADL and IADL total scores. The use of REAC treatment may decrease the need to continually alter pharmacological treatments to achieve optimal results, leading to significant savings in economic resources of rehabilitation programs for AD patients.

REAC treatments alone are not likely to manage all deficits associated with neuropsychiatric disorders in the elderly. However, the results of the present study suggest that REAC treatment has a high safety, tolerability, and efficacy profile and may be useful not only in patients who have experienced poor and/or unstable responses to psychotropic drugs, but also as a first-line therapeutic option. REAC treatment may be useful not only for AD patients, but also for other forms of dementia (ie, vascular dementia or mixed conditions).

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Disclosure

Salvatore Rinaldi and Vania Fontani are the inventors of the Radio Electric Asymmetric Conveyer.

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