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Transcutaneous Electrical Nerve Stimulation (TENS) for dementia (Review)

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[Intervention Review]

Transcutaneous Electrical Nerve Stimulation (TENS) for dementia

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ABSTRACT

Background

Transcutaneous electrical nerve stimulation (TENS) is the application of an electrical current through electrodes attached to the skin. The commonest clinical application of TENS is pain control. TENS is also used occasionally for the treatment of a range of neurological and psychiatric conditions including drug and alcohol dependence, headaches, and depression. TENS is rarely used for the treatment of dementia. However, since the early 1990s a number of studies carried out by a group in the Netherlands, and one study carried out by a group in Japan, suggest that TENS applied to the back or head may improve cognition and behaviour in patients with Alzheimer's disease or multi-infarct dementia. It was claimed that applying TENS could benefit patients with dementia by altering the activity of various neurotransmitters, or by increasing brain activity and thereby retarding neural degeneration and stimulating regenerative processes. It is claimed that application of TENS to the head may also alleviate the sleep disorders associated with dementia.

Objectives

The aim of this review is to determine the effectiveness and safety of transcutaneous electrical nerve stimulation (TENS) in the treatment of dementia. Secondary objectives of this review are to determine whether any effect of treatment of dementia with TENS is influenced by any treatment parameters or patient features, including: the duration of treatment, electrical waveform, current amplitude, pulse duration and frequency and the patient's type or severity of cognitive impairment.

Search methods

The trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 5 December 2005 using the terms TENS, transcutaneous, "transcutaneous electrical nerve stimulation", "electric stimulation", or "cranial electrostimulation" or "cranial stimulation". The CDCIG Specialized Register contains records from all major health care databases and many ongoing trials databases and is regularly updated.

Selection criteria

All RCTs in which TENS was used as an intervention for people with dementia were included in this review. This included peripherally applied transcutaneous electrical stimulation as well as transcutaneous electrical stimulation applied to the head (also known as cranial electrical stimulation (CES)).

Data collection and analysis

All randomized controlled trials (RCTs) that fulfilled the inclusion criteria for the review and for which sufficient data were available were included in this meta-analysis. Two reviewers extracted the data from the included trials. All except one of the included trials used similar outcome measures. Data of the same outcome measures were combined for analysis.

Main results

Nine trials were included in the review but only 3 trials could be included in the meta-analysis. Sufficient data to include the other trials in the meta-analysis could not be obtained. From this limited analysis it appears that TENS produced a statistically significant improvement directly after treatment in: delayed recall of 8 words in one trial, face recognition in two trials and motivation in one trial. However, no effect of TENS was found on any of the many other neuropsychological and behavioural measures evaluated either directly after TENS treatment or 6 weeks after treatment was completed.

Authors' conclusions

Although a number of studies suggest that TENS may produce short lived improvements in some neuropsychological or behavioural aspects of dementia, the limited presentation and availability of data from these studies does not allow definite conclusions on the possible benefits of this intervention. Since most of the currently published studies are well designed, although the numbers of subjects in each study is small, analysis of the complete original data from these and/or future studies may allow more definitive conclusions to be drawn.

PLAIN LANGUAGE SUMMARY

Insufficient data to determine the efficacy of transcutaneous electrical nerve stimulation for dementia

Transcutaneous electrical nerve stimulation (TENS) is rarely used for the treatment of dementia but has been studied in a number of randomized controlled trials. Although the available data suggests TENS may be beneficial for some neuropsychological and/or behavioural aspects of dementia insufficient data was available to these reviewers for definitive conclusions to be drawn.

BACKGROUND

Transcutaneous electrical nerve stimulation (TENS) is the application of an electrical current through electrodes attached to the skin. Many different electrical current waveforms with different characteristics can be used for this application but a biphasic pulsed waveform with alternating positive and negative polarity is most commonly used. By carefully adjusting the intensity and duration of the pulses, a comfortable tingling sensation without pain or muscle contraction, or a tingling with a muscle contraction, can be produced. This is possible because nerves that control muscle contractions and the nerves that transmit pain information to the brain are not as responsive to electrical stimulation as the nerves that transmit other sensory information. Thus, if a low intensity and short pulse is used only the sensory nerves and not the motor or pain transmitting nerves will respond. If a slightly higher intensity, or longer pulse duration, is used, both the sensory and the motor nerves, but not the pain transmitting nerves, will respond. The electrodes used most commonly at this time for the application of TENS are made of fabric or thin plastic and are coated on one side with a self-adhesive conductive gel. A pair of these electrodes, connected by wires to an electrical stimulator, is adhered to the patient's skin in the area where the stimulation is desired. Usually the electrodes are approximately 2 - 5 cm by 2 - 5 cm and are placed about 5 to 20 cm apart. The electrical stimulator is generally battery driven and approximately the size of a pager/ beeper.

The most common clinical application of TENS is for pain management. Two mechanisms for the effectiveness of TENS for this application have been proposed. Firstly, the comfortable sensory stimulus provided by TENS may inhibit transmission of noxious stimuli at the spinal cord. This is frequently referred to as the gate control mechanism. The sensory stimulus provided by the peripherally applied electrical current stimulates afferent A-beta sensory fibers. The A-beta fiber activity causes an increase in activity of neurons in the substantia gelatinosa of the spinal cord. Substantia gelatinosa activation inhibits transmission of painful sensations from A-delta and C fibers to the brain. The sensory stimulation of the A-beta nerves is said to close the gate to transmission of the signal from the nociceptive A-delta and C fibers. Secondly, TENS stimulation with a sufficient pulse duration and current amplitude to cause a muscle contraction, has been shown to stimulate the production of natural opiates, including endorphins and enkephalins. These natural opiates can also centrally inhibit the perception of pain.

Since the 1920s, TENS has occasionally been used for the treatment of a range of neurological and psychiatric conditions including drug and alcohol dependence, headaches, and depression (Wagender 1967, Wageneder 1970, Straus 1964, Rosenthal 1972). It has also been used to potentiate the effects of anaesthetic drugs (Limoge 1999). TENS is rarely used in clinical practice for the treatment of dementia. However, since the early 1990s a number of studies carried out by a group in the Netherlands, and one study carried out by a group in Japan, suggest that TENS may improve cognition and behaviour in patients with early and mid-stage Alzheimer's disease. Specifically, these studies suggest that TENS may improve long- and short-term memory (Scherder 1992, Scherder 1995a, Scherder 1998, Scherder 1999), verbal fluency (Scherder 1998), circadian rest-activity rhythm (Van Someren 1998, Scherder 1999a), and, physical, social and affective functioning of patients (Scherder 1995a). In addition, a few studies have evaluated the effects of applying electrical stimulation via electrodes placed on the earlobes or the head, to produce cranial electrical stimulation (CES) (Hozumi 1996, Scherder 2002). It is proposed that CES may exert effects via stimulation of the peripheral sensory nerves of the head or directly by stimulating the brain itself. One study indicated that CES can improve the sleep-wake cycle and other behaviour in patients with dementia (Hozumi 1996).

The authors of the above mentioned studies propose that TENS applied to the back of patients with dementia may produce benefits by altering the activity of various neurotransmitters. A number of studies in humans have demonstrated that TENS can cause changes in cholinergic (Chen 1981; Romo 1987), serotonergic (Autrum 1982, Belanger 1985, Youing 1985) and noradrenergic (Sherman 1980, Tyce 1981) neurotransmitter systems. In addition, it is proposed that the peripheral stimulus provided by TENS may also enhance higher-level brain function more directly via ascending neural pathways transmitting information to the brain. Animal studies have demonstrated that peripheral somatic stimulation can cause CNS activation in a number of regions, including the hippocampus which is associated with memory functions, as well as acetylcholine release (Dutar 1985, Dudar 1979). It is proposed that the stimulation produced by TENS would have the same effect. By the "use it or lose it" principle, this activation of neurons may prevent or retard cell degeneration and initiate regenerative processes. This may counteract or prevent cell death in the hippocampal region and prevent or retard atrophy of cells in the basal forebrain region. Such effects on the forebrain may be mediated by projections from the locus coeruleus and dorsal raphe nucleus. In addition, the authors of these studies note that an advantage of TENS over many drugs intended to treat dementia is that it does not have to cross the blood-brain barrier. It is proposed that TENS applied to the head may improve the sleep disturbances associated with dementia because this type of treatment has been found to help otherwise healthy people with sleep disorders and prevent drowsiness in the absence of disordered sleep (Iijima 1986, Shimizu 1986, Sato 1985). The mechanism for this effect has not been elucidated.

To determine the value of TENS in the treatment of dementia, including optimal treatment parameters and patient characteristics, a systematic review of this literature is needed. No systematic reviews or meta-analyses on this subject have yet been published.

OBJECTIVES

Primary objective:
The aim of this review is to determine the effectiveness and safety of transcutaneous electrical nerve stimulation (TENS) in the treatment of dementia.

Secondary objectives:
To determine whether any effectiveness of treatment of dementia with TENS is influenced by any treatment parameters or patient features, including:

- Duration of treatment
- Electrical waveform
- Current amplitude
- Pulse duration or frequency

- Patient's type or severity of cognitive impairment

METHODS

Criteria for considering studies for this review

Types of studies

All unconfounded, randomized, placebo-controlled clinical trials with concealed allocation of subjects are included in this review. Interrupted time series trials are excluded.

Types of participants

The report includes patients with dementia of any type. The patients are of either sex and of any age (although almost all are 65 years of age or older). Both in-patients and outpatients (with or without caregivers) are included. The presence and type of dementia, unclassified or diagnosed, is identified according to the classifications provided by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (APA 1994) and the ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research] (WHO 1992). Studies prior to 1994 use criteria for dementia found in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM III) and DSM III Revised. In the absence of these criteria relevant rating scales such as the Mini-Mental State Examination (Folstein 1975), psychiatric evaluation, psychological evaluation, or a medical evaluation are considered acceptable.

Types of interventions

Transcutaneous electrical nerve stimulation (TENS) of any kind and with any pattern or duration of application. Patients may be receiving other types of interventions, including medications and other psychiatric treatment, at the time of study.

Types of outcome measures

Dementia produces change and decline in a host of neuropsychological and functional abilities. The specific outcomes chosen here to assess the potential effects of TENS on dementia are those most frequently described in the limited literature in this area. Although these measures vary in their clinical relevance, in aggregate they represent many of the disabling features of dementia that should be meaningful to clinicians and patients alike. These include:

- Visual and verbal short- and long-term memory
- Semantic verbal fluency
- Circadian rest-activity rhythm
- Affect/depression
- Level of independent functioning
- Adverse effects
- Drop out

Search methods for identification of studies

The trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 5 December 2005 using the search term: tens, transcutaneous, "transcutaneous electrical nerve stimulation", "electric stimulation" or "cranial electrostimulation" or "cranial stimulation".

The Specialized Register at that time contained records from the following databases:

- CENTRAL: July 2005 (issue 3);
- MEDLINE: 1966 to 2005/08, week 2;
- EMBASE: 1980 to 2005/08, week 2;
- PsycINFO: 1887 to 2005/07;
- CINAHL: 1982 to 2004/07;
- SIGLE (Grey Literature in Europe): 1980 to 2004/06;
- ISTP (Index to Scientific and Technical Proceedings): to May 2000;
- INSIDE (BL database of Conference Proceedings and Journals): to June 2000;
- Aslib Index to Theses (UK and Ireland theses): 1970 to March 2003;
- Dissertation Abstract (USA): 1861 to March 2003;
- http://clinicalstudies.info.nih.gov/;
- National Research Register (issue 3/2005);
- ClinicalTrials.gov: last searched 1 September 2005;
- LILACS:Latin American and Caribbean Health Science Literature: last searched April 2003;
- http://www.forestclinicaltrials.com/: last searched 1 September 2005;
- ClinicalStudyResults.org: last searched 1 September 2005;
- http://www.lillytrials.com/index.shtml: last searched 28 August 2005;
- ISRCTN Register: last searched 1 September 2005;
- IPFMA Clinical trials Register: www.ifpma.org/clinicaltrials.html: last searched September 2005

The search strategies used to identify relevant records in MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS can be found in the Group's module.

English and non-English language publications were reviewed. Where indicated, authors of publications and manufacturers of TENS devices were contacted for additional information. A hand search for recent relevant articles available in medical libraries was also carried out.

Data collection and analysis

- Identification of studies:

Searching and screening of the results was performed independently by two reviewers (MHC, EL or HL). The reviewers selected trials for relevance and against defined inclusion criteria. Trials that did not meet the criteria were excluded. Reviewers' selection of trials was compared and the final list of studies was reached by consensus between the reviewers or adjudicated by the third reviewer.

- Inclusion criteria:

Trials were ranked using one of the Cochrane approaches (Mulrow 1997)
Grade A: Adequate concealment (randomization; placebo controlled; concealed allocation).
Grade B: Uncertain.
Grade C: Inadequate concealment; no randomization.

Only trials with a grade A or B ranking were included in the review. Since trials with inadequate concealment have been shown to overestimate treatment effect (Chalmers 1983; Schulz 1994) these will be excluded.

Based on the search strategy, a total of 14 research papers were identified. Of these, 3 were determined to be reports of the same study. Of the 12 studies, 8 met the inclusion criteria and 4 failed to meet the inclusion criteria. Excluded studies used matched groups rather than randomising group assignment.

- Data extraction:

Data was extracted from the published reports. The summary statistics required for each trial and each outcome for continuous data are the mean change from baseline, the standard error of the mean change, and the number of patients for each treatment group at each assessment. Where changes from baseline are not reported, the mean, standard deviation and the number of patients for each treatment group at each time point were extracted.

For binary data the numbers in each treatment group and the numbers experiencing the outcome of interest were sought. For some binary or ordinal outcomes the endpoint itself is of clinical relevance as all patients are by definition at the same baseline score.

The baseline assessment is defined as the latest available assessment prior to randomization, but no longer than two months prior.

For each outcome measure, data was sought on every patient assessed. To allow an intention-to-treat analysis, the data was sought irrespective of compliance, whether or not the patient was subsequently deemed ineligible, or otherwise excluded from treatment or follow-up. If intention-to-treat data are not available in the publications, "on-treatment" or the data of those who complete the trial will be sought and indicated as such.

In studies where a cross-over design was used, only data from the first treatment phase after randomization was eligible for inclusion. Individual patient data was requested for further examination.

- Analysis of data:

The outcomes measured in clinical trials of dementia often arise from ordinal rating scales. Where ordinal scales used in the trials have a reasonably large number of categories (more than 10) the data were treated as continuous outcomes arising from a normal distribution.

Summary statistics (n, mean and standard deviation) were required for each rating scale at each assessment time for each treatment group in each trial for change from baseline. For crossover trials only the data from the first treatment period were used.

When change from baseline results are not reported, the required summary statistics were calculated from the baseline and assessment time treatment group means and standard deviations. In this case a zero correlation between the measurements at baseline and assessment time will be assumed. This method overestimates the standard deviation of the change from baseline, but this conservative approach is considered to be preferable in a meta-analysis.

The meta-analysis requires the combination of data from trials that may not use the same rating scale to assess an outcome. The measure of the treatment difference for any outcome was the weighted mean difference when the pooled trials used the same rating scale or test, and the standardised mean difference, which is the absolute mean difference divided by the standard deviation when they used different rating scales or tests.

For binary outcomes, such as clinical improvement or no clinical improvement, the odds ratio was used to measure treatment effect. A weighted estimate of the typical treatment effect across trials, the 'typical odds ratio' (i.e. the odds of an unfavourable outcome amongst treatment-allocated patients to the corresponding odds amongst controls) was calculated using Peto's log-rank test adapted for ordinal data (EBCTCG, 1990).

For some ordinal outcomes data may be concatenated into the two categories that best represent the contrasting states of interest, and the variable treated as binary.

Overall estimates of the treatment difference are presented. In all cases the overall estimate from a fixed effects model is presented and a test for heterogeneity using a standard chi-square statistic was performed. If there was significant heterogeneity a random effects model is presented.

Although it would be desirable to perform subset analyses for factors such as the age and sex of patients, their type and stage of dementia, the nature of the TENS treatment and the types of other concurrent interventions, the number of patients available in the studies was not large enough to permit such sub-group analysis. Since there were not sufficient patients for subset analysis, the overall effects of treatment with TENS on patients with dementia was evaluated.

RESULTS

Description of studies

The studies in this review readily fall into two groups - the Dutch studies and the Japanese study. Within each group, the studies use similar experimental design, subjects, interventions and outcome measures. Below follows a description of these two groups of studies in general and the features that differentiate the studies within each group.

THE DUTCH STUDIES
Authors: All of these studies are authored by Erik J. A. Scherder and colleagues.

Study design:
All included studies are randomized, placebo-controlled, double-blind trials. Studies were excluded if they used matched rather than randomly assigned groups.

Subjects:
In all studies the subjects were chosen from a group of 350 to 500 residents of a residential home for elderly people. The age range of the subjects was approximately 70 to mid 90 years old. When sex is specified the subjects were mostly female (> 80%). All subjects met NINCDS-ADRDA criteria for the clinical diagnosis of probably AD, mostly with early AD but some with midstage AD. Subjects generally had scores of 17 or less on the Hamilton Depression Rating Scale (Hamilton 1960) indicating that their cognitive impairment was

not due to depression. Exclusion criteria in all studies included a history of psychiatric disorder, alcoholism, cerebral trauma, cerebrovascular disease, hydrocephalus, neoplasm, epilepsy or disturbances of consciousness. For some trials, infection, kidney or lung disease or focal brain abnormalities were also exclusion criteria. When cognitive functioning was assessed, subjects' scores on a limited MMSE or a similar test indicated serious cognitive disturbances. The number of subjects ranged from 8 to 20.

INTERVENTIONS:
All included studies, except the most recent one published in 2002 which addresses cranial electrostimulation, used a similar TENS intervention protocol.

Stimulator type: Premier 10s.
Waveform: Asymmetric biphasic square wave, Burst mode.
Frequency: Bursts of trains, 9 pulses/burst, pulse freq 160Hz, burst freq 2 Hz.
Pulse duration: 100 microseconds.
Amplitude: Visible muscle twitches.
Electrode location: Two 2 x 3 cm electrodes between T1 and T5 on 2cm from the spine.

For the study on cranial electrical stimulation an AlphaStim 100 stimulator was used to apply an electrical current with a bipolar asymmetric rectangular waveform, a frequency of 0.5 Hz, and an intensity between 10 and 600 microAmps, at just below the threshold level for sensation, and the electrodes were applied to the earlobes.
The treatment duration for both types of treatment was generally 30 minutes per day, 5 days per week for 6 weeks, although in one study stimulation was applied for 6 hours per day.

Placebo intervention: Same as experimental except with no current delivered.

Update 2006
Another study by Scherder, Scherder 2003, has been included. It follows the same design and methodology as the previous trials. The treatment was cranial electrostimulation (CES). The hypothesis that was tested was that low frequency CES could decrease sleep disturbance in the sleep-activity rhythm in patients in a relatively early stage of AD. A secondary hypothesis to be investigated was that an improvement in rest-activity rhythm could be reflected in a decrease in the level of cortisol.

OUTCOME MEASURES:
These studies generally used a similar collection of neuropsychological and behavioural outcome measures that are well described and referenced in all reports. These measures include:

NEUROPSYCHOLOGICAL TESTS:

- Digit span: This is a subtest of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler 1984). This is a standard digit span forward/backward task with an ordinal scale starting at 0 and increasing with improved memory.
- Visual memory span: This task is also a subset of the WMS-R (Wechsler 1984) that can be considered as the nonverbal equivalent of the digit span test. For this test, in the forward condition, the examiner taps a number of blocks in a given order which is then copied by the subject. In the backward condition the subject must repeat the sequence in reverse. The number of blocks in a sequence is gradually increased and the score is the total number of correct sequences.
- Fifteen or 8 words test with tests for immediate recall, delayed recall and recognition (Heslinga 1983, Lindeboom 1989): This is a measure of auditory verbal long-term memory. This task requires the subject to memorize 15 or 8 unrelated Dutch words, immediately and also after a delay. Only the initial study, (Scherder 1992) used the 15 word test while all later studies used the 8 word test. The words are first presented orally five times by the examiner. Subjects are required to recall as many words as possible after each presentation. The immediate recall score is the subject's total number of correctly recalled words minus the expected recall score. The expected recall score is a standardised score which, by means of a regression formula, predicts the subject's performance on the basis of age and education. A negative score means that the subject's performance is less than his/her expected performance level. After an occupied interval of 10 minutes, the subject is again asked to recall as many words as possible. The delayed recall score is the total number of correctly recalled words minus the expected delayed recall score. The subjects are then read twice as many words as in the initial test (i.e. 30 words for the 15 word test, 16 words for the 8 word test) in random order, and they are asked to recognize as many words as possible. The recognition score is the number of correctly recognized answers minus the number of incorrectly recognized answers.
- Face recognition: This test is from the Rivermead Behavioural Memory Test (RBMT) (Wilson 1987) that provides a measure of visual, nonverbal long-term memory. Five faces are shown successively to the subject. After an occupied interval of 5 minutes the subject is required to select the original 5 faces from a set of 10. The recognition score is the number of correct answers minus the number of incorrect answers.
- Picture recognition: This test is also from the RBMT (Wilson 1987). It provides a measure of visual, verbal long-term memory. Line drawings of 10 common objects are presented one at a time. After an occupied interval of 5 minutes, the subject is asked to select the original 10 pictures from a set of 20. The recognition score is calculated in the same way as in the face recognition test.
- Word/verbal fluency: This test comes from the Groninger Intelligence Test (Snijders 1983), a Dutch intelligence test. This task measures the ability of subjects to retrieve familiar information from semantic memory. Subjects are required to name as many words as possible in one minute (names of occupations in one condition and names of animals in another condition). The score is the mean scaled score of the two conditions (M = 50; SD = 10).

BEHAVIOURAL OBSERVATIONAL SCALES:

- Beoordelingsschaal voor Oudere Patienten (BOP) (Van der Kam 1971): This is a standard factor-analysed rating scale for elderly patients that produces a total score and scores on six subscales: need of help, aggressiveness, physical invalidity, depressed behaviour, mental invalidity and inactivity. This scale is based on the Stockton Geriatric Rating Scale (Meer 1966). Higher scores on this scale indicate greater impairment.
- Behaviour Inventory: This is a scale developed by the authors that includes 12 main traits which each consist of a varying

number of items, with a total of 44 items. The main traits are depression, elation, shyness, mood, anger, tiredness, activity, anxiety, conscience, indifference, cognition, and contact. Each item was measured on a 5 point scale ranging from -2 to +2. A score of -2 means 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.

For both observational scales, all subjects were evaluated by a nursing staff consisting of 10 nurses trained to observe patients' behaviour. They were blinded to group assignment.
All of the neuropsychological tests and behavioural evaluations were performed the day before treatment began (for pre-treatment scores), a day after completion of six weeks of treatment (for post-treatment scores) and again after a 6 week period without treatment (for delayed scores).

Two of the published studies (Van Someren 1998, Scherder 1999a) evaluated rest-activity/circadian rhythms using a device called an actigraph that was developed by the authors (Van Someren 1993). This device measures acceleration-induced wrist movements and sums them hourly. From this data an Interdaily Stability (IS) (a measure of coupling to Zeitgeber), Intradaily Variability (IV) (a measure of fragmentation) and Relative Amplitude (RA) are calculated. IS is the ratio between the variance of the average 24 hour pattern around the mean and the overall variance. IV is the ratio of the mean squares of the difference between successive hours and the mean squares around the grand mean (overall variance). RA is the difference in activity between the 5 hour period of least activity and the 10 hour period of most activity. Although these measures from the actigraph have been validated as indicators of activity in patients with Parkinson's disease, they have not been validated as measures of circadian rhythms or rest/activity rhythms in any population.

For one study, (Scherder 2000), the Beck Depression Inventory (Beck 1961) was also used to assess mood. For another study, (Scherder 2002), the Philadelphia Geriatric Center Morale Scale (PGCMS) (Lawton 1975) and a symptom checklist, (SCL-90) (Derogatis 1977) were also administered.

DATA ANALYSIS:
For most studies ANOVA were used to evaluate differences between experimental and control subjects and between pre-treatment, post-treatment and delayed scores. In all tests the critical significance level was set at 0.05. Post-hoc corrections for multiple tests on the same group were not used. Scherder 2003 analysed the repeated measures on patients using a multi-level, random coefficients model. The measurements on individual patients were modelled over time. The coefficients of fitted curves are the random effects, and the treatment is the fixed effect. They did not present simple analyses of the change from baseline at endpoint and delayed endpoint for each treatment group, for each outcome.

THE JAPANESE STUDY
There are three reports on the application of TENS for dementia (Hozumi 1992; Hozumi 1996; Okawa 1999) authored by a group in Japan. The reports of these studies are very similar and their authors confirmed that they are all reports of the same single study. The data used in this analysis is from the Hozumi 1996 paper where it is most completely reported.

- Authors: these 3 papers are all authored by the same group, although the authors appear in different orders.
- Study design: double-blind cross-over
- Subjects: in contrast to the Dutch studies where the subjects had probable Alzheimer's disease as the cause of their dementia, the subjects in this study were thought to have multi-infarct dementia or Alzheimer's disease and were selected on the basis of irregular sleep-wake patterns in conjunction with nocturnal behaviour disorders and/or delirium. Twenty seven subjects completed this study.
- Interventions: stimulator type: HESS-10. Waveform: rectangular pulses. Frequency: 6 - 80 Hz. Pulse duration: 0.2 ms maximum, rms of 256 microAmps. Amplitude: 6 - 8 V. Electrode location: transcranial with electrodes attached to the "forehead and inion with a head-band". Treatment duration: 20 minutes daily for 2 weeks. Placebo treatment: same as experimental but electrodes disconnected from the device.
- Outcome measures: only one report documented statistical analysis of their results (Hozumi 1996) although all commented on similar outcomes. The outcomes evaluated were sleep disorder, motivation, behaviour disorder, intelligence, emotion, language, neurological signs, subjective complaints and activities of daily life. All of these were rated on a 5 point scale: absence of the related symptom: 0, mildy disturbed: 1, moderately: 2, markedly: 3, and severely:4. In addition, EEGs were recorded before and after the two week intervention. The EEG was considered improved if the frequency and/or continuity of background alpha or theta waves increased and was considered worse if there was an increase in paroxysmal intermittent delta waves or spike waves after treatment.

Risk of bias in included studies

The studies included in this review have a number of strengths and weaknesses. The strengths of the included studies are that the subjects are a fairly homogeneous sample, of similar age and stage of dementia, and that they are well described. In addition, the interventions and outcomes are well described in most of the reports. These consistencies allow combination of the data from the various studies in a meta-analysis. The placebo intervention of mimicking the active treatment completely except that no current was delivered to the electrodes provides a good comparison with the active treatment. It is not clear from the reports if the clinician applying the treatment could tell whether or not there was current flowing. Ideally, the device would appear to be delivering current for both the true and the placebo intervention. Since it is not possible to deliver a placebo treatment that feels the same to the patient as active TENS treatment, ideally the subjects would be naive to TENS so they would not know what sensation, if any, to expect. None of the reports comment on the subject's prior experience of TENS. The fact that most of the outcome measures used have been validated, or are subscales of validated measures, increases the reliability and validity of any conclusions that might be drawn from a systematic review or meta-analysis.

A consistent weakness of all the studies included in this review is a small sample size, with no study having more than 27 subjects in total and most having fewer than 20. The small sample size reduces the likelihood of detecting an effect of an intervention in a single study but, given the similarities between studies, makes a meta-analysis of the data from multiple studies particularly valuable. The reports from the Dutch studies suggest that all the studies were

carried out in a single institution, making it possible that the same subjects may have been included in multiple studies. If this were so, their data could not readily be combined in a meta-analysis. However, the primary author of these studies stated in a personal communication with the authors of this review that no subjects were used in more than one study. Although different subjects were used for the different studies, the fact that all the subjects were residents of the same facility may still limit the generalizability of the findings. Although most of the outcome measures used in the included studies have been validated a number of measures that have not been validated, or subscales of validated measures that have not been independently validated, are also used in these studies. When a measure has not been validated its interpretation is limited. The feature that most limits interpretation of the included studies is their limited reporting or provision of the actual results of the testing performed. Most of the reports provide only p values for the difference between pre-treatment, post-treatment and delayed scores within each group. They do not present the original mean group scores or analysis of between group comparisons, thus limiting further analysis of their data.

Effects of interventions

Of the 15 reports that met the search criteria for this review 9 met the criteria for inclusion. Two reports (Hozumi 1992, Hozumi 1999) were excluded because the data they reported in relation to the use of TENS for dementia was included and more fully described in another published study (Hozumi 1996). Two reports on the effects of cranial electrical stimulation on circadian rhythm disturbance in patients with Alzheimer's disease were excluded because the subjects were not selected to have circadian rhythm disturbances and because the outcome measure used has not been validated for this application (Van Someren 1998, Scherder 1999a).

Of the 9 studies that met the criteria for this review, only 3 (Scherder 1998, Scherder 1999, Hozumi 1996) were included in the meta-analysis because these were the only studies for which sufficient data could be obtained. Only the data presented in published reports could be analysed because further data could not be obtained from the authors at the time of this review.

Benefits of intervention
A significant effect in favor of treatment of dementia with TENS was found in both delayed recall of 8 words (effect size 1.06, 95% CI 0.21, 1.91) (based on Scherder 1998 only) and face recognition (effect size 2.77, 95% CI 0.04, 5.51) (based on Scherder 1998 and Scherder 1999) immediately after 6 weeks of application of TENS to the back . In addition, a significant effect in favour of treatment with TENS was found in motivation (p=0.00001, effect size 0.85, 95% CI 0.53, 1.17) immediately after 2 weeks of application of TENS to the head (based on Hozumi 1996 only). No significant effects of treatment were found for any of the many (>10 for most studies) other neuropsychological or behavioural measures evaluated immediately or 6 weeks after completion of six weeks of treatment with TENS.

Adverse effects
The only adverse effects mentioned were in one study that one patient to whom cranial electrical stimulation was applied complained of a dull pain the head with active treatment (Hozumi 1996). None of the other reports mentioned any adverse effects from treatment with TENS however it does not appear that adverse effects were monitored for.

DISCUSSION

Although this systematic review and meta-analysis of the currently published and available data on the use of TENS in dementia suggests that this intervention may have some short lived neuropsychological benefits, the limited availability of data does not allow one to draw any reliable conclusions about the presence or level of benefit, or means to optimize such possible effects. Although nine studies, each with approximately 20 subjects in both their treatment and placebo groups, met criteria for inclusion in this review, sufficient data for analysis could only be obtained for three of these studies and the analysis of these three was also limited. Of the three studies where sufficient data for analysis could be obtained, only two used the same outcome measures, allowing their outcomes to be assessed together in a meta-analysis. For the two studies where data could be combined, since the standard error which was estimated from available data was probably an overestimate, the effect of treatment may have been underestimated. Thus, although our search and review indicates that a number of studies that may be able to demonstrate the effects of TENS on dementia have been carried out, the limited presentation and availability of data from these studies limits one's ability to draw clear conclusions. Should the data from more of the reviewed studies become available it may be possible to more clearly assess the effects of TENS on dementia in the populations studied. None the less, since almost all the studies were carried out by one group of researchers working with residents of one home for the elderly, until studies are carried out with more varied samples, these findings should be extrapolated to a wider population with caution.

The electrical stimulation parameters (waveform, pulse duration, pulse frequency, current amplitude, electrode placement and treatment duration) used for the TENS interventions in the reviewed studies were almost always the same. Although this allows one to draw stronger conclusions about the effects of TENS delivered in this manner, it does not allow for evaluation of the effects of variation in specific parameters or for selection of optimal parameters. The parameters used for most of the studies were selected to stimulate large diameter A-beta non-nociceptive afferent sensory nerves, medium diameter efferent motor nerves and small diameter high threshold afferent nociceptive A-delta and C nerves. This type of stimulation is likely to take advantage of a variety of physiological effects of peripheral nerve activation but does not allow one to distinguish the effects of stimulating different nerve types. It is possible that other treatment parameters could be as, or more, effective, if the effects of treatment were dependent on activation of only a subset of peripheral nerves or, if central nervous system activation does not directly correlate with the stimulated peripheral nerve activation. Such differential activation of central and peripheral nerves is likely because some types of peripheral activation can have inhibitory effects on transmission to the central nervous system.

The reports of the reviewed studies indicate that a wide range of possible neuropsychological and behavioural benefits of TENS on dementia were assessed. The breadth of this assessment, and the fact that validated measures were used, makes it likely that positive effects of this intervention would be detected. Most studies did not document monitoring for adverse effects, making it possible that risks associated with with the use of TENS for dementia may have been missed. However, since very few adverse effects

are mentioned in other literature on TENS, it is unlikely that this treatment carries significant risks. In most other applications, the most prominent risks associated with TENS are poor tolerance of the sensation of the electrical stimulation and potential alteration of cardiac rhythm in patients with demand cardiac pacemakers. Thus, TENS should not be used to treat individuals who do not tolerate the sensation of the stimulation or for those with demand cardiac pacemakers. It has also been suggested that TENS may enhance epileptic activity; however, there is no evidence to support this suggestion. Some patients react with an allergic urticarial rash to the adhesive used on TENS electrodes and fragile, thin skin may be damaged by removal of self adhering electrodes. Problems with electrodes can generally be overcome by using different types of electrodes either without adhesive or with different types of adhesive.

This meta-analysis demonstrated a beneficial effect of TENS as compared with placebo TENS on delayed word recall, face recognition and motivation assessed directly after completion of treatment. Although these findings suggest that TENS may improve some neuropsychological aspects of dementia, they should be interpreted with caution because they are isolated positive findings amongst a large number of neuropsychological and behavioural tests. Statistically, using a p value of 0.05, as was done in all the reviewed studies, there is a one in twenty chance of reporting a positive effect even when no such effect exists. Thus, the few positive effects reported may be random variation in the outcome measured rather than a true impact of the treatment provided. In addition, the mechanism or clinical relevance of the isolated positive findings in the context of the many other negative findings is not clear. The fact that these findings are based on a very small number of subjects has mixed implications. On the one hand, detecting a statistically significant effect with a very small number of subjects indicates that the effect size is large. On the other hand, studies with small numbers are more likely to have unknown biases in selection that can exaggerate a treatment effect. It is also of note that the authors of the individual studies reviewed frequently conclude incorrectly that TENS is beneficial for dementia based on comparison of pretreatment status with posttreatment status within groups rather than correctly comparing the change in scores in the treated group with the change in scores in the placebo group. This type of assessment error is likely to over estimate the effect of an intervention. For this meta-analysis, the data presented in the published papers was used to calculate between-group differences and these were then used in the meta-analysis.

The indication of some positive findings for an effect of TENS on dementia lends support to a need for further evaluation of this intervention. It is recommended that such evaluation include further assessment of the data already collected for the reported studies where the data were not published in full or currently made available, should this be obtainable. In addition, in order to increase the generalizability of the findings to a wider population, it is recommended that this work be replicated in a larger group of individuals with dementia, ideally in multiple sites.

AUTHORS' CONCLUSIONS

Implications for practice

Although the use of TENS in patients with dementia is unlikely to have adverse effects, at the present time there is insufficient data available to recommend the use of TENS in the clinical treatment of most individuals with dementia.

Implications for research

The data available from research on the effects of TENS on dementia suggest that this intervention may have some short-lived positive effects on some aspects of neuropsychological function. Strong conclusions however cannot be drawn because sufficient data for meta-analysis could only be obtained for a small number of subjects in a small number of trials. In addition, since the positive findings were found in the context of many tests that did not demonstrate any effect of TENS, it is possible that these findings are spurious. Further analysis of the data already collected but not made available from the currently published studies, and further larger scale studies with more varied samples, would allow one to draw strong conclusions about the possible benefits of TENS in the treatment of dementia.

Given the indication that TENS may benefit people with dementia and the limitations of the current studies and available data, further research in this area is recommended. Future research with similar design and methodology to prior studies, but with larger sample sizes, more varied samples of the population, and where the treatment effect with standard error is fully reported, will allow one to draw clearer conclusions about the possible effects of this intervention.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Hozumi 1996

Methods	Randomised, double-blind, placebo-controlled, 2 weeks
Participants	Japan Single center 27 subjects, 14 expt, 13 control 12M, 15 F Age 58 - 86 Inpatients With multi-infarct dementia with irregular sleep-wake patterns and nocturnal behavior disorders and/or delirium. Exclusion: sleep apnea
Interventions	Stimulator type: HESS-10 Waveform: rectangular pulses Frequency: 6 - 80 Hz Pulse duration: 0.2 ms maximum, rms of 256 microA Amplitude: 6 - 8 V Electrode location: transcranial with electrodes attached to the "forehead and inion with a head-band" Treatment duration: 20 minutes daily for 2 weeks Placebo treatment: same as experimental but electrodes disconnected from the device.
Outcomes	Evaluated the following categories with subitems: Chi square modified by Akaike information criterion. Sleep disorder: improved in both treatment and placebo groups, $p < 0.01$ for both and no significant difference between groups. Motivation: improved, $p < 0.01$ Behaviour disorder: improved $p < 0.05$

Hozumi 1996 *(Continued)*

	Intelligence: no signif change Emotion: no signif change Language: no signif change Neurological signs: no signif change Subjective complaints: improved, $p < 0.01$ Activities of daily life: no signif change All rated on a 5 point scale. EEGs also recorded pre and post and considered improved if the frequency and/or continuity of background alpha or theta waves increased. EEG considered worse if there was an increase in paroxysmal intermittent delta waves or spike waves after treatment. In the active therapy group improvement in background EEG was seen in 10/14 patients. In the placebo group improvement in background EEG was seen in 5/13. This was a significant difference between groups $p < 0.05$. There were no significant differences found in paroxysmal EEG waves between placebo and active therapy groups. Adverse effects: one pt complained of a dull pain in the head with active treatment.
Notes	Transcranial stimulation. This is the same trial as described in Hozumi 1992 and Okawa 1999. 2 cases with improvements described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Scherder 1998

Methods	Randomised, double-blind, placebo-controlled, 6 weeks
Participants	Holland Single center 18 subjects, 9 expt, 9 control Lived in a residential home for elderly people. Age: 78 - 92yrs, mean 83.4 Inclusion: Dutch cognitive screening test (CST) < 12/20 Early stage/moderate disease Met NINCDS-ADRDA criteria for clinical diagnosis of demetia of probable Alzheimers type with symptoms present at least 6 months, all scored 17 or less on Hamilton Rating Scale for Depression. Exclusion: history of psychiatric disorder, alcoholism, cerebral trauma, cerebrovascular disease, hydrocephalus, neoplasm, epilepsy, disturbances of consciousness, focal brain abnormalities, pacemaker. No change in drug use for 3 months preceeding treatment.
Interventions	Stimulator type: Premier 10s Waveform: asymmetric biphasic square wave, Burst mode Frequency: Bursts of trains, 9 pulses/burst, pulse freq 160Hz, burst freq 2 Hz Pulse duration: 100 microsec. Amplitude: Visible muscle twitches Electrode location: Two 2 x 3 cm electrodes between T1 and T5 on 2cm from the spine. Poles switched daily. Treatment duration: 30 min/day, 5 days/week, 6 weeks Placebo intervention: Same as experimental except no current delivered.

Scherder 1998 *(Continued)*

Outcomes	ANCOVA on pre and posttest scores on the following: Neuropsycological tests: Digit span: ns Visual memory span: p < 0.002 post, 0.05 6 wks delayed 8 words test Immed. recall: ns Delayed recall: ns Recognition: ns Face recognition: p < 0.04 post, ns 6 wks delayed Picture recognition: ns Word fluency: p < 0.03 post & 6 wks delayed Behavioural observational scales: Beoordelingsschaal vor Oudere Patienten (BOP) Total: ns Subscales Need of help: p < 0.04 post, ns @ 6wks Aggressiveness: ns Physical invalidity: ns Depressed behaviour: ns Mental invalidity: ns Inactivity: ns Behaviour Inventory: ns
Notes	One expt subject died between the immediate neuropsych. post-testing and the immediate post testing for the behavioural measures. For this meta-analysis an n of 8 was used for the experimental group for all delayed test results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Scherder 1999

Methods	Randomised, double-blind, placebo-controlled, 6 weeks
Participants	Holland Single center 18 subjects, 9 expt, 9 control Lived in a residential home for elderly people. Age: 70 - 91yrs, mean 81.7 Shortened MMSE mean 4.4/12. 7 or less/12 on this scale, (equivalent to 17 or less/20 on regular MMSE) classifies patients as having serious cognitive disturbances. Met NINCDS-ADRDA criteria for clinical diagnosis of demetia of Alzheimers type, GDS stage 6 (midstage) with symptoms present at least 6 months, all scored 17 or less on Hamilton Rating Scale for Depression. Exclusion: history of psychiatric disorder, alcoholism, cerebral trauma, cerebrovascular disease, hydrocephalus, neoplasm, infection, epilepsy, disturbances of consciousness, focal brain abnormalities, pacemaker.
Interventions	Stimulator type: Premier 10s Waveform: asymmetric biphasic square wave, Burst mode Frequency: Bursts of trains, 9 pulses/burst, pulse freq 160Hz, burst freq 2 Hz Pulse duration: 100 microsec.

Scherder 1999 *(Continued)*

	Amplitude: Visible muscle twitches Electrode location: Two 2 x 3 cm electrodes between T1 and T5 on 2cm from the spine. Treatment duration: 30 min/day, 5 days/week, 6 weeks Placebo intervention: Same as experimental except no current delivered.
Outcomes	ANCOVA Neuropsycological tests: Digit span: ns Visual memory span: p < 0.004 post, ns 6 wks delayed 8 words test Immed. recall: ns Delayed recall: ns Recognition: ns Face recognition: ns Picture recognition: ns Word fluency: ns Behavioural observational scales: Beoordelingsschaal vor Oudere Patienten (BOP) Subscales Need of help: ns Other scales, i.e. aggressiveness, physical invalidity, depressed behaviour, mental invalidity, inactivity, are not presented although it is implied that these were evaluated. Behaviour Inventory: ns
Notes	Authors consider this a study evaluating the effects of TENS on midstage AD in contrast with their other studies looking at early stage AD. They conclude that this study demonstrates "that TENS has a very positive effect on the performance of midstage AD patients on Visual Memory Span.... not maintained during a period of 6 weeks without treatment."

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Scherder 1999a

Methods	Randomised, double-blind, placebo-controlled, 6 weeks
Participants	Holland Single center 15 subjects, 8 expt, 7 control (16 initially, one fromthe control group did not tolerate the actigraphic assessment and was therefore excluded from the study) Lived in a residential home for elderly people. Shortened MMSE mean 4.4/12. 7 or less/12 on this scale, (equivalent to 17 or less/20 on regular MMSE) classifies patients as having serious cognitive disturbances. Met NINCDS-ADRDA criteria for clinical diagnosis of demetia of Alzheimers type, GDS stage 6 (midstage) with symptoms. Exclusion: history of psychiatric disorder, alcoholism, cerebral trauma, cerebrovascular disease, hydrocephalus, neoplasm, epilepsy, kidney or lung disease or disturbances of consciousness.
Interventions	Stimulator type: Premier 10s Waveform: asymmetric biphasic square wave, Burst mode Frequency: Bursts of trains, 9 pulses/burst, pulse freq 160Hz, burst freq 2 Hz

Scherder 1999a *(Continued)*

	Pulse duration: 100 microsec. Amplitude: Visible muscle twitches Electrode location: Two 2 x 3 cm electrodes between T1 and T5 on 2cm from the spine. Poles switched daily. Treatment duration: 30 min/day, 5 days/week, 6 weeks Placebo intervention: Same as experimental except no current delivered. Therapist present
Outcomes	t-test Circadian rest-activity rhythm measured by actigraph (see reference Van 1998). This measured acceleration-induced wrist movements and summed them hourly. Checked Interdaily Stability (IS) (a measure of coupling to Zeitgeber), Intradaily Variability (IV) (a measure of fragmentation) and Relative Amplitude (RA). T-tests found IS directly after TENS treatment to be significanctly increased compared with pooled baseline values (p = 0.004). IV and RA were not significantly different after TENS when compared with pooled baseline levels although there was a trend (p = 0.08) for RA being increased. No significant changes were observed for the control group. No improvements were maintained after 6 weeks without treatment.
Notes	Authors consider this a study evaluating the effects of TENS on midstage AD in contrast with their prior study looking at the effect of TENS on circadian rhythm in early stage AD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Scherder 1999b

Methods	Randomised, double-blind, placebo-controlled, 6 weeks
Participants	Holland Single center Study 1: 8 subjects, 4 expt, 4 control Study 2: 16 subjects, 8 expt, 8 control Study 3: 18 subjects, 9 expt, 9 control Lived in a residential home for elderly people. Meeting NINCDS-ADRDA criteria for clinical diagnosis of probable demetia of Alzheimers type. Studies 1-3: early stage of AD (stage 5 of GDS) Study 4: midstage of AD (stage 6 of GDS) Exclusion: history of psychiatric disorder, alcoholism, cerebral trauma, cerebrovascular disease, hydrocephalus, neoplasm, infection, epilepsy, disturbances of consciousness or focal brain abnormalities.
Interventions	Stimulation not described except that Premier 10s stimulator used. Study 1: TENS for 6 hours/day, therapist present throughout Study 2: TENS for 30 min/day, therapist present throughout Study 3: TENS without therapist present (called "isolated TENS" in the report), duration of treatment not indicated. Study 4: no description of TENS intervention given. Therapist present. All studies: 5 days/week, 6 weeks
Outcomes	t-test Neuropsycological tests:

Scherder 1999b *(Continued)*

	Digit span: ns for studies 1 - 4 Visual memory span: ns for study 1, ns study 2, p = 0.002 study 3, p = 0.004 study 4. 8/15 words test (15 word used only in study 1) Immed. recall: p = 0.03 study 1, ns studies 2-4 Delayed recall: ns studies 1-4 Recognition: p = 0.05 studies 1 & 2, ns studies 3 & 4 Face recognition: ns studies 1 & 4, p = 0.01 study 2, p = 0.04 study 3. Picture recognition: ns studies 1, 3 & 4, p = 0.001 study 2. Word fluency: p = 0.04 study 1, ns studies 2 & 4, p = 0.03 study 3 Behavioural observational scales: Beoordelingsschaal vor Oudere Patienten (BOP) Subscales Need of help: ns studies 1 & 4, p = 0.01 study 2, p = 0.04 study 3 Aggressiveness: ns Physical invalidity: ns studies 1, 3 & 4, p =0.02 study 2 Depressed behaviour: ns Mental invalidity: ns Inactivity: ns Behaviour inventory: ns studies 1, 3, 4, p = 0.03 study 2.
Notes	Poor/limited reporting of interventions and results. Authors imply that treatment effect was evaluated directly post-treatment and 6 weeks later but only one set of results given. They note that "Analyses of the data obtained after 6 weeks without stimulation revealed that the majority of the treatment effects observed in the above-mentioned studies disappeared." Consider excluding due to limitations of description of interventions and outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Scherder 2000

Methods	Randomised, double-blind, placebo-controlled, 6 weeks
Participants	Holland Single center 20 subjects, 10 expt, 10 control Institutionalised elderly persons 17 F, 3 M Age: 82-91 yrs, mean 86.9 Inclusion criterion for shortened MMSE 8 - 12/12, BUT a range of 7 - 11, mean of 9.4 described for the experimental group, range 8 - 12, mean 9.7 for controls.
Interventions	Stimulator type: Premier 10s Waveform: asymmetric biphasic square wave, Burst mode Frequency: Bursts of trains, 9 pulses/burst, pulse freq 160Hz, burst freq 2 Hz Pulse duration: 100 microsec. Amplitude: Visible muscle twitches Electrode location: Two 2 x 3 cm electrodes between T1 and T5 on 2cm from the spine. Poles switched daily. Treatment duration: 30 min/day, 5 days/week, 6 weeks Placebo intervention: Same as experimental except no current delivered.

Scherder 2000 *(Continued)*

Outcomes	t-tests Neuropsycological tests: Visual memory span improved: p = 0.02 California Verbal Learning Test (CVLT) Total score Recall Recognition Face recognition increased: p = 0.03 Picture recognition: ns Semantic verbal fluency: p = 0.02 Stroop color word task: ns F statistic for CVLT total and CVLT recall significantly increased over baseline 1 (p = 0.0005 and p = 0.04 respectively) but did increase over baseline 2 for either test. Behavioural observational scales: Beoordelingsschaal vor Oudere Patienten (BOP) Need of help subscale only: ns Behaviour inventory: ns Beck depression inventory: Decreased significantly over pooled baseline p = 0.05
Notes	Authors conclude a beneficial effect on visual short-term memory, verbal long-term memory, nonverbal long-term recognition memory and word fluency and, that subjects depressed mood decreased.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Scherder 2002

Methods	Randomised, double-blind, placebo-controlled, 6 weeks treatment.
Participants	Holland Single center 18 subjects, 9 expt, 9 control Institutionalised elderly persons. Mean age: experimental group 87.1, control group 87.67. Mean education: experimental group 3.11, control group 2.88. MMSE experimental group 18.33, control group 19.67. All met NINCDS-ADRDA criteria for the clinical diagnosis of probably AD and stage 5 of the GDS.
Interventions	Stimulator: Alphastim 100 Waveform: Bipolar asymmetric rectangular waves, Frequency: 0.5 Hz Pulse duration: not given Amplitude: 10 - 600 microA, to just below reported sensation of tingling and/or dizziness or to maximum if no sensation experienced. Electrode Placement: clipped to the earlobes. Treatment duration and frequency: 30 minutes/day between 1500 and 1900 h, 5 days/week, 6 weeks. Placebo intervention: Same as for the experimental group except no current administered.
Outcomes	MANOVA No improvements or treatment effects on any of the following: Cognition evaluation: Digit span and visual memory span 8 word test

Scherder 2002 *(Continued)*

	Face and picture recognition Word fluency Moral/mental/physical evaluation: Philadelphia Geriatric Moral Scale (PGCSM) Symptom Checklist (SCL-90) Affective, independent & psychogeriatric behaviour: Beoordelingsschaal voor Oudere Patienten (BOP) Gedraagsobservatieschaal voor Intramurale Psychogeriatrie (GIP)
Notes	Consider exclusion as ES applied to ears - CES vs TENS. Methods of randomization not described. No dropouts mentioned. Pulse duration not give

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Scherder 2003

Methods	Randomised, double-blind, placebo-controlled, 6 weeks treatment.
Participants	Holland Single center 16subjects, 8 expt, 8 control Lived in a residential home for elderly people. Age: 70 - 91yrs, mean 81.7 Shortened MMSE mean 4.4/12. 7 or less/12 on this scale, (equivalent to 17 or less/20 on regular MMSE) classifies patients as having serious cognitive disturbances. Met NINCDS-ADRDA criteria for clinical diagnosis of demetia of Alzheimers type, GDS stage 5 (midstage) with symptoms present at least 6 months Exclusion: history of psychiatric disorder, alcoholism, cerebral trauma, cerebrovascular disease, hydrocephalus, neoplasm, infection, epilepsy, disturbances of consciousness, focal brain abnormalities, pacemaker.
Interventions	1. Stimulator: Alphastim 100 Waveform: Bipolar asymmetric rectangular waves, Frequency: 0.5 Hz 30mins/day, 5 days a week 2.control appeared the same with electrodes but no current
Outcomes	t-test Circadian rest-activity rhythm measured by actigraph (see reference Van 1998). This measured acceleration-induced wrist movements and summed them hourly. Checked Interdaily Stability (IS) (a measure of coupling to Zeitgeber), Intradaily Variability (IV) (a measure of fragmentation) and Relative Amplitude (RA).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Scherder 2003 *(Continued)*

Allocation concealment?	Unclear risk	D - Not used

Van Someren 1998

Methods	Randomised, double-blind, placebo-controlled, 6 weeks
Participants	Holland Single center 14 subjects (initial sample of 19, 14 completed), 6 treated, 8 placebo. 13 F, 1 M Nursing home patients. Diagnosed with early stage probable AD NINCDS-ADRDA Age mean 84 +/- 1.5 Dutch cognitive screening test (CST): mean 10.2 +/- 0.4(= approx 18 on MMSE) None used neuroloptics, none had severe visual deficiencies.
Interventions	Stimulator type: Premier 10s Waveform: asymmetric biphasic square wave, Burst mode Frequency: Bursts of trains, 9 pulses/burst, pulse freq 160Hz, burst freq 2 Hz Pulse duration: 100 microsec. Amplitude: Visible muscle twitches Electrode location: Two 2 x 3 cm electrodes between shoulder blades. Treatment duration: 30 min/day, 5 days/week, 6 weeks Placebo intervention: Same as experimental except no current delivered.
Outcomes	Circadian rest-activity rhythm measured by author developed actigraph. This measured acceleration-induced wrist movements and summed them hourly. Checked Interdaily Stability (IS) (a measure of coupling to Zeitgeber), Intradaily Variability (IV) (a measure of fragmentation) and Relative Amplitude (RA). ANOVA pre, post and follow up at 6 wks. ANOVA treatment vs. placebo. Only one signifcant effect found, an interaction between treatment group & time for IS. "post hoc contrasts indicated that only in the treatment group was the posttreatment mean significantly higher than both the pretreatment mean F (1,5) = 6.58, p = 0.03, and the follow-up mean F (1,5) = 6.81, p = 0.03.
Notes	Outcome variables IS, IV and RA described in detail in text. Conclude a positive effect of improved coupling to Zeitgeber that returns to baseline after 6 weeks, based on minimal significant results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Luijpen 2004	The patients were suffereing from mild cognitive impairment, but not dementia.
Scherder 1992	Matched groups by age, but no mention of randomization.

Study	Reason for exclusion
Scherder 1995	Matched groups by age and performance on CST. NOTE: many outcomes evaluated and no corrections made for multiple tests on the same groups but the authors conclude that there were significant treatment effects. 2 groups of 8 subjects. Treatment: Premier 10s stimulator, asymmetric biphasic square waves, bursts of trains, 9 pulses/train, pulse freq 160Hz, burst freq 2Hz, pulse duration 40 microseconds with two 2 x 3cm electrodes between the scapulae for the treatment group. Treated 30min/day for 6 weeks. Placebo intervenion: same as experimental except electrodes placed one on the back of each hand. Outcomes: ANCOVA. Digit span n; visual memory 0.08 post test, ns delayed 6 weeks; 8 words test immed and delayed recall ns, recognition 0.05 post, ns delayed 6 wks; Face recognition 0.01 post, 0.09 delayed 6 wks; Picture recognition 0.001 post, ns delayed 6 wks; Verbal fluency ns. Behavior scales: improvement on need of help &, physical invalidity, not on aggressiveness, depressed behaviour, mental invalidity &, inactivity. Also, a significant treatment effect was found for the behaviour inventory total and 3/12 of the subscales.
Scherder 1995a	Matched groups by age and performance on CST. Same method as many of the other studies. Burst mode TENS to the upper back for 30 minutes/day, 5 days/week for 6 weeks. Similar outcome measures also used. Many measures - only few significant, face recognition pre/post in the experimental group p = 0.01, need of help and physical invalidity on BOP subscales.
Scherder 1997	Match groups, not randomized. This is one of the many Dutch studies in this review using similar methodology.

DATA AND ANALYSES

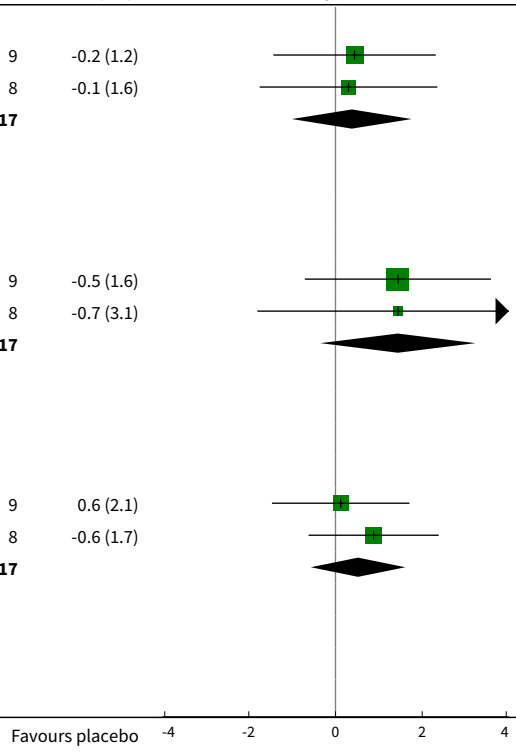
Comparison 1. TENS to the thoracic area Vs placebo (immediate effect)

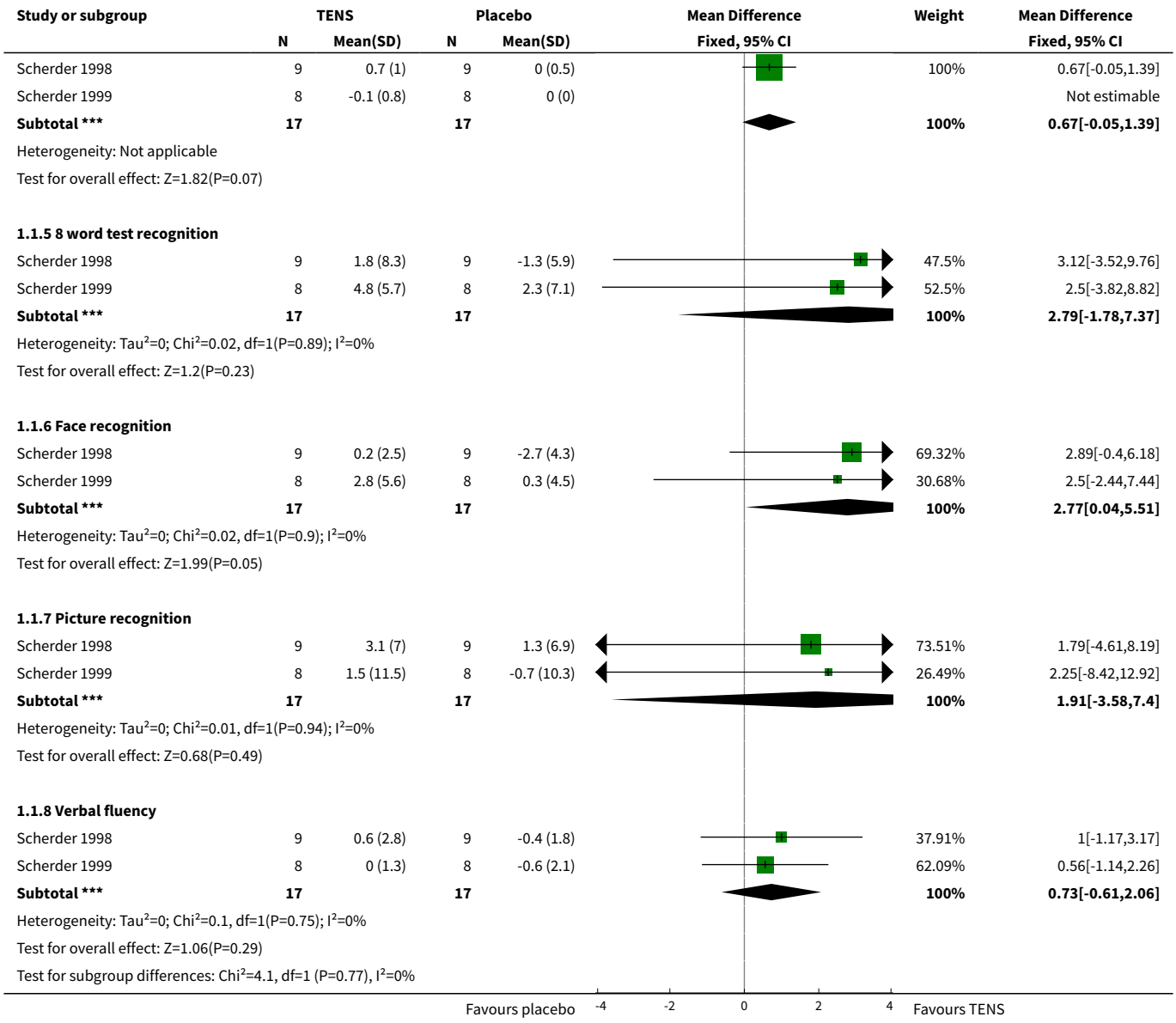
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neuropsychological tests	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Digit span	2	34	Mean Difference (IV, Fixed, 95% CI)	0.38 [-1.01, 1.76]
1.2 Visual memory	2	34	Mean Difference (IV, Fixed, 95% CI)	1.44 [-0.35, 3.23]
1.3 8 word test immediate recall	2	34	Mean Difference (IV, Fixed, 95% CI)	0.52 [-0.57, 1.61]
1.4 8 word test delayed recall	2	34	Mean Difference (IV, Fixed, 95% CI)	0.67 [-0.05, 1.39]
1.5 8 word test recognition	2	34	Mean Difference (IV, Fixed, 95% CI)	2.79 [-1.78, 7.37]
1.6 Face recognition	2	34	Mean Difference (IV, Fixed, 95% CI)	2.77 [0.04, 5.51]
1.7 Picture recognition	2	34	Mean Difference (IV, Fixed, 95% CI)	1.91 [-3.58, 7.40]
1.8 Verbal fluency	2	34	Mean Difference (IV, Fixed, 95% CI)	0.73 [-0.61, 2.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Behavioural observational scales	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 BOP subscale: Need of Help	2	33	Mean Difference (IV, Fixed, 95% CI)	-2.31 [-9.47, 4.84]
2.2 BOP subscale: Aggressiveness	1	17	Mean Difference (IV, Fixed, 95% CI)	0.2 [-2.53, 2.93]
2.3 BOP subscale: Physical invalidity	1	17	Mean Difference (IV, Fixed, 95% CI)	0.24 [-1.22, 1.70]
2.4 BOP subscale: Depressed behaviour	1	17	Mean Difference (IV, Fixed, 95% CI)	-1.16 [-3.02, 0.70]
2.5 BOP subscale: Mental invalidity	1	17	Mean Difference (IV, Fixed, 95% CI)	-0.68 [-2.88, 1.52]
2.6 BOP subscale: Inactivity	1	17	Mean Difference (IV, Fixed, 95% CI)	-2.81 [-6.96, 1.34]
2.8 Behavioral Inventory - overall affective behaviour	1	16	Mean Difference (IV, Fixed, 95% CI)	7.5 [-7.65, 22.65]

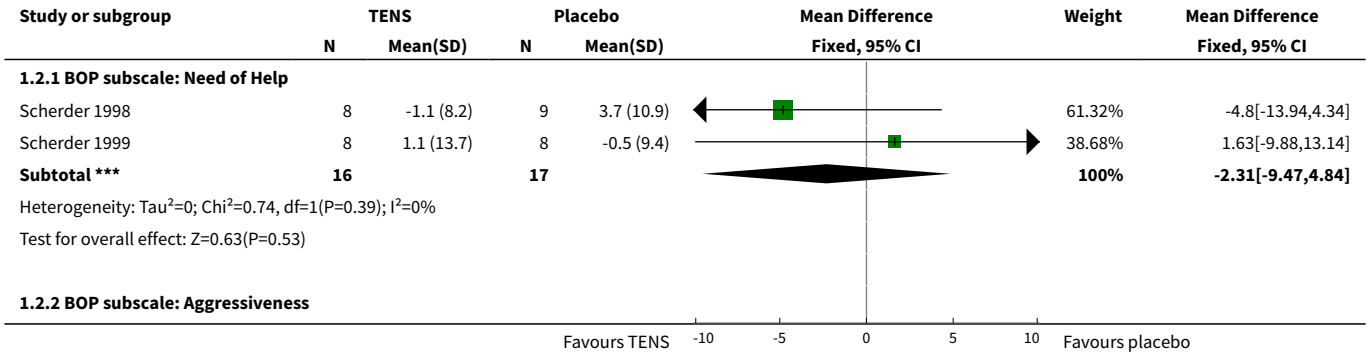
Analysis 1.1. Comparison 1 TENS to the thoracic area Vs placebo (immediate effect), Outcome 1 Neuropsychological tests.

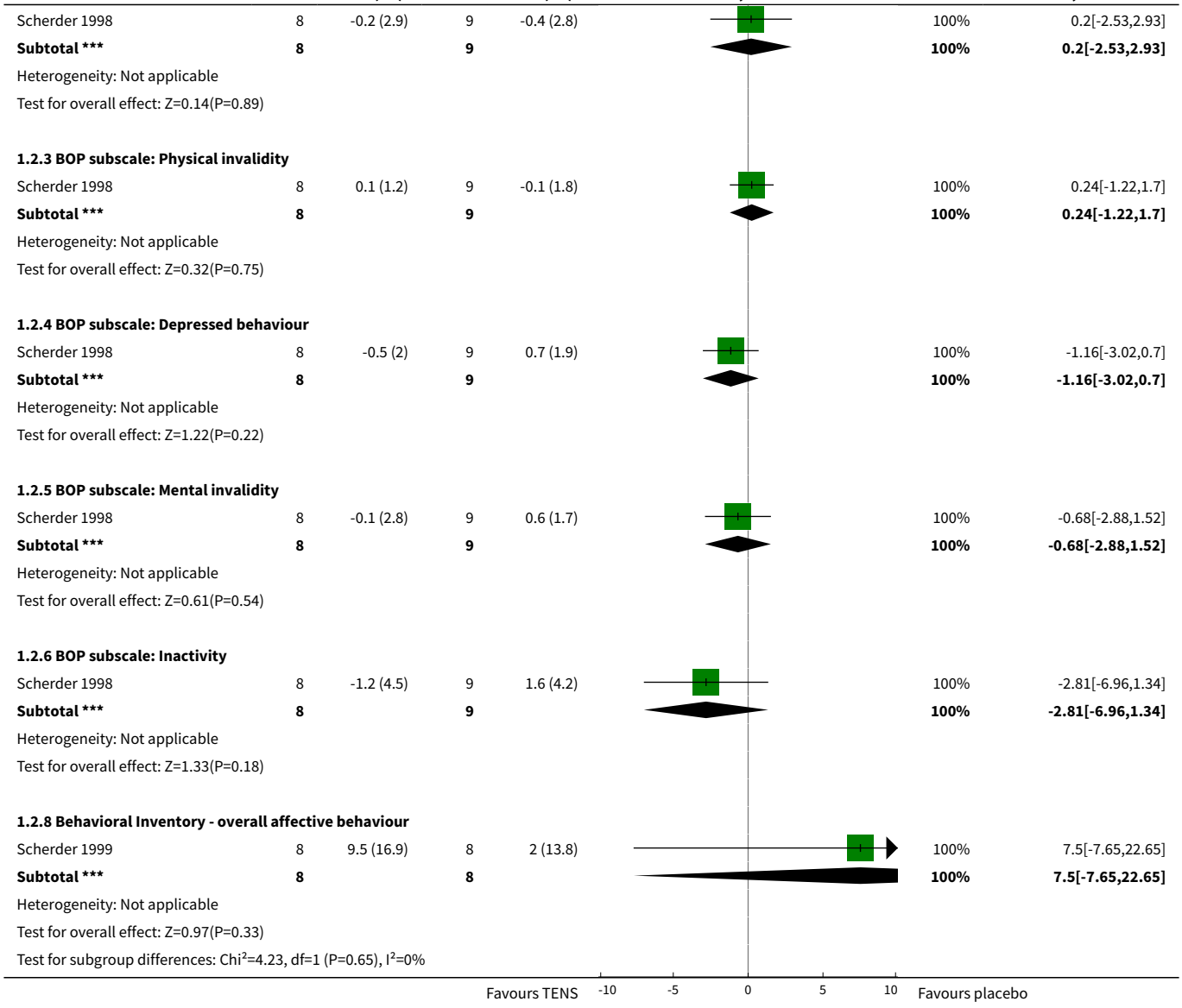
Study or subgroup	TENS N	TENS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.1.1 Digit span							
Scherder 1998	9	0.2 (2.6)	9	-0.2 (1.2)		54.47%	0.44[-1.43,2.31]
Scherder 1999	8	0.2 (2.5)	8	-0.1 (1.6)		45.53%	0.3[-1.75,2.35]
Subtotal ***	**17**		**17**			**100%**	**0.38[-1.01,1.76]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%							
Test for overall effect: Z=0.53(P=0.59)							
1.1.2 Visual memory							
Scherder 1998	9	0.9 (2.9)	9	-0.5 (1.6)		69.52%	1.44[-0.71,3.59]
Scherder 1999	8	0.8 (3.5)	8	-0.7 (3.1)		30.48%	1.44[-1.8,4.68]
Subtotal ***	**17**		**17**			**100%**	**1.44[-0.35,3.23]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%							
Test for overall effect: Z=1.58(P=0.11)							
1.1.3 8 word test immediate recall							
Scherder 1998	9	0.7 (1.3)	9	0.6 (2.1)		47.27%	0.12[-1.47,1.71]
Scherder 1999	8	0.3 (1.3)	8	-0.6 (1.7)		52.73%	0.88[-0.62,2.38]
Subtotal ***	**17**		**17**			**100%**	**0.52[-0.57,1.61]**
Heterogeneity: Tau^2=0; Chi^2=0.47, df=1(P=0.5); I^2=0%							
Test for overall effect: Z=0.94(P=0.35)							
1.1.4 8 word test delayed recall							





Analysis 1.2. Comparison 1 TENS to the thoracic area Vs placebo (immediate effect), Outcome 2 Behavioural observational scales.





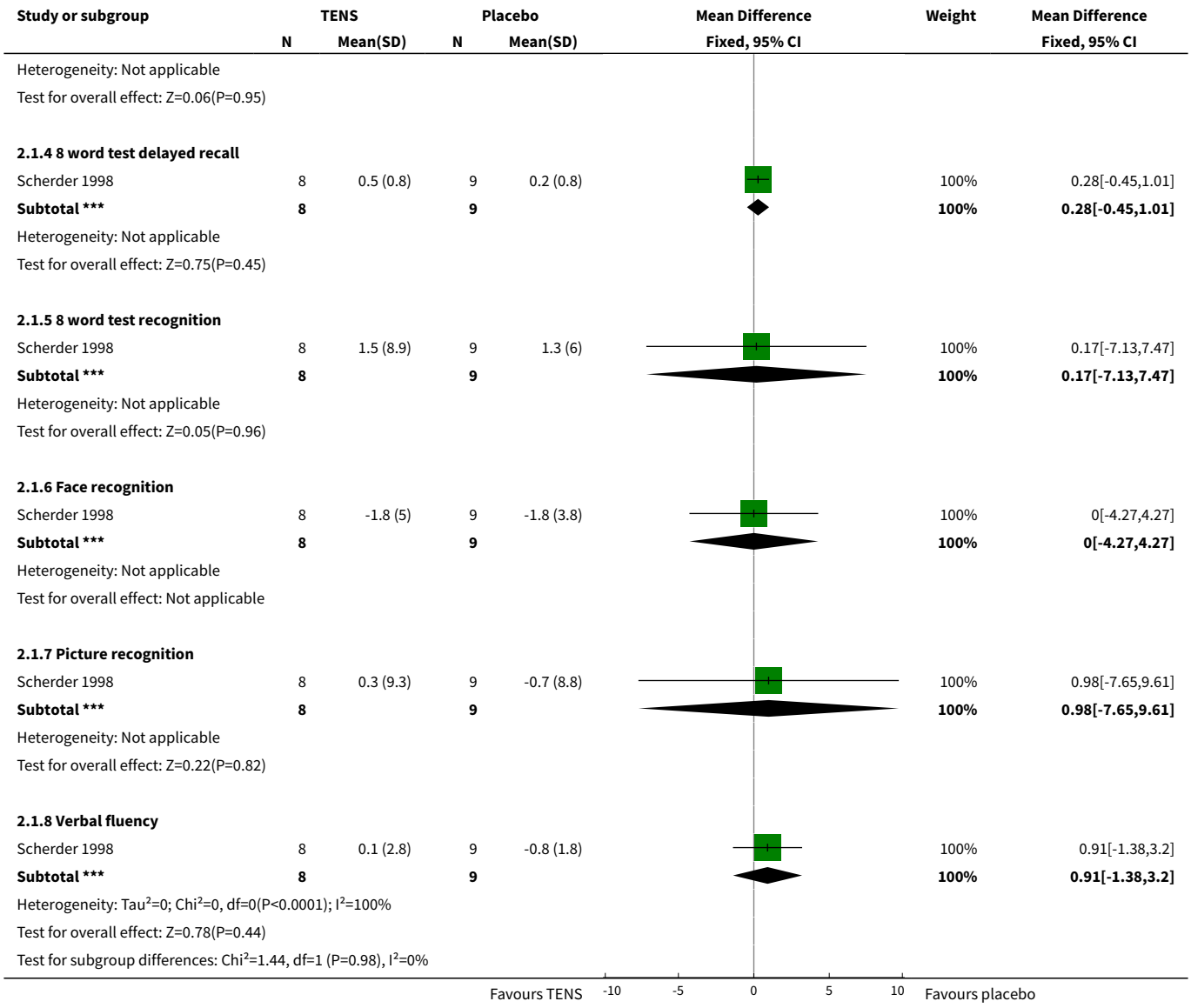
Comparison 2. TENS to the thoracic area Vs placebo (delayed effect)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neuropsychological tests	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Digit span	1	17	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-2.93, 1.53]
1.2 Visual memory	1	17	Mean Difference (IV, Fixed, 95% CI)	0.9 [-1.58, 3.38]
1.3 8 word test immediate recall	1	17	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-1.75, 1.65]

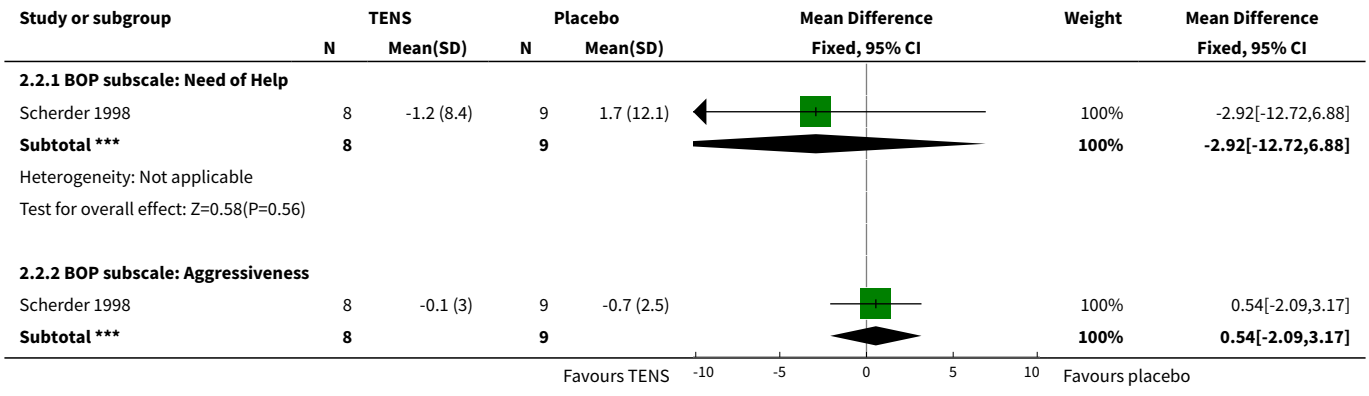
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 8 word test delayed recall	1	17	Mean Difference (IV, Fixed, 95% CI)	0.28 [-0.45, 1.01]
1.5 8 word test recognition	1	17	Mean Difference (IV, Fixed, 95% CI)	0.17 [-7.13, 7.47]
1.6 Face recognition	1	17	Mean Difference (IV, Fixed, 95% CI)	0.0 [-4.27, 4.27]
1.7 Picture recognition	1	17	Mean Difference (IV, Fixed, 95% CI)	0.98 [-7.65, 9.61]
1.8 Verbal fluency	1	17	Mean Difference (IV, Fixed, 95% CI)	0.91 [-1.38, 3.20]
2 Behavioural observational scales	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 BOP subscale: Need of Help	1	17	Mean Difference (IV, Fixed, 95% CI)	-2.92 [-12.72, 6.88]
2.2 BOP subscale: Aggressiveness	1	17	Mean Difference (IV, Fixed, 95% CI)	0.54 [-2.09, 3.17]
2.3 BOP subscale: Physical invalidity	1	16	Mean Difference (IV, Fixed, 95% CI)	0.13 [-1.38, 1.64]
2.4 BOP subscale: Depressed behaviour	1	17	Mean Difference (IV, Fixed, 95% CI)	-1.46 [-3.75, 0.83]
2.5 BOP subscale: mental invalidity	2	19	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-2.65, 1.75]
2.6 BOP subscale: Inactivity	2	19	Mean Difference (IV, Fixed, 95% CI)	-1.88 [-5.68, 1.92]

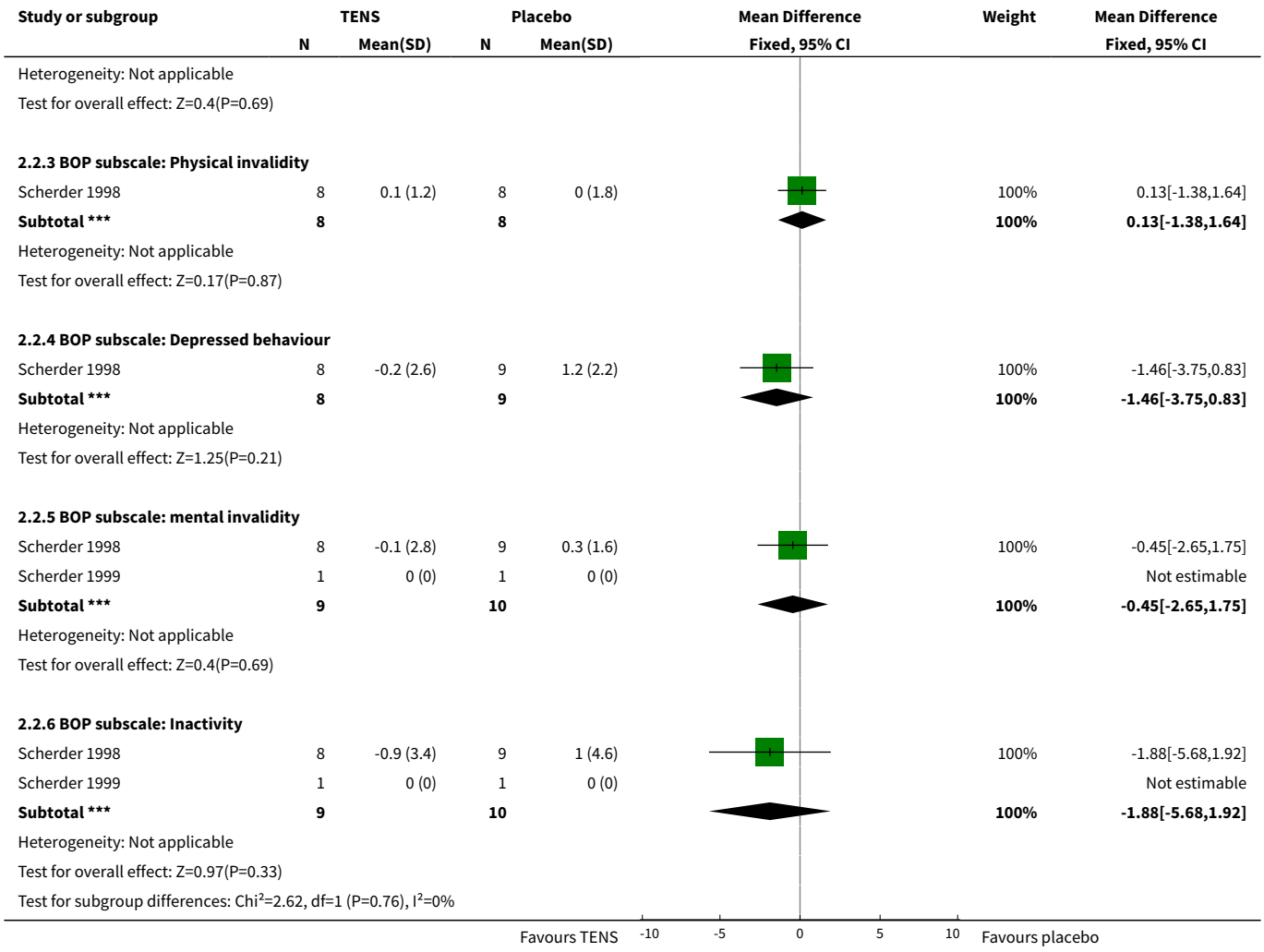
Analysis 2.1. Comparison 2 TENS to the thoracic area Vs placebo (delayed effect), Outcome 1 Neuropsychological tests.

Study or subgroup	TENS N	TENS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 Digit span							
Scherder 1998	8	-0.8 (2.9)	9	-0.1 (1.4)		100%	-0.7[-2.93,1.53]
Subtotal ***	**8**		**9**			**100%**	**-0.7[-2.93,1.53]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.61(P=0.54)							
2.1.2 Visual memory							
Scherder 1998	8	0.4 (3.3)	9	-0.5 (1.6)		100%	0.9[-1.58,3.38]
Subtotal ***	**8**		**9**			**100%**	**0.9[-1.58,3.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.71(P=0.48)							
2.1.3 8 word test immediate recall							
Scherder 1998	8	0.3 (1.9)	9	0.3 (1.7)		100%	-0.05[-1.75,1.65]
Subtotal ***	**8**		**9**			**100%**	**-0.05[-1.75,1.65]**



Analysis 2.2. Comparison 2 TENS to the thoracic area Vs placebo (delayed effect), Outcome 2 Behavioural observational scales.



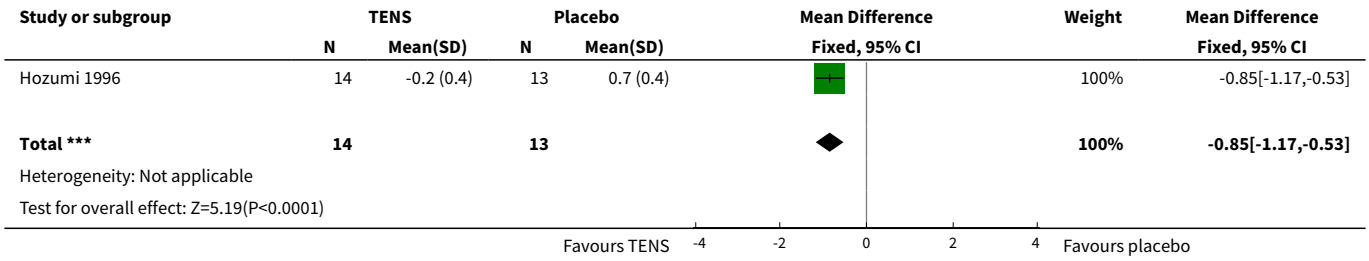


Comparison 3. TENS to the head Vs placebo (immediate effect)

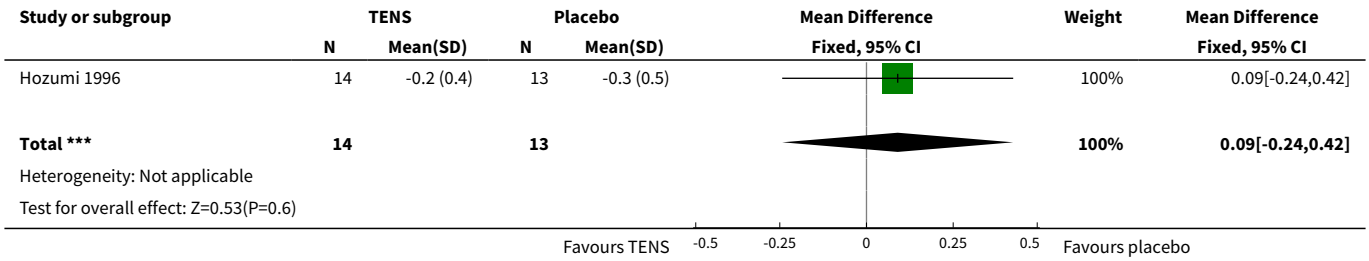
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Motivation	1	27	Mean Difference (IV, Fixed, 95% CI)	-0.85 [-1.17, -0.53]
2 Behaviour disorder	1	27	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.24, 0.42]
3 Sleep disorder	1	27	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.28, 0.38]
4 Intelligence	1	27	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.28, 0.44]
5 Emotion	1	27	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.34, 0.26]
6 Language	1	27	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.37, 0.19]
7 Neurological signs	1	27	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.23, 0.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Subjective complaints	1	27	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.17, 0.19]
9 Activities of daily life	1	27	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.46, 0.40]

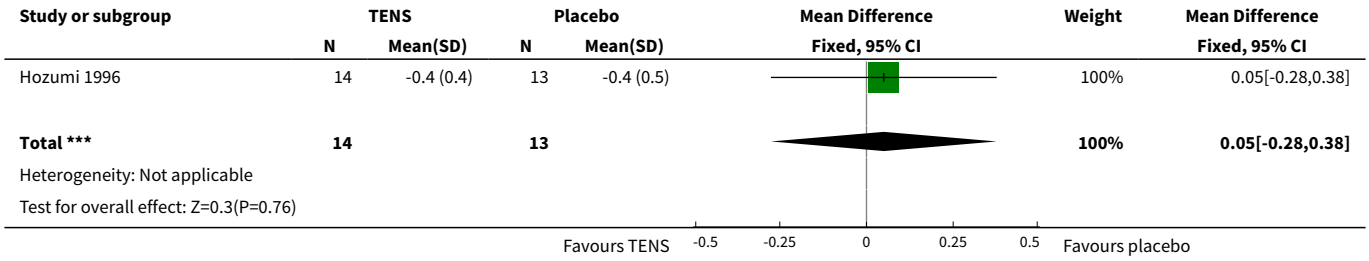
Analysis 3.1. Comparison 3 TENS to the head Vs placebo (immediate effect), Outcome 1 Motivation.



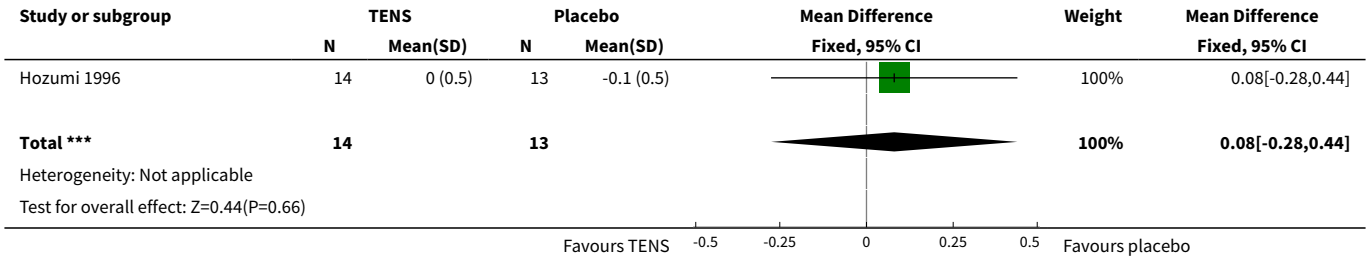
Analysis 3.2. Comparison 3 TENS to the head Vs placebo (immediate effect), Outcome 2 Behaviour disorder.



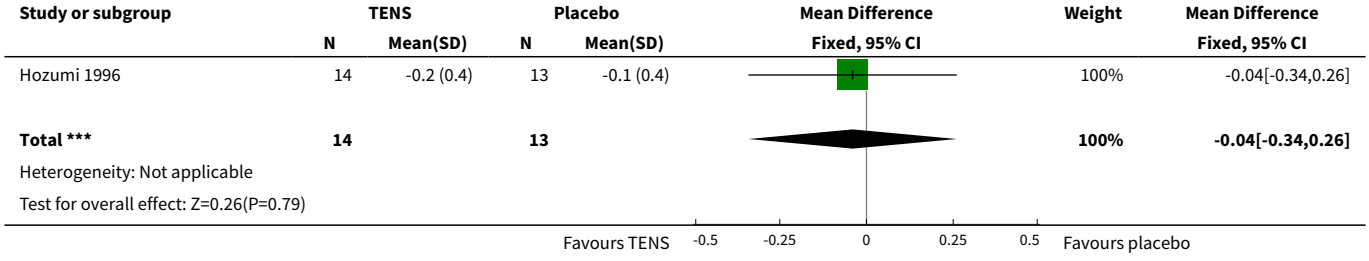
Analysis 3.3. Comparison 3 TENS to the head Vs placebo (immediate effect), Outcome 3 Sleep disorder.



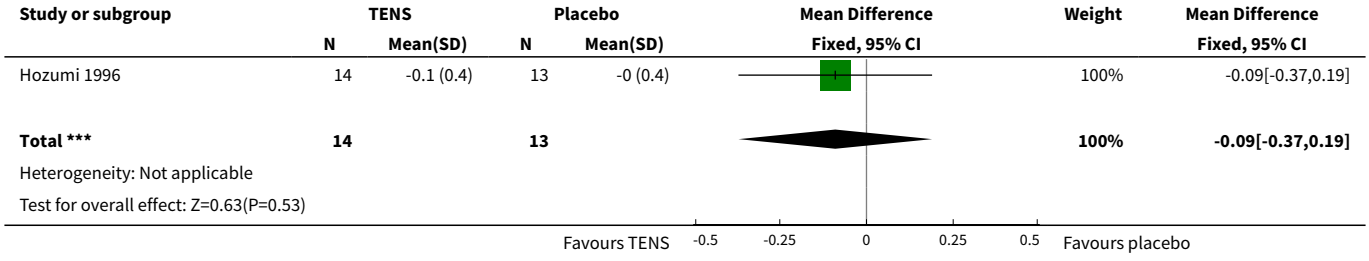
Analysis 3.4. Comparison 3 TENS to the head Vs placebo (immediate effect), Outcome 4 Intelligence.



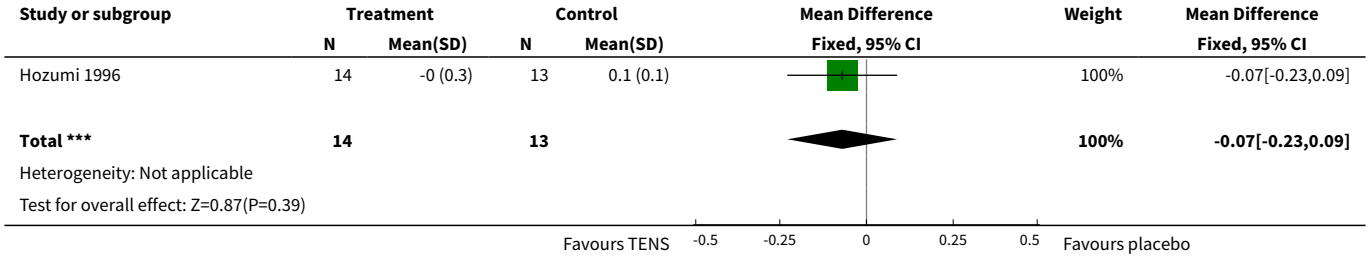
Analysis 3.5. Comparison 3 TENS to the head Vs placebo (immediate effect), Outcome 5 Emotion.



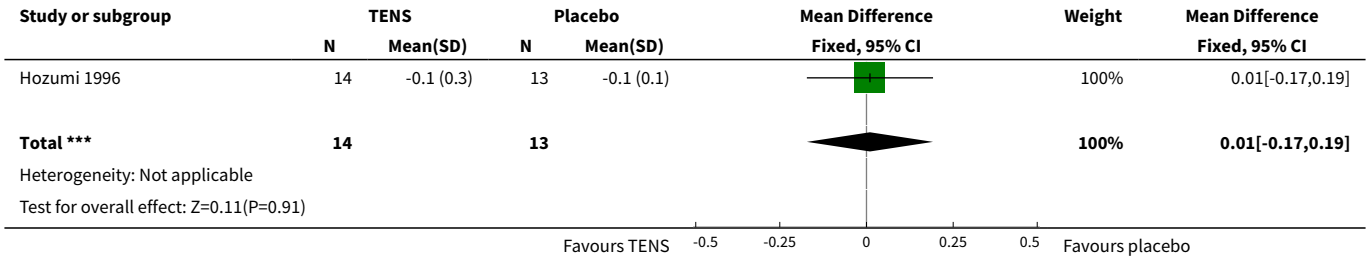
Analysis 3.6. Comparison 3 TENS to the head Vs placebo (immediate effect), Outcome 6 Language.



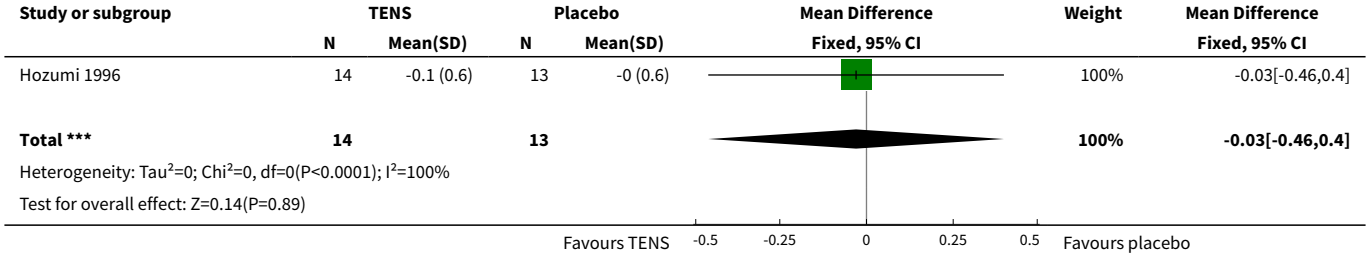
Analysis 3.7. Comparison 3 TENS to the head Vs placebo (immediate effect), Outcome 7 Neurological signs.



Analysis 3.8. Comparison 3 TENS to the head Vs placebo (immediate effect), Outcome 8 Subjective complaints.



Analysis 3.9. Comparison 3 TENS to the head Vs placebo (immediate effect), Outcome 9 Activities of daily life.



WHAT'S NEW

Date	Event	Description
7 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 3, 2003

Date	Event	Description
11 May 2006	New search has been performed	May 2006: Another study by Scherder (Scherder 2003) has been included. It follows the same design and methodology as the previous trials by Scherder. The treatment was cranial electrostimulation (CES) for early stage AD and the outcome was sleep activity rhythm. The statistics needed for inclusion in the meta-analyses were not available. Another new study has been excluded because the participants did not have dementia, but mild cognitive impairment.
25 May 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

-Cameron MH: All correspondence, drafting of review versions, selection of trials for inclusion/exclusion, extraction of data, entry of data (in RevMan), interpretation of data analyses.
-Lonergan ET: Selection of trials for inclusion/exclusion, extraction of data, interpretation of data analyses.
-Lee H: Search for trials, obtaining copies of trial reports, selection of trials for inclusion/exclusion, extraction of data.

-Consumer editor: David Krassner
-Contact editor: Linda Clare
-This review has been peer reviewed anonymously

DECLARATIONS OF INTEREST

Michelle Cameron teaches the use of TENS in rehabilitation

SOURCES OF SUPPORT

Internal sources

- University of California, San Francisco. Dept of Neurology., USA.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Dementia [*therapy]; Randomized Controlled Trials as Topic; Transcutaneous Electric Nerve Stimulation [*methods]

MeSH check words

Aged; Humans