Effects of High-Frequency Cranial Electrostimulation on the Rest-Activity Rhythm and Salivary Cortisol in Alzheimer’s Disease

A Pilot Study

Erik Scherder\textsuperscript{a, b} Dirk Knol\textsuperscript{c} Marie-Jose van Tol\textsuperscript{d} Eus van Someren\textsuperscript{e} Jan-Berend Deijen\textsuperscript{b} Dick Swaab\textsuperscript{e} Philip Scheltens\textsuperscript{f}

\textsuperscript{a}Institute of Human Movement Sciences, University of Groningen, Groningen, \textsuperscript{b}Department of Clinical Neuropsychology, Vrije Universiteit, Amsterdam, \textsuperscript{c}Department of Clinical Epidemiology and Biostatistics, Vrije Universiteit Medical Center, Amsterdam, \textsuperscript{d}Department of Psychiatry, Leiden Universitas Medical Center, Leiden, \textsuperscript{e}Netherlands Institute for Brain Research, Amsterdam and \textsuperscript{f}Department of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands

Key Words
High-frequency cranial electrostimulation \cdot Rest-activity rhythm \cdot Salivary cortisol \cdot Alzheimer’s disease

Abstract

Objective: In a previous study, low-frequency (0.5 Hz) cranial electrostimulation (CES) neither improved the rest-activity rhythm nor reduced the level of salivary cortisol in patients with probable Alzheimer’s disease (AD). To investigate whether the frequency of CES was responsible for these negative findings, we set out to examine the effects of high-frequency CES on the rest-activity rhythm and salivary cortisol of patients with probable AD. We hypothesized that a decreased level of cortisol would parallel a positive effect of high-frequency CES on nocturnal restlessness in AD patients. Methods: Twenty AD patients were randomly assigned to an experimental group (n = 10) and a control group (n = 10). The experimental group was treated with high-frequency CES, the control group received sham stimulation, for 30 min a day, during 6 weeks. The rest-activity rhythm was assessed by actigraphy. Level of cortisol was measured by means of salivette tubes. Results: The rest-activity rhythm and the level of salivary cortisol did not react positively to high-frequency CES. In contrast, both groups showed an increase in the level of cortisol after the 6-week treatment period. Conclusions: High-frequency CES appeared to be ineffective in AD patients.

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In previous studies, transcutaneous electrical nerve stimulation, a type of peripheral nerve stimulation, appeared to strengthen the coupling of the rest-activity rhythm to supposedly stable zeitgebers in patients with Alzheimer’s disease (AD) [1, 2]. Moreover, AD patients showed a decrease in nocturnal restlessness. Another type of mild electrical stimulation that is partly mediated by the peripheral nervous system is cranial electrostimulation (CES). It was observed that CES improved sleep quality after 2 weeks of treatment in older people with vascular dementia [3].

Based on the positive effects mentioned above, we examined in a recent study the effects of low-frequency CES on the rest-activity rhythm and salivary cortisol of patients in a relatively early stage of AD [4]. The motivation to apply particularly low-frequency stimulation was that this type of stimulation preferably stimulates the locus...
coeruleus (LC)/noradrenergic neurotransmitter system [5], which strongly projects to the hypothalamic supra-
chiasmatic nucleus [6]. Salivary cortisol was included as a
dependent variable since an increased level of cortisol is indicative of a hyperactive hypothalamic-pituitary-ad-
renal axis which could cause sleeplessness [7–9]. The re-
results of that study [4] showed that low-frequency CES did
not improve the rest-activity rhythm in AD patients and
did not lower the level of salivary cortisol. One explana-
ration might be that it is insufficient to focus treatment par-
ticularly on the LC/noradrenergic system whereas also
other neurotransmitter systems are affected in AD, e.g.
the serotonergic system that originates in the dorsal ra-
phe nucleus (DRN) [10]. Both the LC/noradrenergic and
the DRN-serotonergic system project to the basal fore-
brain cholinergic neurons [11] and the basal forebrain
cholinergic neurons project to the hypothalamic supra-
chiasmatic nucleus [12]. It is of note that the LC and DRN
not only project to the basal forebrain, they are also in-
nervated by the basal forebrain. Moreover, the LC and
DRN receive projections from the hypothalamus [12].
These mutual connections reflect an integrative system
that plays an important role in circadian rhythms [12].
Since the DRN-serotonergic system preferably responds
to high-frequency stimulation [13] and the LC/noradren-
ergic neurons are also able to react to high-frequency
stimulation [5], the goal of the present study was to ex-
amine the effects of high-frequency CES on the circadian
rest-activity rhythm in patients with AD.

Similar to the previous CES study in AD [4], also in
the present study, it was examined whether the high level
of cortisol, indicative of sleeplessness [7–9], would de-
crease by high-frequency CES.

Materials and Methods

Participants

The sample consisted of 20 subjects, drawn from a sample of
500 institutionalized elderly persons. All subjects met the
NINCDS-ADRDA criteria for the clinical diagnosis of probable
AD [14] and were in stage 5 of the Global Deterioration Scale, in-
dicative of moderate to severe dementia [15]. Exclusion criteria
were a history of psychiatric disorder, alcoholism, cerebral trau-
ma, cerebrovascular disease, hydrocephalus, neoplasm, epilepsy,
disturbances of consciousness, focal brain disorders, and a pace-
maker. Level of general cognitive functioning was measured by
the Mini-Mental State Examination (MMSE), with a maximum
score of 30 [16]. The level of education was quantified on a 5-point
Likert-type scale [for details, see Scherder et al. [4]].

Subjects were randomly assigned to an experimental group
(n = 10) and a control group (n = 10). The gender of the experi-
mental group (10 women) and the gender of the control group
(8 females, 2 males) did not differ significantly (χ² = 2.22, d.f. = 1;
n.s.). The mean age of the participants of the experimental group
(85.70 years) did not differ significantly from the mean age of the
control group (84.50 years) [t(18) = 0.38; n.s.]. The mean MMSE
score of the experimental group (18.20) was not significantly dif-
ferent from the mean MMSE score of the control group (20) [t(18)
= 0.98; n.s.]. There was no significant difference between the lev-
el of education of the experimental group (2.70) and the control
group (3.30) [t(18) = 1.16; n.s.].

The patients and their families were extensively informed
about the aim and procedure of the study and gave their informed
written consent to further participate in the study. Before onset
of the treatment procedure, a trial treatment was applied to both
the experimental and the control group. No negative reactions of
the patients were observed. The patients and their relatives were
not aware of the group in which they participated (experimental
or control group), thus preventing a possible bias. The local Med-
ical Ethics Committee approved the study.

Assessment of the Circadian Rhythms

The Rest-Activity Rhythm

The circadian rest-activity rhythm was assessed noninvasively
by an actigraph (Actiwatch, Cambridge Neurotechnology, Cam-
bridge, UK), 24 h a day, for 1 week. The actigraph has the size and
shape of a watch, is worn on the dominant wrist, and registers ac-
celeration-induced wrist movements. The actigraph quantifies ac-
celerations due to motor activity of the arm and integrates these
over 1-min periods. From the resulting rest-activity rhythms, 3
nonparametric variables were calculated [17], using the Actiwatch
Sleep Analysis 2001 software (Cambridge Neurotechnology):
(1) interdaily stability (IS), a variable that quantifies the strength
of coupling between the rest-activity rhythm and supposedly sta-
ble zeitgebers (e.g. meals); (2) intradaily variability (IV), a variable
that quantifies the fragmentation of the rhythm, that is, the fre-
quency and extent of transitions between rest and activity, and
(3) relative amplitude (RA), a variable that quantifies the differ-
ence between the main activity (day) and rest (night) periods.

Salivary Cortisol Measurement

Results of several studies suggest that salivary cortisol is a reli-
able reflection of cortisol concentrations in blood [18, 19]. It rep-
resents cortisol that is not bound to plasma proteins, and, there-
fore, reflects the biologically active free hormone concentration.
Salivary cortisol concentrations were obtained by means of
salivette tubes (Sarstedt, Rommelsdorf, Germany). The partici-
ants were asked to chew on a cotton-wool swab for about 1 min,
which is sufficient to collect enough material for analyses [19].
Sampling took place at 9 different points during 24 h. The first
sample took place immediately after the moment of awakening,
the final sample was acquired just before the patient went to sleep;
for further information about the specific points, see Scherder et
al. [4]. All saliva sampling was conducted between 7:28 AM and
11:00 PM. Because the duration of the study was 2 years and the
patients were randomly assigned to both groups in parallel, sea-
son effects can be disregarded.

Cortisol Analysis

Salivary cortisol was analyzed by a coated-tube radioimmu-
noassay with the Orion Diagnostica Spectra Cortisol Ria Test
(Orion Corporation Orion Diagnostica, Espoo, Finland).
Effects of CES on Salivary Cortisol

Since the data were not normally distributed, the multilevel model was fitted to the log-transformed data. The parameter estimates of the interaction model are shown in table 2. Data analyses showed that there was no significant interaction effect between group and time, including group × post-treatment (T2) and group × delayed measurement (T3) (likelihood ratio $\chi^2 = 3.32$, d.f. = 2, $p = 0.19$). Because the group × time interaction was not significant, the model was also fitted without interaction. The parameter estimates of this model are also shown in table 2 (no interaction model). The back-transformed mean cortisol curves are shown in figure 1, and the mean cortisol values evaluated at value 0 (at about 11:00 AM) of the periodic function are shown in table 3. As can be seen in figure 1, the minimum cortisol level of 3.51 nmol/l occurred at about 9.39 PM (control group, delayed measurement), whereas the projected maximum

<table>
<thead>
<tr>
<th>Actigraphy</th>
<th>Experimental group</th>
<th>Control group</th>
<th>ANOVA (T1-T2)</th>
<th>Effect size $\eta^2$</th>
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<tbody>
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<td>pre mean SD</td>
<td>post mean SD</td>
<td>del mean SD</td>
<td>F(1, 19) p</td>
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<td>IS</td>
<td>0.63 0.14</td>
<td>0.64 0.12</td>
<td>0.59 0.20</td>
<td>0.65 0.16 0.59 0.18</td>
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<tr>
<td>IV</td>
<td>1.16 0.19</td>
<td>1.18 0.21</td>
<td>1.28 0.27</td>
<td>1.31 0.32 1.34 0.27</td>
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<tr>
<td>RA</td>
<td>0.78 0.09</td>
<td>0.79 0.08</td>
<td>0.77 0.08</td>
<td>0.77 0.14 0.80 0.12</td>
</tr>
</tbody>
</table>

Table 1. Means, standard deviations, and analyses of variance of the three actigraphy variables
**Fig. 1.** The fitted multilevel model for the mean values of saliva cortisol of the experimental and control group between 7:00 AM and 11:00 PM.

**Table 2.** Parameter estimates and standard errors (SE) of the multilevel two-harmonics model to fit the log-transformed cortisol levels in both the experimental group and the control group, at baseline (pre), after a 6-week treatment period (post) and after a 6-week treatment-free period (del).

<table>
<thead>
<tr>
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<th>Interaction model</th>
<th>No interaction model</th>
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<tr>
<td></td>
<td>parameter estimate</td>
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<td>Intercept</td>
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<tr>
<td>Group (treatment vs. control)</td>
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<td>0.145</td>
</tr>
<tr>
<td>Time</td>
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<td></td>
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<tr>
<td>Post (vs. pre)</td>
<td>0.162</td>
<td>0.067</td>
</tr>
<tr>
<td>Del (vs. pre)</td>
<td>-0.012</td>
<td>0.068</td>
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<tr>
<td><strong>Group × time</strong></td>
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<td></td>
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<tr>
<td>Group × post</td>
<td>-0.139</td>
<td>0.097</td>
</tr>
<tr>
<td>Group × del</td>
<td>-0.034</td>
<td>0.103</td>
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<tr>
<td>sin (2πt/24)</td>
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</tr>
<tr>
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<td>0.078</td>
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<tr>
<td>sin (4πt/24)</td>
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<tr>
<td>var(sin (2πt/24))</td>
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<tr>
<td>var(cos (2πt/24))</td>
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<td>0.011</td>
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<tr>
<td>cov(intercept, sin (2πt/24))</td>
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<td>cov(intercept, cos (2πt/24))</td>
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<td>Level 1</td>
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<td>var(intercept)</td>
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<td>–2 log likelihood</td>
<td>639.87</td>
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</table>

Research question is presented in bold.
level of 17.02 nmol/l (not shown in fig. 1) was reached at about 5.46 AM (experimental group, post-treatment). For all 6 curves, the ratio of the maximum to the minimum cortisol levels is 4.2. The results on amplitude and peak time should be considered with caution because the maximum cortisol level has been obtained by extrapolation from the fitted curves.

The mean cortisol values indicate that in both groups the change in cortisol levels increased in the post-treatment period and returned to their pretreatment values after the 6-week period without treatment (fig. 1, table 2 and 3). We tested in this model the main effects of time: likelihood ratio $\chi^2 = 5.15$, d.f. = 2, $p = 0.076$, n.s. (post vs. pre: $z = 1.99$, $p = 0.047$; del vs. pre: $z = -0.04$, $p = 0.96$).

Discussion

The results of the present study suggest that, in contrast to our expectations, high-frequency CES did not have a positive influence on the rest-activity rhythm and cortisol levels in AD patients. After the treatment (treatment-free) period of 6 weeks, both the experimental and control group showed hardly any changes in the rest-activity variables IS, IV and RA (table 1). In addition, cortisol levels in both the experimental and control group increased instead of decreased after the 6-week treatment period and returned to pretreatment values after the 6-week period without treatment (table 2 and 3, fig. 1).

Although in the present study the lowest cortisol level was observed at about 9:30 PM, an hour before and after that time, the cortisol level was close to this lowest point (fig. 1). These findings approach the results of an earlier study in which 24-hour cortisol profiles of patients with AD were analyzed [23]. In that study, the lowest cortisol level was observed at about 8:00 PM and remained level until midnight, after which the level showed a considerable increase. Compared to this latter finding, the level of salivary cortisol increased about 2 h earlier in the present study. One explanation might be that our patients were institutionalized and preparations for the night are often considered a stressful factor that triggers an increase in cortisol [24].

Considering the absence of treatment effects, together with very small effect sizes with respect to the actigraphy variables IS, IV and RA and the changes in cortisol levels in an opposite direction, clinically relevant treatment effects cannot be expected. In other words, similar to the low-frequency CES study, we must conclude that also high-frequency CES is not effective in AD and research concerning its effects on circadian rhythms in AD should not be continued in its present form.

Acknowledgement

The authors are very grateful to Fontis Amsterdam for financial support.

References


