Research report

Effects of transcutaneous electrical nerve stimulation (TENS) on memory in elderly with mild cognitive impairment

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Abstract

In previous studies, transcutaneous electrical nerve stimulation (TENS) was shown to have a positive effect on memory in Alzheimer’s disease (AD) patients. Moreover, the reported effects appeared to be more beneficial in early stages of Alzheimer’s disease compared to later stage intervention. Based on this stage-dependency, the present study examined the effects of TENS on memory in a preclinical stage of AD, i.e. in subjects with mild cognitive impairment (MCI). Our results suggest that TENS did not improve memory in a MCI population. Mechanisms that might underlie the absence of positive effects of the TENS treatment in a MCI population are discussed.

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1. Introduction

Mild cognitive impairment (MCI) is considered to be a transitional phase between normal aging and dementia [36]. The most prominent feature is an isolated mild decline in memory, whereas other cognitive functions remain intact. This type of MCI has been called ‘amnestic MCI’ [35] and is probably caused by degeneration of various structures of the medial temporal lobe such as the hippocampus, the parahippocampus, the entorhinal cortex and the perirhinal cortex [6]. Compared to healthy age-matched individuals, subjects with MCI have a higher risk for developing probable Alzheimer’s disease (AD). Several studies [1,7,10,36,51] report a rate of progression from MCI to dementia or AD in the range between 6 and 15% per year. In contrast, the annual age-specific incidence rate for AD found in a meta-analysis by Gao et al. [18], is considerably lower (0.51% ages 70 to 74–3.86% ages 85 to 89). The increased risk for the elderly that suffer from MCI to progress to AD, makes it an appropriate condition for therapeutic intervention.

In a series of clinical studies, the effect of transcutaneous electrical nerve stimulation (TENS) was examined on various aspects of memory and other cognitive functions in different stages of AD [41,43-45] and in non-demented elderly individuals [22,46]. TENS appeared to improve visual short-term and verbal long-term (recognition) memory, and semantic verbal fluency. Important with respect to the goal of the present study is that the effects of the TENS treatment were robust in earlier stages of AD than in later stage intervention [22,42]. A limitation of these studies is the relatively small number of participants, rendering firm conclusions concerning the effectiveness impossible.

In the above mentioned studies, it was hypothesized that TENS could stimulate the hippocampus and the cholinergic basal forebrain (CBF) system. Both the hippocampus and the CBF system play a major role in memory processes [39,49] and are affected in aging and AD [40,49]. The TENS signal may stimulate the hippocampus through direct spinoseptal pathways [2,19], and indirectly, mediated by two brain stem...
nuclei, the locus coeruleus (LC) [11,12] and the dorsal raphe nucleus (DRN) [14]. The LC and the DRN are major sources of the noradrenergic and serotonergic neurotransmitter systems, respectively [28,52]. Furthermore, the LC and DRN may relay the TENS signal and stimulate the CBF system through rostral noradrenergic and serotonergic projections into the basal forebrain [4,16,27]. The hypothesis that TENS could be effective in AD was based on the observation that a major neuropathological hallmark of aging and AD is brain atrophy [49,50]. Brain atrophy is characterized by shrinkage of cells and decreased metabolic neuronal activity [50]. These authors suggested that neuronal stimulation might slow down further degeneration and even initiate regenerative processes in aging and AD [49,50].

Based on the above mentioned theories and the positive effects TENS appeared to have on memory in both demented and non-demented elderly in previous TENS studies, the present study examined the effects of TENS on various aspects of memory in the elderly with MCI. In contrast to the former TENS studies, a larger number of patients were included here.

2. Methods

2.1. Subjects

Fifty-six, native Dutch speakers, were recruited from a population of 500 nursing home residents. Statistical power analysis performed before the start of the study indicated that the inclusion of approximately 60 subjects in combination with four moments of measurement with a conservative estimated effect size of 0.25 [3], would result in a power of 0.80.

The nursing staff of each participating nursing home was extensively informed about the procedure and implications of the study and asked for their subjective evaluation of residents showing signs of isolated memory deficiencies. Next, the selected residents were visited by a member of the research team and were informed about the nature and the purpose of the study. After informed consent, a first global cognitive screening was performed by the mini-mental state examination (MMSE) [15]. Following this initial screening subjects were required to have a diagnosis: MCI [17], i.e.: (1) the participant had to report mild forgetfulness, confirmed by the nursing staff; (2) the decline in memory function had to be objectively assessed by the memory items of the MMSE; (3) other cognitive functions had to be unimpaired, as supported by the nursing staff and the non-memory items of the MMSE; (4) the activities of daily living had to be intact; (5) no signs of dementia were to be present and confirmed by the medical staff and medical records. Furthermore, participants were excluded from the study, if their medical records reported a history of either psychiatric disorder, alcoholism, cerebral trauma, cerebrovascular disease, hydrocephalus, neoplasm, epilepsy, disturbances of consciousness, or focal brain disorders. Subjects having a pacemaker were also excluded from participating.

Subjects meeting the above criteria were randomly assigned to either an experimental group (n = 30) or a placebo group (n = 26). Both groups did not differ significantly in age (experimental group: M = 87.27, S.D. = 5.55, placebo group: M = 87.15, S.D. = 4.75), M (s) = 87.27, S.D. = 7.84, and mean MMSE score (experimental group: M = 22.43, S.D. = 3.73, placebo group: M = 23.35, S.D. = 2.23), M (s) = 23.35, S.D. = 1.09, p = 0.28. The educational level was measured with a seven-point scale, i.e.: (1) uncompleted elementary school; (2) six grades elementary school; (3) eight grades; (4) and (5) three and four years lower general secondary education, respectively; (6) pre-university education, technical college, higher vocational education; (7) university. The mean level of education of the experimental group (M = 3.20, S.D. = 1.29) showed no significant difference compared to the placebo group (M = 2.96, S.D. = 1.57), M (s) = 2.96, S.D. = 0.56. The experimental group contained 6 male and 24 female subjects, the placebo group 8 male and 18 female subjects. The difference in gender between both groups was not significant (Fisher’s exact: p = ns).

Prior to the actual treatment, both groups were familiarized with TENS treatment, i.e. the experimental received a trial TENS treatment in which the actual signal was generated by a TENS device. The placebo group was familiarized with a sham-stimulation treatment, i.e. treatment without current. Following this trial treatment, subjects were asked again if they were willing to participate in the actual 6 weeks treatment period.

3. Material and procedure

3.1. Neuropsychological tests

To evaluate possible treatment effects of TENS on various aspects of memory such as visual and verbal short-term and long-term memory, verbal and visual recognition memory and working memory, the following tests were administered:

- Digit span forward and backward from the Wechsler memory scale-revised (WMS-R) [53]. In the forward condition subjects were asked to repeat sequence of digits that are named aloud by the examiner. The forward condition commenced with sequences containing three different digits, the longest sequence included eight digits. After the subject has replicated two consecutive sequences containing the same number of digits correctly, the number of digits in a sequence was increased by one digit. If the subject failed to replicate sequences containing the same number of digits twice, the test was aborted. For the backward condition, subjects were required to repeat the sequence of digits spoken by the examiner in reverse order. This backward condition begins with sequences containing two different digits, whereas the longest possible sequence includes seven digits. The total score is the number of correct replicated and reversed sequences (maximum score: 24). Studies show that the digit span test forward of the WMS-R loads high on verbal short-term memory, whereas the digit span test backward loads high on extra working memory component.

- Visual memory span forward and backward from the WMS-R [53]. This subset of the WMS-R is considered the non-verbal equivalent of the digit span test. Like the digit span test, the test also consists of a forward and a backward condition. In this test, the examiner taps a number of blocks in
a given order. This sequence has to be copied by subjects in the forward condition, whereas in the backward condition subjects have to reverse the order the blocks are tapped in. The number of blocks included in a sequence are increased by one when a subject copies or reverse a consecutive sequence twice correctly. The test is terminated if a subject fails to copy or reverse two consecutive sequences including the same number of blocks tapped. The forward condition begins with a sequence including two blocks, while the most difficult pattern in this condition includes eight blocks. The backward condition of the visual memory span also begins with two blocks patterns and ends with a pattern including seven blocks. The score is the number of correctly copied and reversed sequences (maximum score: 26).

**The verbal learning and memory test (VLMT)** [9] , a Dutch version of the California verbal learning test (CVLT) [32] , is the number of correct responses from the Rivermead Behavioural Memory Test (RBMT) [54] . This subtest of the RBMT is designed to assess subject’s visual, non-verbal long-term memory. The test consists of a set of 10 cards (the extended version) depicting different faces. Each card is presented in a fixed order for 5 s. After an interval of 5 min, during which the subject was occupied with another test, subjects were required to select the original 10 faces from a set of 20 cards. The score of the face recognition test is the number of correct responses minus the number incorrectly recognized faces (maximum score: 20). To control for test–retest effects in this study, two different sets of cards were used.

**Picture recognition from the RBMT** [54] . This subtest provides a measure of the verbal component of the visual long-term memory. A set of 20 cards (extended version) depicting line drawings of various objects was presented for 5 s in a fixed order. The subject was instructed to recall and name the depicted object. After a 5 min occupied interval, a set of 40 cards was presented from which the subject was asked to select the 20 cards depicting objects shown before. The score is calculated as the difference of the correct answers and the incorrectly recognized cards (maximum score: 40). Similar to the face recognition subtest of the RBMT described earlier, two different sets of cards were used in this study.

**Word fluency (category fluency)** from the Groninger Intelligence Test [47] . In this subtest, subjects are instructed to name as many words belonging to a particular category in 1 min. The test includes an animal word category condition, i.e. the words required have to be animal names, and an occupational word category condition, i.e. the words named must represent an occupation. The test assesses the subject’s ability to retrieve familiar information from semantic memory. The score is the total of correctly named words over both categories.

### 3.2. Administration of the tests

#### 3.2.1. Sequence

The tests were administered in the following order: digit span (forward condition), digit span (backward condition), visual memory span (forward condition), visual memory span (backward condition), VLMT wordlist (immediate recall), RBMT face recognition (stimulus presentation), GIT word fluency (occupation names category), RBMT face recognition (response condition), RBMT picture recognition (stimulus presentation), GIT word fluency (occupation names category), RBMT picture recognition (response condition), VLMT wordlist (delayed recall), VLMT wordlist (delayed recognition), Trailmaking Test (version A). The administration of the neuropsychological test battery took, depending on a subjects’ capacity, about 1 h.

#### 3.2.2. Investigator

An independent investigator, who was blind to the experimental or placebo treatment, administered the neuropsychological test battery. Although it was not possible to test all 56 subjects by the same examiner, each individual subject was tested by the same investigator during the 18 weeks research period. Moreover, the test protocol was rigidly standardized. All examiners were trained in advance to give the same instructions and act uniformly during testing.

#### 3.2.3. Moments of measurements

The study included four measurement moments, during which the neuropsychological test battery was administered, i.e. a pre-treatment baseline measurement (T1) followed by a 6-week treatment- and examination-free period, a second baseline measurement (T2) administered a day before the 6-week TENS treatment period, a post-treatment measurement (T3) administered directly after cessation of the 6 weeks TENS intervention, and a delayed measurement (T4) administered after a 6-week treatment and examination free period.
Each individual subject who completed the study was followed for 18 weeks. This extended number of assessments provided the investigators more information about participants’ pre-treatment and post-treatment levels of memory functioning compared to studies that include two or three moments of measurements. Moreover, it resulted in an enhancement in power of the study. The whole study ran from May 2000 until September 2003.

### 3.3. TENS treatment

#### 3.3.1. Duration

In this study, participants were treated 30 min-a-day, 5 days-a-week, for six consecutive weeks. This treatment duration and period are based on earlier pain relief studies which reported analgesia after a peripheral stimulation duration of 20–30 min [13,20,38] that were maintained after a treatment period of at least 4 weeks [17,30]. TENS studies showed that a 30 min per day treatment for a 6-week period in groups of demented and non-demented elderly improved cognitive and behavioural functioning [45,46]. Unlike the sustained effect of TENS found in the analgesic studies, the beneficial effect of TENS on behaviour and cognition was not found to be sustained in the 6-week period after cessation of the intervention [41].

#### 3.3.2. Location

The TENS signal was administered using two self-adhesive carbon gel electrodes (2 cm × 3 cm) attached on both sides of the spinal column, between Th1 and Th5. This location was selected for practical reasons, i.e. participants did not have to undress and could not reach for the electrodes. Moreover, afferent spinoseptal pathways originate at this location [2,19].

#### 3.3.3. Frequency and intensity

TENS intervention studies hypothesize that the TENS signal, via afferent peripheral nerve fibres of the somato-sensory system, i.e. thick-myelinated A-Beta fibres, thin-myelinated A-Delta fibres, and unmyelinated C fibres [5,23], might (re)activate higher-level brain regions involved in memory functioning (see Section 1).

Animal experimental studies on analgesia indicate these three types of afferent nerve fibres to be unequally responsive to frequency and intensity of stimulation. The thick-myelinated A-Beta fibres respond optimally to both high-frequency stimulation (100 Hz) with concurrent low intensity [20,21,34] and to a low frequency (2 Hz)—high intensity (visible muscular contraction) stimulation type [26]. The thin-myelinated A-Delta fibres and the unmyelinated C fibres are triggered by a low-frequency (<10 Hz)—high intensity (visible muscular contractions) type of stimulation [25,31,48,55].

To achieve maximum effectiveness for the TENS intervention, the TENS signal applied in this study assembled various frequencies and intensities and, therefore, utilized the different transmission characteristics of the three types of nerve fibres.

### Table 1

<table>
<thead>
<tr>
<th>Neuronal afferent fibres</th>
<th>Summary of the separate memory tests</th>
<th>Treatment Placebo MANOVA d.f.</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMS-R digit span</td>
<td>Mean 8.11 S.D. 2.67</td>
<td>Mean 8.81 S.D. 2.08</td>
<td>Mean 8.11 S.D. 2.50</td>
<td>Mean 8.75 S.D. 2.22</td>
</tr>
<tr>
<td>WMS-R visual memory span</td>
<td>Mean 9.50 S.D. 3.06</td>
<td>Mean 10.14 S.D. 3.26</td>
<td>Mean 9.96 S.D. 2.50</td>
<td>Mean 9.64 S.D. 2.07</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>Mean 4.52 S.D. 4.70</td>
<td>Mean 3.52 S.D. 3.68</td>
<td>Mean 4.28 S.D. 4.03</td>
<td>Mean 4.13 S.D. 3.31</td>
</tr>
</tbody>
</table>

WMS-R: Wechsler memory scale-revised; Rivermead behavioural memory test; GIT: Groninger intelligence test.

*Printed in boldface: the mean scores on the various memory tests administered a day before the 6 week TENS treatment period (T2), and directly after cessation of the 6 week TENS intervention (T3).*
fibres best. This so-called BURST-TENS signal [13] consists of asymmetric biphasic square shaped impulses. It is 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 μs. The intensity of the signal evokes painless muscular contractions. The BURST-TENS signal was generated by a type Premier 10s electro stimulator.

### 3.3.4. Experimental versus placebo treatment

In the present study the experimental group was treated with the actual TENS signal consisting of the parameters described in the previous section, while the placebo group received sham stimulation. This sham stimulation was applied with an identical electro stimulator, not generating a TENS signal. Both groups were told that the TENS signal would be administered as soon as the green LED of the electro stimulator started to flash. Electrodes were attached following the same procedure and at the same location in both groups. Since the actual TENS signal is perceptible for experimental participants (evoking muscular contractions) and the sham stimulation is not, the subjects in the present study were treated individually. During the trial and actual treatment participants from both groups were informed that the perceptibility of the TENS signal varies for each individual. The therapist applying the TENS treatment could not be blinded for the experimental or placebo condition.

### 4. Data analysis

All statistical analyses were performed using SPSS-PC software [33]. In a preliminary analysis, the scores on each dependent variable for both groups were first explored using box plots of which the bottom and the top represent the 25th and 75th percentiles. Scores that fall between 1.5 and 3 box lengths, i.e. respectively outliers and extreme scores, were excluded from further analysis. Subsequently, independent-samples t-tests were applied on each separate neuropsychological test to find any significant between-group differences on the two pre-treatment measurement scores (T1, T2). Those tests that showed any significant group differences were excluded from further examination.

A repeated measures multivariate analysis of variance (MANOVA) with time (four levels: pre-treatment 1 (T1); pre-treatment 2 (T2); post-treatment (T3); delayed (T4)) as a repeated measurements factor, and group (experimental and placebo) as an independent factor, was used to analyze the scores of the separate memory tests over the four measurement moments.

Since the study has a strong explorative character, univariate analyses of variance (ANOVA) were performed on four different orthogonal contrasts [29] – i.e. T2–T3, an indication for treatment effects; T1–T2, indicative for cognitive stability before treatment starts; T3–T4, an indication for cognitive stability after cessation of treatment; and T1–T4, an indication of an overall effect over the 18 weeks research period – irrespective of a significant interaction between group and time in the MANOVA.

The data were analyzed on a separate test level and in addition, on a global measure of memory function. This global memory score was created by transforming the raw scores of all the included memory tests into z-scores and, subsequently, by calculating the overall mean z-score of the memory tests on each of the four moments of measurements.

Considering the fact that the MANOVA was performed over eight separate memory tests, the Bonferroni correction was applied to the significance level of \( p < 0.05 \). This resulted in a critical value of \( p < 0.006 \). The significance level with respect to the global memory score analysis remained at \( p < 0.05 \).

### 5. Results

An independent-samples t-test conducted over the T1 and T2 measurements of the individual tests showed no significant differences between the placebo and experimental conditions.
Consequently, a repeated measures MANOVA was performed over all eight separate memory tests.

5.1. Separate memory tests

Data-analysis with a repeated measures MANOVA did not reveal a significant interaction between group (experimental, placebo) and time (T1, T2, T3, T4) for any of the separate memory tests (for means, standard deviation and $F$-statistics, see Table 1). Further one degree of freedom interaction $F$-statistics were performed to explore the data. Results showed no significant interactions between group and time at the four defined orthogonal contrasts: T2–T3, T1–T2, T3–T4, T1–T4 (see Table 2). Fig. 1 shows the mean score of each separate memory test for the four moments of measurement for both the experimental and the placebo groups. Compared to
orthogonal contrasts for the global measure of memory, significance level at $p < 0.05$

<table>
<thead>
<tr>
<th></th>
<th>$d_i$</th>
<th>$F$</th>
<th>$p$</th>
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<tbody>
<tr>
<td>Global memory score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2–T3</td>
<td>1.52</td>
<td>0.63</td>
<td>0.43</td>
</tr>
<tr>
<td>T1–T2</td>
<td>1.52</td>
<td>0.01</td>
<td>0.93</td>
</tr>
<tr>
<td>T5–T4</td>
<td>1.52</td>
<td>2.98</td>
<td>0.09</td>
</tr>
<tr>
<td>T1–T4</td>
<td>1.52</td>
<td>7.26</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Contrast T2–T3, indication for treatment effects; contrast T1–T2, indication for cognitive stability after treatment starts; contrast T3–T4, indication for cognitive stability after cessation of treatment; T1–T4, indication for an overall effect over the 18 weeks research period.

Fig. 2. Mean scores and standard error of the mean for the global measure of memory on the four moments of measurement.

T1–T2, which depicts the natural fluctuation in mean memory scores during the 6 weeks treatment free period, the absence of a treatment effect between the experimental and the placebo group in the following 6 weeks treatment period T2–T3 is noticeable.

5.2. Global measure of memory

The repeated measures MANOVA revealed a significant group $\times$ time interaction effect for the overall mean memory $z$-scores, $F(3, 50) = 4.01, p = 0.01$. Further univariate analysis showed a significant group $\times$ time interaction for the contrast T1–T4, indicating a significant overall effect over the 18 weeks research period. The results of the four defined orthogonal contrasts are presented in Table 3. A paired samples $t$-test performed for this contrast showed a significant increase in global memory score for the placebo group ($t(24) = 2.58, p = 0.02$), whereas the score of the experimental group did not decrease significantly ($t(28) = -1.54, p = 0.14$). The significant interaction effect found in the orthogonal contrast between T1–T4 and group of the global memory score is depicted in Fig. 2.

6. Discussion

The present findings suggest that TENS did not have a positive effect on the performance of any of the neuropsychological tests. A repeated measures MANOVA performed over the global measure of memory showed a significant interaction between group (experimental, placebo) and time (T1, T2, T3, T4). This interaction effect was due to a significant increase in score in the placebo group and a non-significant decrease in score in the experimental group over the total 18 weeks research period (T1–T4). Thus, TENS did not have a positive influence on the global memory score.

The present results are in contrast to our hypothesis which was based on earlier TENS studies, in which TENS appeared to have a beneficial effect on memory of demented and non-demented elderly [43–46]. Moreover, these studies showed TENS to be more effective in an early stage of AD than in a more advanced stage [42]. The present study was designed to examine the effects of TENS on memory at a pre-clinical stage of dementia, i.e. in elderly with MCI.

This is the first study to examine the effect of TENS on memory in a MCI population. One can only speculate about the mechanisms underlying the absence of the hypothesized treatment effect. An explanation might be related to neurotransmitter changes in the cholinergic basal forebrain found in this transitional stage between normal and pathological aging. DeKosky et al. [8] observed a counter-intuitive up-regulation of choline acetyltransferase (ChAT) activity, the enzyme that is responsible for acetylcholine (ACh) synthesis, in the hippocampus and the superior frontal cortex of MCI elderly compared to normal aged individuals and AD patients. Deficits in ACh production and, therefore, dysfunction of the cholinergic system have been associated with cognitive disturbances and memory dysfunction [24]. It appears that the cholinergic system in this preclinical phase of AD responds in a unique chemoplastic fashion [8]. TENS is hypothesized to, among others, reactivate the hippocampal region and the pre-frontal cortex through cholinergic basal forebrain neurons. However, in MCI elderly, ChA T activity levels in the hippocampus and superior frontal cortex are elevated above those measured in normal aged and AD individuals. TENS stimulation might render no effect or a negative effect by overactivating this intricate compensatory mechanism. Neuroimaging techniques such as fMRI may provide useful information considering alterations in brain activity following TENS treatment in MCI.

Compared to earlier TENS studies, the strength of the present study is threefold. In the first place, the present group of participants was larger, i.e. 56 subjects, compared to sample sizes of former TENS studies, i.e. 16–18 subjects. In the second place the present study was multi-centered, whereas the former studies took place in one institute. In the third place, the number of therapists applying the TENS treatment in the present study was larger, i.e. 10, compared to earlier studies in which two to three therapists applied the treatment. These three factors make the present study a more realistic trial for possible future implementation of TENS treatment. If these three factors are related to the absence of a beneficial effect on memory, one could conclude that TENS treatment is not relevant for clinical practice.

Taken together, compensatory chemoplastic changes in the cholinergic neurotransmitter system specifically found
in MCI elderly might underlie the deficiency of the TENS treatment. On the other hand, the strength of the present study supports the reliability of the present findings and cautions us on how to interpret the results of previous studies.

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