Effects of "Isolated" Transcutaneous Electrical Nerve Stimulation on Memory and Affective Behavior in Patients with Probable Alzheimer's Disease

Erik J.A. Scherder, Anke Bouma, and Louis M. Steen

Background: *In previous studies, transcutaneous electrical nerve stimulation (TENS), tactile stimulation, and a combination of the two resulted in cognitive and affective improvements in patients with Alzheimer's disease (AD). As in those studies the therapist was present during the treatment of the experimental and control group (sham stimulation), a positive effect of the combination of TENS with interpersonal communication could not be excluded. Therefore, the effects of "isolated" TENS, i.e., in the absence of the therapist, on memory and affective disturbances in AD patients were examined.*

Methods: *Eighteen subjects (78–92 years old) met the NINCDS-ADRDA criteria for the clinical diagnosis of probable AD. To evaluate treatment effects, the experimental group (9) and the control group (9) underwent a number of neuropsychological tests and two observation scales.*

Results: *Treatment effects were observed for nonverbal short-term (Visual Memory) and long-term (Face Recognition) memory, word fluency (Verbal Fluency), and need of help, whereas patients' affective behavior did not improve.*

Conclusions: *The results of the present study show that isolated TENS has a positive effect on patients' cognitive and independent functioning; however, isolated TENS appeared not to have a therapeutic effect on patients' affective behavior.* Biol Psychiatry 1998;43:417–424

Key Words: TENS, Memory, Affective Behavior, Alzheimer's Disease

Introduction

In a series of studies, patients in an early stage of Alzheimer's disease (AD) were treated with transcutaneous electrical nerve stimulation (long-term and short-term TENS), tactile nerve stimulation, and a combination of the two for 5 days a week during a 6-week period (Scherder et al 1992, 1995a, 1995b, 1995c, 1995d, in press). Compared to the patients of the control group who received sham stimulation (placebo), AD patients of the experimental group improved in visual short-term and long-term memory, verbal long-term memory, and word fluency. Moreover, stimulated AD patients participated more independently in activities of daily living, were looking more for social contacts, and felt less withdrawn, irritable, moody, dejected, and gloomy.

The rationale underlying these studies was that peripheral nerve stimulation, mediated through the somatosensory system, might activate e.g. the hippocampus and hypothalamus, which are involved in memory processes and affective behavior, respectively (Salzmann 1992; Carpenter and Grossberg 1993; Raadsheer et al 1995), and are affected in AD (Scheltens et al 1992; Swaab et al 1992). The assumption that these structures would be stimulated by peripheral nerve stimulation was based upon animal experimental studies that observed an increase in activity of the hippocampus, including a release of acetylcholine, and the hypothalamus (Huan-Ji and Yan-Fang 1976; Dutar et al 1985). The increase in activity of the hippocampus and hypothalamus by peripheral nerve stimulation is possibly mediated through the locus coeruleus and nucleus raphe dorsalis (Huan-Ji and Yan-Fang 1976; Dutar et al 1985). It is known that the locus coeruleus and nucleus raphe dorsalis, origins of the noradrenergic and serotonergic neurotransmitter systems, respectively (Rossor 1988), project to the hippocampus and hypothalamus (Bobillier et al 1976; Legoratti-Sanchez et al 1989; Vertes 1991; Petrov et al 1992). Moreover, both brain stem nuclei are affected in AD (Rossor 1988). Interestingly, also other studies confirm that neuronal stimulation might in general result in functionally relevant effects in AD (for review, see Swaab 1991). In a recent study, transcranial electrostimulation in elderly patients with multi-infarct dementia was also found to be effective in decreasing wandering and nocturnal delirium and increasing patients' interaction with others (Hozumi et al 1996). In explaining these

From the Department of Clinical Psychology, Vrije Universiteit, Amsterdam, The Netherlands (EJAS, AB); and Centre of Informatics, Universiteit van Amsterdam, Amsterdam, The Netherlands (LMS).

Address reprint requests to Dr E.J.A. Scherder, Department of Clinical Psychology, Vrije Universiteit, De Boelelaan 1109, 1081 HV Amsterdam, The Netherlands.

Received August 6, 1996; revised December 2, 1996; revised February 17, 1997; accepted February 25, 1997.

0006-3223/98/$19.00
PII S0006-3223(97)00208-4

findings, the authors suggest a possible role of the somatosensory system in mediating transcranial electrostimulation. In several other studies, application of bright light, mediated through the visual sensory system, activated the hypothalamus of AD patients, resulting in a decrease in agitation, wandering, and delirium (Okawa et al 1991; Satlin et al 1992; Lovell et al 1995).

In the former studies concerning peripheral nerve stimulation in AD (Scherder et al 1992, 1995a, 1995b, 1995c, 1995d, in press), the therapist was present during both the peripheral nerve stimulation of the experimental group and the sham stimulation of the control group. Hence, although interpersonal communication might be considered as a possible way of stimulation (Karlsson et al 1985; Widerlöv et al 1989), it cannot explain the treatment effects; however, a positive effect of the combination of TENS with interpersonal communication could not be excluded. Therefore, in the present study, we examined the effects of "isolated" TENS, i.e., in the absence of the therapist, on memory and affective disturbances in AD patients.

Methods and Materials

Subjects

The sample consisted of 18 subjects, drawn from a larger sample of 500 elderly persons who lived in a residential home for elderly people. The subjects ranged in age from 78 to 92 years, with a mean age of 83.4 years. Level of cognitive functioning was assessed by using a Dutch cognitive screening test (CST) (de Graaf and Deelman 1991), a modified version of the Short Portable Mental Questionnaire of Pfeiffer (Pfeiffer 1975). The CST consists of 20 items evaluating recent and remote memory, personal orientation, and orientation to time and place. Subjects with a score of 12 or less were classified as having a cognitive decline (maximum total score = 20). The mean score of the CST of our sample was 10.4, ranging from 8 to 13, suggesting that the subjects were in a relatively early stage of AD. All subjects had completed elementary school. After this first global screening, the subjects and their family were informed extensively about the aim and procedure of this investigation. After their consent, we continued with the screening procedure.

All subjects met the NINCDS-ADRDA criteria for the clinical diagnosis of probable Alzheimer's disease (McKhann et al 1984). The clinical symptoms of the dementia were present for at least 6 months. In addition, a score of 17 or less on the Hamilton Depression Rating Scale (Hamilton 1960) was considered to indicate that the cognitive decline of the subject was not due to depression. The mean score on the Hamilton Depression Rating Scale of our sample was 5.9.

Subjects were excluded from participation in this study if they had a history of psychiatric disorder, alcoholism, cerebral trauma, cerebrovascular disease, hydrocephalus, neoplasm, epilepsy, disturbances of consciousness, or focal brain disorders. The subjects' drug use had not changed during the 3 months preceding treatment. None of the subjects had a pacemaker.

After this screening procedure, the subjects were randomly assigned to the experimental (n = 9) and control group (n = 9), but they were not told to which group they belonged. The subjects in the two groups appeared to match for age and performance on the CST. To examine whether the provided information had been understood correctly, a trial treatment was applied to both the experimental and the control group. The subjects of the experimental group were familiarized with the electrostimulation method by applying a trial treatment, during which they could experience the electrical stimulus. The subjects of the control group were familiarized with a sham electrostimulator, i.e., during the trial treatment no electrical current was applied (placebo). During the trial treatment of both the experimental and the control group no negative reactions of the subjects were observed. The subjects and their family subsequently gave their final informed consent. The family, who also did not know in which group their relative participated, was weekly contacted only to detect possible disturbances in patients' life by our daily visits.

Neuropsychological Tests

The 18 subjects underwent a number of neuropsychological tests to evaluate the effects of treatment on various aspects of memory, including verbal and visual short-term and long-term memory, and semantic memory. The test battery consisted of the following tasks:

Digit Span from the Wechsler Memory Scale–Revised (WMS-R) (Wechsler 1984) was used to assess patients' verbal short-term memory abilities.

Visual Memory Span from the WMS-R (Wechsler 1984) can be considered as a nonverbal equivalent of the Digit Span test.

The 8 Words Test (Lindeboom and Jonker 1989) was used as a measure of auditory, verbal long-term memory. This task provides measures of Immediate Recall, Delayed Recall, and Recognition.

Face Recognition from the Rivermead Behavioural Memory Test (RBMT) provides a measure of visual, nonverbal long-term memory (Wilson et al 1987).

Picture Recognition from the RBMT provides a measure of visual, verbal long-term memory (Wilson et al 1987).

Word Fluency from the Groninger Intelligence Test, a Dutch intelligence test (Snijders and Verhage 1983), measures the ability of subjects to retrieve familiar information from semantic memory by asking them to name as many animals and occupations as possible, each during 1 min.

All subjects did these tests the day before (pretreatment test scores) and the day after a period of 6 weeks (posttreatment test scores) during which the experimental and placebo treatments were applied. In addition, a follow-up measurement was performed 6 weeks after the experimental and placebo treatment had ended (delayed test scores).

The tests were administered by an independent investigator who was not informed about which subjects belonged to the experimental or the control group. The tests were given in the

following order: Digit Span, Visual Memory Span, 8 Words Test (Immediate Recall), Face Recognition (stimulus presentation), Word Fluency (names of animals), Face Recognition (response), Picture Recognition (stimulus presentation), Word Fluency (names of occupations), Picture Recognition (response), 8 Words Test (Delayed Recall and Recognition).

Observation Scales

All subjects were evaluated on the basis of two observation scales to evaluate the effects of treatment on various aspects of affective behavior.

One observation scale was a standard factor-analyzed rating scale for elderly patients (Beoordelingsschaal voor Oudere Patiënten: BOP) (Van der Kam et al 1971), a revision of the Stockton Geriatric Rating Scale (Meer and Baker 1966). The scale has been divided into six subscales, i.e., Need of Help (BOP1; 23 items); Aggressiveness (BOP2; 5 items); Physical Invalidity (BOP3A; 3 items); Depressed Behavior (BOP3B; 3 items); Mental Invalidity (BOP3C; 4 items); and Inactivity (BOP4; 7 items). The administration of the BOP subscales took place a day before (pretreatment test scores) and a day after a treatment period of 6 weeks (posttreatment test scores), and again after a 6-week period without treatment (delayed test scores).

The other observation scale was a Behavior Inventory, constructed by the authors. This inventory includes 12 main traits, i.e., depression, elation, shyness, mood, anger, tiredness, activity, anxiety, conscience, indifference, cognition, and contact. Each item was measured on a five-point rating scale, ranging from −2 to +2. A score of −2 meant that, in comparison with 6 weeks ago, a particular item was applicable to the patient to a much lesser extent; a score of +2 indicated the opposite. Scores in between implied a moderate change or no change (score of zero). This inventory was administered twice. The first administration occurred 6 weeks after the experimental and placebo treatments were applied, the second evaluation took place following a 6-week period without treatment.

All subjects were evaluated by a nursing staff consisting of 10 nurses, trained to observe patients' behavior. They did not know whether the subjects belonged to the experimental or the control group. The nursing staff filled in the two inventories together, which resulted in a joint judgment.

Stimulation

Activation of the hippocampus and hypothalamus via the locus coeruleus and nucleus raphe dorsalis by TENS is supposed to be mediated by afferent nerve fibers, i.e., thickly myelinated A-beta fibers, thinly myelinated A-delta fibers, and unmyelinated C fibers (Howson 1978; Coffey and Mahon 1982). The selection of stimulation parameters under which these three types of afferent nerve fibers in AD patients could be optimally stimulated was based upon animal studies dealing with analgesia. Because peripheral tactile and electrical stimulation seems to activate the same afferent nerve fibers (Guieu et al 1990), animal studies dealing with analgesia by either type of stimulation seem to be suitable for providing the parameters for location, intensity, and duration of the stimulation.

FREQUENCY AND INTENSITY. A-beta fibers respond very well to high-frequency stimulation, e.g., 100 Hz with an intensity just above threshold (Omura 1987; Guieu et al 1990). In another study, A-beta fibers appeared to respond also to low-frequency stimulation (2 Hz), however, with an intensity that triggered visible muscular twitches (Jorum and Shyu 1988). Activation of A-delta and C fibers is usually caused by low-frequency stimulation (less than 10 Hz) with an intensity well above threshold (Pauser 1980; Jones and Gebhart 1987), triggering strong muscular contractions (Duranti et al 1988).

To activate all three types of afferent nerve fibers, high-frequency and low-frequency stimulation had to be combined in one treatment. For this purpose, patients of the experimental group were treated with an electrostimulator, type Premier 10 s. This stimulator generates transcutaneous electrostimulation, which consists of asymmetric biphasic square impulses, applied in bursts of trains, nine pulses per train, with an internal frequency of 160 Hz, a repetition rate of 2 Hz, and a pulse width of 100 μsec. This type of TENS is known as BURST-TENS (Eriksson et al 1979). The intensity of the stimulation triggered visible muscular twitches which, as appeared by means of feedback from the patients, were painless. A flickering green light placed on the electrostimulator indicated stimulation.

The same electrostimulator was applied to patients of the control group; however, for sham stimulation no current was administered to the patients. The patients were told that the stimulator gave off signals which they could not feel, and that the stimulation began at the moment a green light started to flicker on the apparatus.

LOCATION. The patients of the experimental group were sitting in a chair. Two 2 × 3 cm (height × width) standard carbon rubber electrodes with gel were fixed on the patients' back with tape between Th1 and Th5, each on one side of the spinal column, 2 cm from the diameter. Because asymmetric biphasic impulses were used, one electrode had a negative pole, the other a positive one. To divide the possible effect of BURST-TENS equally over both sides of the spinal column, the poles were switched every day. The same procedure took place for the control group.

ABSENCE OF THERAPIST. The therapist went out after application of the stimulator and only returned a few times just to check whether the treatment progressed as planned.

DURATION. Studies concerning analgesia indicate that a peripheral stimulation time of 20–30 min per treatment is necessary to provide analgesia (Wolf et al 1981; Robaina et al 1989). To evaluate the analgesic effect of peripheral stimulation and to maintain the acquired relief from pain, these studies report a total duration of a treatment period of at least 4 weeks (Frampton 1982). Based on these data, in the present study a 30-min-a-day treatment of TENS and of sham electrostimulation was applied to the experimental and control group, respectively, for 5 days a week, during a 6-week period.

Data Analyses

NEUROPSYCHOLOGICAL TESTS. The pretreatment scores were submitted to a multivariate analysis of variance (MANOVA) to verify that no difference existed between the two groups at the start of the experiment.

Cognitive testing took place immediately before the 6 weeks of stimulation (pretreatment, T1), after this period (posttreatment, T2), and following another period of 6 weeks without stimulation (delayed, T3). There are two important questions of investigation in this study: 1) Does stimulation improve memory functions more in the experimental group than in the placebo group? To answer this question, an analysis of the test scores from T1 and T2 (pre/post) is required. 2) Do effects, if any, last over a period of 6 weeks without further stimulation? To answer this question we compared T1 and T3 (pre/delayed).

For the first question of investigation, an one-factor analysis of covariance (ANCOVA) was applied for each neuropsychological test, with the posttreatment scores (T2) as dependent variable and the pretreatment scores (T1) as covariate. For the second question also, an ANCOVA was used for each test, with the delayed scores (T3) as dependent variable and the pretreatment scores (T1) as covariate. The data were analyzed by means of the SPSS-PC program (Norusis 1988).

OBSERVATION SCALES. The BOP scale has been constructed primarily to evaluate patient's behavior on *fixed* moments, in the present study the day before (pretreatment scores, T1) and the day after the treatment period of 6 weeks (posttreatment scores, T2). The difference between the two measurements T1 and T2 might indicate a change in the patient's behavior. The Behavior Inventory, however, is primarily aimed at recording a possible change in affective behavior, rendering pretreatment scores superfluous. Consequently, the first evaluation took place after the 6-week treatment period (posttreatment scores, T2). To investigate whether treatment improved overall affective behavior, a total score of changes was calculated by summing up the recoded scores of all items employed in the Behavior Inventory. To evaluate whether the treatment effects could be maintained over a 6-week period without treatment (delayed scores, T3), a comparison with the pretreatment situation is necessary. Therefore, an overall effect score was calculated by adding up the posttreatment scores (T2) and the delayed scores (T3). For example, a posttreatment score of +2 and a delayed score of 0 leads to an overall effect score of +2. This score would mean that the treatment effect observed during the treatment period could be maintained during the no-treatment period. The SPSS-PC program was used for statistical analyses, including ANCOVAs and t tests (Norusis 1988). A p value of $< .05$ was considered to be significant.

Results

Neuropsychological Tests

The test scores showed a normal pattern of distribution, and no outliers were found in the sample. The results of the MANOVA on the pretreatment scores showed no significant differences between the experimental and placebo groups on any of the pretreatment scores. This finding was confirmed by univariate analyses.

For the experimental as well as for the control group, the pretreatment, posttreatment, and delayed test scores (means and standard deviations) on the various neuropsychological tests as well as the ANCOVAs are presented in Table 1.

The results of the pre–post (T1–T2) analyses revealed significant treatment effects for Visual Memory, Face Recognition, and Verbal Fluency. The treatment effect on Picture Recognition tended to be significant. The results showed that after treatment the experimental group performed better or slightly better on all four of these tasks, whereas the control group declined in performance (Visual Memory, Face Recognition, and Verbal Fluency) or showed a lesser improvement (Picture Recognition). No treatment effects were found on the Digit Span test and the Immediate Recall and Delayed Recall subtests of the 8 Words Test. The results of the pre–delayed (T1–T3) analyses revealed that the treatment effects could still be observed over a period of 6 weeks without treatment for Visual Memory and Verbal Fluency. On both tasks, the experimental group performed slightly better after the treatment-free period than before the treatment period. The control group remained level for Visual Memory and declined in Verbal Fluency during this period.

Observation Scales

Directly after the treatment period of 6 weeks, 1 patient of the experimental group died. The administration of the neuropsychological tests had just finished, but in the circumstances, the nursing staff was not able to fill in the two observation scales for this patient (Table 1).

BOP SUBSCALES. For the experimental group as well as for the control group, the pretreatment, posttreatment, and delayed scores (means and standard deviations) on the BOP subscales as well as the ANCOVAs are presented in Table 1. The pretreatment scores on the BOP subscales revealed no significant differences between the two groups as indicated by t tests.

Treatment effects were examined by means of a one-factor ANCOVA, separately for each test, with the posttreatment scores (T2) as dependent variable and the pretreatment scores (T1) as covariate (see Table 1). A significant treatment effect was observed for Need of Help (BOP1), indicating that the experimental group improved, whereas the control group declined. No treatment effects were found for the other five subscales. The results of the pre-delayed analyses (T1-T3) showed that the observed

Table 1. Means, Standard Deviations (SD), and Analyses of Covariance (ANCOVAs) of the Neuropsychological Tests and BOP Subscales, and Means, SD, and *t* Tests of the Behavior Inventory (Overall Affective Behavior)

	Experimental group						Control group									
	Pre (n = 9)		Post (n = 9)		Del (n = 8)		Pre (n = 9)		Post (n = 9)		Del (n = 9)		ANCOVA post		ANCOVA delayed	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	$F(1,15)$	$p <$	$F(1,14)$	$p <$
Tests																
Digit Span	5.06	2.02	5.28	1.62	4.25	2.17	4.22	0.79	4.00	0.94	4.11	1.19	2.67	.13	0.64	.44
Visual Memory	4.28	2.03	5.17	2.03	4.63	2.55	4.94	1.26	4.39	0.99	4.39	.96	13.70	.002	4.82	.05
8 Words Test																
Immediate Recall	0.22	0.83	0.89	0.93	0.50	1.69	−0.33	1.22	0.22	1.09	0.00	1.12	0.60	.46	0.00	.96
Delayed Recall	0.00	0.00	0.67	1.00	0.50	0.76	0.11	0.33	0.11	0.33	0.33	.71	2.10	.17	0.11	.75
Recognition	6.00	6.16	7.78	5.52	7.50	6.39	6.67	4.36	5.33	4.00	8.00	4.12	1.98	.18	0.05	.84
Face Recognition	7.78	1.56	8.00	2.00	6.00	4.78	7.56	2.60	4.89	3.48	5.78	2.73	5.26	.04	0.02	.91
Picture Recognition	14.44	6.06	17.56	3.43	14.75	7.09	12.89	5.67	14.22	3.93	12.22	6.67	3.58	.08	0.48	.50
Verbal Fluency	2.06	1.91	2.61	2.01	2.19	2.10	2.06	1.24	1.61	1.36	1.28	1.30	6.26	.03	6.61	.03

	Pre (n = 8)		Post (n = 8)		Del (n = 8)		Pre (n = 9)		Post (n = 9)		Del (n = 9)		ANCOVA post		ANCOVA delayed	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	$F(1,14)$	$p <$	$F(1,14)$	$p <$
BOP subscales																
Need of Help	13.63	6.16	12.50	5.45	12.38	5.66	11.89	7.37	15.56	8.08	13.56	9.58	5.31	.04	2.17	.17
Aggressiveness	2.38	2.26	2.13	1.81	2.25	1.98	2.78	1.86	2.33	2.12	2.11	1.62	0.00	.98	0.19	.67
Physical Invalidity	1.75	0.89	1.88	0.83	1.88	0.83	2.00	1.12	1.89	1.45	2.00	1.41	0.04	.85	0.00	1.00
Depressed Behavior	3.12	1.89	2.63	0.74	2.88	1.73	2.00	1.32	2.67	1.32	3.22	1.79	1.05	.33	3.00	.11
Mental Invalidity	1.75	2.12	1.63	1.77	1.63	1.85	2.00	0.87	2.56	1.42	2.33	1.32	2.08	.18	1.22	.31
Inactivity	8.63	2.20	7.38	3.93	7.75	2.55	6.22	2.68	7.78	3.23	7.22	3.73	1.27	.28	1.82	.20

	Post (n = 8)		Del (n = 8)		Post (n = 9)		Del (n = 9)		t test post		t test delayed	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	$t(15)$	$p <$	$t(15)$	$p <$
Behavior inventory												
Overall affective behavior	0.37	19.24	−8.50	27.58	−5.56	10.08	−16.56	21.82	0.71	.49	0.67	.52

Del, delayed scores.

treatment effects did not persist in the period without treatment.

BEHAVIOR INVENTORY. For the experimental group as well as for the control group, the posttreatment and delayed scores (means and standard deviations) on the Behavior Inventory are presented in Table 1.

The effect of treatment was analyzed by administering the Behavior Inventory after the treatment period of 6 weeks (posttreatment scores, T2). The total score of changes (overall affective behavior) appeared not to be significant. Each main trait was analyzed by summing up the recoded scores of all items belonging to that particular trait. The results showed no significant treatment effects for the main traits. The overall effect score (T3) revealed no significant difference between the experimental and control group as indicated by a *t* test, nor did the main traits reveal significant effects between the two groups.

Discussion

The results of the present study show that TENS, in the absence of the therapist, has a positive effect on nonverbal short-term memory (Visual Memory) and nonverbal long-term recognition memory (Face and Picture Recognition) as well as on word fluency (Verbal Fluency). Besides its effect on memory, the present findings also suggest that TENS has a beneficial influence on patients' independent participation in activities of daily life (Need of Help, BOP1); however, TENS appeared not to have a therapeutic effect on patients' affective behavior (overall affective behavior, Behavior Inventory). The results further indicate that the treatment effects, although declining, could still be observed after a period of 6 weeks without treatment for the neuropsychological tests Visual Memory and Verbal Fluency.

It is interesting to compare the present findings with

those of a previous TENS study in which the therapist was present during treatment (Scherder et al 1995b). In both studies, treatment effects were observed for visual short-term memory (Visual Memory) and visual long-term memory (Face and Picture Recognition). Furthermore, a treatment effect was observed for the patients' verbal long-term memory (Recognition subtest of the 8 Words Test) if the therapist was present, and for the patients' word fluency (Verbal Fluency) if the therapist was absent. With respect to the observation scales, the results of both studies revealed that stimulated patients participated more independently in activities of daily life (BOP1). In contrast, only patients who were treated in the presence of the therapist acquired more physical skills (BOP3A) and were looking for more social contacts (BOP4). They also showed an improvement in overall affective behavior (Behavior Inventory), indicating that they felt less depressed (Depression), more cheerful (Elation), less irritable and moody (Mood), and less withdrawn (Shyness). They also showed more initiative and interest in daily life (Activity), and were less forgetful and confused (Cognition). Although comparisons drawn between the two TENS studies are tentative, since they concern independent groups of patients, and a slightly different pulse width and a different location of the electrodes in the control group in the present study, the results suggest that TENS has a similar effect on patients' cognitive functioning and need of help, irrespective of the presence or absence of the therapist; however, isolated TENS appears to have no beneficial effect on patients' affective functioning.

The present study has several caveats, one of which is the relatively small number of patients; however, the results of the present study are not an isolated observation, but were also found in earlier studies with TENS (Scherder et al 1992, 1995b) and tactile stimulation (Scherder et al 1995a, 1995c, in press). Furthermore, the present findings provide, of course, no direct evidence that the locus coeruleus–noradrenergic system and the nucleus raphe dorsalis–serotonergic system are indeed activated by TENS with subsequent activation of the hippocampus or hypothalamus of AD patients. Another caveat might be that although this study is a randomized double-blind placebo-controlled study, the therapist knew which patients belonged to the experimental and control group, thus creating a bias. On the other hand, compared to the former TENS study, in which the therapist was present during treatment (Scherder et al 1995b), the absence of therapist in the present study (isolated TENS) has certainly lowered the bias. In other words, isolated TENS might be considered as a replication with an improved blinded design.

Since the influence of peripheral nerve stimulation on various neurotransmitter systems, including the cholinergic system, has been assumed (Dutar et al 1985), one could compare the present results with those observed after administration of, e.g., Tacrine (tetrahydroaminoacridine or THA), a cholinesterase inhibitor. Tacrine appears to have beneficial effects on, particularly, simpler memory tasks like, e.g., delayed matching to sample with only a short delay of 4 sec (Eagger et al 1991). Indeed, in the present study we found improvements in Face and Picture Recognition, tasks that do not require complex memory processes. In contrast to Tacrine, however, isolated TENS seemed to have an additional effect on visual short-term memory (Visual Memory) and word fluency (Verbal Fluency). For a better performance on the Visual Memory task, patients had to improve storing, reversing, and producing of visual information. A higher score on Verbal Fluency implied that patients' capacity for retrieval of familiar, categorized information from their memory store had improved. As for behavior, AD patients participated more independently in activities of daily life after application of both TENS and Tacrine (Ashford et al 1989). A major limitation of Tacrine is the occurrence of side effects that include, among others, nausea, vomiting, transient dysphoria, headache, and aggression (Eagger et al 1991). In contrast, TENS has no known side effects, is perceived by the patient as a type of neutral, friendly stimulation, is easy to apply, and, except for patients with a pacemaker (Howson 1978), seems completely safe.

Finally, it should be emphasized that TENS does not claim to cure AD. Instead, it should be viewed as an example of a new therapeutic strategy that tries to improve the quality of life of demented patients by stimulation of the central nervous system.

E.J.A.S. was financially supported by NOG-Insurances.

The authors are very grateful to the staff members of the St. Jacob Nursing Home for their hospitality and help in conducting the study, and to the firm of Xytron Medical for their kind permission to use their apparatus. We would like to thank H.E. Ravesteijn for his invaluable assistance with the administration of the neuropsychological tests. We sincerely thank D.F. Swaab, MD, PhD, for his critical reading of the manuscript and his constructive comments.

References

Ashford JW, Sherman KA, Kumar V (1989): Advances in Alzheimer therapy: Cholinesterase inhibitors. *Neurobiol Aging* 10:99–105.

Bobillier P, Seguin S, Petitjean F, Salvert D, Touret M, Jouvet M (1976): The raphe nuclei of the cat brain stem: A topographical atlas of their efferent projections as revealed by autoradiography. *Brain Res* 11:449–486.

Carpenter GA, Grossberg S (1993): Normal and amnesic learning, recognition and memory by a neural model of cortico-hippocampal interactions. *Trends Neurosci* 16:131–137.

Coffey GH, Mahon MV (1982): Pain: Theories and a new approach to treatment. *J Natl Med Assoc* 74:147–153.

de Graaf A, Deelman BG (1991): *Cognitive Screening Test.* Lisse, The Netherlands: Swets & Zeitlinger.

Duranti R, Pantaleo T, Bellini F (1988): Increase in muscular pain threshold following low frequency-high intensity peripheral conditioning stimulation in humans. *Brain Res* 452:66–72.

Dutar P, Lamour Y, Jobert A (1985): Activation of identified septohippocampal neurons by noxious peripheral stimulation. *Brain Res* 328:15–21.

Eagger SA, Levy R, Sahakian BJ (1991): Tacrine in Alzheimer's disease. *Lancet* 337:989–992.

Eriksson MBE, Sjölund BH, Nielzen S (1979): Long term results of peripheral conditioning stimulation as an analgesic measure in chronic pain. *Pain* 6:335–347.

Frampton VM (1982): Pain control with the aid of transcutaneous nerve stimulation. *Physiotherapy* 68:77–81.

Guieu R, Tardy-Gervet MF, Blin O, Pouget J (1990): Pain relief achieved by transcutaneous electrical nerve stimulation and/or vibratory stimulation in a case of painful legs and moving toes. *Pain* 42:43–48.

Hamilton M (1960): A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62.

Howson DC (1978): Peripheral neural excitability. Implications for transcutaneous electrical nerve stimulation. *Phys Ther* 58:1467–1473.

Hozumi S, Hori H, Okawa M, Hishikawa Y, Sato K (1996): Favorable effect of transcranial electrostimulation on behavior disorders in elderly patients with dementia: A double-blind study. *Int J Neurosci* 88:1–10.

Huan-Ji D, Yan-Fang C (1976): Localization of central structures involved in descending inhibitory effect of acupuncture on viscero-somatic reflex discharges. *Sci Sin* 19:137–148.

Jones SL, Gebhart GF (1987): Spinal pathways mediating tonic, coerulospinal and raphe-spinal descending inhibition in the rat. *J Neurophysiol* 58:138–159.

Jørum E, Shyu BC (1988): Analgesia by low-frequency nerve stimulation mediated by low-threshold afferents in rats. *Pain* 32:357–366.

Karlsson I, Widerlöv E, Melin EV, Nyth A, Brane GAM, Rybo E, et al (1985): Changes of CSF neuropeptides after environmental stimulation in dementia. *Nord Psykiatr Tidsskr* 39:75–81.

Legoratti-Sanchez MO, Guevara-Guzman R, Solano-Flores LP (1989): Electrophysiological evidences of bidirectional communication between the locus coeruleus and the suprachiasmatic nucleus. *Brain Res Bull* 23:283–288.

Lindeboom J, Jonker C (1989): *Amsterdamse Dementie-Screeningstest, Handleiding.* Lisse, The Netherlands: Swets & Zeitlinger.

Lovell BB, Ancoli-Israel S, Gevirtz R (1995): Effect of bright light treatment on agitated behavior in institutionalized elderly subjects. *Psychiatry Res* 57:7–12.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (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.

Meer B, Baker JA (1966): The Stockton Geriatric Rating Scale. *J Gerontol* 21:392–403.

Norusis MJ (1988): *Statistical Packages for the Social Sciences, SPSS/PC+.* New York: McGraw-Hill.

Okawa M, Hishikawa Y, Hozumi S, Hori H (1991): Sleep-wake disorder and phototherapy in elderly patients with dementia. In: Racagni G, editor. *Biological Psychiatry.* Amsterdam: Elsevier, pp 837–840.

Omura Y (1987): Basic electrical parameters for safe and effective electro-therapeutics [electro-acupuncture, TES, TENMS (or TEMS), TENS and electro-magnetic field stimulation with or without drug field] for pain, neuromuscular skeletal problems, and circulatory disturbances. *Acupunct Electrother Res Int J* 12:201–225.

Pauser G (1980): Neurophysiologische und Neuropharmakologische Untersuchungen über (mögliche) Mechanismen der peripheren Stimulationsanalgesie. *Wien Klin Wochenschr* 92: 1–20.

Petrov T, Krukoff TL, Jhamandas JH (1992): The hypothalamic paraventricular and lateral parabrachial nuclei receive collaterals from raphe nucleus neurons: A combined double retrograde and immunocytochemical study. *J Comp Neurol* 318: 18–26.

Pfeiffer E (1975): A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc* 23:433–441.

Raadsheer FC, van Heerikhuize JJ, Lucassen PJ, Hoogendijk WJG, Tilders FJH, Swaab DF (1995): Corticotropin-releasing hormone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. *Am J Psychiatry* 152:1372–1376.

Robaina FJ, Rodriquez JL, de Vera JA, Martin MA (1989): Transcutaneous electrical nerve stimulation and spinal cord stimulation for pain relief in reflex sympathetic dystrophy. *Stereotact Funct Neurosurg* 52:53–62.

Rossor M (1988): Neurochemical studies in dementia. In: Iversen LL, Iversen SD, Snijder SH, editors. *Handbook of Psychopharmacology.* New York: Plenum Press, pp 107–130.

Salzmann E (1992): Importance of the hippocampus and parahippocampus with reference to normal and disordered memory function. *Fortschr Neurol Psychiatr* 60:163–176.

Satlin A, Volicer L, Ross V, Herz L, Campbell S (1992): Bright light treatment of behavioral and sleep disturbances in patients with Alzheimer's disease. *Am J Psychiatry* 149:1028–1032.

Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, et al (1992): Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: Diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry* 55:967–972.

Scherder EJA, Bouma A, Steen AM (1992): Influence of transcutaneous electrical nerve stimulation on memory in patients with dementia of the Alzheimer type. *J Clin Exp Neuropsychol* 14:951–960.

Scherder EJA, Bouma A, Steen AM (1995a): Effects of peripheral tactile stimulation on memory in patients with Alzheimer's disease. *Am J Alzheimer Dis* May/June: 15–21.

Scherder EJA, Bouma A, Steen AM (1995b): Effects of short-term transcutaneous electrical nerve stimulation on memory

and affective behavior in patients with probable Alzheimer's disease. *Behav Brain Res* 67:211–219.

Scherder EJA, Bouma A, Steen AM (1995c): Effects of simultaneously applied short-term transcutaneous electrical nerve stimulation and tactile stimulation on memory and affective behavior of patients with probable Alzheimer's disease. *Behav Neurol* 8:3–13.

Scherder EJA, Bouma A, Steen AM, Swaab DF (1995d): Peripheral nerve stimulation in Alzheimer's disease. A meta-analysis. *Alzheimer Res* 1:183–184.

Scherder EJA, Bouma A, Steen AM (in press): Effects of peripheral tactile nerve stimulation on affective behavior of patients with probable Alzheimer's disease. *Am J Alzheimer Dis.*

Snijders JT, Verhage F (1983): *Groninger Intelligentie Test.* Lisse, The Netherlands: Swets & Zeitlinger.

Swaab DF (1991): Brain aging and Alzheimer's disease, "wear and tear" versus "use it or lose it." *Neurobiol Aging* 12:317–324.

Swaab DF, Grundke-Iqbal I, Iqbal K, Kremer HPH, Ravid R, Van de Nes JAP (1992): Tau and ubiquitin in the human hypothalamus in aging and Alzheimer's disease. *Brain Res* 590:239–249.

Van der Kam P, Mol F, Wimmers MFHG (1971): *Beoordelingsschaal voor Oudere Patiënten.* Deventer, The Netherlands: Van Loghum Slaterus.

Vertes R (1991): A PHA-L analysis of ascending projections of the dorsal raphe nucleus in the rat. *J Comp Neurol* 313:643–668.

Wechsler D (1984): *Wechsler Memory Scale–Revised.* New York: The Psychological Corporation.

Widerlöv E, Brane G, Ekman R, Kihlgren M, Norberg A, Karlsson I (1989): Elevated CSF somatostatin concentrations in demented patients parallel improved psychomotor functions induced by integrity-promoting care. *Acta Psychiatr Scand* 79:41–47.

Wilson B, Cockburn J, Baddeley A (1987): *The Rivermead Behavioral Memory Test.* Titchfield, U.K.: Thames Valley Test Company.

Wolf SL, Gersh MR, Rao VR (1981): Examination of electrode placements and stimulating parameters in treating chronic pain with conventional transcutaneous electrical nerve stimulation (TENS). *Pain* 11:37–47.