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ESTIMATING THE EFFECTS OF RIGHT MEDIAN NERVE STIMULATION ON MEMORY IN ALZHEIMER'S DISEASE: A RANDOMIZED CONTROLLED PILOT STUDY

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The goal of the present study was to examine possible effects of right median nerve stimulation (RMNS) on memory in patients in a relatively early stage of probable Alzheimer's disease (AD). Seventeen AD patients were randomly assigned to an experimental group (n = *8) and a control group* (n = *9) and treated with RMNS and sham RMNS, respectively, for 30 min a day, 5 days a week, for 6 weeks. Neuropsychological tests were used to assess memory processes. The results show that the various aspects of memory did not respond positively to RMNS. A study with a much longer treatment period is suggested before firm conclusions about the ineffectiveness of RMNS on memory in AD can be drawn.*

In previous studies, the effects of transcutaneous electrical nerve stimulation (TENS) on various aspects of memory were examined in patients with probable Alzheimer's disease (AD). In those studies,

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various aspects of memory, particularly episodic and semantic memory, showed a statistically significant improvement, despite the relatively small number of patients that participated in each study (Scherder, Bouma, & Steen, 1995, 1998; Scherder & Bouma, 1999). Of note is that a recent larger study failed to find positive effects of TENS on memory in AD patients (Van Dijk, Scheltens, Luijpen, Sergeant, & Scherder, 2005). One rationale that underlies these studies is that TENS enhances the activity of the ascending reticular activating system (ARAS) through stimulation of the locus coeruleus and dorsal raphe nucleus, brain stem areas that are the origin of the noradrenergic and serotonergic neurotransmitter systems, respectively (Kayama & Koyama, 1999). To activate the ARAS, the electrical current in the TENS studies was applied through two electrodes placed on the musculus trapezius pars descendens, between the first and fifth thoracic vertebrae, with an intensity high enough to provoke mild non-nociceptive muscular contractions of the musculus trapezius.

However, the application of the electrodes on the musculus trapezius is quite impractical on a psychogeriatric ward with a large number of patients and a small nursing staff. The electrodes are hidden underneath the clothing and, consequently, the muscular contraction of the musculus trapezius pars descendens can only be controlled for by a close inspection. A more practical alternative might be to stimulate the patient through electrodes over the median nerve of, e.g., the right forearm, called right median nerve stimulation (RMNS). This electrode placement requires hardly any undressing and enables the nursing staff to control for muscular contractions at a distance because there is no need to cover the electrodes by clothing. In clinical studies, RMNS has only been applied to coma patients and appeared to accelerate awakening from deep coma (Cooper, Jane, Alves, & Cooper, 1999; Peri et al., 2001; Cooper & Cooper, 2003; Liu et al., 2003). Similar to the TENS studies in AD, the rationale underlying the coma studies is that RMNS stimulates the ARAS (Cooper et al., 1999; Cooper, Scherder, & Cooper, 2005). Based on the positive effects of RMNS in coma, we investigated in the present study whether RMNS could improve memory in patients with probable AD.

METHODS

Subjects

Seventeen subjects met the NINCDS-ADRDA criteria for the clinical diagnosis of probable AD (McKhann et al., 1984) and stage 5 of the Global Deterioration Scale (GDS) (Reisberg, Ferris, De Leon, &

Crook, 1982), in the absence of a history of psychiatric disorder, alcoholism, cerebral trauma, cerebrovascular disease, hydrocephalus, neoplasm, epilepsy, disturbances of consciousness, or focal brain disorders. None of the subjects had a pacemaker. Patients were randomly assigned to an experimental group ($n = 8$) and a control group ($n = 9$). The level of cognitive functioning was measured by the Mini-Mental State Examination (MMSE), with a maximum score of 30 (Folstein, Folstein, & McHugh, 1975).

After description of the study to the patients and their families, written informed consent was obtained from both. The local Medical Ethical Committee approved the study.

Procedures

Treatment

RMNS was applied to the patients in the experimental group by an electrostimulator, type Premier 10 s. This stimulator generated asymmetric biphasic square electrical impulses in bursts of trains (Scherder et al., 1995) via two surface rubber electrodes placed on the volar side of the patient's right distal forearm over the median nerve (Cooper et al., 1999). The AD patients in the control group received sham stimulation, i.e., no current was administered. All 17 patients received a 30-min/day treatment between 15:00 and 19:00 h, for 5 days/week, during a 6-week period.

Assessment of Memory

To evaluate possible treatment effects of RMNS on memory, the following neuropsychological tests were administered. Digit Span Forward and Backward (Forward + Backward = Total score) and Visual Memory Span Forward and Backward (Forward + Backward = Total Total Score) (Wechsler, 1987) were used to assess patients' verbal and nonverbal short-term memory capacities, respectively. The California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987) includes a list of 16 words (groceries and clothing) and was used to assess various types of recall from episodic memory, i.e., recall immediately after the presentation of the words: Immediate Recall (total score after presenting the words five times), Delayed Recall (recall after 15 min), and Recognition (recall by means of recognition). Face and Picture Recognition (Wilson, Cockburn, & Baddeley, 1987) provided a measure of visual and verbal long-term recognition memory, respectively, and Word Fluency (Snijders & Verhage, 1983) was meant to measure semantic memory. An independent investigator who was not informed about which subjects belonged to which group administered the tests.

Data Analyses

Neuropsychological testing took place immediately before the 6 weeks of stimulation (pretreatment), directly after this period (post treatment), and following another period of 6 weeks without stimulation (delayed). The pretreatment scores were submitted to t tests to verify that no difference existed between the two groups at the start of the experiment.

To calculate a possible treatment effect of RMNS on cognitive functioning, the pretreatment scores were subtracted from the post-treatment scores of both the experimental and the control group (difference scores). To evaluate whether possible treatment effects remained or disappeared after cessation of stimulation, the scores obtained after the treatment-free period (delayed scores) were subtracted from the post-treatment scores (difference scores) in both groups. Independent-sample t tests for the main effect of treatment were performed on these difference scores. A confidence coefficient of 95% was used for confidence interval (CI). A Bonferroni correction was applied to the significance level of $p < .05$, resulting in a critical value of $p < .006$. When a significant difference between both groups after treatment failed, but the mean post-treatment scores were in the expected direction, i.e., a higher mean score in the experimental group and a hardly unchanged or a lower mean score in the control group, the number of patients necessary to reach the level of significance was calculated by means of a power analysis (PASS; NCSS Statistical Software, Kaysville, UT). The SPSS-PC program (Norusis, 1992) was used to analyze the data.

RESULTS

Demographic Characteristics

The experimental group and the control group did not differ significantly in age ($t(15) = 0.17$; $p = .87$), education ($t(15) = 0.44$; $p = .67$), and level of cognitive functioning measured by the MMSE ($t(15) = 0.31$; $p = .76$). Details on demographic variables and MMSE scores are presented in Table 1.

Treatment Effects

The test scores showed a normal pattern of distribution, and no outliers were found in the sample. The results of the t tests on the pretreatment scores showed no significant differences between the experimental and control group (for means, standard deviations, and t tests, see Table 2).

Table 1. Demographic characteristics of the subject sample

	Experimental group ($n = 8$)		Control group ($n = 9$)	
	2/6		2/7	
Male/female ratio	Mean	*SD*	Mean	*SD*
Age (range)	85.00 (76–92)	6.21	85.44 (77–90)	4.77
Education	3.25	.71	3.11	0.60
MMSE (range)	19.50 (12–24)	4.18	18.89 (12–25)	4.95

Note. MMSE: Mini-Mental State Examination.

Analyses of treatment efficacy by applying independent t tests to the difference scores of post-treatment minus pretreatment scores and post-treatment minus delayed treatment scores of both the experimental and control group are presented in Tables 3 and 4. Compared to sham stimulation, RMNS did not significantly improve the performance on the various memory tests.

Of note is that the mean (difference) scores in Tables 3 and 4, respectively, show that the performance on only two tests, i.e., the CVLT Immediate Recall and Word Fluency were in the expected direction (see Data Analyses). For the two tests to reach a level of significance, a power analyses with $\beta = .80$ and $\alpha = .006$ revealed that 21 and 155 patients, respectively, should be included in each group (Table 3). With respect to the other tests, patients of the experimental group showed a *lower* performance on Digit Span Total score, CVLT Delayed and Recognition, and Face Recognition after treatment. On two tests, i.e., Visual Memory Span Total score and CVLT Recognition, the mean scores of the control group were even higher compared to the mean scores of the experimental group.

DISCUSSION

The results of the present study show that right median nerve stimulation (RMNS) did not improve the various aspects of memory in AD patients. Compared to the mean pretreatment scores, only the mean post-treatment scores on the CVLT Immediate Recall and Word Fluency were higher in the experimental group and remained level in the control group (Tables 3 and 4). A power analysis showed that for the two tests to become statistically significant, each group should include 21 and 155 patients, respectively. Although in the

Table 2. Means and standard deviations (*SD*) of the scores on the various neuropsychological tests at three moments of measurement: pretreatment (Pre), post treatment (Post), and after 6 weeks without treatment (Del)

	Experimental group						Control group						*t* tests[a]		Reference	
	Pre		Post		Del		Pre		Post		Del		Pre		MCI*	
Neuropsychological Tests	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	*t*(15)	*p*	Mean	*SD*
Digit Span Total Score	8.88	4.22	8.75	3.28	8.88	4.09	8.11	2.52	8.89	3.10	9.35	2.40	.46	.65	10.30	2.92
Visual Memory Span Total Score	9.25	3.19	10.13	3.18	9.38	2.83	8.00	3.12	10.11	2.67	8.67	1.50	.82	.43	10.98	2.95
CVLT Immediate Recall	18.13	6.75	21.50	7.37	20.63	7.15	16.89	7.57	16.44	6.00	18.38	6.58	.35	.73	33.16	14.31
CVLT Delayed Recall	.38	.74	.13	.35	.25	.46	.00	.00	.00	.00	.13	.33	1.52	.15	5.14	4.85
CVLT Recognition	18.75	12.56	18.50	6.48	11.25	12.14	15.33	9.11	17.33	10.86	15.26	11.28	.65	.53	34.52	9.41
Face Recognition	11.75	4.20	9.50	7.15	10.00	6.93	8.67	7.14	6.22	6.36	8.25	5.80	1.06	.30	12.63	5.74
Picture Recognition	23.25	8.75	25.50	14.99	28.45	12.52	14.67	12.57	16.00	12.77	19.29	13.32	1.61	.13	35.16	7.93
Word Fluency	14.75	8.33	15.88	9.05	16.25	9.30	15.10	7.39	14.81	8.95	17.54	6.45	.09	.93	22.86	9.41

Note. CVLT: California Verbal Learning Test.

[a] *t* tests for possible differences in pretreatment scores (pre) between the experimental and control groups.

*Scores of patients with Mild Cognitive Impairment (MCI) on the various neuropsychological tests are provided as a reference (Scherder et al., 2005).

Table 3. ***t*** **tests on the post-treatment (Post) minus pretreatment (Pre) scores (difference scores) of the neuropsychological tests of the experimental (Exp) and control (Co) groups**

Neuropsychological tests	Group	Post minus Pre: difference scores			*t* tests			
		M	*SE*	95%CI	*t*	*df*	*p*	N^*
Digit Span Total score	Exp	−.13	.64	−1.64–1.38	.79	15	.44	
	Co	.78	.91	−1.32–2.87				
Vis. Mem. Span Total score	Exp	.88	.30	−1.59– − .17	1.20	15	.25	
	Co	2.11	.94	−.06–4.28				
CVLT Immediate Recall	Exp	3.37	1.46	−.07–6.83	2.16	15	.054	21
	Co	−.45	1.04	−3.28–2.40				21
CVLT Delayed Recall	Exp	−.25	.16	−.63–2.12	1.63	15	.13	
	Co	.00	.00					
CVLT Recognition	Exp	−.25	2.71	−6.66–6.16	.55	15	.59	
	Co	2.00	3.04	−5.01–9.01				
Face Recognition	Exp	−2.25	2.84	−8.97–4.47	.05	15	.96	
	Co	−2.44	2.82	−8.94–4.06				
Picture Recognition	Exp	2.25	2.79	−4.35–8.85	.23	15	.92	
	Co	1.33	2.73	−4.97–7.63				
Word Fluency	Exp	1.13	1.34	−2.04–4.30	.78	15	.45	155
	Co	−.29	1.22	−3.10–2.52				155

Note. CVLT: California Verbal Learning Test.

N^* = Number of patients necessary to reach the level of significance: $p < .006$; only calculated for those tests of which the post-treatment scores were in the expected direction, i.e., a higher mean score in the experimental group and an unchanged or lower score in the control group.

present study the inclusion of a homogeneous group of seventeen AD patients took about 2 years, a number of 21 patients in each group (42 in total) would still be feasible. However, a statistically significant effect on CVLT Immediate Recall—an episodic memory test—does not automatically mean a *clinical relevant* effect. In previous studies, in which statistically significant effects were observed for tests appealing to episodic memory, patients did not show a 'clinical' improvement (Scherder et al., 1995, 1998; Scherder & Bouma, 1999). A possible clinical effect of RMNS on episodic memory in case of a larger sample size is further weakened by the finding that after 6 weeks of treatment the experimental group showed *lower* scores on other episodic memory tests: the subtests Delayed Recall and Recognition of the CVLT and Face Recognition. The improved performance on the episodic memory test Picture Recognition has been observed in both the experimental and control group and can therefore not be ascribed to RMNS.

Table 4. ***t*** **tests on the post-treatment scores (Post) minus delayed scores (Delayed) (difference scores) of the neuropsychological tests of the experimental (Exp) and control (Co) groups**

		Post minus Delayed: difference scores			*t* tests		
Neuropsychological tests	Group	*M*	*SE*	95%CI	*t*	*df*	*p*
Digit Span Total score	Exp	– .13	.55	– 1.43–1.17	.32	15	.75
	Co	– .46	.85	– 2.42–1.50			
Visual Memory Span Total score	Exp	.75	.45	– .31–1.81	.86	15	.41
	Co	1.44	.65	– .06–2.94			
CVLT Immediate Recall	Exp	.88	1.39	– 2.41–4.17	1.45	15	.17
	Co	– 1.94	1.34	– 5.03–1.15			
CVLT Delayed Recall	Exp	– .13	.23	– .67– – .41	.03	15	.59
	Co	– .13	.11	– .38– – .12			
CVLT Recognition	Exp	7.25	4.73	– 3.94–18.44	1.06	15	.30
	Co	2.07	1.87	– 2.35–6.49			
Face Recognition	Exp	– .50	1.30	– 3.57–3.57	.51	15	.62
	Co	– 2.13	2.78	– 8.70–4.44			
Picture Recognition	Exp	– 2.95	2.30	– 8.39–2.49	.09	15	.93
	Co	– 3.29	2.84	– 9.84–3.26			
Word Fluency	Exp	– .38	1.10	– 2.98–2.22	1.06	15	.31
	Co	– 2.73	1.84	– 6.97–1.51			

Note. CVLT: California Verbal Learning Test.

In order to obtain a statistically significant effect of RMNS on Word Fluency, a homogeneous group of 310 AD patients should participate. To include such a large number of patients is not realistic. Moreover, similar to an improvement in episodic memory tests, a statistically significant higher score on Word Fluency alone does not imply an observable clinical improvement of patient's cognitive functioning (Scherder et al., 1998).

Because this is the first study on RMNS in AD, effect sizes, and consequently, the number of patients that should participate, could not be estimated before the start of the study. In our opinion, a pilot study on a new type of intervention that is very time-consuming and therefore costly requires an evaluation of the direction of the scores in each group, after an initial phase with a feasible number of patients. The present data show that in this group of AD patients clinically relevant effects will not be obtained with this RMNS procedure. Therefore, we feel it is justified to discontinue the present study of RMNS as a treatment of memory in AD patients and make suggestions about modifications of stimulation-parameters that might result in more profound cognitive improvements.

One suggestion for a more effective RMNS treatment concerns the duration of the treatment period. For the sake of comparability, the study design of the present study and of the TENS studies (Scherder et al., 1995, 1998; Scherder & Bouma, 1999) was exactly the same: stimulation took place for 30 min each day, 5 days a week, during a period of 6 weeks. However, studies examining other types of non-pharmacological interventions such as daily physical activity observed some cognitive improvement in patients with dementia after 6 weeks but more pronounced after 12 weeks of treatment (Van de Winckel, Feys, de Weerdt, & Dom, 2004). In a recent review on the effects of fitness on cognitive functioning of elderly people, long-term training programs (>6 months) were more effective than programs of shorter duration (Colcombe & Kramer, 2003). Considering the possible clinical importance of RMNS in dementia, e.g., easy to apply and little side effects, it is suggested that a study with a much longer treatment period is required before definite conclusions about the ineffectiveness of RMNS in AD can be drawn.

REFERENCES

Colcombe, S. & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults. A meta-analytic study. *Psychological Science*, *14*, **125–130.**

Cooper, E. B. & Cooper, J. B. (2003). Electrical treatment of coma via the median nerve. *Acta Neurochirurgica*, *87(Suppl)*, **7–10.**

Cooper, E. B., Scherder, E. J. A., & Cooper, J. B. (2005). Electrical treatment of reduced consciousness: Experience with coma and Alzheimer's disease. *Neuropsychological Rehabilitation*, *15*, **389–405.**

Cooper, J. B., Jane, J. A., Alves, W. M., & Cooper, E. B. (1999). Right median nerve electrical stimulation to hasten awakening from coma. *Brain Injury*, *13*, **261–267.**

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). *California verbal learning test, research edition*. **New York: Psychological Corporation Harcourt Brace Jovanovich.**

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*, **189–198.**

Kayama, Y. & Koyama, Y. (1999). Brain stem neural mechanisms of sleep and wakefulness. *European Urology*, *33*, **12–15.**

Liu, J. T., Wang, C. H., Chou, I. C., Sun, S. S., Koa, C. H., & Cooper, E. (2003). Regaining consciousness for prolonged comatose patients with right median nerve stimulation. *Acta Neurochirurgica*, *87(Suppl)*, **11–14.**

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Reports of the NINCDS-ADRDA work-group under the auspices of the department of health and human services task force on alzheimer's disease. *Neurology*, *34*, **939–944.**

Norusis, M. J. (1992). *Statistical packages for the social sciences*, SPSS/PC+. New York: McGraw-Hill.

Peri, C. V., Shaffrey, M. E., Farace, E., Cooper, E., Alves, W. M., Cooper, J. B., Young, J. S., & Jane, J. A. (2001). Pilot study of electrical stimulation on median nerve in comatose severe brain injured patients: 3-month outcome. *Brain Injury*, *15*, 903–910.

Reisberg, B., Ferris, S. H., De Leon, M. J., & Crook, T. (1982). The global deterioration scale for assessment of primary dementia. *American Journal of Psychiatry*, *139*, 1136–1139.

Scherder, E. J. A. & Bouma, A. (1999). Effects of transcutaneous electrical nerve stimulation on memory and behavior in alzheimer's disease may be stage-dependent. *Biological Psychiatry*, *45*, 743–749.

Scherder, E. J. A., Bouma, A., & Steen, A. M. (1995). Effects of short-term transcutaneous electrical nerve stimulation on memory and affective behaviour in patients with probable Alzheimer's disease. *Behavioural Brain Research*, *67*, 211–219.

Scherder, E. J. A., Bouma, A., & Steen, L. M. (1998). Effects of 'isolated' transcutaneous electrical nerve stimulation on memory and affective behavior in patients with probable alzheimer's disease. *Biological Psychiatry*, *43*, 417–424.

Scherder, E. J., Van Paasschen, J., Deijen, J. B., Van der Knokke, S., Orlebeke, J. F., Burgers, I., Devriese, P. P., Swaab, D. F., & Sergeant, J. A. (2005). Physical activity and executive functions in the elderly with mild cognitive impairment. *Aging and Mental Health*, *9*, 272–280.

Snijders, J. T. & Verhage, F. (1983). *Groninger intelligentie test*. Lisse: Swets & Zeitlinger.

Van Dijk, K. R. A., Scheltens, P., Luijpen, M. W., Sergeant, J. A., & Scherder, E. J. (2005). Peripheral electrical stimulation in Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *19*, 361–368.

Van de Winckel, A., Feys, H., de Weerdt, W., & Dom, R. (2004). Cognitive and behavioral effects of music-based exercises in patients with dementia. *Clinical Rehabilitation*, *18*, 253–260.

Wechsler, D. (1987). *Wechsler memory scale—revised*. New York: The Psychological Corporation.

Wilson, B., Cockburn, J., & Baddeley, A. (1987). *The rivermead behavioural memory test*. Titchfield, UK: Thames Valley Test Company.