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Peripheral electrical nerve stimulation and rest-activity rhythm in Alzheimer's disease

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SUMMARY Rest-activity rhythm disruption is a prominent clinical feature of Alzheimer's disease (AD). The origin of the altered rest-activity rhythm is believed to be degeneration of the suprachiasmatic nucleus (SCN). In accordance with the 'use it or lose it' hypothesis of Swaab [*Neurobiol Aging* 1991, **12**: 317–324] stimulation of the SCN may prevent age-related loss of neurons and might reactivate nerve cells that are inactive but not lost. Previous studies with relatively small sample sizes have demonstrated positive effects of peripheral electrical nerve stimulation on the rest-activity rhythm in AD patients. The present randomized, placebo-controlled, parallel-group study was meant to replicate prior findings of electrical stimulation in AD in a substantially larger group of AD patients. The experimental group ($n = 31$) received peripheral electrical nerve stimulation and the placebo group ($n = 31$) received sham stimulation. Effects of the intervention on the rest-activity rhythm were assessed by using wrist-worn actigraphs. Near-significant findings on the rest-activity rhythm partially support the hypothesis that neuronal stimulation enhances the rest-activity rhythm in AD patients. Interestingly, *post-hoc* analyses revealed significant treatment effects in a group of patients who were not using acetylcholinesterase inhibitors concomitantly. We conclude that more research is needed before firm general conclusions about the effectiveness of electrical stimulation as a symptomatic treatment in AD can be drawn. In addition, the present *post-hoc* findings indicate that future studies on non-pharmacological interventions should take medication use into account.

KEYWORDS alzheimer's disease, circadian rhythm, dementia, rest-activity rhythm, transcutaneous electrical nerve stimulation

INTRODUCTION

Disruption of the daily rest-activity rhythm is a prominent clinical feature of Alzheimer's disease (AD) (Ancoli-Israel *et al.*, 1997; McCurry *et al.*, 1999; Paavilainen *et al.*, 2005; Satlin *et al.*, 1995; Van Someren *et al.*, 1996). In a large study, the prevalence of symptoms of disordered sleep in AD ranged from 34% (waking up at night thinking it is daytime) to 82% (getting up during the night) (Tractenberg *et al.*, 2003). Moreover, a recent study reported significantly more subjective sleep disturbances in AD patients when compared with non-demented elderly patients, and in addition, greater sleep disturbance appeared to be associated with greater functional

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impairment (Tractenberg *et al*., 2005). Therefore, it is not surprising that institutionalization is best predicted by rest-activity rhythm disruption and not by the level of cognitive functioning or by the number of psychiatric symptoms of the AD patient (Chenier, 1997; Hart *et al*., 2003; Hope *et al*., 1998; Kesselring *et al*., 2001; Lieberman and Kramer, 1991; Pollak and Perlick, 1991).

The origin of the altered rest-activity rhythm in AD is believed to be a degeneration of the suprachiasmatic nucleus (SCN) (Liu *et al*., 2000; Swaab *et al*., 1996), which is part of the hypothalamus and considered the biological clock of the brain (Inouye and Shibata, 1994). Higher daytime light exposure seems to have a positive impact on night-time sleep consolidation in both demented and non-demented elderly patients (Shochat *et al*., 2000). Interestingly, application of bright light has been shown to positively influence rest-activity rhythm disturbances in some AD patients (Fetveit and Bjorvatn, 2004; Fetveit *et al*., 2003; Koyama *et al*., 1999; Lyketsos *et al*., 1999; Satlin *et al*., 1992; Van Someren *et al*., 1997; Yamadera *et al*., 2000). One explanation for this therapeutic action is that light stimulates the SCN through a central pathway, i.e. the retino-hypothalamic nerve tract, and prevents age-related loss of neurons in this nucleus (Van Someren *et al*., 1997). The latter has been found in animal experiments (Lucassen *et al*., 1995) and is in line with the 'use it or lose it' hypothesis which states that an organism profits from neuronal stimulation (Swaab, 1991).

The biological clock may also be stimulated through pathways originating in the peripheral nervous system. An intervention aimed at stimulating peripheral nerves is application of electrical stimuli to the skin. Two placebo-controlled studies have demonstrated positive effects of transcutaneous electrical nerve stimulation (TENS) on the rest-activity rhythm in institutionalized AD patients in terms of improved stability (Scherder *et al*., 1999; Van Someren *et al*., 1998). It was argued that stimulation of peripheral nerves with electrical stimuli might activate the SCN through four projections that were identified in animal experimental studies. First, the spino-hypothalamic tract: a direct pathway from the spinal cord to the SCN (Cliffer *et al*., 1991). Second, a spino-septal-hypothalamic tract: an indirect pathway from the spinal cord to the septal nuclei (Burstein and Giesler, 1989), and subsequently to the SCN (Pickard, 1982). Third and fourth are spino-brainstem-hypothalamic tracts: from the spinal cord to the brain stem locus coeruleus (LC) (Kawano *et al*., 1996) and further to the SCN (Krout *et al*., 2002) and from spinal cord to the raphe nuclei (Hay-Schmidt *et al*., 2003; Kawano *et al*., 1996) and subsequently to the SCN (Krout *et al*., 2002; Moga and Moore, 1997).

In addition, the LC and the raphe nuclei are known to innervate the basal forebrain (Jones, 2003). From the basal forebrain, including the nucleus basalis of Meynert, cholinergic cells project to the cerebral cortex (Jones, 2004) and to the SCN (Yamadera *et al*., 2000). The noradrenergic LC and serotonergic raphe nuclei are parts of the ascending reticular activating system (Kayama and Koyama, 1998), which is known to play an important role in the regulation of sleep and wakefulness (Siegel, 2004). Hence, assuming homologous pathways exist in these animals and humans, stimulation of peripheral nerves could account for the effects of electrical stimulation previously found in AD patients. These positive results of electrical stimulation in AD were based on samples of 14 and 16 patients (Scherder *et al*., 1999; Van Someren *et al*., 1998) and should therefore be interpreted with caution.

The present, randomized, placebo-controlled, parallel-group clinical study, was an attempt to replicate previous findings of electrical stimulation in AD in a larger number of patients. Based on the earlier studies, it was hypothesized that after a treatment period of 6 weeks, the experimental group, which received electrical stimulation, would show improved functioning of the rest-activity rhythm compared with the placebo group, which received sham stimulation.

METHODS

Subjects

Participants were recruited from the Alzheimer Center of the VU University Medical Center, from the Department of Neurology, Sint Lucas Andreas Hospital, and from the community home care agency in Amsterdam, the Netherlands. Both men and women were eligible if they met the diagnostic criteria of the NINCDS/ADRDA for probable AD (McKhann *et al*., 1984). A Mini Mental State Examination (MMSE) (Folstein *et al*., 1975) score of 26 or lower and sufficient hearing and vision were required. It was essential that the AD patient was living at home with a partner or other family member who served as primary caregiver. Concomitant use of acetylcholinesterase inhibitors (AChEIs) for symptomatic treatment of AD was allowed only if the dose was stable before the first assessment and remained unchanged during the trial. Patients with a diagnosis of dementia other than AD, cerebrovascular disease or clinical depression were excluded, as were patients who had a history of cerebral trauma, disturbances of consciousness, seizures, epilepsy, or an infectious disease. Patients with a cardiac pacemaker were excluded because of reported interference between a pacemaker and an electrical stimulator (Rasmussen *et al*., 1988).

After the procedure of the study had been fully explained, written informed consent was obtained from the patient and/or the family caregiver. The study was approved by the local medical ethics committees and by the Committee on Research Involving Human Subjects in The Hague, the Netherlands.

Sixty-eight patients were included and randomly allocated to either an experimental group that received electrical stimulation or to a placebo group that received sham stimulation. Sixty-five patients (96%) completed the study. Discontinuation during the treatment phase occurred only in the placebo group and was due to refused treatment ($n = 1$), stroke ($n = 1$), and a partner who sustained an arm fracture ($n = 1$). Three additional cases were excluded from analysis because no actigraph data were available. Finally, 62 patients (91%)

Table 1 Characteristics of the patients

	Experimental group (n = 31)	*Placebo group (n = 31)*
No. males/females	16/15	22/9
Age, years		
Mean (SD)	71.5 (8.6)	72.8 (8.3)
Range	52–89	55–87
Education, years		
Mean (SD)	10.5 (3.9)	10.7 (3.3)
Range	6–20	6–20
MMSE		
Mean (SD)	15.7 (6.9)	14.8 (7.1)
Range	0–26	1–26
AChEI use		
Rivastigmine (*n*)	13	12
Donepezil (*n*)	2	1

AChEI use, acetylcholinesterase inhibitor use, subdivided in Rivastigmine (Exelon®) and Donepezil (Aricept®). SD, standard deviation; MMSE, Mini Mental State Examination; AChEI, acetylcholinesterase inhibitor.

entered the analysis phase. The two groups did not differ significantly with regard to sex, age, education, and MMSE as indicated by chi-squared and *t*-tests (see Table 1 for group characteristics).

In view of the hypothesized involvement of the cholinergic system in the mechanism underlying the effects of electrical stimulation in AD and the use of AChEIs in a part of the sample, we explored the possible interaction between AChEIs and electrical stimulation. The experimental and placebo group were both split into AChEI users (AChEI +) and AChEI non-users (AChEI −), resulting in four groups: experimental AChEI − ($n = 16$), experimental AChEI + ($n = 15$), placebo AChEI − ($n = 18$), and placebo AChEI + ($n = 13$). *Post-hoc* multiple analyses of variance (MANOVA) and chi-squared tests indicated no significant differences between the groups with respect to age, education, MMSE, and sex.

Randomization and blinding

Using simple randomization by tossing a coin, the participants were allocated to the experimental or placebo group. Those assigned to the experimental group were given the real treatment, i.e. electrical stimuli applied to the skin (see Intervention section below for more details) whereas participants in the placebo group were told that the stimulator was working as soon as a green light was blinking, without actual current being applied. To maintain the participants' blindness and as the participants knew there was an experimental and a placebo condition, the two groups were informed as follows. The experimental group was told that different pulse frequencies were applied to both groups: one frequency that may have the desired effect and one that, on theoretical grounds, was unlikely be effective. Hence, patients who received the experimental treatment, i.e. the patient felt the stimulus and the caregiver observed muscle contraction, would still be under the assumption that they might be treated with non-effective stimuli. The participants in the placebo group were also told that different pulse frequencies were applied in two groups, but that the pulse frequencies were in a range that could not be perceived. Patients, family caregivers, and test administrators were blinded to group allocation. After the treatment period and final assessment, group assignment was disclosed to all participants and the individuals of the placebo group were offered to undergo the experimental treatment as well.

Study design

In this 12-week, randomized, placebo-controlled, parallel-group study, assessment of the rest-activity rhythm by means of actigraphy took place at baseline (Pre-assessment), after the treatment period of 6 weeks (post-assessment) and following a treatment-free period of 6 weeks (delayed assessment).

Intervention

A standard TENS device and two self-adhesive medical electrodes (type: Premier 10s and Xytrode, respectively; Xytron Medical, Apeldoorn, the Netherlands) were used. The electrodes were placed on the back at the first thoracic vertebra, lateral to the spine. The electrical stimulator produced biphasic square pulses with a width of 100 μs, applied in bursts of nine pulses with a frequency of 160 Hz and a repetition rate of 2 Hz. The intensity of the stimuli was set at a level that produced painless, visible muscular twitches. These stimulation parameters were chosen to target afferent nerve fibers which convey the pulses to cortical and sub-cortical areas (Scherder *et al*., 1995, 2003). The family caregiver applied the treatment 30 min a day, 7 days a week, for a period of 6 weeks. The patient and family caregiver were free to decide what time of the day they administered the treatment in order to minimize interference in the daily routine of the participants.

Assessment of rest-activity rhythm

Actigraphy is considered a valid measure of rest-activity rhythms (Ancoli-Israel *et al*., 2003) and has been successfully used in healthy elderly and demented elderly patients (Harper *et al*., 2004; Van Someren *et al*., 1996). Traditionally, actigraphy has been recorded from the non-dominant wrist but studies that investigated different placement locations found no differences between the dominant wrist, non-dominant-wrist, ankle, or trunk (Jean-Louis *et al*., 1997; Sadeh *et al*., 1994) or favored the dominant wrist when assessment of optimal variability of motor movement was of interest (Middelkoop *et al*., 1997). Therefore, an actiwatch (Cambridge Neurotechnology Ltd, Cambridge, UK) was worn on the dominant wrist. The small ($3 \times 4 \times 1$ cm) and light-weight actigraph made home recordings of circadian rhythm possible during several days and caused minimal burden to the participant. The participants were asked to wear the actigraph

for 7 days. A rather large number of participants provided a maximum of 4 days of rest-activity rhythm data. Based on the minimum of 3 days recommended by the American Association of Sleep Medicine Consensus report on the use of actigraphy (Littner *et al.*, 2003) and based on the fact that group differences and treatment effects have previously been reported using only 3 days of actigraphy (see for example: Harper *et al.*, 2001; Mormont *et al.*, 2000), we chose to analyze four consecutive days (M = 96 h, SD = 2, range: 72–96).

The following nonparametric variables were computed and are described in more detail elsewhere (Witting *et al.*, 1990). First, interdaily stability (IS) is a measure of the strength of coupling of the rest-activity rhythm to Zeitgebers (environmental time-cues). High values represent a stable rhythm and are considered positive. Second, intradaily variability (IV) serves as a measure of fragmentation of the rhythm. A normal rest-activity pattern will show one major active period (day) and one major resting period (night) and thus a low IV, whereas a fragmented rhythm will show many transitions between rest and activity during the 24-h cycle and high IV values. Third, the relative amplitude (RA) is a normalized variable based on the most active period in the 24-h cycle in relation to the least active period. A normal pattern will display a large difference between daytime activity and nightly rest. Thus, a high RA is considered positive.

Statistical analysis

Missing data

Two values (< 1%) were missing from 62 participants at three assessments because of noncompliance, i.e. the patient did not wear the actigraph long enough to compute rest-activity rhythm variables. Twenty-one values (11%) were missing due to technical failure of actigraphs. Patterns of missing data were analyzed per treatment group to evaluate whether data were Missing Completely at Random (MCAR) (Little and Rubin, 2002). Little's MCAR tests suggested that data were MCAR for all three dependent variables [chi-squares with 6 degrees of freedom ranged from 4.49 ($P = 0.61$) to 11.50 ($P = 0.12$)]. Missing values on dependent variables IS, IV, and RA were imputed using the expectation maximization (EM) method (Dempster *et al.*, 1977) available in the SPSS software. The EM method allowed for analysis of the entire sample of 62 participants.

Analyses of effects of electrical stimulation

Paired samples *t*-tests indicated no differences between the pre-assessment (baseline before treatment) and the Delayed-assessment (after a washout period of 6 weeks) on any of the dependent variables, justifying pooling of data from these two assessments (Kirk, 1995). This procedure resulted in reduced variability and increased statistical power. The two assessments combined are further referred to as pooled baseline assessment. To evaluate the effects of the treatment, repeated measures analyses of variance (ANOVA) with 'group' (two levels: experimental versus placebo) as between-subjects factor and 'time' (two levels: pooled baseline versus post) as within subjects factor were conducted. When interactions between 'group' and 'time' occurred, within group *t*-tests were conducted.

Analyses of interactions between electrical stimulation and AChEI use

Post-hoc analyses of possible interaction effects between electrical stimulation and AChEI use were performed. The experimental and placebo group separately were subject to repeated measures ANOVA with AChEI use (two levels: AChEI + versus AChEI −) as between-subjects factor and time (two levels: pooled baseline versus post) as within-subjects factor. All statistical tests were two-tailed and the critical value for significance was $P < 0.01$ to compensate for the use of multiple tests. SPSS Base software for Windows Version 11.5 was used for all statistical analyses.

RESULTS

The experimental group and the placebo group did not differ on the actigraphy variables IS, IV, or RA at baseline as indicated by independent samples *t*-tests. Overall IS before treatment was 0.60 ± 0.015 (mean ± SEM), IV was 1.07 ± 0.037 and RA was 0.85 ± 0.013. These values are comparable to previous values found in AD patients and indicative of a less stable and more fragmented rest-activity rhythm compared with non-demented elderly patients (Harper *et al.*, 2004; Scherder *et al.*, 1999; Van Someren *et al.*, 1998).

Effects of electrical stimulation

Repeated-measures ANOVA with group (two levels: experimental versus placebo) as between-subjects factor and time (two levels: post versus pooled baseline) as within-subjects factor revealed a significant group × time interaction effect for RA ($F(2,60) = 13.76$, $P < 0.001$) and near-significant effects for IS ($F(2,60) = 5.90$, $P = 0.02$) and IV ($F(2,60) = 4.24$, $P < 0.04$). Further analyses using within-group *t*-tests revealed a trend for improved IS and IV in the experimental group ($t(30) = 1.85$, $P = 0.07$ and $t(30) = -1.98$, $P = 0.06$, respectively) and a significant worsening of RA in the placebo group ($t(30) = -3.35$, $P = 0.002$). Note that the decrement of RA after the treatment period in the placebo group was temporary and that there was no significant difference between the assessment before the treatment and after the washout period of 6 weeks (Table 2).

Interactions between electrical stimulation and AChEI use

To investigate a possible interaction effect between AChEIs and electrical stimulation, the experimental and placebo group

Table 2 Mean and SEM of the actigraph variables in the experimental and in the placebo group

	Experimental group (n = 31), mean ± SEM			*Placebo group (n = 31), mean ± SEM*			*Pooled baseline vs. post statistics*	
	Pre	*Post*	*Delayed*	*Pre*	*Post*	*Delayed*	*P*	η^2
IS	0.58 ± 0.023	0.60 ± 0.020	0.58 ± 0.018	0.61 ± 0.020	0.57 ± 0.023	0.60 ± 0.022	0.018	0.09
IV	1.02 ± 0.049	0.98 ± 0.055	1.11 ± 0.051	1.11 ± 0.055	1.08 ± 0.055	0.96 ± 0.056	0.044	0.07
RA	0.86 ± 0.015	0.86 ± 0.017	0.85 ± 0.018	0.84 ± 0.022	0.79 ± 0.027	0.86 ± 0.019	0.001	0.19

IS, interdaily stability; IV, intradaily variability; RA, relative amplitude; Pre, baseline; Post, after 6 weeks treatment; delayed, after 6 weeks treatment-free; pooled baseline, pre and delayed pooled; SEM, standard error of the mean; η^2, partial eta squared effect size.

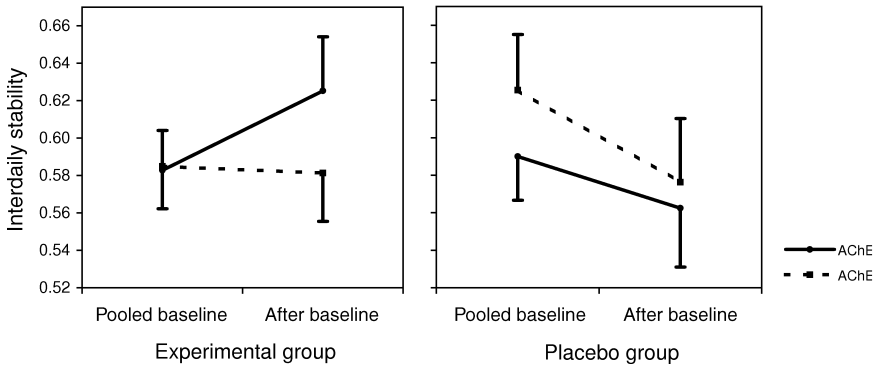

Figure 1. Mean values for interdaily stability of the experimental (left panel) and placebo (right panel) group at pooled baseline and after treatment. There are separate lines for acetylcholinesterase inhibitor users (AChEI users) and non-users (AChEI non-users). Error bars indicate standard errors of the mean (SEM), shown only one sided for reasons of clarity.

separately were subject to repeated-measures ANOVA with AChEI use (two levels: AChEI + versus AChEI −) as between-subjects factor and time (two levels: post versus pooled baseline) as within-subjects factor. The experimental group revealed a near-significant AChEI × time interaction effect for IS ($F(2,29) = 5.00$, $P = 0.03$), whereas the placebo group showed no significant interaction. The effect size in the experimental group was large, i.e. η^2 (Cohen, 1977) was 0.15, which means that 15% of the variance of treatment outcome in the experimental group could be attributed to AChEI use, with better outcome for the group not using an AChEI. Furthermore, within-group *t*-tests revealed a significant effect of the experimental treatment on IS ($t(15) = 3.12$, $P = 0.007$) and a near-significant effect on IV ($t(15) = -2.53$, $P = 0.02$) in the AChEI − group, but no significant effects in the AChEI + group ($t(17) = -0.87$, $P = 0.40$ and $t(17) = 1.60$, $P = 0.13$, respectively) (see Fig. 1). All individual changes in IS within the experimental and placebo group are shown in Fig. 2. To further illustrate the above-mentioned findings on IS and IV, Fig. 3 shows normalized rest-activity data of a single case that showed improvement.

DISCUSSION

This paper presents data from a randomized clinical trial on peripheral electrical nerve stimulation in AD with at least three times as many participants as any earlier study on this topic to date. The previous studies (Scherder *et al.*, 1999; Van Someren *et al.*, 1998) were performed in a nursing home setting and the treatment in those studies was applied by a professional trained therapist. In the present study the participants still lived at home and the treatment was applied by an informal caregiver, mostly the partner of the patient. Effects of peripheral electrical stimulation, compared with placebo, on the rest-activity rhythm in AD patients living at home were examined. Results indicated near-significant group effects on the stability (IS) and fragmentation (IV) of the rhythm and a significant group effect on the amplitude of the rhythm (RA). The latter could be attributed to a temporary significant worsening in the placebo group, not to improvement in the experimental group.

The temporary worsening of RA in the placebo group is a peculiar finding and we can only speculate about origins of this result. One possible explanation is that the temporary worsening was caused by the so-called nocebo reaction, i.e. the opposite of the placebo reaction (Benedetti *et al.*, 1997; Kennedy, 1961). Perhaps the treatment procedure with application of electrodes and the use of an electrical apparatus had a negative connotation to the participants which caused a negative effect. This nocebo response may have been counterbalanced in the experimental group by the positive influence of the real treatment. We also report a temporary worsening of the same type of treatment in a different group of subjects in another paper by our group (Luijpen *et al.*, 2004) which points in the direction of a true effect rather than unreliable data.

The positive results on IS and IV point in the direction of effects found in earlier studies which showed a more stable rest-activity rhythm after treatment (Scherder *et al.*, 1999; Van Someren *et al.*, 1998) and a trend toward a positive effect on the fragmentation of the rhythm (Scherder *et al.*, 1999).

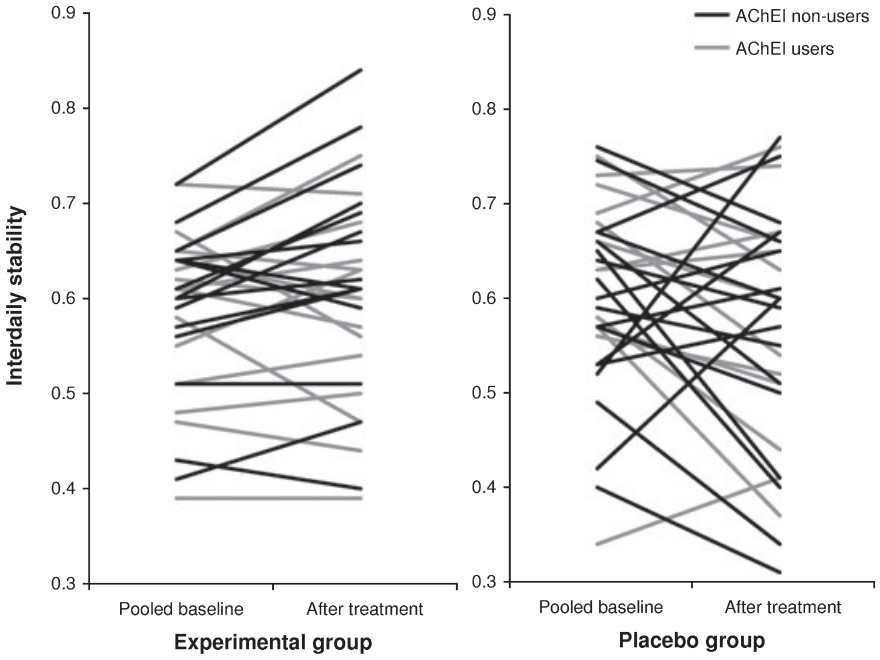

Figure 2. Individual changes of interdaily stability in the experimental group (left panel) and placebo group (right panel) at pooled baseline and after treatment. Note in the left panel the improvement in most of the acetylcholinesterase inhibitor non-users (AChEI non-users, black lines) in comparison with the variable changes in the acetylcholinesterase inhibitor users (AChEI users, gray lines).

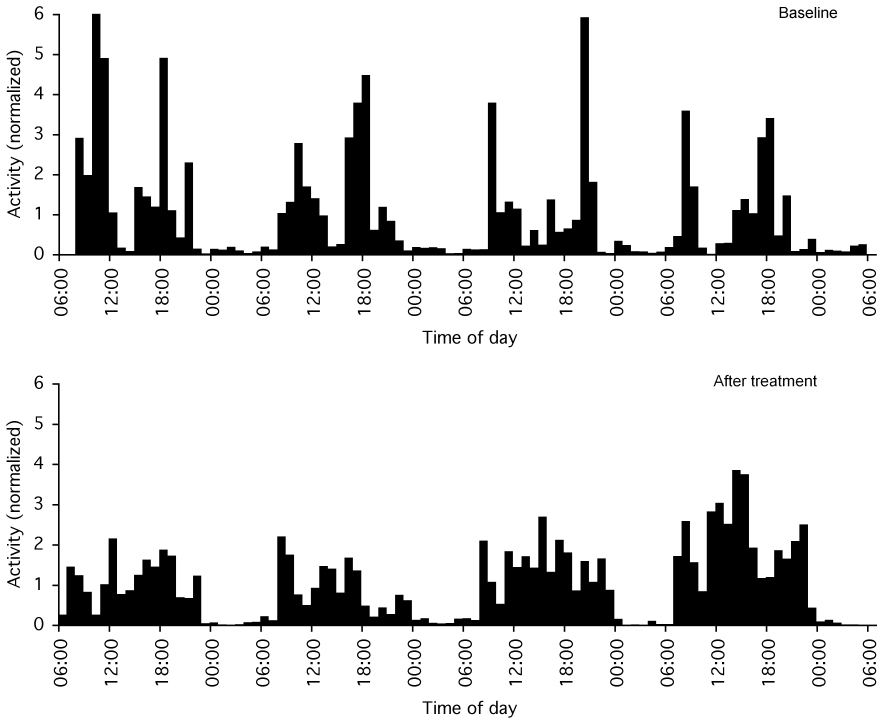

Figure 3. Activity profile (4 days of normalized hourly data) of an Alzheimer's disease patient before (upper graph) and after treatment (lower graph). This participant was assigned to the experimental group and was not using an acetylcholinesterase inhibitor (AChEI) concomitantly. Note the decreased fragmentation (i.e., less alternating periods of high and low activity) and more stability between days after treatment.

Therefore, we believe that the near-significant findings on the rest-activity rhythm, in part, support the hypothesis that neuronal stimulation enhances the rest-activity rhythm in AD patients.

Interestingly, the present sample permitted studying the interaction between electrical stimulation and AChEI intake as half of the participants were using AChEIs during the trial. *Post-hoc* analyses indicated that 15% of the variance of treatment outcome on IS in the experimental group could be attributed to AChEI use, with better outcome for the group not using AChEIs. In addition, the part of the experimental group not using AChEIs displayed a significant within-group treatment effect for stability of the rhythm and a near-significant effect for fragmentation, whereas the part of the experimental group also using AChEIs displayed no effects of electrical stimulation at all.

The finding that effects were most pronounced in the subgroup that was not using AChEIs gives food for thought.

First, AChEIs are aimed at improving cholinergic function (Scarpini *et al*., 2003) and electrical stimulation, among others, was hypothesized to enhance acetylcholine concentration in the brain. Concentration–effect curves are often asymmetrically shaped like an inverted U curve (Giraldo *et al*., 2002) and therefore it is possible that the subgroup using AChEIs benefited optimally from the pharmacological treatment, and electrical stimulation did not have an additional effect. Of course, this is merely speculation and future research using positron emission tomography to measure cholinergic function is necessary. Secondly, if indeed patients that are not using AChEIs benefit from electrical stimulation, this treatment may be of importance for those patients who do not tolerate AChEIs due to side effects like nausea, vomiting, diarrhea, and anorexia (Birks and Harvey, 2003; Birks *et al*., 2000; Loy and Schneider, 2004). Perhaps for those patients an improved rest-activity rhythm may positively influence cognitive and/or behavioral symptoms after long-term treatment periods, a relation that has been suggested in several studies (Bonanni *et al*., 2005; Van Someren *et al*., 2002). Finally, it is important to acknowledge that, although we did not find any differences between the AChEI users and AChEI non-users on any demographic variable, effects of electrical stimulation in the subgroup *not* formed by experimental allocation (in this case AChEI non-users) may be the result of selection bias prior to entering the study and should therefore be confirmed in future experiments.

An interesting issue is whether the near-significant effects on the rhythm have any clinical relevance. On one hand, data about behavioral outcomes in the participants from the present study showed no significant effects on subjective self-report and informant-based questionnaires after the 6-week treatment period. These data have been published elsewhere (Van Dijk *et al*., 2005). On the other hand, effects on the rest-activity rhythm may not show immediate measurable clinical effects. One might argue that long-term daily stimulation (e.g. during several months or more) may induce effects on the rest-activity rhythm that are noticed by the partner or other caregivers in the present study. Future investigations with longer treatment periods and clinically relevant outcome measures – such as number of participants admitted to a professional care facility – may provide answers to this important question.

In conclusion, the results of the present study show near-significant effects of electrical stimulation on the rest-activity rhythm in AD. This partially lends support to the hypothesis that neuronal stimulation enhances the rest-activity rhythm in AD patients. The fact that treatment effects were specifically pronounced in those patients who were not concomitantly using AChEIs warrants further investigation. Future studies of non-pharmacological interventions, including peripheral electrical nerve stimulation, should take medication use into account.

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