Effects of Transcutaneous Electrical Nerve Stimulation (TENS) on self-efficacy and mood in elderly with mild cognitive impairment

Luijpen, M.W.; Swaab, D.F.; Sergeant, J.A.; Scherder, E.J.A.

published in
Neurorehabilitation and Neural Repair
2004

DOI (link to publisher)
10.1177/0888439004268785

document version
Publisher's PDF, also known as Version of record

Effects of Transcutaneous Electrical Nerve Stimulation (TENS) on Self-Efficacy and Mood in Elderly with Mild Cognitive Impairment

Marijn W. Luijpen, Dick F. Swaab, Joseph A. Sergeant, and Erik J. A. Scherder

In previous studies, transcutaneous electrical nerve stimulation (TENS) has been applied to patients with either Alzheimer's disease (AD) or incipient dementia, resulting in an enhancement in memory and verbal fluency. Moreover, affective behavior was shown to improve. Based on the positive effects of TENS in AD, it was hypothesized that TENS would improve self-efficacy in nondemented elderly with mild cognitive impairment (MCI) who live in a residential home. Four outcome measures, that is, a Dutch translation of the General Self-Efficacy Scale (Algemene Competentie Schaal), the Groninger Activity Restriction Scale, the Philadelphia Geriatric Center Morale Scale, and the Geriatric Depression Scale, were administered. Overall, the results suggest that the experimental group showed a mild improvement in self-efficacy and mood. In contrast, the placebo group showed a considerable reduction in self-efficacy and an increase in depression. Limitations of the present study and suggestions for future research are discussed.

Key Words: *Transcutaneous electrical nerve stimulation (TENS)—Mild cognitive impairment (MCI)—Self-efficacy—Mood.*

Recent reviews indicate that the clinical hallmark of patients with mild cognitive impairment (MCI) is impaired memory in combination with a preservation of general cognition and activities of daily life.[1,2] This type of MCI has also been called "amnestic" MCI[2] or "single-domain" MCI[3] and is probably caused by degeneration of various structures of the medial temporal lobe such as the hippocampus, the parahippo- campus, the entorhinal cor-tex, and the perirhinal cortex.[4] As opposed to single-domain MCI, patients with MCI may also show additional impairments in other cognitive functions, for example, orientation.[5,6] Patients with this type of MCI—called "multi-domain" MCI—have an even higher risk of developing probable Alzheimer's disease (AD) than those with single-domain MCI.[3]

Support for multi-domain MCI emerges from the finding that following the involvement of the medial temporal lobe,[4] the prefrontal cortex is also involved in MCI.[7-9] Indeed, an increased choline acetyltransferase (ChaT) activity has been observed in both the hippocampus and the frontal cortex of patients with MCI.[10] This finding suggests a compensatory upregulation of the cholinergic system. The prefrontal cortex has been associated with executive functions such as planning, taking initiatives, and purposeful action/goal-directed behavior.[11] In view of the nature of executive functions, it is logical that they are related to an individual's independent functioning. Specifically, executive functions appear to be a strong predictor for performance of (instrumental) activities of daily living.[12,13]

In addition to a frontal lobe *dysfunction* as observed in MCI associated with decline in independent functioning, the institutional environment of a residential home for the elderly might augment an elderly resident's decline in independent functioning, irrespective of cognitive impairment. Richardson et al.[14] observed that a 1-year institutionalization caused an increase in functional limitations and a decrease in activities of daily living in about one third of the residents. Indeed, instrumental daily activities such as shopping, preparing meals, and cleaning the room are not required anymore in a residential home for the

From the Department of Clinical Neuropsychology, Vrije Univer-siteit, Amsterdam, the Netherlands (MWL, EJAS, JAS), and the Netherlands Institute for Brain Research, Amsterdam (DFS).

Address correspondence to Marijn W. Luijpen, MSc, Department of Clinical Neuropsychology, Vrije Universiteit, Van der Boechorst-straat 1, 1081 BT Amsterdam, the Netherlands. E-mail: mw.luijpen@psy.vu.nl.

Luijpen MW, Swaab DF, Sergeant JA, Scherder EJA. Effects of transcutaneous electrical nerve stimulation (TENS) on self-efficacy and mood in elderly with mild cognitive impairment. Neurorehabil Neural Repair 2004;18:166–175.

DOI: 10.1177/0888439004268785

elderly. Particularly, these latter activities are itemized in most activities of daily living (ADL) scales, rendering them less suitable for the assessment of independent functioning among institutionally based elderly. Therefore, as an alternative, the concept of self-efficacy was used as an outcome measure in the present study. Self-efficacy refers to the way the person perceives her or his own independent functioning in daily life.[15] Replacing independent functioning with self-efficacy is justified in that executive functions are involved in certain aspects of self-efficacy such as self-regulation.[16]

The question arises whether frontal lobe functioning, as measured by the patient's self-efficacy, could be enhanced. Interestingly, certain types of peripheral electrical nerve stimulation appeared to be effective in stimulating areas of the prefrontal cortex and its functions. For example, in an fMRI-study, transcutaneous electrical nerve stimulation (TENS) applied to the right median nerve activated the anterior cingulate cortex, a frontal area also involved in executive functions.[17] The effects of TENS, applied to the back at the level of the 1st thoracic vertebra, have also been examined in AD patients[18-20] and elderly with mild forgetfulness.[21] In these studies, executive functions represented by verbal fluency were found to improve, and depressive symptoms declined. This latter finding is important for the present study, in that a strong relation has been observed between self-efficacy and depression in other patients such as those with asthma.[22]

The rationale underlying the application of TENS relates to the observation that the neuropathological hallmark of MCI is brain atrophy, not cell death.[23-25] Shrunken cells characterize brain atrophy but are still able to respond to neuronal stimulation as reflected in an increase in metabolism.[23-25] TENS is a type of neuronal stimulation and could increase cortical activity by activating the locus coeruleus and dorsal raphe nucleus. These 2 brain stem areas are the sources of the noradrenergic and serotonergic neurotransmitter systems, and they appear to play an important role in the ascending reticular activating system (ARAS),[26] which has strong connections with the prefrontal cortex.[27]

Thus far, the positive effects of TENS on executive functions and depression have been observed in patients with mild forgetfulness and AD. TENS has not been applied to patients with MCI. Because executive functions and depression are strongly related to independent functioning/self-efficacy, it was hypothesized in the present study that TENS could improve self-efficacy and depression in patients with MCI who live in a residential home for the elderly.

METHODS

Participants

A sample of 34 patients with MCI was drawn from a larger population of 500 institutionally based elderly. In a preliminary recruitment procedure, participants and nursing staff were informed about the purpose and nature of the study. Patients who agreed to participate in the study gave their informed consent. Over an 18-month study period, the participants were randomly assigned into 2 groups, that is, an experimental group (n = 17) and a placebo group (n = 17), by an independent investigator.

Demographic characteristics. The experimental group included 2 males and 15 females. The placebo group consisted of 6 males and 11 females. The difference in gender between both groups was not significant (Fisher's Exact: P = ns). The experimental and placebo group did not differ significantly in age (mean = 88.06, range: 79-96, and mean = 87.35, range: 76-98, respectively; t[32] = .42; P = 0.68). The level of education was measured with a 7-point scale: 1) uncompleted elementary school; 2) completed 6 grades of elementary school; 3) completed 8 grades of elementary school; 4) completed 3 years of lower general secondary education; 5) completed 4 years of lower general secondary education; 6) preuniversity education, technical college, higher vocational education; 7) university. The mean level of education of the experimental group showed no significant difference compared to the placebo group (mean = 3.29, range = 2-6, and mean = 3.13, range = 1-6, respectively; t[28] = .28; P = 0.78). The Mini-Mental State Examination (MMSE)[28] was used as an initial cognitive screening instrument. Both groups differed significantly in mean MMSE score (see Table 1 for mean scores, standard deviation, norms, and group comparison). In view of the very old group of elderly included in this study, concurrent decline in other cognitive domains (e.g., attention) could not be avoided and is expressed in a relatively low overall MMSE score (mean =

21.82; *SD* = 3.45). Corrected for age, this score is still representative of an MCI population, that is, between the 25th and 50th percentile.[29]

Cognitive functioning. Patients were screened using the 5 criteria for the diagnosis "MCI" established by Petersen et al.[30] as guidelines: 1) in an initial clinical interview, the patient herself or himself, supported by the opinion of the personal nursing assistant, noticed mild forgetfulness; 2) the reported decline in memory was objectively assessed by the memory items of the MMSE and neuropsychological tests; 3) largely unimpaired general cognitive functioning as reported by the participant himself or herself, the nursing staff, the MMSE, and neuropsychological test scores; 4) the activities of daily living appeared to be normal; 5) consulting the medical and nursing staff and reviewing participant's medical records revealed no signs of dementia. Patients were excluded from participation if they met the NINCDS-ADRDA criteria for probable AD[31] and if medical records showed a history of psychiatric disorder, alcoholism, cerebral trauma, cerebrovascular disease, hydrocephalus, neoplasm, epilepsy, disturbances of consciousness, or focal brain disorders.

A short neuropsychological test battery was administered to measure cognitive functioning more thoroughly (see Table 1 for means, standard deviations, norms, and group comparison). The Digit Span from the Wechsler Memory Scale–Revised (WMS-R)[32] assesses participants' verbal short-term memory abilities. The test consists of a *Forward* condition, in which participants were asked to replicate sequences of spoken digits, and a *Backward* condition, in which the sequences were repeated in reverse order. Episodic memory was measured with the California Verbal Learning and Memory Test,[33] Dutch-version: the Verbal Learning and Memory Test (VLMT): List A.[34] The VLMT contains 3 subtests, that is: *Direct Recall*, participants were invited to recall as many items as possible from a shopping list (containing 16 items) that was presented for 5 times; *Delayed Recall*, participants were asked to recall as many items as possible from the previously trained shopping list after a 15-min filled interval; and *Recognition*, participants were asked to recognize items of the previously presented shopping list from an orally presented list of 44 words. Frontal executive functioning was measured with 2 tests: Category Naming[35] and Trailmaking version A.[36] In the 1st test, which measures the ability to retrieve information from semantic memory, participants were asked to name as many words belonging to a particular category in 1 min, that is, an *Animal word category* and a *Occupational word category*. The 2nd test, Trailmaking version A, is a paper-and-pencil test in which participants are required to connect numbers on a paper in the correct order as quickly as possible, and this involves visual scanning, speed, and attention.

Taken together, with respect to cognition, lowest scores were observed for attention (Digit Span Forward condition, Trailmaking A), working memory (Digit Span Backward Condition), and short- and long-term retrieval from memory (VLMT Direct Recall and Delayed Recall). These findings further support the diagnosis of MCI.

MATERIAL AND PROCEDURE

To evaluate the effects of TENS on self-efficacy and depression, the following scales were administered and used as outcome measures.

Self-Efficacy

Algemene Competentie Schaal (ALCOS)[37] is a Dutch translation of the General Self-Efficacy Scale.[38] The ALCOS is a 5-point scale that consists of 3 subscales: 1) Competence (4 items), 2) Perseverance When Experiencing Adversity (5 items), and 3) Taking Initiatives (3 items). A higher score is indicative for more self-efficacy. The maximum score is 60. The test-retest reliability of the ALCOS appears to be adequate (r = 0.84), whereas the internal consistency varies from Cronbach's α = 0.86 for the test to Cronbach's α = 0.89 for the retest.[39] Another study that included 144 elderly with an age ranging from 55 to 90 years reported an internal consistency of Cronbach's α = 0.87.[40]

The Groninger Activity Restriction Scale (GARS)[41,42] is an 18-item functional status scale. More specific, each item has a response range from 1 to 4, reflecting an increasing extent of dependency. For example, 1 item refers to the extent of independent dressing. Item scores range from 1 (completely independent) to 4 (completely dependent). The lower the score, the less the impairment of the patient (range in scores: 18-72). The GARS is not a self-efficacy scale by nature but a mixed ADL/IADL scale. During instruction of the scale, we emphasized that it was not important

Table 1. Overall and Group Mean Memory and Executive Function Test Scores, Standard Deviations, Norms or Maximum Scores, and *t* Test Group Comparison

	Overall Group Score (N = 34)			Experimental Group (n = 17)		Placebo Group (n = 17)		*t* Test (Experimental-Placebo)		
Tests	*M*	*SD*	Population Norms (Age Range)	*M*	*SD*	*M*	*SD*	*t*	*df*	*P*
MMSE	21.82	3.45	25th-50th percentile (89 years)	20.24	3.70	23.41	2.35	2.99	32	0.005
WMS-R digit span										
Forward condition	4.82	1.53	6th-12th percentile (70-74 years)	4.44	1.31	5.21	1.67	1.49	32	ns
Backward condition	3.91	1.28	14th-26th percentile (70-74 years)	3.50	1.02	4.32	1.41	1.95	32	ns
VLMT										
Direct recall	27.68	11.32	Maximum score: 80	28.79	12.55	26.56	10.21	0.57	32	ns
Delayed recall	2.91	3.49	Maximum score: 16	3.24	4.05	2.59	2.92	0.53	32	ns
Recognition	37.31	4.64	Maximum score: 44	36.91	4.89	37.71	4.50	0.49	32	ns
Category naming										
Animal word category	11.40	3.54	T-score 48-50 (89-93 years)	11.65	4.06	11.15	3.02	0.41	32	ns
Occupational word category	8.37	3.31	T-score 46-48 (85-88 years)	8.41	3.13	8.32	3.58	0.08	32	ns
Trailmaking version A	105.56	44.42	25th percentile (70-79 years)	107.88	30.31	103.09	56.72	0.31	31	ns

MMSE = Mini-Mental State Examination; WMS-R = Wechsler Memory Scale-Revised; VLMT = Verbal Learning and Memory Test; *M* = mean; *SD* = standard deviation; ns = not significant.

whether the requested activity (e.g., doing heavy domestic labor or cleaning the bed) was still appropriate for the setting they were in. The manual of the GARS evaluates the test-retest reliability and internal consistency obtained from several studies in the Netherlands.[43] The test-retest reliability coefficient ranged from $r = 0.53$ ($P < 0.1$) to $r = 0.74$ ($P < 0.1$), whereas the internal consistency varied between Cronbach's $\alpha = 0.83$ and Cronbach's $\alpha = 0.94$.

The Philadelphia Geriatric Center Morale Scale (PGCMS)[44,45] is a 17-item battery that consists of 3 subscales: 1) Agitation (8 items), 2) Attitude toward Aging (6 items), and 3) Dissatisfaction (4 items). Sixteen items have only 2 dichotomous response categories, that is, yes-no, often–not often, and not satisfied–satisfied. One item includes a statement in which the participant is asked to fill in 1 of the following words: better, worse, the same. The total score is 18. A higher score indicates better morale. In a study that included 1086 elderly, Lawton[44] found an internal consistency of Cronbach's $\alpha = 0.85$ for the subscale Agitation; Cronbach's $\alpha = 0.81$ for Attitude toward Aging; and Cronbach's $\alpha = 0.85$ for Dissatisfaction. The test-retest reliability found in a study that administered the Dutch translation of the PGCMS was $r = 0.82$ ($P < 0.0001$).[46]

Depressive Symptoms

The Geriatric Depression Scale (GDS)[47,48] is a valid and reliable self-rating scale,[49] which has been developed for application in an elderly population and which is also suitable for the assessment of treatment effects.[50] Laprise and Vézina[51] reported an adequate test-retest correlation coefficient of 0.70 ($P < 0.0001$). The GDS consists of 30 items with no or yes responses (maximum score: 30). A score equal to or greater than 11 indicates depression, whereas a score of 10 or less indicates the absence of depression.[47,48] However, a cutoff score of 14 has higher agreement with a "clinical diagnosis of depression."[51]

Stimulation

The TENS signal is thought to (re)activate cortical brain regions involved in cognitive functioning through afferent peripheral nerve fibers of the somatosensory system. This hypothesis is based on animal experimental studies, which reported an increase in hippocampal and hypothalamic activity, possibly mediated through supraspinal areas, as a result of tactile and electrical stimulation of the somatosensory system.[52-54] An activation of supraspinal areas, for example, the dorsal raphe nucleus, the locus coeruleus, and subsequently the prefrontal cortex, by TENS might be transmitted by afferent nerve fibers, that is, thick-myelinated A-Beta fibers, thin-myelinated A-Delta fibers, and un- myelinated C fibers.[55,56] The conditions (stimulation- parameters) under which these 3 types of afferent nerve fibers in patients with MCI could be optimally stimulated originate from animal studies dealing with analgesia.[57-64]

Frequency and intensity. A-Beta fibers respond very well to both high- (e.g., 100 Hz) and low-frequency stimulation (e.g., 2 Hz).[57,58,60] A-Delta and C fibers preferably respond to low-frequency stimulation (less than 10 Hz) with a nonpainful intensity that triggers strong muscular contractions.[61-65]

To activate all 3 types of afferent nerve fibers, high-frequency and low-frequency stimulation had to be combined in 1 treatment. Therefore, TENS characterized by asymmetric biphasic square impulses was applied in bursts of trains, 9 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.[66] Importantly, a burst signal is most appropriate to stimulate the prefrontal cortex.[67] The intensity of the stimulation was high enough to provoke muscular twitches, which were painless.

Participants in the experimental group were treated with an electrostimulator, type Premier 10s. The same electrostimulator was applied to participants of the placebo group. However, no current was administered to the patients (sham stimulation). To avoid possible effects resulting from this difference, each participant was informed that the perceptibility for the TENS signal varies for each individual. Both groups were told that the TENS signal was applied as soon as a green LED on the electrostimulator began to flash.

Location. The participant was sitting in a chair. Two 2×3 cm self-adhesive standard carbon rubber electrodes with gel were fixed on the participant's back, between the 1st and 5th thoracic level on each side of the spinal column.

Treatment time and period. Participants were treated 30 min a day, 5 days a week, for 6 consecu-

tive weeks. These parameters are based on earlier TENS studies, which reported enhancement in cognitive and behavioral functioning in both demented and nondemented elderly applying this treatment duration and period.[19,21]

Measurement Moments

The self-efficacy scales and the depression scale (GDS) were applied at 4 points, that is, 6 weeks before the TENS treatment started (pretreatment 1: T1), just before the onset of the 6-week treatment period (pretreatment 2: T2), directly after the 6 weeks of treatment (post: T3), and again after a 6-week treatment- free period (delayed: T4). An independent investigator, unaware of the group identity of participants, administered the scales.

Statistical Analyses

First, it was calculated whether the pretreatment measurement scores (T1 and T2) of each scale could be pooled to reduce within-subjects variability. This procedure results in a gain of discriminative power and is appropriate when the pretreatment scores do not differ significantly.

Next, to answer the main question of the investigation, Does TENS treatment improve self-efficacy and mood? each self-efficacy and mood (sub)scale was submitted to a 1-way analysis of covariance (ANCOVA) with group (2 levels: experimental and placebo) as independent variable, the posttreatment score (T3) as dependent variable, and, if appropriate, the pooled pretreatment baseline score ($T_{(1,2)}$) as covariate. If an ANCOVA revealed a significant group effect for an outcome measure, post hoc single-tailed paired-samples *t* tests at a 0.05 significance level were performed to evaluate differences within the experimental and placebo group.

Furthermore, although an independent-samples *t* test did show a significant group difference in MMSE score (see Methods, subsection Participants), it was calculated whether the MMSE score should be included in the analysis as a 2nd covariate. For this purpose, each self-efficacy or mood (sub)scale was submitted to an ANCOVA—with group as independent variable (2 levels: experimental and placebo), the posttreatment score (T3) as dependent variable, and both the MMSE score and the *pooled* pretreatment score ($T_{(1,2)}$) as covariates. The SPSS-PC program was applied for data analyses.[68]

RESULTS

A preliminary series of paired-samples *t* tests showed no significant differences between the pretreatment scores (T1 and T2) of the experimental group and placebo group for each self-efficacy and mood (sub)scale. Therefore, it was justified to pool both pretreatment scores ($T_{(1,2)}$). Subsequently, an ANCOVA with group as independent variable (2 levels: experimental and placebo), the posttreatment score (T3) as dependent variable, and both the MMSE score and the pooled pretreatment score ($T_{(1,2)}$) as covariates showed that the MMSE scores did not have a significant influence on the self-efficacy and mood (sub)scale scores. Consequently, the MMSE scores were not included as a covariate in further analyses.

Algemene Competentie Schaal (ALCOS)

The results of the ANCOVA (Group [experimental, placebo] × Measurement moment [T3]) (see Table 2) showed a significant main effect for group for the ALCOS scores. This effect is explained by a significant decrease in scores within the placebo group as indicated by post hoc paired-samples *t* tests ($t[16] = 1.74$, $P = 0.05$). A lower score implies a decline in self-efficacy. The slight increase in scores within the experimental group was not significant ($t[16] = .43$, $P = 0.34$). The ANCOVA performed on the 3 subscales, that is, Competence, Perseverance When Experiencing Adversity, and Taking Initiatives, revealed a significant main effect for group for the ALCOS subscale Taking Initiatives. Paired-samples *t* tests showed a significant decline on this subscale within the placebo group ($t[16] = 2.13$, $P < 0.03$), whereas the change in score within the experimental group over time was not significant ($t[16] = .65$, $P < 0.27$).

Groninger Activity Restriction Scale (GARS)

The 1-way ANCOVA (Group [experimental, placebo] × Measurement moment [T3]) conducted on the GARS scores revealed a significant main effect for group (see Table 2). Post hoc paired-samples *t* tests indicated a nonsignificant decrease in score (improvement in self-efficacy) within the experimental group ($t[16] = 1.35$, $P < 0.10$) and an increase in score (decline in self-efficacy) within the placebo group ($t[16] = 1.49$, $P < 0.08$).

Table 2. Means, Standard Deviations, and Analyses of Covariance of the Self-Efficacy and Depression Scales

	Experimental Group						Placebo Group								
	Pretreatment Pooled ($T_{1,2}$)		Posttreatment (T3)		Delayed (T4)		Pretreatment Pooled ($T_{1,2}$)		Posttreatment (T3)		Delayed (T4)		ANCOVA Pre-Post		
Self-Efficacy and Mood Scales	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*df*	*P*
GDS	7.94	3.25	7.35	3.22	7.00	4.63	10.35	5.68	11.82	6.79	9.25	4.93	4.35	1,31	0.02
GARS	40.65	9.32	39.35	10.14	39.37	10.46	44.00	13.31	45.41	13.71	45.31	13.31	3.90	1,31	0.03
ALCOS (overall)	40.18	4.81	40.65	6.59	41.63	4.90	39.35	6.84	36.71	7.42	39.00	5.77	3.17	1,31	0.04
Subscales															
Competence	12.79	2.91	12.88	3.87	13.56	3.29	12.15	4.07	11.82	4.38	12.13	4.30	0.27	1,31	0.30
Perseverance when experiencing adversity	20.88	3.31	20.88	3.33	22.00	2.73	20.82	3.21	20.35	3.12	20.81	3.15	0.29	1,31	0.29
Taking initiatives	6.50	2.30	6.88	3.26	6.06	2.44	6.38	2.00	5.12	2.57	6.06	2.35	4.04	1,31	0.03
PGCMS (overall)	11.85	2.85	11.94	3.96	11.56	3.39	9.65	4.59	9.35	5.24	10.06	4.30	0.23	1,31	0.64
Subscales															
Agitation	5.32	1.79	5.65	1.58	5.38	2.58	4.74	2.73	4.71	2.89	4.94	2.52	1.11	1,31	0.15
Attitude toward aging	3.00	1.06	3.24	1.68	2.75	1.39	2.15	1.34	2.06	1.68	2.19	1.68	1.02	1,31	0.16
Dissatisfaction	3.53	0.45	3.29	0.77	3.44	1.03	2.76	1.17	2.59	1.42	2.94	1.06	0.01	1,31	0.46

GDS = The Geriatric Depression Scale; GARS = The Groninger Activity Restriction Scale; ALCOS = Algemene Competentie Schaal; PGCMS = The Philadelphia Geriatric Center Morale Scale; *M* = mean; *SD* = standard deviation.

Philadelphia Geriatric Center Morale Scale (PGCMS)

The ANCOVA (Group [experimental, placebo] × Measurement moment [T3]) performed on the PGCMS revealed no significant main effect for group (see Table 2). As a result, no additional paired- samples *t* tests were conducted. ANCOVA of the 3 subscales, that is, Agitation, Attitude toward Aging, and Dissatisfaction, showed no significant main effects for group.

Geriatric Depression Scale (GDS)

ANCOVA (Group [experimental, placebo] × Mea- surement moment [T3]) indicated a significant main effect for group for the GDS scores (see Table 2). Specifically, the scores of the experimental group on the GDS became smaller, whereas the scores of the placebo group increased. Paired samples *t* tests showed that the GDS score increased significantly within the placebo group ($t[16] = 2.14$; $P < 0.03$), whereas the decrease in GDS score within the experimental group did not reach significance ($t[16] = .86$; $P < 0.20$).

DISCUSSION

The main finding in the present study was the absence of a statistically significant beneficial effect of TENS treatment on self-efficacy and mood in an MCI population. More specific, the experimental group showed hardly any change on the questionnaires, whereas self-efficacy and mood within the placebo group declined. This decline was statistically significant for the ALCOS overall score and its subscale Taking Initiatives, and the GDS score, whereas the GARS score declined nonsignificantly. The decline in self-efficacy and mood observed within the placebo group was relatively stronger than the enhancement found in the experimental group, and therefore primarily responsible for the significant main effects for group observed in the ANCOVA of the GDS, and the ALCOS overall and its subscale Taking Initiatives. The only scale that did not show a significant main effect for group was the PGCMS. A possible explanation might be that compared to the other scales, this scale has a limited number of items and dichotomous response categories.

The question that arises from the present findings is 2-fold: 1st, why did not TENS improve self-efficacy and mood in the experimental group? and 2nd, why did the placebo group show a decline in self-efficacy and mood during the treatment period?

With respect to the 1st question, one of the major risk factors for MCI is the presence of the apolipoprotein E ε4 allele (APOE ε4).[69] In AD, APOE ε4 is associated with a reduction in regional cerebral metabolic rate of glucose in, among others, the prefrontal regions.[70] Importantly, although findings are equivocal, APOE ε4 may decrease the effectiveness of specific types of interventions such as tacrine, a cholinesterase inhibitor, and estrogen in AD.[71,72] The possibility that APOE ε4 also hinders the effectiveness of TENS in an MCI population should be examined in future research.

With respect to the 2nd question, the decline in self-efficacy and mood in the placebo group might be explained by the so-called nocebo reaction, that is, the opposite of a placebo reaction.[73-76] The nocebo reaction might, as the placebo effect, involve 2 possible underlying mechanisms: conditioning and cognitive factors.[77,78] With regard to conditioning, context and environment (e.g., color of pills, instruments used for the treatment, hospital setting) represent the conditioned stimulus, and the associated valence of these cues may cause a placebo or nocebo response. More specific, the application of electrical current and electrodes in the present study may have been perceived as conditioned stimuli with a negative valence and trigger a nocebo response. This response is reflected in a substantial decline in self-efficacy and mood in the placebo group. In the experimental group, the nocebo reaction may have been counteracted by the positive influence of the TENS treatment.

Cognitive processes (e.g., expectations, beliefs) may also play a role in the nature of the response, that is, placebo or nocebo. We hypothesize that unmet expectations might have played a role in inducing a nocebo effect. Participating in the study required high commitment from the participants—the treatment was applied 30 min a day, 5 days a week, for 6 consecutive weeks—and the lack of experiencing any beneficial effects as a result of the sham treatment might have triggered a nocebo response.

Taken together, a suggestion for future TENS research is to control for the presence of the APOE ε4 allele and examine possible differences in efficacy of the treatment related to the presence or absence of this specific genotype. Considering the previous discussed factors that might cause a nocebo reaction, future TENS research should

include a short questionnaire in which participants are asked how they experienced the application of electrodes, the use of electrical current, and the daily visits of the investigator. Another proposal is to assess expectations regarding TENS treatment with a questionnaire asking whether those expectations are met after cessation of the treatment.

ACKNOWLEDGMENT

This study was financially supported by ZON (Zorg Onderzoek Nederland), FONTIS Amsterdam, and RIDE-NWO.

REFERENCES

1. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;56(9):1133-42.
2. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol* 2001;58(12):1985-92.
3. Meyer J, Xu G, Thornby J, Chowdhury M, Quach M. Longitudinal analysis of abnormal domains comprising mild cognitive impairment (MCI) during aging. *J Neurol Sci* 2002;201(1-2):19-25.
4. Collie A, Maruff P. The neuropsychology of preclinical Alzheimer's disease and mild cognitive impairment. *Neurosci Biobehav Rev* 2000;24(3):365-74.
5. Wang QS, Zhou JN. Retrieval and encoding of episodic memory in normal aging and patients with mild cognitive impairment. *Brain Res* 2002;924(1):113-15.
6. Wolf H, Grunwald M, Ecke GM, et al. The prognosis of mild cognitive impairment in the elderly. *J Neural Transm Suppl* 1998;54:31-50.
7. Raz N, Gunning FM, Head D, et al. Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cereb Cortex* 1997;7(3):268-82.
8. Bartres-Faz D, Junque C, Lopez-Alomar A, et al. Neuropsychological and genetic differences between age-associated memory impairment and mild cognitive impairment entities. *J Am Geriatr Soc* 2001;49(7):985-90.
9. Huang C, Wahlund LO, Almkvist O, et al. Voxel- and VOI-based analysis of SPECT CBF in relation to clinical and psychological heterogeneity of mild cognitive impairment. *Neuroimage* 2003;19(3):1137-44.
10. Morris JC. Challenging assumptions about Alzheimer's disease: mild cognitive impairment and the cholinergic hypothesis. *Ann Neurol* 2002;51(2):143-4.
11. Grimes AL, McCullough LB, Kunik ME, Molinari V, Workman RH Jr. Informed consent and neuroanatomic correlates of intentionality and voluntariness among psychiatric patients. *Psychiatr Serv* 2000;51(12):1561-7.
12. Cahn-Weiner DA, Boyle PA, Malloy PF. Tests of executive function predict instrumental activities of daily living in community-dwelling older individuals. *Appl Neuropsychol* 2002;9(3):187-91.
13. Grigsby J, Kaye K, Baxter J, Shetterly SM, Hamman RF. Executive cognitive abilities and functional status among community-dwelling older persons in the San Luis Valley Health and Aging Study. *J Am Geriatr Soc* 1998;46(5):590-6.
14. Richardson J, Bedard M, Weaver B. Changes in physical functioning in institutionalized older adults. *Disabil Rehabil* 2001;23(15):683-9.
15. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev* 1977;84(2):191-215.
16. Barkley RA. The executive functions and self-regulation: an evolutionary neuropsychological perspective. *Neuropsychol Rev* 2001;11(1):1-29.
17. Davis KD, Taylor SJ, Crawley AP, Wood ML, Mikulis DJ. Functional MRI of pain- and attention-related activations in the human cingulate cortex. *J Neurophysiol* 1997;77(6):3370-80.
18. Scherder EJ, Bouma A, Steen AM. Effects of short-term transcutaneous electrical nerve stimulation on memory and affective behaviour in patients with probable Alzheimer's disease. *Behav Brain Res* 1995;67(2):211-19.
19. Scherder EJ, Bouma A, Steen LM. Effects of "isolated" transcutaneous electrical nerve stimulation on memory and affective behavior in patients with probable Alzheimer's disease. *Biol Psychiatry* 1998;43(6):417-24.
20. Scherder EJ, Bouma A. Effects of transcutaneous electrical nerve stimulation on memory and behavior in Alzheimer's disease may be stage-dependent. *Biol Psychiatry* 1999;45(6):743-9.
21. Scherder EJ, Van Someren EJ, Bouma A, Berg M. Effects of transcutaneous electrical nerve stimulation (TENS) on cognition and behaviour in aging. *Behav Brain Res* 2000;111(1-2):223-5.
22. Mancuso CA, Rincon M, McCulloch CE, Charlson ME. Self-efficacy, depressive symptoms, and patients' expectations predict outcomes in asthma. *Med Care* 2001;39(12):1326-38.
23. Swaab DF, Dubelaar EJ, Hofman MA, Scherder EJ, Van Someren EJ, Verwer RW. Brain aging and Alzheimer's disease; use it or lose it. *Prog Brain Res* 2002;138:343-73.
24. Swaab DF. Nuclei of the human hypothalamus. Part 1. In: Aminos MJ, Boller S, Swaab DF, eds. *Handbook of clinical neurology*. Amsterdam: Elsevier Science; 2003.
25. Swaab DF. Neuropathology of the human hypothalamus and adjacent structures. Part 2. In: Aminos MJ, Boller S, Swaab DF, eds. *Handbook of clinical neurology*. Amsterdam: Elsevier Science; 2004.
26. Kayama Y, Koyama Y. Brainstem neural mechanisms of sleep and wakefulness. *Eur Urol* 1998;33(Suppl 3):12-15.
27. Van Gaalen M, Kawahara H, Kawahara Y, Westerink BH. The locus coeruleus noradrenergic system in the rat brain studied by dual-probe microdialysis. *Brain Res* 1997;763(1):56-62.
28. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12(3):189-98.
29. Dufouil C, Clayton D, Brayne C, et al. Population norms for the MMSE in the very old: estimates based on longitudinal data. Mini-Mental State Examination. *Neurology* 2000;55(11):1609-13.
30. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56(3):303-8.
31. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34(7):939-44.
32. Wechsler D. *Wechsler Memory Scale–Revised*. New York: The Psychological Corporation; 1984.
33. Delis DC, Kramer JH, Kaplan E, Ober BA. *California Verbal Learning Test. Research edition*. New York: The Psychological Corporation Harcourt Brace Jovanovich Inc; 1987.
34. Mulder JL, Dekker R, Dekker PH. *Verbale Leer en Gebeugen Test*. Lisse, the Netherlands: Swets & Zietlinger; 1995.

35. Snijders JTh, Verhage F. *Groninger Intelligentie Test*. Lisse, the Netherlands: Swets & Zeitlinger; 1983.
36. Reitan RM, Wolfson D. *The Halstead-Reitan Neuropsychology Test Battery*. Tuscon, AZ: Neuropsychology Press; 1985.
37. Bosscher RJ, Smith JH, Kempen GIJM. Algemene competentieverwachtingen bij ouderen. *Nederlands Tijdschrift voor de Psychologie* 1997;52:239-48.
38. Sherer M, Maddux JE, Mercandante B, Prentice-Dunn S, Jacobs B, Rogers RW. The self-efficacy scale: construction and validation. *Psychol Rep* 1982;51:663-71.
39. Bosscher RJ, Baardman I. Het meten van gepercipeerde competentie bij psychiatrische patienten. *Bewegen en Hulpverlening* 1989;6:312-22.
40. Bosscher RJ, Laurijssen L, Boer Ed. Competentie op latere leeftijd: een exploratieve studie. *Bewegen en Hulpverlening* 1992;9:255-65.
41. Suurmeijer TP, Doeglas DM, Moum T, et al. The Groningen Activity Restriction Scale for measuring disability: its utility in international comparisons. *Am J Public Health* 1994;84(8): 1270-3.
42. Kempen GIJM, Suurmeijer ThPBM. The development of a hierarchical polychotomous ADL-IADL scale for noninstitutionalized elders. *The Gerontologist* 1990;30:497-502.
43. Kempen GIJM, Doeglas DM, Suurmeijer TPBM. *Het meten van problemen met zelfredzaambeid op verzorgend en huisboudelijk gebied met de Groningen Activiteiten Restrictie Schaal (GARS). Een handleiding [Grongingen Activity Restriction Scale]*. Groningen, the Netherlands: University of Groningen, Northern Centre for Health Care Research; 1993.
44. Lawton MP. The Philadelphia Geriatric Center Morale Scale: a revision. *J Gerontol* 1975;30(1):85-9.
45. Lawton MP. The dimensions of morale. In: Kent D, Kastenbaum R, Sherwood S, eds. *Research, planning and action for the elderly*. New York: Behavioral Publications; 1972.
46. Rai GS, Jetten E, Collas D, Hoefnagels W, Froeling P, Bor H. Study to assess quality of life (morale and happiness) in two continuing care facilities—a comparative study in the UK and the Netherlands. *Arch Gerontol Geriatr* 1995;20:249-53.
47. Brink TL, Yesavage JA, Heersema PH, Adey M, Rose TL. Screening tests for geriatric depression. *Arch Gen Psychiatry* 1982;4: 53-63.
48. Sheikh JL, Yesavage JA. Geriatric Depression Scale (GDS). Recent evidence of development of a shorter version. *Clin Gerontol* 1986;5:165-73.
49. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982;17(1):37-49.
50. Kok RM, Heeren ThJ, van Hemert AM. De Geriatric Depression Scale. *Tijdschrift voor Psychiatrie* 1993;35(6):416-21.
51. Laprise R, Vézina J. Diagnostic performance of the Geriatric Depression Scale and the Beck Depression Inventory with nursing home residents. *Can J Aging* 1998;17(4):401-13.
52. Dudar JD, Whishaw IQ, Szerb JC. Release of acetylcholine from the hippocampus of freely moving rats during sensory stimulation and running. *Neuropharmacology* 1979;18(8-9):673-8.
53. Dutar P, Lamour Y, Jobert A. Activation of identified septo-hippocampal neurons by noxious peripheral stimulation. *Brain Res* 1985;328(1):15-21.
54. Huan-Ji D, Yan-fang C. Localization of central structures involved in descending inhibitory effect of acupuncture on viscero-somatic reflex discharges. *Sci Sin* 1976;19:137-48.
55. Coffey GH, Mahon MV. Pain: theories and a new approach to treatment. *J Natl Med Assoc* 1982;74(2):147-53.
56. Howson DC. Peripheral neural excitability. Implications for transcutaneous electrical nerve stimulation. *Phys Ther* 1978;58(12):1467-73.
57. Guieu R, Tardy-Gervet MF, Blin O, Pouget J. Pain relief achieved by transcutaneous electrical nerve stimulation and/or vibratory stimulation in a case of painful legs and moving toes. *Pain* 1990;42(1):43-8.
58. Guieu R, Tardy-Gervet MF, Roll JP. Analgesic effects of vibration and transcutaneous electrical nerve stimulation applied separately and simultaneously to patients with chronic pain. *Can J Neurol Sci* 1991;18(2):113-19.
59. Omura Y. 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* 1987;12(3-4):201-25.
60. Jorum E, Shyu BC. Analgesia by low-frequency nerve stimulation mediated by low-threshold afferents in rats. *Pain* 1988;32(3):357-66.
61. Jones SL, Gebhart GF. Spinal pathways mediating tonic, coeruleospinal, and raphe-spinal descending inhibition in the rat. *J Neurophysiol* 1987;58(1):138-59.
62. Mokha SS, McMillan JA, Iggo A. Descending control of spinal nociceptive transmission. Actions produced on spinal multi- receptive neurones from the nuclei locus coeruleus (LC) and raphe magnus (NRM). *Exp Brain Res* 1985;58(2): 213-26.
63. Soric R, Devlin M. Transcutaneous electrical nerve stimulation. Practical aspects and applications. *Postgrad Med* 1985;78(4): 101-7.
64. Wolf SL. Perspectives on central nervous system responsiveness to transcutaneous electrical nerve stimulation. *Phys Ther* 1978;58(12):1443-9.
65. Duranti R, Pantaleo T, Bellini F. Increase in muscular pain threshold following low frequency-high intensity peripheral conditioning stimulation in humans. *Brain Res* 1988;452(1-2):66-72.
66. Eriksson MB, Sjolund BH, Nielzen S. Long term results of peripheral conditioning stimulation as an analgesic measure in chronic pain. *Pain* 1979;6(3):335-47.
67. Scherder EJ, Luijpen MW, van Dijk KR. Activation of the dorsal raphe nucleus and locus coeruleus by transcutaneous electrical nerve stimulation in Alzheimer's disease: a reconsideration of stimulation-parameters derived from animal studies. *Chin J Physiol* 2003;46(4):143-50.
68. Norusis MJ. *Statistical Packages for the Social Sciences, SPSS/PC+*. New York: McGraw-Hill; 1988.
69. Lopez OL, Jagust WJ, Dulberg C, et al. Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. *Arch Neurol* 2003;60(10):1394-9.
70. Van Dyck CH. Neuroimaging in Alzheimer's disease: relevance for treatment. *Curr Psychiatry Rep* 2001;3(1):13-19.
71. Sjogren M, Hesse C, Basun H, et al. Tacrine and rate of progression in Alzheimer's disease—relation to ApoE allele genotype. *J Neural Transm* 2001;108(4):451-8.
72. Yaffe K, Haan M, Byers A, Tangen C, Kuller L. Estrogen use, APOE, and cognitive decline: evidence of gene-environment interaction. *Neurology* 2000;54(10):1949-54.
73. Benedetti F, Amanzio M, Casadio C, Oliaro A, Maggi G. Blockade of nocebo hyperalgesia by the cholecystokinin antagonist proglumide. *Pain* 1997;71(2):135-40.
74. Kennedy WP. The nocebo reaction. *Med Exp Int J Exp Med* 1961;95:203-5.
75. Hahn RA. A sociocultural model of illness and healing. In: White L, Tursky B, Schwartz GE, eds. *Placebo: theory, research, and mechanisms*. New York: Guilford; 1985:167-95.
76. Hahn RA. The nocebo phenomenon: scope and foundations. In: Harrington A, ed. *The placebo effect: an interdisciplinary exploration*. Cambridge, MA: Harvard University Press; 1997.
77. Ader R. Conditioned responses in pharmacotherapy research. *Psychol Med* 1993;23(2):297-9.
78. Kirsch I. Specifying nonspecifics: psychological mechanisms of placebo effects. In: Harrington A, ed. *The placebo effect*. London: Harvard University Press; 1997.