Peripheral electrical nerve stimulation in Alzheimer's disease

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ter verkrijging van de graad Doctor aan
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in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Psychologie en Pedagogiek
op dinsdag 6 september 2005 om 15.45 uur
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door
Koene Riemer Albert van Dijk
geboren te Rotterdam

promotoren: prof.dr. E.J.A. Scherder
prof.dr. Ph. Scheltens

“Ik poets mijn tanden en zoek ondertussen naar woorden, een formulering voor wat ik voel. Alsof er iemand in mij zit die zich een ander huis herinnert, waarvan de indeling soms dwars door die van dit huis loopt. Kamers horen absolute zekerheden te zijn. De manier waarop zij in elkaar overlopen hoort eens en voor altijd vast te liggen. Een deur moet vanzelfsprekend geopend kunnen worden. Niet in angst en onzekerheid omdat je geen idee hebt wat je erachter zult vinden.”

(J. Bernlef, Hersenschimmen, p. 42, 1984)

“While I brush my teeth I search for words, an expression for what I feel. As if there is someone inside of me who remembers another house, with a layout that sometimes blends with the layout of this house. Rooms should be absolute certainties. Their mutual position should be permanent and you should be able to open a door with confidence. Not in fear and doubt of what you will find.”

(J. Bernlef, Hersenschimmen, p. 42, 1984, freely translated)

Contents

Chapter 1

General introduction

Alzheimer's disease (AD) is the most common cause of dementia affecting approximately 1% of the population of 65 years old and up to 22% of the persons of 90 years and older (Lobo et al. 2000). Progressive neurodegeneration results in overall cognitive impairment (Katzman 1986) difficulty with activities of daily living (Galasko et al. 1997), a variety of neuropsychiatric symptoms (Assal & Cummings 2002; Mega et al. 1996), circadian rhythm disruption (Van Someren et al. 1996), and sleep disturbances (Tractenberg et al. 2003). Caring for an AD patient places an enormous strain on family members (Pinquart & Sorensen 2003; Rabins 1998) and the economic burden of the disease to society is large and expected to rise considerably due to aging of the population (Hebert et al. 2003).

Pathophysiology

The pathogenesis of neurodegeneration in AD is not yet fully understood. A sequence of events starting with production and accumulation of beta-amyloid peptide leading to formation of neurofibrillary tangles and neuritic plaques followed by cell death is articulated in the amyloid cascade hypothesis (Hardy 1992; Hardy & Selkoe 2002). This theory is, however, not without controversy (for a review, see: Neve & Robakis 1998) and evidence has been put forward by Swaab et al. indicating that presence of beta-amyloid, tangles, plaques, and cell death are independent phenomena (Swaab et al. 1998; Swaab et al. 2003). For instance, the amyloid burden in the superior temporal sulcus of AD patients appears to be independent of neuronal cell loss and number of neurofibrillary tangles (GomezIsla et al. 1997). In addition, neuritic plaques can be present in up to 100% of the tissue of certain brain areas of non-demented persons of 100 years and older (Delaere et al. 1993). Moreover, neurofibrillary tangles and neuritic plaques can occur independently in brain tissue of AD patients (Armstrong et al. 1993) and, finally, although neurofibrillary tangles coincide with cell death in some brain areas, such as CA1 of the hippocampus (West et al. 1994), cell loss in the neocortex of AD patients appeared insignificant despite presence of plaques (Regeur et al. 1994).

Several studies have shown that cell death in aging and AD is less widespread than presumed earlier (Pakkenberg & Gundersen 1997; Regeur et al. 1994; Wickelgren 1996) and Swaab et al. argue that not cell death but decreased neuronal metabolism is

the major pathological hallmark of AD (Swaab 1991; Swaab et al. 1994; Swaab et al. 1998; Swaab et al. 2003). Diminished neuronal activity is indicated by a decreased size of the Golgi apparatus of cells in the nucleus basalis of Meynert (Salehi et al. 1994) and the hippocampus (Salehi et al. 1995), brain areas typically affected in AD. Moreover, decreased metabolic rate in AD seems consistently correlated with clinical symptoms (for a review, see: Blass et al. 2002). Finally, there is evidence that presence of an apolipoprotein (APOE) ε4 allele, a major risk factor for late onset AD (Corder et al. 1993; Saunders et al. 1993), is related to extra diminished metabolism in the nucleus basalis of Meynert in patients with AD (Salehi et al. 1998), and elderly who do not, yet, have AD (Dubelaar et al. 2004).

"Use it or lose it"

Swaab et al. also state that high or enhanced metabolism during the process of aging may have a beneficial effect on neuronal functioning and survival and that neuronal stimulation may protect neurons against degenerative changes in aging and AD, a hypothesis which is paraphrased as "use it or lose it" (Swaab 1991; Swaab et al. 1998; Swaab et al. 2003). According to Swaab et al., therapeutic strategies in AD should focus on reactivation of metabolically impaired neurons through manipulation of trophic factors, hormones, neurotransmitters, and environmental stimuli (Swaab 1991; Swaab et al. 1998; Swaab et al. 2003). Several observations underline this theory. First, the notion that higher educational and occupational attainment appear to have some protective value for AD symptomatology (Stern 2002), second, findings that cognitively stimulating activities may protect against dementia (Fratiglioni et al. 2004), third, the fact that physical activity holds the promise for better mental health of older adults (Lautenschlager et al. 2004) and finally, the observation that exposure to bright light seems to have a positive effect on the rest-activity rhythm as well as on cognition, mood, and behavioral functioning in old age (for a review, see: Van Someren et al. 2002).

Peripheral electrical nerve stimulation in AD

Another way of stimulating the central nervous system externally, i.e. through the environment, is the use of peripheral electrical nerve stimulation applied to the skin. In the past decades, the effects of peripheral electrical stimulation in AD have been studied in a series of placebo-controlled experiments (Scherder et al. 1992; Scherder et al. 1995; Scherder et al. 1998; Scherder et al. 1999b; Scherder & Bouma 1999; Van Someren et al. 1998). Improvements were found in certain aspects of cognition, behavior, and the

rest-activity rhythm. Moreover, a Japanese group replicated effects on cognition and found a positive effect on the pupillary light reflex (Guo et al. 2002). Although these findings are encouraging, the positive effects of electrical stimulation in AD must be interpreted with caution considering the small sample sizes, ranging from 6 (Guo et al. 2002) to 18 (Scherder et al. 1998).

Aim of this thesis

The present thesis examines the effects of peripheral electrical stimulation in a substantially larger group of AD patients than any other study on this topic to date. In **Chapter 2** the literature regarding the effects of peripheral electrical stimulation on cognitive and behavioral functioning in several conditions affecting the central nervous system will be reviewed including the studies on AD and aging. **Chapter 3** deals with the stimulation parameters that have been used since the early studies of electrical stimulation in AD. These parameters were based on knowledge from animal experimental studies up to 1991. The goal of this chapter is to examine whether the animal experimental literature since 1991 still supports the originally selected stimulation parameters. **Chapter 4** examines the effects of electrical nerve stimulation on cognition and behavior in a randomized, placebo-controlled, parallel-group clinical trial including 62 AD patients. The participants still lived at home and a partner or other family caregiver applied the daily treatment, 30 minutes a day, seven days a week, during six weeks. **Chapter 5** presents data on the effects of electrical stimulation on the rest-activity rhythm in AD, derived from the same clinical study as described in the previous chapter. **Chapter 6** deals with executive dysfunctions in terms of neuropsychological deficits in AD patients compared with healthy elderly controls. The executive functions are suitable outcome measures for evaluating treatment and the use of computerized tests to measure these executive functions is discussed. In **Chapter 7**, a summary and conclusions are offered.

Chapter 2

Effects of Transcutaneous Electrical Nerve Stimulation on non-pain related cognitive and behavioral functioning

Abstract

An extensive search through 9 electronic bibliographic databases (PubMed, Cochrane Library, Web of Science, ERIC, PsychINFO, Psyndex, Cinahl, Biological Abstracts, Rehabdata) was performed in order to review the effects of Transcutaneous Electrical Nerve Stimulation (TENS) on non-pain related cognitive and behavioral functioning. Eight studies were identified on neglect due to stroke, six studies on Alzheimer's disease (AD), one study on aging, and two studies on coma due to traumatic brain injury. The results of the various studies revealed that TENS has a variety of effects. These consist of enhancement in somatosensory functioning, visuospatial abilities, and postural control in neglect, improved memory, affective behavior, and rest-activity rhythm in AD, and acceleration of awakening in coma. Effectiveness of TENS is discussed in relation to various stimulation parameters: duration, frequency, pulse width, and intensity. It is argued that arousal may underlie the beneficial influence of TENS in various conditions. Finally, suggestions are offered for future research.

Van Dijk KRA, Scherder EJA, Scheltens P, Sergeant JA. Effects of Transcutaneous Electrical Nerve Stimulation (TENS) on non-pain related cognitive and behavioral functioning. *Reviews in the Neurosciences* 2002;13(3):257-70.

Introduction

Transcutaneous Electrical Nerve Stimulation (TENS), a type of peripheral nerve stimulation, is particularly known for its analgesic effects in a variety of painful conditions, e.g. postoperative pain, cancer pain, and lower back pain (Carrol & Badura 2001; Mann 1983; Pan et al. 2000). The results of clinical studies on the analgesic effects of TENS are, however, equivocal (White et al. 2001) primarily due to methodological issues (Wright & Sluka 2001). Lack of standardization of the various stimulation parameters (frequency, intensity, and duration of stimulation) makes comparison between the various studies difficult. In addition, evaluation of the effects of TENS is complicated by the different pain conditions studied (Wright & Sluka 2001). It is clear that randomized controlled studies are necessary before firm conclusions can be drawn concerning the analgesic effectiveness of TENS.

It is noteworthy that in recent studies the effects of TENS have also been examined using measures of non-pain related cognitive and behavioral functioning. The present paper reviews studies on the effects of TENS on cognitive and behavioral functioning in terms of attention, memory, arousal, rest-activity rhythm as well as affective behavior and quality of life.

To avoid confusion concerning the various types of electrical stimulation, the present review will include only those studies in which the original type of TENS has been used, i.e. an electrical stimulus applied to the skin and exclusively mediated through peripheral afferent nerve fibers. Electrical stimulation applied to the earlobes or on the skin of the cranium is sometimes called 'Cranial TENS' (Taylor et al. 1989), 'Cranial Electro Stimulation' (CES) (Klawansky et al. 1995) or 'Transcranial Electro Stimulation' (TCES or TES) (Limoge et al. 1999). A possible explanation for the observed effects of Cranial TENS, CES, and TCES/TES on cognition and behavior is increased microcirculation in the brain (Omura 1983). Because Cranial TENS, CES and TCES/TES might only be partly mediated through the peripheral nervous system (Hozumi et al. 1996; Taylor et al. 1989), these types of stimulation will not be included in this review.

TENS has also been applied to enhance functional ability of a hemiparetic arm or leg. This type of TENS is often called 'functional electrical stimulation' (FES) (Glanz et al. 1996; Johansson et al. 2001; Sonde et al. 2000). Successful rehabilitation of a hemiparetic extremity requires, among other things, an increase in muscle strength, improved co-ordination between agonists and antagonists (Glanz et al. 1996), and (re)learning of motor activity. Although cognitive processes are involved, an early report by Ashby and Verrier (1976) suggests that peripheral electrical nerve stimulation

might reduce muscle tone by activating a spinal inhibitory mechanism. Such a spinal mechanism possibly underlies the positive effects of FES and, therefore, a review of the effects of FES is beyond the scope of this paper.

Following an extensive search[1] through nine electronic bibliographic databases (PubMed, Cochrane Library, Web of Science, ERIC, PsychINFO, Psyndex, Cinahl, Biological Abstracts, Rehabdata), studies on the effects of TENS on cognitive and behavioral functioning were narrowed down to the following domains: neglect due to stroke, Alzheimer's disease (AD), and aging, and coma due to traumatic brain injury. Articles written in English and with more than a single subject were included. After examination of the reference lists of relevant studies, eight studies on neglect were identified, six studies on AD, one on aging, and two on coma.

The review is organized as follows: the results of clinical studies in which the effects of TENS on the various patients groups noted above will be discussed. With respect to statistical significance, effect sizes[2] will be stated if the data were provided in the specific article. Subsequently, the effectiveness of TENS on cognition will be related to four stimulation parameters: duration, frequency, pulse width, and intensity of stimulation. Next, it will be argued that an increase in arousal may underlie the effects of TENS on cognition and behavior. Finally, suggestions will be made for future research.

Clinical studies

TENS in neglect

Vallar et al. (1995) were among the first to examine the effects of TENS on left visuospatial hemineglect in patients who suffered a stroke in the right hemisphere. In one experiment the superficial electrodes were placed either to the left or right posterior neck, improving performance in 13 out of 14 patients (93%). In another experiment TENS was applied either to the left neck or to the dorsal surface of the left hand, both leading to improved left visuospatial hemineglect (Vallar et al. 1996). The results

[1] The most recent search was performed November 2001

[2] Cohen's $d = M_1 - M_2 / \sqrt{[(\sigma_1^2 + \sigma_2^2) / 2]}$, where $d = 0.2$ is small, $d = 0.5$ is medium, and $d = 0.8$ is large (Cohen, 1988)

Table 2.1 Studies of TENS and neglect *(nsa = not stated in article)*

author	population (male/female)	n	age	stimulation parameters: site	duration	frequency	intensity	pulse width	results
Vallar et al., 1995	visual-spatial hemineglect, right hemisphere lesions (nsa[1])	14	*M* = 59.07 range = 34-80	posterior neck, below the occiput, just LEFT of the spine	single stimulation period of 15-min	100 Hz	0.5 µA/mm^2	100 µs	when subjects were free to move their head and trunk left stimulation improved performance on letter cancellation task right stimulation did not improve performance
				posterior neck, below the occiput, just RIGHT of the spine					
		8	*M = 59* range = 43-67	posterior neck, below the occiput, just LEFT of the spine	single stimulation period of 15-min	100 Hz	0.5 µA/mm^2	100 µs	when subjects were not free to move their head and trunk, stimulation temporarily improved cancellation performance as well
				posterior neck, below the occiput, just RIGHT of the spine					
		6	*M* = 70.67 range = 65-85	posterior neck, below the occiput, just LEFT of the spine	single stimulation period of 15-min	100 Hz	0.5 µA/mm^2	100 µs	both hand and neck stimulation improved performance levels
				dorsal surface of the LEFT hand					
Karnath, 1995	visual neglect due to stroke or intracranial neoplasm (2/2)	4	*M* = 54 range = 48-61	vibration: LEFT posterior neck muscle	nsa	100 Hz	0.4 mm	-	improvement of performance on cancellation and copy task
				TENS: LEFT posterior neck muscle	nsa	100 Hz	substantial non-painful tingling sensation	nsa	little or no effect
				vibration: LEFT hand muscle	nsa	100 Hz	0.4 mm	-	little or no effect
Vallar et al., 1996	somatosensory neglect due to stroke in the right hemisphere(4/6)	10	*M* = 67.6 range = 42-81	posterior neck, below the occiput, just LEFT of the spine	single stimulation of 15-min	100 Hz	0.5 µA/mm^2	100 µs	temporary improvements of contralesional somatosensory deficits
					no stimulation	-	-	-	
	somatosensory neglect due to stroke in the left hemisphere (1/3)	4	*M* = 69.75 range = 59-79	posterior neck, below the occiput, just RIGHT of the spine	single stimulation of 15-min	100 Hz	0.5 µA/mm^2	100 µs	beneficial effects in one out of four patients only
					no stimulation	-	-	-	
Pizzamiglio et al., 1996	somatosensory hemineglect due to stroke in the right hemisphere (2/2)	4	*M* = 60 range = 47-69	TENS: posterior neck, below the occiput, just LEFT of the spine	8 weeks, 5 days per week, 60 minutes	100 Hz	0.5 µA/mm^2	100 µs	positive effects in two out of four patients
				general cognitive rehabilitation treatment	-	-	-	-	generalized positive effects in all patients

(Table 2.1 continued)

Guariglia et al., 1998	hemi neglect due to stroke in the right hemisphere (nsa[1])	9	*M* = 65.25 *SD* = 8.88	LEFT neck muscle	single stimulation of >20-min	100 Hz	0.5 µA/mm^2, non-noxious cutaneous prickling	100 µs	significantly affecting imaginal neglect compared to nostimulation
				RIGHT neck muscle					no clear effect compared to no stimulation
				no stimulation	-	-	-	-	
Guariglia et al., 2000	Hemispatial neglect due to stroke in the right hemisphere (nsa[1])	12	nsa	positive electrode: LEFT neck muscle below the occiput, just lateral to the spine negative electrode: LEFT shoulder	single stimulation of >20-min	100 Hz	0.5 µA/mm^2	100 µs	TENS significantly improved (greatly impaired) ability to code shape-based representations compared to no stimulation and was ineffective in improving (less impaired) coding of non-geometric representations (e.g. color).
					no stimulation	-	-	-	
Pérennou et al., 2001	neglect related postural instability due to stroke with spatial neglect (5/1)	6	*M* = 58.3 *SD* = 2.5	dorsal neck muscle, contralateral to the damaged hemisphere	TENS condition: single stimulation of >10-min	100 Hz	mild tingling sensation, roughly 10mA	200 µs	strong improvement of postural imbalance
					sham/control condition: single stimulation of >10-min	100 Hz	0.01 x perception threshold	200 µs	
	neglect related postural instability due to stroke without spatial neglect (11/5)	16			TENS condition: single stimulation of >10-min	100 Hz	mild tingling sensation, roughly 10mA	200 µs	no significant effect of TENS
					sham/control condition: single stimulation of >10-min	100 Hz	0.01 x perception threshold	200 µs	
	healthy subjects (9/5)	14	*M* = 54.7 *SD* = 3	no stimulation	-	-	-	-	
Richard et al., 2001	neglect due to stroke in the right hemisphere (1/1)	2	*M* = 66.5	medial sagittal plane of the foot (LEFT vs. RIGHT stimulation in both TENS and vibration condition)	TENS	100 Hz	adjusted to 2/3 of the interval between perception and unpleasantness	100 µs	decreased rightward orientational bias after LEFT and RIGHT stimulation
					vibration	100 Hz	moderate pressure 0.5 mm	-	decreased rightward orientational bias after LEFT stimulation
					no stimulation	-	-	-	postural imbalance
	neglect due to stroke in the right hemisphere (0/2)	2	*M* = 47		TENS	100 Hz	adjusted to 2/3 of the interval between perception and unpleasantness	100 µs	no effect
					vibration	100 Hz	moderate pressure 0.5 mm	-	no effect
					no stimulation	-	-	-	no postural imbalance
	healthy subjects (1/2)	3	*M* = 52	no stimulation	-	-	-	-	no effect

suggest that TENS has a non-specific effect regarding the anatomical site (hand versus neck), but a specific effect regarding the body laterality (left versus right) which is stimulated.

In another study, patients with left-sided visuospatial neglect due to stroke were treated with either vibration of the left-neck muscle, TENS stimulation of the left neck, or vibration of the left hand muscle (Karnath 1995). Because vibration of the left neck muscle had clearly more effect than TENS stimulation of the neck and vibration of the muscle of the hand, this effect may be considered specific. In contrast, TENS activates afferent nerve fibers in a rather non-specific way, resulting in an increased level of arousal (Karnath 1995).

In a recent study, treatment with both TENS and muscle vibration, applied to the left and right side of the neck, had positive effects on a right sided orientation bias in patients with visuospatial neglect. In contrast, there was no beneficial effect in subjects without neglect (Richard et al. 2001). This non-specific laterality effect needs to be interpreted with caution due to the small sample size (n=4).

In another study by Vallar et al. (1996), TENS was applied to 14 patients with neglect hemianesthesia following a vascular lesion in the right or left hemisphere. The site of stimulation was the posterior neck, contralateral to the lesion. Recovery from the somatosensory deficit was observed in all patients with a lesion in the right hemisphere, irrespective of the presence or absence of visuospatial hemineglect. In one right brain damaged patient, the right posterior neck was stimulated with TENS, resulting in an increase in the left somatosensory deficit (Vallar et al. 1996). This latter finding strengthens the suggestion that TENS has a specific effect on cognitive functioning regarding laterality of stimulation.

Similar positive and specific effects of TENS in 9 right brain damaged patients with visuospatial hemineglect have been observed by Guariglia et al. (1998). TENS was applied to the left neck muscle. This appeared to be highly beneficial (effect size: d = 1.05). In contrast, right neck muscle TENS yielded no significant effects (Guariglia et al. 1998).

In a study on neglect, it was argued that spatial orientation is dependent on different neuronal mechanisms (Guariglia et al. 2000). TENS applied to the left side of the neck in stroke patients with neglect improved only orientation guided by the shape of the environment (d = 1.08) and not by a visual environmental cue, e.g. color (Guariglia et al. 2000). This finding suggests a specific effect of TENS not only for laterality of stimulation but also a specific effect for function. Findings from a recent study, in which TENS restored the postural instability in neglect patients (n = 6) who

had a lesion in the temporoparietal area showing a very strong effect (d = 1.90), support the idea of TENS acting upon a specific brain function (Perennou et al. 2001).

In most studies on neglect, TENS was applied in a single session with a duration of 10 to 20 minutes (Guariglia et al. 1998; Guariglia et al. 2000; Karnath 1995; Perennou et al. 2001; Vallar et al. 1995; Vallar et al. 1996). In the study by Richard et al. (2001) duration of stimulation was unfortunately not stated. There is only one publication that reports more than a single stimulation session, i.e. 60 minutes per day, five days a week, for a period of eight weeks (Pizzamiglio et al. 1996). In this study, TENS was applied to four patients with visuospatial hemineglect in addition to a general cognitive intervention. In the eight weeks immediately following TENS treatment, patients underwent a purposebuilt rehabilitation training program for neglect. Assessment of visuospatial neglect after the first eight weeks revealed no effect of TENS. Significant change was observed after the eight weeks of specific rehabilitation training (Pizzamiglio et al. 1996). A treatment free period between the two interventions, in order to minimize carry-over effects, would have given more insight in the effectiveness of TENS. Unfortunately, that was not part of the study design and hence, no firm conclusions about the effectiveness of TENS can be drawn.

Taken together, TENS appears to have a beneficial effect on somatosensory deficits and postural control. Effects on the visuospatial component of neglect are equivocal. A major limitation of all studies is the small sample size, i.e. groups ranged from 2 to 14 subjects. All studies used a within-subjects design and in only one study subjects received sham stimulation (Perennou et al. 2001). See Table 2.1 for an overview of the studies of TENS and neglect.

TENS in Alzheimer's disease (AD) and aging

In a series of studies, TENS was applied to patients in both an early and an advanced stage of AD (Scherder et al. 1992; Scherder et al. 1995; Scherder et al. 1998; Scherder et al. 1999b; Scherder & Bouma 1999; Van Someren et al. 1998). Patients were stimulated five days a week for six weeks. In one study, TENS was applied for 6 hours a day in which high and low frequency were alternated every 1.5 hours (Scherder et al. 1992). In the other studies, the stimulation period consisted of 30 minutes burst-TENS (see section: stimulation parameters).

Various aspects of memory were assessed in four of these studies. The results suggest that TENS has a beneficial influence on visual short-term memory (d = 0.30) (Scherder & Bouma 1999), (d = 0.44) (Scherder et al. 1998), (d = 1.49) (Scherder et al. 1995), a medium to strong effect on visual long-term memory (d = 0.50) (Scherder et al. 1998), (d = 1.92) (Scherder et al. 1995), and a high effect on verbal long term memory (d = 3.40) (Scherder et al. 1992; Scherder et al. 1995). No effects were found on verbal

short term memory in any of the studies (Scherder et al. 1992; Scherder et al. 1995; Scherder et al. 1998; Scherder et al. 1999b). Results further suggest that TENS has a modest positive effect on verbal fluency (d = 0.28) (Scherder et al. 1992; Scherder et al. 1998) and affective behavior (d = 0.82) (Scherder et al. 1995), and a small positive effect on activities of daily living (ADL), (d = 0.19) (Scherder et al. 1995; Scherder et al. 1998). The effect on ADL consisted of a small but significant decline in service need. Two other studies report large improvement in coupling between the rest-activity rhythm and supposedly stable Zeitgebers in early and advanced AD patients (d = 1.04) (Scherder et al. 1999b), (d = 1.86) (Van Someren et al. 1998). This latter finding suggests improved functioning of the suprachiasmatic nucleus (SCN), the biological clock of the brain (Rusak & Zucker 1979; Van Someren et al. 1998). In addition, a medium effect was found for improved activity during the day and less activity during the night (d = 0.58) (Scherder & Bouma 1999). This latter finding is particularly important, since nocturnal restlessness is one of the main reasons for institutionalization of the elderly (Pollak & Perlick 1991).

In one study, the effects of TENS were examined in non-demented elderly with benign forgetfulness (Scherder et al. 2000). Similar to the effects found in AD, verbal and nonverbal long term memory and nonverbal short term memory showed strong effects (d = 1.65, d = 2.07, d = 2. 91, respectively). Moreover, strong effects were found for verbal fluency and affective behavior which paralleled those observed in AD patients (d = 0.96, d = 1.45, respectively). However, a decline in service need was not observed (Scherder et al. 2000).

It is noteworthy that in all of the above studies in AD and non-demented elderly, observed TENS effects were not maintained after six weeks without treatment. A major limitation of the TENS-studies in demented and non-demented elderly is that the participating groups are relatively small, i.e. experimental and placebo group ranged from four to ten subjects. On the other hand, all studies included a control group which received sham stimulation.

In summary, the effects of TENS in both AD and aging must be interpreted with caution considering the relatively small number of patients in each study. The fact that the results could be replicated in various studies might be considered as support for treatment effects. Treatment effects of TENS in AD and aging are further supported by the observation that the effects disappeared after cessation of stimulation. Indeed, TENS is not intended to cure AD and, hence, without stimulation the disease progresses further. See Table 2.2 for an overview of the studies of TENS and AD.

Table 2.2 Studies of TENS and AD *(nsa = not stated in article)*

author	population (men/women)	N	age	stimulation parameters					results
				site	duration	frequency	intensity	pulse width	
Scherder et al., 1992	early stage AD (1/7)	4 (TENS)	*M* = 81.4 range = 74-91	two electrodes between T1 and T5, each on one side of the spinal column	6 weeks, 6 hours a day: alternating 100 (1.5 hours) Hz and 2 Hz.(1.5 hours)	100 Hz	perceptual threshold	40 µs	TENS improved verbal long-term memory and verbal fluency. No improvement visual long-term memory and verbal/non-verbal short term memory
						2 Hz	strongly perceptual, non-noxious	250 µs	
		4 (sham)				-	-	-	
Scherder et al., 1995	early stage AD (nsa)	8 (TENS)	*M* = 84.6 range = 76-92	two electrodes between T1 and T5, each on one side of the spinal column	6 weeks, 5 days per week, 30 minutes	160 Hz, 2 bursts per sec	visible painless muscular twitches	40 µs	TENS improved some aspects of verbal and non-verbal short term and long term memory. Improved affective behavior.
		8 (sham)				-	-	-	
van Someren et al., 1998	early stage AD (4/18)	6 (TENS)	*M* = 84 *SD* = 1.5	two electrodes between T1 and T5, each on one side of the spinal column	6 weeks, 5 days per week, 30 minutes	160 Hz, 2 bursts per sec	visible painless muscular twitches	100 µs	TENS improved rest-activity rhythm, i.e. nightly restlessness decreased
		8 (sham)				-	-	-	
		8 (control)	*M* = 77 *SD* = 3.5	-	-	-	-	-	
Scherder et al., 1998	AD (nsa)	9 (TENS)	*M* = 83.4 range = 78-90	two electrodes between T1 and T5, each on one side of the spinal column	6 weeks, 5 days per week, 30 minutes	160 Hz, 2 bursts per sec	visible painless muscular twitches	100 µs	TENS improved nonverbal short-term and long term memory, word fluency. Less need of help. No improvement in affective behavior.
		9 (sham)				-	-	-	
Scherder et al., 1999a	midstage AD (nsa)	8 (TENS)	*M* = 81.7 range = 70-91	two electrodes between T1 and T5, each on one side of the spinal column	6 weeks, 5 days per week, 30 minutes	(burst TENS)	nsa	nsa	TENS improved rest-activity rhythm
		7 (sham)				-	-	-	
Scherder et al., 1999b	midstage AD (nsa)	8 (TENS)	*M* = 81.7 range = 70-91	two electrodes between T1 and T5, each on one side of the spinal column	6 weeks, 5 days per week, 30 minutes	160 Hz, 2 bursts per sec	visible painless muscular twitches	100 µs	TENS improved nonverbal short-term memory. No treatment effects in physical, social and affective functioning.
		8 (sham)				-	-	-	
Scherder et al., 2000	non-demented elderly (3/17)	10 (TENS)	*M* = 85.90 range = 80-89	two electrodes between T1 and T5, each on one side of the spinal column	6 weeks, 5 days per week, 30 minutes	(burst TENS)	nsa	nsa	TENS improved visual short-term memory, verbal long-term memory, semantic verbal fluency and stimulated subjects felt less depressed.
		10 (sham)	*M* = 87.90 range = 82-91			-	-	-	

Table 2.3 Studies of TENS and coma *(nsa = not stated in article)*

				stimulation parameters					
author	**population (men/women)**	**N**	**age (years)**	**site**	**duration**	**frequency**	**intensity**	**pulse width**	**results**
Ingvar and Ciria, 1975	severely brain damaged unresponsive patients	nsa	nsa	right thumb	nsa	nsa	nsa	nsa	increased cortical blood flow
Cooper et al., 1999	comatose	3	*M* = 32 range = 13-42	right median nerve	TENS, 2 weeks, 8 hours a day, 20 sec/min	40Hz	20 mA	300 µs	results indicate earlier awakening from coma
		3			sham, 2 weeks, 8 hours a day, 20 sec/min	-	-	-	
		3	*M* = 15.3 range = 14-16		2 weeks, 12 hours a day, 20 sec/min	40Hz	20 mA	300 µs	
		22	-	no stimulation	-	-	-	-	

TENS in Coma

In the last 20 years, sensory stimulation has become part of brain injury rehabilitation programs. LeWinn (1980) describes a Coma Arousal Team which attempted to achieve arousal by applying stimulation to all five senses, including tactile stimulation to the skin. Compatible types of stimulation applied in a Coma Arousal Procedure produced significant (d = 0.59) (Mitchell et al. 1990) and non-significant (Pierce et al. 1990) effects in terms of reducing the duration of coma. Cutaneous electrical stimulation increased cortical blood flow in, among others, patients who were comatose due to severe brain injury (Ingvar & Ciria 1975). In this latter study, low and high intensity electrical stimulation of the right thumb provoked a moderate increase in cerebral blood flow. Unfortunately, no details were provided on frequency and intensity of stimulation (Ingvar & Ciria 1975). Right median nerve stimulation (RMNS), which results in sensory evoked potentials (SEPs), has been used to assess brain function and predict clinical outcome in comatose patients (Cusumano et al. 1992; Facco et al. 1993). More recently, eight to twelve hours daily RMNS by TENS was applied as a therapeutic tool in the treatment of brain-injured comatose patients (Cooper et al. 1999). In one experiment, three treated patients showed a more rapid recovery from coma, spending an average of 7.7 days in the intensive care unit, as opposed to 17.0 days for three control patients who were treated with a sham stimulator (Cooper et al. 1999).

In another experiment, clinical observations revealed improved language capacities (Cooper et al. 1999). The language improvements, shown by recovery of speech and capacity to read aloud, might be mediated through stimulation of Broca's motor speech area. Although no placebo group was included in this experiment, the improvements in the TENS-treated patients appeared to be much faster than the rate of recovery of a control group that was not treated (Cooper et al. 1999). See Table 2.3 for an overview of the studies of TENS and coma.

Stimulation parameters

In the previous section, studies on TENS effects on cognition and behavior in various patient groups have been described in some detail. Study design and number of subjects have been critically reviewed. This section will address the duration, frequency, pulse width and intensity of stimulation, employed in the various studies.

Duration

In studies of neglect, TENS was applied once for 10 to 20 minutes and effects were measured immediately following stimulation (Guariglia et al. 1998; Guariglia et al. 2000; Karnath 1995; Perennou et al. 2001; Vallar et al. 1995; Vallar et al. 1996). Follow-up measurement after a delay of 20 to 30 minutes (Perennou et al. 2001; Vallar et al. 1995; Vallar et al. 1996) revealed that the effects disappeared. These data suggest that the effects of a single stimulation period in neglect are of short duration. Unfortunately, in other studies, there was no follow-up measurement at all (Guariglia et al. 1998; Guariglia et al. 2000; Perennou et al. 2001; Richard et al. 2001).

As far as the authors are aware, there is only one study in which patients with visuospatial hemineglect were treated with TENS for more than a single session, i.e. 60 minutes per day, five days a week, for a period of eight weeks (Pizzamiglio et al. 1996). However, no clear treatment effects were observed in that study.

AD patients were stimulated 30 minutes a day, five days per week, during six consecutive weeks. In one study, the patients were stimulated six hours a day (Scherder et al. 1992), but the longer stimulation time yielded no more effects than a treatment of 30 minutes a day. In contrast, Cooper et al. (1999) stimulated coma patients eight to twelve hours per day after which a significant reduction in the duration of coma was observed. Because of heterogeneity between the patient groups, no firm conclusions can be drawn concerning the most effective duration of stimulation.

Frequency

Low-frequency TENS generally implies frequencies between 2 and 10 Hz whereas frequencies above 10 Hz are considered high (Roche & Wright 1990). In the studies with neglect patients (Guariglia et al. 1998; Guariglia et al. 2000; Karnath 1995; Perennou et al. 2001; Pizzamiglio et al. 1996; Richard et al. 2001; Vallar et al. 1995; Vallar et al. 1996) and comatose patients (Cooper et al. 1999), 100 Hz and 40 Hz was used, respectively. Effects were enhanced somatosensory functioning, visuospatial abilities, and postural control in neglect ($1.05 < d < 1.90$), and reduction in duration of coma.

In the first TENS study of AD patients (Scherder et al. 1992), high (100 Hz) and low frequency (2 Hz) alternated every 1.5 hours during 6 hours per day. Effects observed in that study included enhancement in verbal long-term memory and verbal fluency. In the other studies on AD and on aging, a combination of 2 Hz and 160 Hz (burst-TENS) was used. In those studies, TENS appeared to exert effects on daily life activities, ($d = 0.19$) (Scherder et al. 1995; Scherder et al. 1998), on rest-activity rhythm ($0.58 < d < 1.86$) (Scherder et al. 1999b; Van Someren et al. 1998) as well as on

memory (0.28 < *d* < 3.40) (Scherder et al. 1995; Scherder et al. 1998; Scherder et al. 1999b; Scherder et al. 2000) and verbal fluency (*d* = 0.28, d = 0.96) (Scherder et al. 1998; Scherder et al. 2000).

Pulse width and intensity

The intensity of the stimulation in the reviewed studies was non-noxious and varied from at to above threshold and, in several studies, provoking mild muscular twitches. The pulse width was either 40 µsec, 100 µsec, 200 µsec, or 300 µsec. Strength-duration curves on various types of afferent nerve fibers indicate that a stimulus with a pulse width of at least 10 µsec but not exceeding 1 msec, in combination with an non-painful intensity varying from just at to above threshold is particularly suitable to excite thin-myelinated A-Delta afferent nerve fibers (Howson 1978). Such a specific combination of pulse width and intensity can be applied in either a low- or high-frequency stimulation mode. In one study, it was observed that low-frequency TENS (2 Hz) with a pulse width of 100 µsec and an intensity 6 times threshold, activated the locus coeruleus (LC)/noradrenergic system (Hitoto et al. 1998). On the other hand, high-frequency stimulation (e.g. 200 Hz) with a pulse width of 100 µsec and an intensity that provoked muscular contractions appeared to be mediated by the raphe-serotonergic system (Cheng & Pomeranz 1981). Interestingly, low-frequency stimulation (2 Hz) and a combination of high- and low-frequency stimulation (e.g. burst-TENS) with an intensity high enough to provoke muscle contractions, are supposed to be conveyed by A-Delta nerve fibers (Duranti et al. 1988; Hitoto et al. 1998).

In sum, depending on the specific combination of stimulation parameters, the LC/noradre-nergic system or the raphe-serotonergic system may be stimulated by low-frequency and high-frequency TENS, respectively. TENS-bursts might create the possibility to stimulate both systems at the same time.

Arousal: a possible mechanism underlying TENS

It is argued that an increase in arousal might underlie the observed effects of TENS in the various conditions. Robertson et al. (1998) suggested that in right brain damaged patients with unilateral neglect, the cortical tonic arousal system is damaged. They observed that a non-spatial warning signal presented at the right side improved the deficit in left spatial awareness in these patients. This was probably mediated by the ascending reticular activating system (ARAS) (Robbins & Everitt 1995). The results of another study confirmed a more general attention deficit underlying persistent neglect

(Samuelsson et al. 1998). Compared to a control group, the simple reaction times measuring cognitive speed were increased in patients with contralateral neglect. The phasic arousal system mediated by the projections of e.g. the thalamus to the posterior association areas (Samuelsson et al. 1998) might still be intact in these patients (Robertson et al. 1998).

The ARAS includes several brain stem areas, e.g. the LC and the nucleus raphe dorsalis (NRD) (Kayama & Koyama 1998). The LC and NRD are the origins of the noradrenergic and serotonergic neurotransmitter systems, respectively (Mann 1983; Rossor 1988; Saper 1988). Both brain stem areas have strong connections with the nucleus basalis of Meynert (NBM), the prefrontal cortex, the hippocampus, the amygdala, the hypothalamus, and the SCN (Bobillier et al. 1976; Legoratti-Sanchez et al. 1989; Petrov et al. 1992; Vertes 1991). These areas, which play a role in (working) memory, (affective) behavior, and the rest-activity rhythm (Carpenter & Grossberg 1993; Collette et al. 1997; Salzmann 1992; Swaab 1997), are affected in AD (Blin et al. 1997; Braak & Braak 1991a; Goudsmit et al. 1990; Haroutunian et al. 1998; Swaab 1997). In addition, the LC and NRD show severe neuropathology in AD (Arendt et al. 1997; Braak & Braak 1996; O'Mahony et al. 1994). Atrophy of, among others, the frontal lobe, the hippocampus, the amygdala, the hypothalamic SCN, and the LC has also been observed in aging (Brody 1992; Coffey et al. 1992; Coleman & Flood 1987; Decarli et al. 1994; Swaab 1997). One could speculate that through the ARAS, stimulation of these brain structures indirectly contributes to the observed treatment effects of TENS.

In addition to the role of the ARAS in conveying TENS to subcortical and cortical areas, the influence of TENS in AD and aging might also be mediated through more direct pathways. TENS could activate e.g. the hippocampus and the hypothalamus through spinoseptal and spinohypothalamic pathways, respectively (Burstein & Giesler 1989; Giesler et al. 1994). In sum, one might argue that the improvements in memory, (affective) behavior, and the rest-activity rhythm in AD and aging by TENS result from activation of either the ARAS or, indirectly, of adjacent cortical and subcortical areas.
The rationale underlying the effects on comatose patients was that RMNS also activates the ARAS (Cooper et al. 1999). Due to its strong connections with, among others, the NBM, which is the origin of the cholinergic ascending pathways to the cerebral cortex (Cummings & Back 1998), the ARAS plays a crucial role in wakefulness (Cooper et al. 1999). In other words: stimulating the ARAS might shorten the duration of coma.

Discussion

Compared to the impressive number of articles on the role of TENS in analgesia, only a relatively small number of studies has focused on the influence of TENS on non-pain related cognitive and behavioral functioning. As far as the authors are aware, the influence of TENS on cognition and behavior has been examined in three patients groups, i.e. neglect due to stroke, AD and aging, and coma. Effects of TENS range from enhancement in somatosensory functioning, visuospatial abilities and postural control in neglect, to improved memory, affective behavior and rest-activity rhythm in AD and aging and acceleration of awakening in coma.

A major difference across the studies is the duration of stimulation. In the AD studies, patients were stimulated daily for six weeks, while in the majority of the neglect studies stimulation consisted of a single session of 10 to 30 minutes. The treatment effects in AD could not be maintained after a stimulation-free period of six weeks, while in the neglect studies, effects disappeared within 20 to 30 minutes. In the AD studies, administration of tests and scales to assess treatment effects always took place the day following the last stimulation session. Cognitive and behavioral assessment was never conducted immediately after application of TENS. Future research could possibly provide more information about the rate of decline in treatment effects to the pre-treatment level of functioning. The fact that effects in AD declined during the six weeks without treatment is not surprising considering the progressive nature of the disease. Consequently, maintenance of treatment effects in AD probably requires continuous stimulation.

In stroke, one might expect a more structural recovery because of mechanisms such as adaptive plasticity (Nudo et al. 2001). Future studies must show whether a longer application of TENS in neglect patients, e.g. six or eight weeks, will prevent a decline of treatment effects. The effectiveness of prolonged treatment with TENS is supported by the finding that comatose patients showed a structural recovery after they were treated with TENS for a longer period, i.e. eight weeks (Cooper et al. 1999).

The possibility that TENS stimulates specific (sub)cortical areas, which are part of the ARAS, is supported by a recent study using functional Magnetic Resonance Imaging (fMRI) (Kwan et al. 2000). In that study, it was observed that TENS applied to the right median nerve with an intensity that provoked pain, activated the posterior part of the anterior cingulate cortex (ACC). The ACC plays a crucial role in attention (Pardo et al. 1990); its stimulation though TENS might have contributed to the treatment effects observed in the various studies. Although in the TENS-studies reviewed here, the intensity of stimulation was not painful, the intensity did cause motor activity, i.e. visible muscular contractions. Interestingly, another fMRI study showed that fine co-coordinated motor activity of the hand and fingers enhanced the activity of the ACC

(Davis et al. 1997). It seems worthwhile to examine whether the ACC might react to TENS with an intensity which is painless but which is high enough to cause motor activity. This would support the assumption that TENS has an effect on specific supraspinal brain areas. In addition, fMRI might reveal whether improved performance on cognitive or behavioral functioning is indeed related to an enhanced activity in specific areas of the brain.

A point of concern is the applicability of TENS in clinical practice. The more distal location of the electrodes on the forearm to stimulate the right median nerve of comatose patients (Cooper et al. 1999) seems much more practical than the proximal location of the electrodes on the trapezius muscle of the AD patients (Scherder et al. 1995). Placing both electrodes on the trapezius muscle cannot take place without personal assistance whereas the subject himself can apply the electrodes on the right forearm without additional help. Therefore, in future studies, the effectiveness of RMNS should be further examined in other groups of patients, e.g. AD patients. Note that applying TENS without personal assistance is not recommended in moderate and severely cognitive impaired patients.

Finally, TENS might become an attractive non-pharmacological alternative for the treatment of cognitive and behavioral disturbances. TENS is simple to apply, very well tolerated by elderly persons and is completely safe except for subjects with a pacemaker and subjects with epileptic activity (Scherder et al. 1999a). However before firm conclusions about the effectiveness of TENS in cognitive and behavioral disorders can be drawn, further research in the neurophysiological basis for the mechanisms underlying TENS is a prerequisite.

Chapter 3

Activation of dorsal raphe nucleus and locus coeruleus by Transcutaneous Electrical Nerve Stimulation in Alzheimer's disease

A reconsideration of stimulation parameters derived from animal experimental studies

Abstract

In 1990 a series of studies started, in which the effects of Transcutaneous Electrical Nerve Stimulation (TENS) were examined on cognition, behavior, and the rest-activity rhythm of patients with Alzheimer's disease (AD). In those studies, TENS aimed primarily at stimulating the dorsal raphe nucleus (DRN) and the locus coeruleus (LC) by a combination of low- and high-frequency stimulation (2 Hz and 160 Hz, respectively), a pulse width of 0.1 ms, and an intensity that provoked muscular twitches. TENS was applied 30 minutes a day, during a six-week period. In order to make reliable comparisons between studies, identical stimulation parameters were used in all studies thus far. TENS appeared to have a positive effect on cognition, behavior, and the rest-activity rhythm, but the effects disappeared after cessation of stimulation. In order to optimize TENS treatment in AD, the present paper is meant to reconsider the once selected stimulation parameters by reviewing the relevant literature published since 1991. The results derived from animal experimental studies show that for an optimal stimulation of the LC and DRN, the pulse width should be more than 0.1 ms. Limitations and suggestions for future research will be discussed.

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Alzheimer's disease

Epidemiology

At the age of 65, the prevalence of dementia is about 1.5% and increases to about 30% at the age of 80 (Ritchie & Lovestone 2002). Within dementia, Alzheimer's disease (AD) is the most common cause, affecting 60% to 70% of all cognitively impaired elderly. The number of AD patients has been estimated at 2.3 million in the USA (Cummings & Cole 2002). The number of new cases of AD each year (incidence) is approximately 360.000, implying 40 new cases each hour (Cummings & Cole 2002). Besides problems for the individual patients and their surroundings, the increasing proportion of elderly people in most countries will cause great burden to health care systems and economy in the near future.

Since there is no cure for AD at this moment, research on (non-) pharmacological interventions that may stabilize or even improve the clinical course of the disease is crucial.

Neuropathology in AD

AD is characterized by a progressive neuropathology in the temporoparietal, frontal and occipital lobes (Coleman & Flood 1987). More specifically, the hippocampus, which plays a crucial role in memory (Lisman & Otmakhova 2001), is affected (Braak & Braak 1991b; Salehi & Swaab 1999) even in a preclinical stage (Fox et al. 1996). The prefrontal cortex, which is involved in executive functions like cognitive flexibility, planning, and response inhibition (Duke & Kaszniak 2000) also degenerates in AD (Coleman & Flood 1987). Furthermore, the hypothalamus and particularly the hypothalamic suprachiasmatic nucleus (SCN), involved in affective behavior and the regulation of the circadian rest-activity rhythm, respectively (Swaab 1997; Swaab et al. 1998; Van Someren et al. 2002), show neuropathological changes in AD (Swaab 1997; Swaab et al. 1998). Importantly, nightly restlessness is often the main reason for institutionalization (Pollak & Perlick 1991).

"Use it or lose it"

It is noteworthy that the neuropathological hallmark of AD is not cell death but atrophy (Swaab et al. 2002). Shrunken cells that still have some metabolism characterize brain atrophy. Swaab et al. (2002) provide convincing evidence that the decreased metabolism in AD can be enhanced by the reactivation of shrunken cells. This reactivation may result from neuronal stimulation that subsequently slows down or even restores degenerative processes, a hypothesis that has been paraphrased as "use it or lose it" (Swaab 1991). In other words, despite the severe neuropathology in cortical and subcortical areas, suppressing clinical symptoms and positively influencing the course of this progressive disease by neuronal stimulation is still possible. Neuronal stimulation could take place by various types of pharmacological and, interestingly, also by non-pharmacological stimuli. An example of a non-pharmacological treatment strategy that might enhance the decreased metabolism in AD is Transcutaneous Electrical Nerve Stimulation (TENS).

Transcutaneous Electrical Nerve Stimulation (TENS) in AD

In the preceding twelve years, TENS has been widely studied in AD patients (Scherder et al. 1992; Scherder et al. 1995; Scherder et al. 1998; Scherder et al. 1999b; Van Someren et al. 1998). In all but one study, a 30 minutes-a-day and five days-a-week TENS treatment was applied to patients in a relatively early stage of AD, based on the assumption that the earlier the intervention, the more effective. Each study also included a control group that received sham stimulation. Neuropsychological functions, behavior, and rest-activity rhythm were assessed at three moments, i.e. before and directly after the six-week treatment period, and again after a treatment-free period of six weeks.

Except for the first pilot-study (Scherder et al. 1992), the stimulation parameters used were exactly the same in all studies. The TENS-device (Premier 10s) generated two 'bursts' per second (2 Hz) of biphasic impulses with an internal frequency of 160 Hz (burst-TENS) (Eriksson et al. 1979). The pulse width was 100 µsec. Based on animal experimental studies (Cedarbaum & Aghajanian 1978; Cheng & Pomeranz 1981) available at that time, it was argued that low-frequency TENS (2 Hz) comprising high intensity 0.1 ms spikes could activate the locus coeruleus (LC) whereas high-frequency (≥10 Hz) stimulation comprising the same pulse width and intensity increased the activity of the dorsal raphe nucleus (DRN). The DRN and LC are the origin of the ascending serotonergic and noradrenergic neurotransmitter systems, respectively (Kayama & Koyama 1998), and show neuronal loss in early AD (Lyness et al. 2003). Importantly, studies have shown afferent and efferent pathways that connect the DRN and LC with the hypothalamus, and specifically with the SCN (Cedarbaum &

Aghajanian 1978; Kawano et al. 1996; Krout et al. 2002; Vertes 1991), the septal/hippocampal region (Font et al. 1997; Foote et al. 1983; Legoratti-Sanchez et al. 1989; Vertes 1991), and the frontal lobe (Ritchie & Lovestone 2002; Vertes 1991).

Results of the TENS-studies show that, in comparison with a placebo treatment, TENS improved nonverbal short-term memory, nonverbal and verbal long-term recognition memory, and executive functioning (verbal fluency) in AD patients. Moreover, TENS had a positive effect on affective behavior, e.g. depressive symptoms declined. Another important finding was that nightly restlessness decreased in TENS-treated patients.

Notably, in all studies, after cessation of stimulation the observed improvements disappeared. In order to optimize TENS treatment in AD, e.g. maintaining positive effects after ending the treatment, the present paper reconsiders the once selected stimulation parameters to stimulate primarily the DRN and LC, by reviewing relevant literature published since 1991. All reviewed studies are animal experimental studies. A frequency of <10 Hz will be considered low and a frequency of ≥10 Hz will be considered high (Scherder et al. 1995).

The present paper will first focus on indirect electrical stimulation, i.e. stimulation through the peripheral nervous system, of the DRN/serotonergic system and the LC/noradrenergic system. Subsequently, studies on direct stimulation of both brain stem nuclei and its effect on supraspinal areas, particularly the hippocampus, the hypothalamus including the hypothalamic SCN, and the prefrontal cortex will be presented. Limitations and suggestions for future research are discussed.

Indirect DRN and LC stimulation

Increased activity of the DRN, measured by c-fos protein expression, has been observed after low-frequency (3 Hz) electro-acupuncture (EA) of Zusanli (St 36) in the hind leg of rats (Dai et al. 1992). The intensity was high enough (20 V) to provoke slight muscular twitches of the hind limb. The pulse width was 10 ms and the duration of EA was 1 hour. An increase in activation of the LC-hypothalamic pathway of aged rats has been observed after EA of Shenshu (UB23) (Zhu et al. 2000). Stimulation parameters were: a frequency of 4 Hz, an intensity of 1-3 V, a continuous wave pulse form, and a duration of stimulation of 3 minutes. No information on the pulse width was provided. The LC-noradrenergic neurons of rats could also be activated by sciatic nerve stimulation with a frequency of 0.1 Hz, a pulse width of 0.5 ms, and an intensity of 1.3 mA (Rouzade-Dominguez et al. 2001). The trial consisted of 60 pulses. Again, no information on the waveform was provided.

In one study, activation of both the DRN and LC was measured (Kwon et al. 2000). Zusanli was stimulated with a frequency of 4 Hz or 100 Hz and a pulse width of 0.5 ms. An intensity of 5 times threshold (mean value 6 V) provoked a muscle twitch. Duration of stimulation was 2 hours and the pulse form was biphasic. Results show that low-frequency stimulation of 4 Hz had a larger effect on the LC compared to the DRN. However, both brain stem areas were equally activated by high-frequency stimulation of 100 Hz.

Taken together, although both brain stem nuclei respond to low- and high-frequency indirect stimulation, the LC reacts somewhat stronger to low-frequency stimulation than the DRN. The various stimulation parameters and concurrent results are presented in Table 3.1.

Table 3.1 Indirect stimulation of the dorsal raphe nucleus (DRN) and the locus coeruleus (LC)

Indirect DRN stimulation	**Pulse form**	**Pulse width**	**Intensity**	**Frequency**	**Duration of stimulation**	**Results**
Dai and Zhu, 1992	na	10 ms	20 V	3 Hz	1 hour	Increased activity DRN
Kwon et al., 2000	Biphasic impulses	0.5 ms	6 V	4 Hz and 100 Hz	2 hours	Increased activity DRN, particularly with 100 Hz
Indirect LC stimulation						
Rouzade-Dominquez et al., 2001	na	0.5 ms	1.3 mA	0.1 Hz	trial of 60 pulses	Increased activity LC
Zhu et al., 2000	Continuous wave	na	1-3 V	4 Hz	3 minutes	Increased activity in the brain stem-hypothalamus pathway
Kwon et al., 2000	Biphasic impulses	0.5 ms	6 V	4 Hz and 100 Hz	2 hours	Increased activity LC, particularly with 4 Hz

na = not available

Direct DRN and LC stimulation

Direct DRN stimulation and the hippocampus

Ezrokhi et al. (1999) observed that direct high-frequency stimulation of the DRN of rats had a beneficial influence on the long-term potentiation (LTP) decay at the synapses of the hippocampus. LTP implies an activity-dependent increase in synaptic transmission efficiency that may last for hours and represents the mechanism underlying conscious memory (Bliss & Collingridge 1993). In the study of Ezrokhi et al. (1999), the stimulation parameters were: a frequency of 100 Hz, a pulse width of 0.4 ms, and intensity between ± 100 – 400 µA. Biphasic square constant current pulses were used

and the duration of stimulation varied from hours to days. Unfortunately, there was no further information on which intensity was the most effective.

In another study, the effects of direct DRN stimulation on various brain areas were examined (McQuade & Sharp 1997). The amount of 5-hydroxytryptamine (5-HT) increased in, among others, the ventral hippocampus and the medial septum. No effect was observed in the dorsal hippocampus. Stimulation parameters were: a frequency of 5 Hz, an intensity of 300 µA and 1 ms pulse width. Duration of stimulation was 20 minutes. The waveform was not mentioned. In an earlier study, McQuade and Sharp (1995) applied the same intensity and pulse width in four different frequencies, i.e. 2, 3, 5 and 10 Hz. The results show that the higher the frequency, the more release of 5-HT in the hippocampus of the anaesthetized rat.

Direct DRN stimulation and the hypothalamus

Activity of several hypothalamic nuclei can be enhanced by electrical stimulation of the DRN neurons. Saphier (1991) observed that subgroups of neurons in the hypothalamic paraventricular nucleus (PVN) of rats responded differently to DRN stimulation. The PVN plays a role in autonomic and neuroendocrine processes (Swanson & Sawchenko 1980). Direct stimulation of the DRN took place at a frequency of 0.2 Hz – 0.5 Hz, a pulse width of 1 ms and an intensity of 1 mA. The pulse form was a bipolar square wave. Eight out of 15 neurons were activated (53%), two cells showed an inhibition (13%) whereas four cells (33%) did not respond at all. Considering the latency of the response after stimulation of the DRN, a monosynaptic pathway between the DRN and the PVN is suggested (Saphier 1991).

Interestingly, Weidenfeld et al. (2002) observed in a recent animal experimental study that, by DRN stimulation, the PVN showed an increase in its extracellular release of 5-HT, with a subsequent activation of the hypothalamus-pituitary-adrenocortical (HPA) axis. The stimulation parameters were: a frequency of 100 Hz, a pulse width of 1 ms, an intensity of 0.5 mA, and duration of stimulation of 5 minutes. No information about the waveform was available.

Direct DRN stimulation and the frontal lobe

Gartside et al. (2000) compared single-pulse stimulation with twin-pulse stimulation (burst firing) of the DRN with respect to the release of 5-HT in the medial prefrontal cortex of rats. Stimulation parameters included a frequency of 3 Hz, a pulse width of 1 ms, and an intensity of 300 µA. The pulse-form was a square-wave and duration of stimulation was 10 minutes. The stimuli were applied singly or in pairs with an interval

of 10 ms between the pulses (burst firing). The results show that, compared to the single pulses, the twin pulses doubled the release of 5-HT in the medial prefrontal cortex.

In sum, the literature points to a positive relationship between the frequency of DRN stimulation and release of 5-HT in adjacent brain areas. The utilization of a burst signal resulted in a higher release of 5-HT in the medial prefrontal cortex (for details, see Table 3.2).

Table 3.2 Direct dorsal raphe nucleus (DRN) stimulation and its effect on the hippocampus, hypothalamus and prefrontal cortex. PVN: Paraventri-cular nucleus; 5-HT: 5- hydroxytryptamine; LTP: long-term potentiation

	Pulse form	**Pulse width**	**Intensity**	**Frequency**	**Duration of stimulation**	**Results**
Ezrokhi et al., 1999	Biphasic square -wave	0.4 ms	±100-400 µA	100 Hz	1 minute	Restoration of a decay in LTP in CA1
McQuade and Sharp, 1997	na	1 ms	300 µA	5 Hz	20 minutes	Release of 5-HT in ventral hippocampus and medial septum
McQuade and Sharp, 1995	na	1 ms	300 µA	2,3,5,10 Hz	20 minutes	The higher the frequency, the more the release of 5-HT in the hippocampus
Saphier, 1991	Bipolar square -wave	1 ms	1 mA	0.2 – 0.5 Hz	na	Excitation (53%) and inhibition (13%) of PVN neurons
Weidenfeld et al., 2002	na	1 ms	0.5 mA	100 Hz	5 minutes	Increase in the hypothalamic PVN extracellular 5-HT levels
Gartside et al., 2000	Square-wave	1 ms	300 µA	3 Hz: single or twin-pulses	10 minutes	Release of 5-HT in the medial prefrontal cortex. Twin twice as much as single

na = not available

Direct LC stimulation and the hippocampus

In the study of Ezrokhi et al. (1999), it was observed that decay in LTP at synapses of the perforant pathway and dentate gyrus of the hippocampal formation could be restored by high-frequency (50-100 Hz) stimulation of the LC. Other stimulation parameters were: a pulse width of 0.1 – 0.4 ms, an intensity of 65 – 300 µA, and a biphasic square constant current waveform. The study design included variability in stimulation frequency, pulse width and intensity but information about the most effective combination of these three parameters is lacking. The duration of stimulation was 1 min.

It has been suggested that both LTP and short-term potentiation of the perforant-path in the awake rat results from a phasic instead of tonic LC cell firing (Klukowski & Harley 1994). Interestingly, particularly non-noxious stimuli yield a phasic activation of LC cells (AstonJones & Bloom 1981).

Direct LC stimulation and the hypothalamus

LC-stimulation with 100 Hz, pulse width of 0.2 ms, a sinusoidal waveform, and an intensity of 60 µA, increased the density of α2-receptor sites in the hypothalamus of rats (Velley et al. 1991). The authors argue that this sequence of events causes a reduction in stress reaction and hence improves cognitive functioning. In another animal experimental study, direct LC stimulation increased the activity in the hypothalamic paraventricular nucleus (PVN), reflected in an increase in the noradrenergic metabolite 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) (Lookingland et al. 1991). Electrical stimulation of the LC took place by monophasic pulses, with a pulse width of 1 ms, an intensity of 400 µA, and a frequency of 15 Hz.

Direct LC stimulation and the frontal lobe

Florin-Lechner et al. (1996) stimulated the LC of rats either with a tonic stimulation (evenly spaced pulses) or with a phasic stimulation (bursts of pulses). In the tonic stimulation condition, 3, 5, or 10 Hz was used for 20 minutes. The results showed a frequency-dependent release of norepinephrine in the prefrontal cortex, i.e. the higher the frequency, the higher the release. Interestingly, compared to the 3 Hz tonic stimulation, bursts of 3 pulses (presented at 6, 12, and 24 Hz, every second) produced a much larger increase in norepinephrine, with the largest increase at 12 Hz. It is concluded that the physiologically relevant ‘burst’ activity of LC neurons releases norepinephrine in the prefrontal cortex in the most effective way.

In sum, similar to the DRN, frequency of direct LC-stimulation and release of norepinephrine in associated areas show a positive relationship. A summation of the effects of the various stimulation parameters is presented in Table 3.3.

Discussion

The goal of the present study is to examine whether studies on the effects of indirect and direct stimulation of the DRN and LC published from 1991 until now still support the originally selected stimulation parameters that were used in our TENS-studies. In those

Table 3.3 Direct locus coeruleus (LC) stimulation and its effect on the hippocampus, hypothalamus and prefrontal cortex. LTP: long-term potentiation; PVN: paraventricular nucleus (hypothalamus)

	Pulse form	Pulse width	Intensity	Frequency	Duration of stimulation	Results
Ezrokhi et al., 1999	Biphasic square constant current	0.1 – 0.4 ms	65 – 300 µA	50-100 Hz, one to two trains: 15-20 seconds interval	1 minute	Restoration of a decay in LTP in perforant pathway and dentate gyrus
Velley et al., 1991	Sinusoidal waveform	0.2 ms	60 µA	100 Hz	15 minutes	Increase in α_2-receptor sites density in the hypothalamus
Lookingland et al., 1991	Monophasic pulses	1 ms	400 µA	15 Hz	10 minutes	Increase in the noradrenergic metabolite 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) in the PVN
Florin-Lechner et al., 1996	na	0.2 ms	700 µA	Tonic: 3,5,10 Hz	20 minutes	The higher the frequency, the higher the norepinephrine increase in prefrontal cortex
				Bursts of 6 Hz Bursts of 12 Hz Bursts of 24 Hz		Bursts more effective than tonic Highest increase in norepinephrine at 12 Hz

na = not available

TENS-studies, it was argued that low-frequency TENS (2 Hz) with a pulse width of 0.1 ms could stimulate the LC whereas high-frequency stimulation of 160 Hz, in combination with the same pulse width, could increase the activity of the DRN. Except in the pilot-study (Scherder et al. 1992), the intensity of the TENS signal used provoked muscular twitches. Both frequencies were combined into one TENS-mode, i.e. burst-TENS (Eriksson et al. 1979).

Frequency

The results of the present review indicate that the LC, compared to the DRN, responds more strongly to indirect low-frequency stimulation, i.e. < 10 Hz. In addition, direct high-frequency stimulation of the LC with frequencies varying from 10 Hz to 100 Hz resulted in the highest activity increase in the hippocampus, the hypothalamus, and the prefrontal cortex. With respect to the DRN, the results of both direct and indirect stimulation studies show that this brain stem nucleus preferably responds to high-frequency stimulation of 10 Hz, 20 Hz, and 100 Hz.

The finding that both the LC and the DRN respond positively to a burst-firing rate is not so surprising considering the electrophysiological characteristics of the neurons of the DRN and LC. It has been observed that a considerable number of DRN

and LC neurons are capable of firing in bursts (Gartside et al. 2000; Hajos et al. 1995; Hajos & Sharp 1996; Wrenn & Crawley 2001).

Pulse width

As mentioned before, the pulse width used in our TENS-studies was 0.1 ms (Scherder et al. 2000). Although in the direct and indirect stimulation studies reviewed here, the pulse width varied between 0.1 ms and 10 ms, the most frequently applied pulse widths were 0.4, 0.5, and 1 ms. Future research is necessary to find out whether an increase in pulse width is indeed more effective in the treatment of cognitive and behavioral disturbances in AD, reflected in e.g. the maintenance of improvements in cognition and behavior after cessation of stimulation.

Intensity and pulse form

Intensity shows considerable variation among the various studies, ranging from 65 µA to 1300 µA and 1 V to 20 V in some indirect stimulation studies provoking muscular twitches. Specific information on the pulse form is often lacking. The role these two stimulation parameters can play in an optimal stimulation of the DRN and LC as an intervention strategy in AD, should be addressed in studies to be performed.

Limitations and suggestions

In the first place, studies on indirect and direct stimulation of the DRN and LC reviewed here are not intervention studies and hence information on the most efficient stimulation-time and treatment-period is lacking. Although in our TENS-studies a stimulation-duration of 30 minutes a day and a treatment period of six weeks proved to be effective (Scherder et al. 2000), future studies should examine whether an extension of both parameters may be even more effective, for example by maintaining the observed effects after cessation of stimulation. Next, the studies reviewed here are all animal experimental studies. Hence, generalization of the results to humans should take place with care. In the third place, one should be cautious when deducing stimulation parameters for a non-invasive treatment like TENS from direct stimulation studies and invasive techniques like electro-acupuncture.

Finally, the present review does not explain why TENS is effective in AD. It is known that both the DRN and LC are part of the ascending reticular activating system (ARAS) which plays a central role in arousal (Kayama & Koyama 1998). Until now it has been assumed that an increase in arousal is responsible for the effects of TENS on

cognition and behavior in several conditions that effect the central nervous system (Van Dijk et al. 2002). On the other hand, in an fMRI study by Davis et al (1997) increased activity in the anterior cingulate cortex, a frontal lobe area involved in attention, was found as a from median nerve stimulation by TENS. These findings imply that future studies should include brain imaging techniques that will enhance the insight into the mechanisms underlying the effects of TENS in AD.

Chapter 4

Peripheral electrical nerve stimulation in Alzheimer's disease

A randomized controlled trial on cognition and behavior

Abstract

In a number of studies, peripheral electrical nerve stimulation has been applied to Alzheimer's disease (AD) patients who lived in a nursing home. Improvements were observed in memory, verbal fluency, affective behavior, activities of daily living, rest-activity rhythm and pupillary light reflex. The aim of the present, randomized, placebo-controlled, parallel-group clinical trial was to examine the effects of electrical stimulation on cognition and behavior in AD patients still living at home. Repeated measures analyses of variance revealed no effects of the intervention in the experimental group (n = 32) compared to the placebo group (n = 30) on any of the cognitive and behavioral outcome measures. However, the majority of the patients and the caregivers evaluated the treatment procedure positively, and applying the daily treatment at home caused minimal burden. The lack of treatment effects calls for reconsideration of electrical stimulation as a symptomatic treatment in AD.

Van Dijk KRA, Scheltens P, Luijpen MW, Sergeant JA, Scherder EJA. Peripheral electrical stimulation in Alzheimer's disease. A randomized controlled trial on cognition and behavior. *Dementia and Geriatric Cognitive Disorders* 2005; 19:361-368

Introduction

Dysfunction of the cholinergic neurotransmitter system is one of the characteristics of Alzheimer's disease (AD) (Francis et al. 1999). Early studies considered cell death in the nucleus basalis of Meynert (NBM) to be the cause of the diminished level of acetylcholine (ACh) (Mann et al. 1984; Whitehouse et al. 1982). However, only a small proportion of cells in the NBM is actually lost in AD (Vogels et al. 1990) and the observed lowered number of cholinergic markers is due to NBM atrophy rather than cell loss (Swaab 1991). Swaab argued that therapeutic strategies in AD could be directed towards stimulation of neurons to improve metabolism and possibly reactivate impaired neurons in e.g. the NBM (Swaab 1991; Swaab et al. 2002; Swaab et al. 2003). Accordingly, improved functioning might be established by stimulating the central nervous system exogenously, for example through an enriched environment.

In enriched environments, the organism typically is subject to multi-sensory input (Kobayashi et al. 2002). Unisensory stimulation techniques, such as bright light (visual sensory system) and tactile stimulation (somatosensory system) have yielded positive effects on several brain functions in mild cognitively impaired and demented patients (Luijpen et al. 2003). Walking, another type of somatosensory stimulation, resulted in an increased release of extracellular ACh in the hippocampus of rats (Nakajima et al. 2003). Somatosensory stimulation by means of peripheral electrical stimulation applied to the skin of rats showed an increased activity of the hippocampus and an elevated release of ACh in the hypothalamus (Dutar et al. 1985).

Somatosensory stimulation through Transcutaneous Electrical Nerve Stimulation (TENS) has been applied to AD patients in a number of placebo-controlled experiments (Scherder et al. 1992; Scherder et al. 1995; Scherder et al. 1998; Scherder et al. 1999b; Scherder & Bouma 1999; Van Someren et al. 1998). In those studies, a small electrical current was applied to the skin of the upper back of AD patients. After application of the electrical stimulus five days a week for a period of six weeks, improvements were found in memory, verbal fluency, affective behavior, activities of daily living and the rest-activity rhythm (for a review, see: Van Dijk et al. 2002). A Japanese group replicated effects on cognition and found a positive effect on pupillary light reflex (Guo et al. 2002). The latter is considered an indication that the cholinergic function has improved (Tales et al. 2001). Despite these encouraging findings, the positive effects of electrical stimulation must be interpreted with caution because of the small sample sizes: ranging from 6 (Guo et al. 2002) to 18 (Scherder et al. 1998).

In the studies described above, the participating AD patients lived in a nursing home. The research question of the present study was whether peripheral electrical

nerve stimulation would also demonstrate positive effects on cognition and behavior of patients who still live at home. This randomized, placebo-controlled, parallel-group clinical trial is unique since the treatment was applied by a family caregiver. Based on previous positive findings, it was hypothesized that after a treatment period of six weeks the experimental group would show improved functioning in cognition and behavior compared to the control group.

Materials and Methods

Participants

Participants were recruited from the Alzheimer Center of the VU University Medical Center, the Department of Neurology of the Sint Lucas Andreas Hospital, and the community home care agency in Amsterdam, The Netherlands. Men and women were eligible if they had a diagnosis of probable AD according to the NINCDS/ADRDA criteria (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. In addition, it was essential that the AD patient lived at home with a partner or other family member who served as primary caregiver (the partner or other family member will further be referred to as family caregiver). 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. Also, 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 ethical committees and by the Committee on Research Involving Human Subjects in The Hague, The Netherlands.

Study design

In this 12-week, randomized, placebo-controlled, parallel-group study, assessment of cognition and behavior took place at baseline (Pre), after the treatment period of six weeks (Post), and following a treatment-free period of six weeks (Delayed). Additionally, a questionnaire covering applicability and efficacy of the treatment according to the patient and the caregiver was administered after treatment.

Intervention

A standard commercially available TENS device (Premier 10s) was used. It produced biphasic square pulses with a width of 100 μsec, applied in bursts of nine pulses with a frequency of 160 Hz and a repetition rate of 2 Hz. Self-adhesive medical electrodes for electrical stimulation (XyTrode) were placed on the back at the first thoracic vertebra, lateral to the spine. The intensity of the stimuli was set at a level that produced painless, visible muscular twitches. These stimulation parameters were chosen to optimally target afferent nerve fibers, i.e. A-Beta, A-Delta, and C-fibers, which convey the pulses to sub-cortical and cortical areas (for more details, see: Scherder et al. 1995). The family caregiver applied the treatment 30 minutes a day, seven days a week, for a period of six weeks. To minimize interference in the daily routine of the participants, the patient and the family caregiver were free to decide at what time of the day they would administer the treatment.

Randomization and blinding

Participants were allocated to either the experimental or the placebo treatment using simple randomization by tossing an unbiased coin. Participants assigned to the experimental group received experimental treatment, whereas participants in the placebo group were told that the stimulator was working as soon as the green light was blinking without current being applied. To maintain the participants' blindness and because they 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 might have the desired effect and one that, on theoretical grounds, was unlikely to be effective. Hence, patients who received the experimental treatment, i.e. the patient felt the stimulus and the caregiver would observe 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 we were applying different pulse frequencies in two groups, but that the pulse frequencies were in a range that could not be perceived. The neuropsychologist, who instructed the participants about the use of the electrical stimulator (K.R.A.v.D), was not blinded to group allocation because a different instruction was required when explaining the use of the electrical stimulator to the experimental and placebo groups. Patients, family caregivers, and test administrators were blinded to group allocation.

Cognitive measures

Digit Span, a subtest of the Wechsler Memory Scale (Wechsler 1945), consists of a Forward and a Backward condition. The Forward condition serves as a measure of attention for verbally presented stimuli and the Backward condition is used as a measure of working memory for verbally presented stimuli. The score for each condition is the number of correct reproduced sequences.

Visual Memory Span (Wechsler 1945) is the non-verbal equivalent of the Digit Span test. The Forward and the Backward condition serve as a measure of attention and working memory for visually presented stimuli, respectively. The score for each condition is the number of correct reproduced sequences.

The Eight Words Test of the Amsterdam Dementia Screening test (Lindeboom & Jonker 1989) was used to assess verbal episodic memory. The immediate recall score is the total number of correct words after five trials and is used as a measure of the patients' ability to process and learn verbal stimuli. The delayed recall score is the total number of correctly reproduced words after a delay of approximately 10 min, measuring active retrieval of information from verbal memory. The recognition score is the total of correct responses minus incorrect responses and measures recognition of the previously presented stimuli.

Face Recognition of the Rivermead Behavioural Memory Test (Wilson et al. 1985) was used as a measure of visual, non-verbal long-term recognition memory.

Picture Recognition of the Rivermead Behavioural Memory Test (Wilson et al. 1985) serves as a measure of visual, verbal long-term recognition memory.

The Stroop Color Word test (Stroop 1935) was used to obtain a measure of interference control, i.e. the ability to disregard an automated response. The interference score is computed by subtracting the colors named correctly in 45 seconds on the Color Card from the colors named correctly in 45 seconds on the Color/Word Card. A high interference score is an indication of poor interference control.

Category Fluency test was used to measure verbal fluency (Benton & Hamster 1978). Categories were animals and professions. The total score for each category is the number of correct words produced in 60 seconds.

Self-report questionnaires assessing emotional status

The patients reported the status of their emotional condition using the following questionnaires that were administered by an interviewer.

The Geriatric Depression Scale (GDS) (Yesavage et al. 1983), a Dutch 30-item version, was administered to assess symptoms of depression. Because the sample in the present study included cases of severe AD and because of known limited validity and

reliability of the GDS when administered to cognitively impaired populations (Burke et al. 1989), a selection of twelve items was used to calculate the total score. The twelve selected items make up the GDS-12R, a screening measure appropriate for use with older people in nursing and residential care settings, including persons with cognitive impairment (Sutcliffe et al. 2000). Internal reliability of the GDS-12R was .81 and .78 for those patients with an MMSE score below 10 (Sutcliffe et al. 2000).

The Philadelphia Geriatric Center Morale Scale (PGCMS) (Lawton 1975) was administered to obtain a measure of subjective well-being. This seventeen-item questionnaire is designed to measure dimensions of emotional adjustment in people aged 70 to 90. The total score on the seventeen items is used as a measure of global life satisfaction.

Informant-based ratings of functional and emotional status

The Philadelphia Geriatric Center Affect Rating Scale (PGCARS) (Lawton et al. 1996) is an observation scale designed to rate affective states in dementia.

The 28-item Dutch Behavioral Observation Scale for Psychogeriatric Inpatients (GIP-28) (De Jonghe et al. 1997) was used to assess psychiatric symptoms. This shortened version is a modification of the original 82-item GIP (Verstraten & Van Eekelen 1987) that is based on the Physical and Mental Impairment-of-Function Evaluation (Linn 1988). Three symptom dimensions were used as dependent variables: negative symptoms, cognitive symptoms, and mood/affective symptoms (De Jonghe et al. 2003).

Activities of Daily Living (ADL) is a list of selected items obtained from Katz et al. (1963) that are part of a larger Patient Informant Interview (Holmes et al. 1990). It was used as a measure of functional independence.

Applicability and efficacy questionnaire

In a questionnaire designed by the authors, applicability and efficacy of the treatment according to both the patient and the family caregiver were assessed. Part A consists of questions for the patient receiving the treatment and includes two subscales. 1) “Perceived burden”, ranging from 0 (no burden) to 12 (highest burden) and 2) “Perceived efficacy”, ranging from 0 (no benefit) to 4 (most benefit). Part B consists of items for the family caregiver and includes four subscales. 1) “Difficulties using the apparatus” ranging from 0 (no burden) to 8 (highest burden), 2) “Perceived burden for the family caregiver” ranging from 0 (no burden) to 8 (highest burden), 3) “Perceived

burden for the patient" ranging from 0 (no burden) to 12 (highest burden), and 4) "Perceived efficacy" ranging from 0 (no benefit) to 4 (most benefit).

Statistical analysis

Complete case method was used in which all patients with a missing response on an outcome variable were excluded from analysis regarding that variable. Comparisons of group characteristics were made using independent sample *t*-tests for normally distributed data and Mann-Whitney *U* tests for categorical data. Dependent variables that were not normally distributed were transformed using square root or log transformation. For purposes of clarity, all means printed in the tables are the original values. To determine treatment effects, dependent variables were subject to repeated univariate analyses of variance (ANOVAs), employing transformed scores when applicable, with Group (two levels: experimental and placebo) as between subjects factor and Time (three levels: Pre, Post, and Delayed) as within subjects factor. Treatment effects were hypothesized to emerge after the treatment period: therefore, Post versus Pre contrasts were computed. To investigate if any effects lasted when the treatment was discontinued, Delayed versus Pre contrasts were computed. Group differences on the applicability and efficacy questionnaire were analyzed using univariate analyses of variance (ANOVAs). To compensate for the use of multiple comparisons, a significance level of .01 was applied. SPSS Base for Windows Version 11.5 was used for all analyses.

Results

Patient characteristics

Of the 68 patients who were included and randomly allocated to either treatment group, 65 (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 ($n = 1$). An additional three cases were excluded from analysis because of missing data. Finally, 62 patients (91%) entered the analysis phase. An overview of the progress through the different phases of the trial is provided in Figure 4.1.

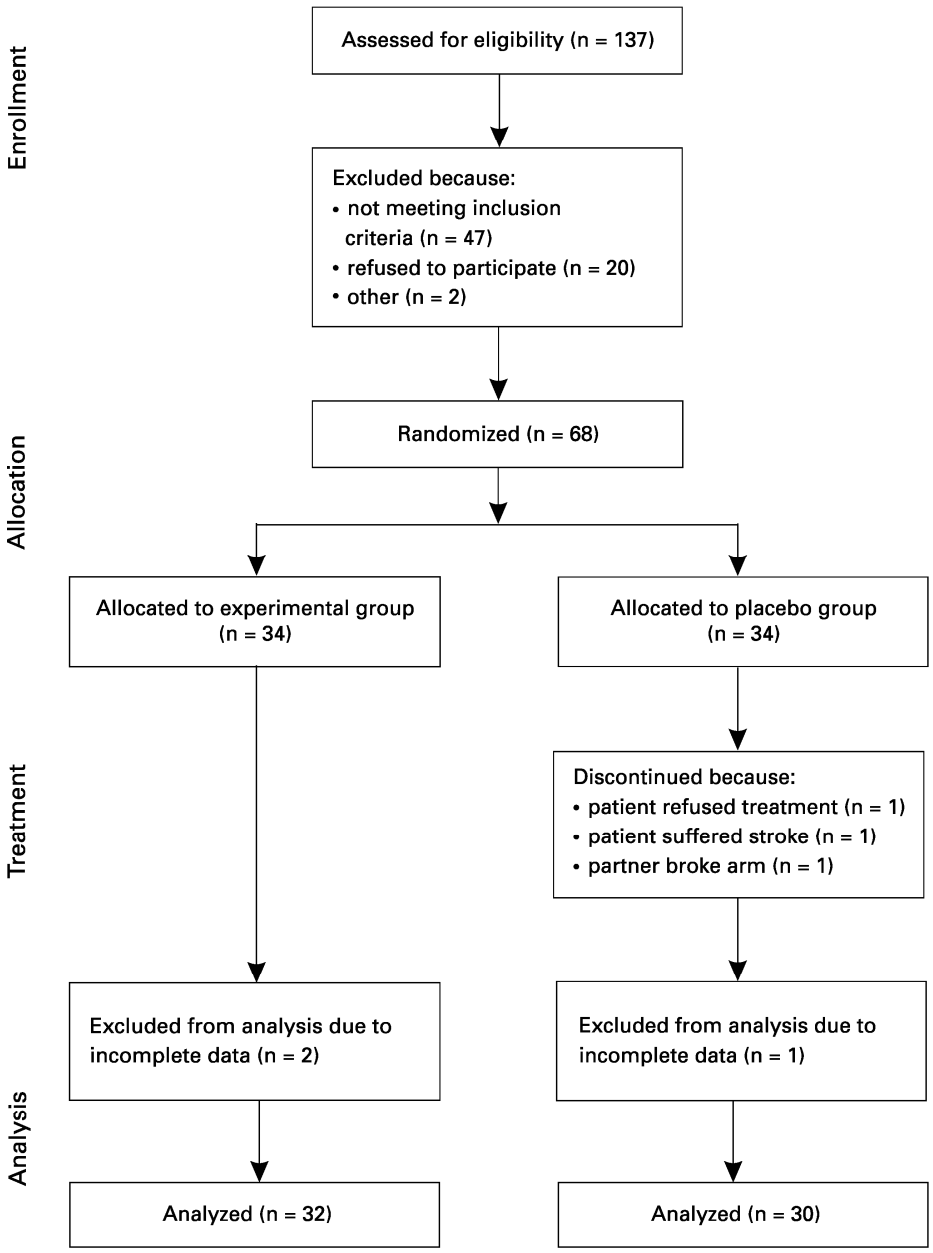

Figure 4.1 Flow diagram of the progress through the phases of the trial

The two treatment groups were not significantly different with regard to sex, age, education, and MMSE (see Table 4.1). In total, there were 39 men and 23 women; their mean age was 71.7 years (*SD* 8.0; range 52 – 87). Mean years of education was 10.5 (*SD* 3.6; range 6 – 20) and mean MMSE score at baseline was 15.2 (*SD* 6.9; range 0 – 26). All patients lived with a partner/spouse or family member.

Table 4.1 Characteristics of the patients

	experimental (n = 32)	**placebo (n = 30)**	**total (n = 62)**
Males / females	17 / 15	22 / 8	39 / 23
Age, years			
Mean (*SD*)	71.0 (7.8)	72.5 (8.2)	71.7 (8.0)
Range	52-87	55-87	52-87
Education, years			
Mean (*SD*)	10.3 (3.9)	10.7 (3.3)	10.5 (3.6)
Range	6-20	6-20	6-20
MMSE			
Mean (*SD*)	15.7 (6.8)	14.7 (7.2)	15.2 (6.9)
Range	0-26	1-26	0-26

Treatment effects

Cognitive measures

Independent samples *t*-tests indicated no significant differences between groups on cognitive measures before treatment. Results of repeated measures ANOVAs suggested no significant differences on any of the cognitive measures between groups after treatment (Table 4.2).

Self-report questionnaires assessing emotional status

Groups did not differ on the GDS-12R or PGCMS before the treatment period. Repeated measures ANOVAs revealed no significant differences between groups after treatment.

Table 4.2 Means (*M*), standard deviations (*SD*), and repeated analyses of variance (ANOVA) of the cognitive measures before treatment (Pre), after treatment (Post), and after a treatment free period (Delayed) of the experimental group and placebo group

	experimental			**placebo**			**ANOVA**					
	pre	**post**	**delayed**	**pre**	**post**	**delayed**	**pre-post**			**pre-delayed**		
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*F*	*df*	*p*	*F*	*df*	*p*
Digit Span Forward	4.54 (1.8)	5.00 (2.1)	4.61 (2.2)	4.17 (2.0)	4.34 (2.0)	4.31 (2.0)	.59	1,55	.45	.03	1,55	.86
Digit Span Backward	3.25 (1.9)	3.36 (1.7)	3.29 (1.8)	3.41 (2.2)	3.28 (1.8)	3.14 (1.9)	.48	1,55	.49	1.1	1,55	.30
Visual Memory Span Forward	3.89 (1.7)	3.79 (2.1)	4.18 (2.1)	4.28 (2.1)	4.00 (2.2)	3.90 (2.5)	.25	1,55	.62	2.8	1,55	.10
Visual Memory Span Backward	3.21 (2.8)	3.36 (2.1)	2.93 (2.1)	3.00 (2.2)	3.24 (2.4)	3.38 (2.4)	.07	1,55	.79	9.3	1,55	.10
Eight Words Test												
Immediate Recall	15.43 (6.6)	15.00 (8.1)	16.11 (7.4)	13.00 (8.1)	13.62 (8.1)	14.17 (9.0)	1.2	1,55	.28	1.7	1,55	.69
Delayed Recall	.89 (1.6)	.71 (1.3)	1.11 (1.8)	.41 (1.0)	.76 (1.3)	.76 (1.7)	3.6	1,55	.06	.09	1,55	.77
Cued Recall	7.86 (5.7)	8.14 (5.1)	7.43 (5.0)	5.07 (5.7)	6.07 (5.5)	6.59 (6.2)	.33	1,55	.57	2.4	1,55	.12
Face Recognition	5.14 (5.2)	6.36 (3.0)	6.71 (3.9)	6.14 (4.1)	6.21 (3.8)	7.31 (3.3)	.94	1,55	.34	.05	1,55	.83
Picture Recognition	14.21 (6.2)	13.39 (5.8)	11.71 (8.6)	12.00 (7.6)	12.14 (7.5)	12.00 (7.3)	.00	1,55	.97	.31	1,55	.58
Stroop Interference	31.10 (17.0)	32.7 (17.1)	30.5 (16.2)	26.65 (14.5)	30.3 (15.7)	28.1 (13.7)	.18	1,35	.68	.22	1,36	.64
Verbal Fluency Animals	10.00 (6.9)	9.39 (6.1)	8.82 (7.1)	7.72 (6.2)	7.83 (6.1)	7.69 (6.8)	1.1	1,55	.31	2.2	1,55	.14
Verbal Fluency Professions	6.79 (5.3)	7.46 (5.5)	6.64 (5.9)	4.79 (4.2)	5.24 (5.2)	4.79 (4.6)	1.1	1,55	.30	.003	1,55	.96

Table 4.3 Means (*M*), standard deviation (*SD*), and repeated analyses of variance (ANOVA) of the behavioral measures before treatment (Pre), after treatment (Post), and after a treatment free period (Delayed) of the experimental group and placebo group

	experimental			**placebo**			**ANOVA**					
	pre	**post**	**delayed**	**pre**	**post**	**delayed**	**pre-post**			**pre-delayed**		
	***M* (*SD*)**	***M* (*SD*)**	***M* (*SD*)**	***M* (*SD*)**	***M* (*SD*)**	***M* (*SD*)**	***F***	***df***	***p***	***F***	***df***	***p***
GDS12R ˅	1.25 (1.4)	1.64 (1.8)	1.43 (1.7)	.92 (1.2)	1.32 (1.6)	1.14 (1.2)	.05	1,54	.92	.59	1,54	.45
PGCMS ^	13.32 (2.9)	13.04 (3.7)	13.04 (3.5)	14.21 (3.3)	14.50 (3.8)	14.39 (3.4)	.66	1,54	.42	.358	1,54	.42
PGARS												
Pleasure ^	4.03 (1.2)	3.75 (1.2)	3.69 (1.2)	3.83 (1.2)	4.03 (1.0)	3.69 (1.1)	2.9	1,59	.09	.35	1,59	.56
Anger ˅	1.97 (1.2)	1.72 (1.1)	1.84 (.95)	1.90 (1.2)	1.90 (.97)	2.00 (1.1)	1.7	1,59	.19	1.3	1,59	.27
Anxiety ˅	2.28 (1.5)	2.06 (1.4)	2.13 (1.5)	2.34 (1.3)	2.14 (1.2)	2.24 (1.3)	.001	1,59	.98	.01	1,59	.91
Sadness ˅	2.00 (1.1)	2.19 (1.1)	2.06 (1.2)	1.97 (1.5)	1.93 (1.0)	1.86 1.1)	.74	1,59	.39	.38	1,59	.54
Interest ^	3.59 (1.3)	3.69 (1.3)	3.34 (1.4)	3.10 (1.3)	3.83 (1.3)	3.66 (1.3)	4.4	1,59	.04	6.0	159	.017
Content ^	4.19 (.8)	4.03 (.86)	3.94 (.84)	4.17 (.93)	4.48 (.69)	4.24 (.91)	3.7	1,59	.06	1.5	1,59	.23
GIP-28												
Negative symptoms ˅	7.03 (3.5)	6.75 (2.9)	6.94 (2.8)	7.5 (4.0)	7.79 (3.0)	8.00 (3.7)	.61	1,59	.44	.51	1,59	.48
Cognitive symptoms ˅	12.75 (5.2)	10.37 (4.3)	10.97 (5.6)	12.66 (5.6)	9.93 (6.1)	12.00 (6.25)	.18	1,59	.67	1.1	1,59	.31
Mood/affective symptoms ˅	5.69 (5.1)	3.44 (4.9)	3.78 (5.3)	5.10 (5.3)	3.41 (4.1)	3.52 (4.4)	1.2	1,59	.28	1.1	1,59	.29
ADL ˅	7.38 (6.6)	7.78 (6.5)	8.00 (6.7)	8.21 (6.8)	8.52 (7.8)	10.03 (9.2)	2.1	1,59	.15	.35	1, 59	.56

^ High values are considered positive, ˅ Low values are considered positive

Informant-based ratings assessing functional and emotional status

Family caregivers of patients in the experimental group and in the placebo group did not rate functional status on the ADL scale and emotional status on the PGCARS and GIP-28 differently. Repeated measures ANOVAs revealed no effects of the intervention on any of the functional and emotional measures based on the caregiver's judgments (Table 4.3).

Applicability and efficacy of the treatment

Questions for patients

Patients in both the experimental and the placebo group did not differ significantly on the subscales of the applicability and efficacy questionnaire. Thus, burden caused by the treatment and perceived efficacy of the treatment were not rated differently by the two groups. The means show that both burden and perceived efficacy were quite low in both groups.

Questions for family caregivers

Family caregivers who applied the real electrical stimulus also did not score differently on any of the subscales compared to those who applied sham stimulation. Mean scores indicate hardly any difficulty using the apparatus, low burden and low perceived efficacy in both groups (see Table 4.4).

Table 4.4 Means (M), standard deviation (SD) of scores on the Applicability and Efficacy Questionnaire subscales of the experimental group and placebo group

Subscale (possible range)	**experimental** ***M (SD)***	**placebo** ***M (SD)***	**total** ***M (SD)***
Part A (questions for the patient)			
Perceived burden (0-12)	2.22 (1.9)	1.60 (1.1)	1.97 (1.6)
Perceived efficacy (0-4)	1.10 (1.4)	0.77 (1.1)	0.97 (1.3)
Part B (questions for the family caregiver)			
Difficulties using the apparatus (0-8)	1.54 (1.3)	1.70 (1.6)	1.61 (1.4)
Perceived burden for the family caregiver (0-8)	1.22 (1.3)	1.26 (1.4)	1.24 (1.3)
Perceived burden for the patient. (0-12)	1.56 (1.3)	1.00 (0.8)	1.30 (1.1)
Perceived efficacy (0-4)	1.13 (1.3)	1.26 (1.2)	1.19 (1.2)

Discussion

Treatment effects

We found that peripheral electrical nerve stimulation had no beneficial influence on the measures of cognitive and behavioral functioning in patients in the experimental group compared to the placebo group after a treatment period of six weeks.

These results differ from the positive outcomes observed in previous studies using electrical stimulation in AD (Guo et al. 2002; Scherder et al. 1992; Scherder et al. 1995; Scherder et al. 1998; Scherder et al. 1999b; Scherder & Bouma 1999; Van Someren et al. 1998) and the question rises how this discrepancy can be explained. Firstly, the number of participating patients here is three times the number included in the earlier studies. The lack of treatment effects in the present study could imply that the earlier findings observed in relatively small numbers of patients were not real treatment effects. Secondly, the present study included patients at all stages of AD, ranging from mild to severe, with a lower mean level of cognitive functioning than patients in previous studies using electrical stimulation. Le Bars et al. (2002) observed a treatment effect of a ginkgo biloba extract on, among others, the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), irrespective of the stage of dementia. However, an improvement was particularly observed in very mild to mild demented patients whereas stabilization or hindering a further progression of the disease was characteristic for the effects in more advanced stages of dementia. In other words, a treatment effect should not automatically be considered the same as an improvement in functioning. In addition, results from a recent review indicate that pharmacological treatment in AD stabilizes cognitive functioning and enhances activities of daily living (Standridge 2004). In other words, patient groups that are more homogenous with regard to disease severity may have generated different treatment effects than those reported here. A third difference between the current and former studies is the age of disease onset: i.e. earlier in the present study. There is ample evidence that early onset is associated with more severe cognitive impairment, more aggressive course of the disease, more AD pathology, greater neocortical cholinergic cell loss, and a higher prevalence of apolipoprotein (APOE) ε4 (Cedazo-Minguez & Cowburn 2001; Ho et al. 2002). Therefore, the number of patients with early-onset AD included in this study may have reduced average treatment effects.

Taken together, the lack of treatment effects in the present study with its considerable number of patients may question the treatment effects observed in earlier studies with fewer participants. However, patients' characteristics (level of cognitive functioning and age of onset of AD) differed between this study and previous studies. Perhaps the theory that stimulating the central nervous system improves metabolism and

reactivates impaired neurons (Swaab 1991; Swaab et al. 2002; Swaab et al. 2003) does not hold for AD patients in a more advanced stage and/or patients with early onset AD. This suggestion is supported by Geddes and Cotman (1991) who note that when neuropathology in AD is more severe, functional benefits of plasticity become less certain.

A large replication study with AD patients in an earlier phase of the disease might provide a more definitive conclusion about the beneficial effect of peripheral electrical nerve stimulation in AD.

Treatment applicability

We also examined how the patients underwent the treatment and how the family caregiver experienced applying the treatment. Interestingly, the majority of the patients and the caregivers were very positive about the procedure, and applying the daily treatment was accompanied with minimal burden.

Several studies have focused on the effects of providing care to a demented relative and found an increased strain on psychological and physical health of the family caregiver (Pinquart & Sorensen 2003; Sadik & Wilcock 2003). Other studies report a positive gain from caregiving (Kramer 1997; Schulz et al. 1997) or captured the caregivers' experience in the term "vigilance", operationalized as "supervising" and "being there" (Mahoney 2003). Another group found that when caregivers provided end-of-life care at home they showed faster recovery from depression and psychological stress after death of their relatives than caregivers of patients who were institutionalized (Schulz et al. 2003). Also, a study on nursing-home placement of cognitively impaired elderly who were cared for by their relatives, found that caregivers expressed a higher preference for institutionalization if he or she experienced less caregiving satisfaction (Spruytte et al. 2001). In sum, to our knowledge, the present study is the first to show that an active role for the family caregiver is feasible in symptomatic treatment of a demented relative.

Chapter 5

Peripheral electrical nerve stimulation in Alzheimer's disease

A randomized controlled trial on the rest-activity rhythm

Abstract

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). Stimulation of the SCN may prevent age-related loss of neurons and might reactivate nerve cells that are inactive but not lost. Previous studies have demonstrated positive effects of peripheral electrical nerve stimulation on the rest-activity rhythm in AD patients living in a nursing home. The present randomized controlled study examined the effects of electrical stimulation on the rest-activity rhythm in AD patients still living at home. Sixty-two AD patients were randomly assigned to either electrical stimulation or sham-stimulation. Effects on the rest-activity rhythm were assessed using actigraphy before and after treatment. Results show no significant effects of electrical stimulation when all participants were analyzed. Interestingly, however, post hoc analyses revealed significant effects in a subgroup of patients who were not using aceteylcholinesterase inhibitors (AChEIs) concomitantly. The interaction between AChEIs and electrical stimulation in the present sample of AD patients warrants further investigation.

Van Dijk KRA, Luijpen MW, Van Someren EJW, Sergeant JA, Scheltens P and Scherder EJA. Peripheral electrical stimulation in Alzheimer's disease. A randomized controlled trial on the rest-activity rhythm (submitted for publication)

Introduction

Rest-activity rhythm disruption is a prominent clinical feature of Alzheimer's disease (AD) (Ancoli-Israel et al. 1997; McCurry et al. 1999; Prinz 1982; Satlin et al. 1995; Van Someren et al. 1996). In a recent 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). Therefore, it is not surprising that institutionalization is best predicted by rest-activity rhythm disruption and not by the level of cognitive functioning or number of psychiatric symptoms of the AD patient (Chenier 1997; Hart et al. 2003; Hope et al. 1998; Kesselring et al. 2001; Lieberman & Kramer 1991; Pollak & Perlick 1991).

The origin of the altered rest-activity rhythm in AD is believed to be 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). Interestingly, application of bright light has shown to positively influence rest-activity rhythm disturbances in some AD patients (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 thus 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. 1999b; Van Someren et al. 1998). It was argued that stimulation of peripheral nerves with electrical stimuli might activate the SCN through four projections that have been identified in animal experimental studies. First, the spino-hypothalamic tract: a direct pathway from 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 & 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 the 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 & 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 (NBM), 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 part of the ascending reticular activating system (ARAS) (Kayama & 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.

Considering the positive effects of electrical stimulation on the rest-activity rhythm in AD patients living in a nursing home, the present, randomized, placebo-controlled, parallel-group clinical study examined the effects of peripheral electrical stimulation in AD patients still living at home. Based on earlier studies, it was hypothesized that after a treatment period of six weeks, the experimental group that received electrical stimulation would show improved functioning of the rest-activity rhythm, compared to the placebo group.

Methods

Participants

Participants were recruited from the Alzheimer Center of the VU University Medical Center, from the Department of Neurology of the 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 changed 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 ethical 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%) entered the analysis phase. The two groups did not differ significantly with regard to sex, age, education, and MMSE as indicated by chi-square and t-tests (see Table 5.1 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 (MANOVAs) and chi-square tests indicated no significant differences between the groups with respect to age, education, MMSE, and sex.

Table 5.1 Characteristics of the patients

	Experimental group (n = 31)	**Placebo group (n = 31)**
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 (n)		
Rivastigmine (n)	13	12
Donepezil (n)	2	1

AChEI use = acetylcholinesterase inhibitor use, subdivided in Rivastigmine (Exelon®) and Donepezil (Aricept®)

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, whereas participants in the placebo group were told that the stimulator was working as soon as a green light was blinking, without an actual current being applied. To maintain the participants' blindness and since 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 to 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.

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 six weeks (Post-assessment) and following a treatment-free period of six 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 μsec, 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, i.e. A-Beta, A-Delta, and C-fibers, which convey the pulses to cortical and sub-cortical areas (Scherder et al. 1995; Scherder et al. 2003). The family caregiver applied the treatment 30 minutes a day, seven days a week, for a period of six 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 (Pollak et al. 2001) and has been successfully used in healthy elderly and demented elderly patients (Huang et al. 2002; Martin et al. 2000; Van Someren et al. 1996). Traditionally, actigraphy has been recorded from the non-dominant wrist but studies that investigated different placement locations found no difference 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, Great Britain) was worn on the dominant wrist. The small (3 x 4 x 1 cm) and light-weight actigraph made home recordings of circadian rhythm during several days possible and caused minimal burden to the participant. Analyses were based on data obtained in 1 min epochs during 4 consecutive days (M = 96 hours, SD = 2, range: 72-96).

The following non-parametric variables were computed and are described in more detail elsewhere (Van Someren et al. 1998). 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-hour cycle and high IV values. Third, the relative amplitude (RA) is a normalized variable based on the most active period in the 24-hour 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 were missing from 62 participants (<1%) at three assessments due to non-compliance, 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 & 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 = .61) to 11.50 (p = .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 six 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 (ANOVAs) with Group (two levels: experimental versus placebo) as between subjects factor and Time (two levels: Post versus Pooled baseline) 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. Separately, the experimental and placebo group were subject to repeated measures ANOVAs with AChEI use (two levels: AChEI + versus AChEI −) as between subjects factor and Time (two levels: Post versus Pooled baseline) as within subject factor. All statistical tests were two-tailed and the critical value for significance was $p < .01$ to compensate for 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 .60 ± .015 ($M \pm SEM$), IV was 1.07 ± .037 and RA was .85 ± .013. These values are comparable to previous values found in AD patients in a nursing home setting and indicative of a less stable and more fragmented rest-activity rhythm compared to non-demented elderly (Scherder et al. 1999b; Van Someren et al. 1998).

Effects of electrical stimulation

Repeated measures ANOVAs 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 x Time interaction effect for RA ($F(2,60) = 13.76$, $p < .001$) and near significant effects for IS ($F(2, 60) = 5.90$, $p = .018$) and IV ($F(2,60) = 4.24$, $p < .04$). Further analyses using within group t-tests revealed a trend for improved IS and IV in the experimental group ($t(30) = 1.85$, $p = .07$, and $t(30) = -1.98$, $p = .06$, respectively) and a significant worsening of RA in the placebo group ($t(30) = -.35$, $p = .002$).

Table 5.2 Means (*M*) and standard errors of the mean (*SEM*) of the experimental and placebo group

	experimental group (n=31)			**placebo group (n=31)**					
	pre	**post**	**delayed**	**pre**	**post**	**delayed**	**ANOVA pooled baseline vs post**		
Actigraphy	***M* (*SEM*)**	***M* (*SEM*)**	***M* (*SEM*)**	***M* (*SEM*)**	***M* (*SEM*)**	***M* (*SEM*)**	***F*(2,60)**	η^2	***p***
IS	.58 (.023)	.60 (.020)	.58 (.018)	.61 (.020)	.57 (.023)	.60 (.022)	5.90	.09	0.018
IV	1.02 (.049)	.98 (.055)	1.11 (.051)	1.11 (.055)	1.08 (.055)	.96 (.056)	4.25	.07	0.044
RA	.86 (.015)	.86 (.017)	.85 (.018)	.84 (.022)	.79 (.027)	.86 (.019)	13.76	.19	0.001

IS = interdaily stability, IV = intradaily variability, RA = relative amplitude, pre = baseline, post = after six weeks treatment, delayed = after six weeks treatment free, pooled baseline =the average of pre and delayed, η^2 *= partial eta squared effect size*

Interactions between electrical stimulation and AChEI use

To investigate a possible interaction effect between AChEIs and electrical stimulation, the experimental and placebo group separately were subject to repeated measures ANOVAs 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 x Time interaction effect for IS ($F(2,29) = 5.00$, $p = .03$), whereas the placebo group showed no significant interaction. The effect size in the experimental group was large, i.e. partial η^2 (Cohen 1977) was .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 ($t(15) = 3.12$, $p = .007$) and a near significant effect on IV ($t(15) = -2.53$, $p = .02$) in the AChEI − group, but no significant effects in the AChEI + group ($t(17) = -.87$, $p = .40$, and $t(17) = 1.60$, $p = .13$, respectively) (see Figure 5.1).

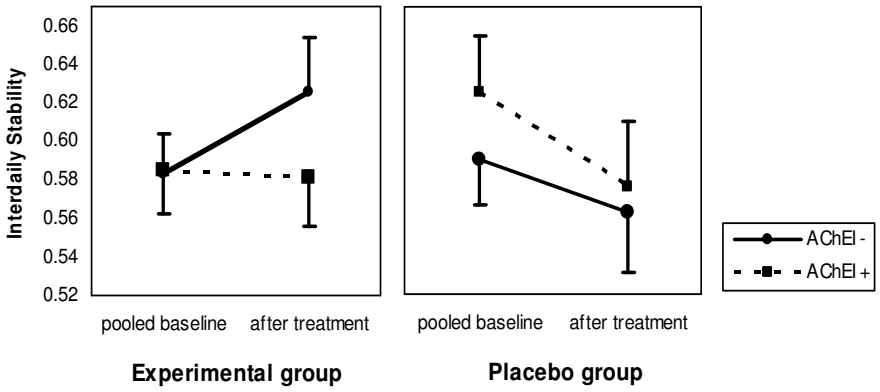

Figure 5.1 Mean values for Interdaily Stability of the experimental (left) and placebo (right) group at pooled baseline and after treatment. There are separate lines for acetylcholinesterase inhibitors users (AChEI +) and non-users (AChEI −). Error bars indicate standard errors of the mean (SEM), shown only one sided for reasons of clarity.

Discussion

This paper presents data from a randomized clinical trial on peripheral electrical nerve stimulation in AD with three times as many participants as any earlier study on this topic to date. Effects of peripheral electrical stimulation, compared to placebo, on the rest-activity rhythm in AD patients living at home were examined. Results indicated a group effect for the amplitude of the rhythm (RA). However, this effect was due to a significant worsening in the placebo group, not to improvement in the experimental group. Furthermore, a near significant group effect was observed for the stability (IS) and fragmentation (IV) of the rhythm. The latter two could be attributed to improvements in the experimental group.

These results are similar to effects found in earlier studies which showed a more stable rest-activity rhythm after treatment (Scherder et al. 1999b; Van Someren et

al. 1998) and a trend towards a positive effect on the fragmentation of the rhythm (Scherder et al. 1999b). 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 since 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 ACh 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 e.g. positron emission tomography (PET) to measure cholinergic function is necessary. Second, 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 et al. 2000; Birks & Harvey 2003; Loy & Schneider 2004). Perhaps, in those patients an improved rest-activity rhythm may positively influence cognitive and/or behavioral symptoms, a relation that has been suggested in several studies (Van Someren et al. 2002).

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. Use of imaging techniques such as PET may disentangle the complex interactions between AChEIs and electrical stimulation and may also provide more insight into the underlying mechanisms of this non-pharmacological treatment.

Chapter 6

Assessment of executive functions in Alzheimer's disease using computerized tests

Abstract

Executive functions (EFs) are often impaired early in the course of Alzheimer's disease (AD). Since EFs play a crucial role in self-care, communicative functioning, and financial capacity, and because executive dysfunction has been linked to more neuropsychiatric symptomatology, evaluation of EFs is essential. In the past decades there has been a growing interest in computerized tests of cognitive functions but only a limited number of studies employed computerized tests of EFs in AD patients. The goal of the present study was to administer computerized EF tests of planning, inhibition, working memory, and attention in AD. Sixteen AD patients who met the NINCDS/ADRDA diagnostic criteria for probable AD and seventeen healthy elderly controls participated in the study. Results show that the AD patients score significantly lower on tests of planning and near significantly lower on attention. Differences on the tests of working memory and inhibition were in the expected direction but not significant. Although replication with larger groups is required, the current study indicates that a battery of computerized EF tests can be used in AD patients and healthy elderly persons and partially differentiates between groups.

Van Dijk KRA, Holleman MA, De Sonneville LMJ, Oosterlaan J, Sergeant and JA. Scherder EJA. Assessment of executive functions in Alzheimer's disease using computerized tests (submitted for publication)

Introduction

Memory impairment is among the first signs of Alzheimer's disease (AD) and an essential symptom for a clinical diagnosis (American Psychiatric Association 1994; Brandt & Rich 1995; McKhann et al. 1984). However, there is growing evidence that executive functions (EFs) are often also impaired early in the course of AD (Binetti et al. 1996; Collette et al. 1999; Lafleche & Albert 1995). A recent study including 137 cases with AD, classified 64% of the AD patients as having executive dysfunctions (Swanberg et al. 2004), and even individuals who do not meet clinical criteria for AD but who are likely to be in a prodromal phase of the disease, showed executive dysfunctions (Albert et al. 2001; Lam et al. 2004). EFs can be defined as higher order cognitive capabilities necessary for the synthesis of external stimuli, formations of goals and strategies, preparation for action, and the use of feedback (Luria 1988). They include cognitive functions such as planning, working memory, inhibition, attention and fluency, and they are known to be primarily, but not solely, mediated by the prefrontal cortex (Pennington & Ozonoff 1996; Stuss & Alexander 2000). Since EFs play a crucial role in self-care (Boyle et al. 2003), communicative functioning (Bayles 2003), and financial capacity (Earnst et al. 2001), and because executive dysfunctions have been linked to more neuropsychiatric symptomatology (Chen et al. 1998), evaluation of EFs of AD patients in clinical practice is essential.

In the past decades there has been a growing interest in computerized tests of cognitive functions (Butcher et al. 2000; Collie & Maruff 2003; Kane & Kay 1992). Although a computer should not be used as a substitute for the human examiner (Tien et al. 1996) and cannot replace clinical judgment (Butcher et al. 2000), there are evident advantages of computers in terms of ease of administration, detailed objective measures of speed and accuracy, automated scoring, and availability of different parallel versions. Moreover, studies that have examined the use of computerized measures to detect memory deficits in healthy elderly persons (De Jager et al. 2002) and patients with questionable dementia (Fowler et al. 2002), found deterioration with computerized measures before significant decline was noted on standard paper-and-pencil tests.

Only a limited number of studies employed computerized tests of EFs in AD patients. Swainson et al. (2001) administered a battery of traditional paper-and-pencil tests and computerized measures to patients with mild AD. One of the computerized measures included in that study was a modified Tower of London (TOL) planning test (Shallice 1982) which was taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Owen et al. 1990). Results of this computerized TOL showed that the group of AD patients performed significantly worse when compared

with groups of patients with questionable dementia, major depression, and healthy elderly controls (Swainson et al. 2001). In a study by Amieva et al. (2002) on inhibitory breakdown using a Stop-Signal motor inhibition task (Logan & Cowan 1984), a significant difference between AD patients and normal elderly controls was found regarding the number subjects in each group committing at least one error.

The goal of the present study was to administer computerized EF tests in AD which are comparable to the tests used by Swainson et al. (2001) and Amieva et al. (2002) in order to assess planning and inhibition. In addition, the battery was extended with computerized tests of working memory and attention and a group of normal elderly controls was included for comparison.

Method and material

Participants

A sample of AD patients and normal elderly controls was recruited among residents of a nursing home in Amsterdam, The Netherlands. The main inclusion criterion for the AD group was a diagnosis of probable AD according to the NINCDS/ADRDA guidelines (McKhann et al. 1984). Exclusion criteria for the AD group were cerebrovascular disease, clinical depression, a history of cerebral trauma, disturbances of consciousness, seizures, epilepsy, infectious diseases, and hearing and vision loss. The inclusion criteria for the normal control group were absence of diagnosis of probable AD or other types of dementia and exclusion criteria were the same as those for the AD group.

Participants were 16 AD patients (4 men and 12 women) and 17 healthy elderly persons (2 men and 15 women). The two groups were not significantly different with regard to sex, age and education. Mean age was 83.3 (*SD* 4.5; range 74 – 90) and 84.8 (*SD* 4.8; range 77 – 92) years for the AD and control group, respectively. Mean years of education was 8.3 (*SD* 2.4; range 6 – 13) and 7.5 (*SD* 2.2; range 6 – 12). The mean MMSE score of the AD group was 19.8 (*SD* 3.8; range 12 – 26) and differed significantly from the mean MMSE score of the control group which was 26.1 (*SD* 2.1; range 22 – 29) ($t(31) = 6.1$, $p < 0.001$).

Neuropsychological measures

All participants were administered four computerized EF tests, two control measures for basic psychomotor functions and one widely used non-computerized EF test (see Table 6.1 for an overview).

Planning

The Stockings of Cambridge closely resembles the classical TOL (Shallice 1982) and is first described by Owen et al. (1990). It is part of the CANTAB which ran on a standard PC with a 12-inch touch sensitive screen. Participants were seated approximately 0.5 m from the screen. Prior to the test, participants are familiarized with the touch screen in a "motor screening task" in which they are instructed to touch the screen at a cross that appears at a pseudo-random location on the screen. The planning task involves an example set of three colored balls (red, blue and green) in a certain configuration at the top half of the screen and a set of colored balls in another configuration in the lower half of the screen. The participants are instructed to rearrange the balls in the lower half in such a way that it is the same as the example at the top half of the screen. A ball can be moved by touching it and, after the rim of the ball starts flashing, touching a desired new location.

An extensive instruction is followed by six practice items, which can be solved within one or two moves, and twelve subsequent test trials: two items with two and three moves, and four items with four and five moves. The test trials are the same problems as used in the original TOL (Shallice 1982). The participants are instructed to try to solve the problems in a minimum possible number of moves and encouraged to plan their moves before actually enacting the solution to the problems. The correct solution of the trials can be attained in a minimum of two, three, four and five moves, respectively. The minimum number of moves required is included in the oral instructions and stated on the screen during presentation of the problems. The program registers the number of moves that the subject needs to reach the solution from which the following variables are computed: "number of problems solved in the minimum moves" and "mean number of moves above the minimum". The latter is the average of number of moves needed above the minimum for two, three, four and five move problems. After the planning task, a motor control condition is presented. In the motor condition, the participant is instructed to move the balls in the lower display promptly as the upper display changes. Moves in the control condition correspond to moves in the planning condition and latencies are recorded for the motor initiation and execution time of each response. The motor initiation and execution times are used to obtain the measure "mean initial thinking time". This measure is calculated as the time between presentation of the problem in the main planning condition on the screen and the first touch, minus the corresponding latency to make the same move in the control condition. Using this method, measures of thinking time are not confounded by the time needed to perform the motor initiation and execution. This measure is an average of the mean initial thinking time for two, three, four and five move problems.

Working memory

Spatial Span is another CANTAB subtest and was used as a measure of working memory. Traditionally, working memory was believed to be assessed, among others, by the backward conditions of the digit span and spatial span tasks from the Wechsler Memory Scale-Third Edition (WMS-III: Wechsler 1997) (Groeger et al. 1999; Lezak 1995). Recent data of 1030 persons of the original WMS-III standardization sample (Wechsler 1997) indicated that not only backward but also forward span tasks recruit working memory resources (Hester et al. 2004). The Spatial Span test that was administered in the present study was a computerized version of the Corsi Block Tapping test (Milner 1971), in which a pseudo random pattern of nine white squares was shown on the touch sensitive screen. A sequence of squares changes color for three seconds each and at the end of the presentation of the sequence, a tone indicates the participant to touch the same boxes in the same order. The number of boxes in the sequence increases from two to nine boxes with three sequences per level. The test terminates after failure on all sequences at a particular level. The main working memory measure "span length" is the final level at which the subject successfully recalled at least one sequence of boxes. A secondary measure was the "number of errors" (boxes not in sequence).

Attention

The Amsterdam Neuropsychological Tasks (ANT) (De Sonneville 1999) is a computerized battery of tests that has been shown to be highly sensitive in detecting cognitive deficits in several clinical populations (De Sonneville et al. 2002; Huijbregts et al. 2002; Kalff et al. 2005). Focused Attention is a subtest of the ANT in which a schematic fruit bowl with pieces of fruit is presented at the centre of a 15-inch computer screen. The bowl is oval shaped and the pieces of fruit are located on the top, bottom, left and right. There is one target object (apple) and several non-target objects (e.g. pear, banana and cherries). In addition, there are two target locations: the vertical locations (top and bottom) of the fruit bowl. The participant is instructed only to press a button when a target object is presented at a target location. A target presented in a non-target location should be ignored and a response suppressed. Stimulus duration is 2000 ms, the event rate is 3000 ms, and the valid response window is 200-2300 ms. There are 12 practice trials and 40 test trials. Of the 40 test trials, 50% are relevant targets at relevant locations, 25% are relevant targets at irrelevant locations, and 25% are trials without relevant targets. "Number of hits of relevant targets" is the main outcome variable and represents the ability to focus attention on the target object at the target locations.

Inhibition

A Stop-Signal Task was used as measure of inhibition of a prepotent response (Logan 1994; Logan & Cowan 1984). The task involves two types of trials: "go" trials and

"stop" trials presented on a 15-inch computer screen. Go trials start with a fixation cross presented at the center of the screen during 500 ms, followed by a cartoon airplane pointing either to the left or right for a duration of 1000 ms. The inter-stimulus-interval is 500 ms. Participants are instructed to press the button on the right when an airplane is pointing to the right and the button on the left when an airplane is pointing to the left. Stop trials consist of a go trial and an auditory Stop-Signal presented through headphones (1000 Hz, 50 ms, volume adjusted to audible level for each participant). Stimuli are presented in blocks of 64 trials, 25% of which are stop trials. To ensure familiarity with the paradigm, the task starts with two practice blocks. During the first practice block, consisting of go trials only, the instruction is to respond as quickly and accurately as possible to the airplanes. In the second practice block, with 25% randomly presented stop trials, the instruction is to respond as quickly and accurately as possible but to try to suppress a response when a stop-signal is presented. Two practice blocks are followed by four test blocks.

In this version of the Stop-Signal Task a tracking mechanism varies the interval between the go and the stop-signal. The use of a tracking mechanism has several theoretical and practical advantages: for instance, it establishes that each participant has a 50% chance of response inhibition on stop trials (for more information, see: Band et al. 2003). This version of the task is described in further detail by Scheres et al. (2003). The dependent variable in the Stop-Signal Task is the "stop-signal reaction time" which reflects the latency of the inhibition process and is calculated by subtracting the mean time at which the participant is still able to inhibit a response from the mean go trial reaction time.

Control measures

Information processing

Baseline Speed from the ANT was used as a simple reaction time measure with minimal cognitive demands. Participants are instructed to press a button as quickly as possible when a fixation cross at the target location at the center of the screen changes into a square. The valid response window is 150-6000 ms, the stimulus disappears after a response, and the post-response interval varies randomly between 500 and 2500 ms. There are 10 practice trials and 32 test trials for both right and left hand. The outcome variable was the average of the simple reaction times for the left and right hand and served as a measure of information processing.

Motor skills

Finger Tapping from the ANT resembles the classical finger tapping test from the Halstead-Reitan Battery (Reitan & Wolfson 1993). Participants are instructed to tap a button with their index finger as many times as possible during a certain interval. After

the instruction, the test starts with a practice run of 5 seconds followed by a test run of 13 seconds. Only taps in the last 10 seconds are scored as valid taps. There is a right hand and a left hand condition. The outcome measure was the average number of taps for the left and the right index finger and served as a measure of simple motor skills.

Verbal fluency

The Category Fluency test (Benton & Hamster 1978) was used to measure verbal fluency. This task, which is known to be affected in AD (Henry et al. 2004), was included in order to get an indication of whether, and two what extent, a classical widely used EF measure is affected in the present sample of AD patients. In this test, participants are asked to produce as many words as possible belonging to a specific semantic category in a 60 seconds interval. The categories were animals and professions, and the dependent variable was the sum of the total correct words for each category. When the same item was named more than once, only the first was counted.

Table 6.1 Overview of the neuropsychological measures

Neuropsychological function	Test	Dependent variable
Planning	Stockings of Cambridge	Number of problems solved in minimum moves Mean number of moves above minimum Mean initial thinking time (s)
Working memory	Spatial Span	Span length Number of errors (boxes not in sequence)
Attention	Focused Attention	Number of hits of relevant targets
Inhibition	Stop Signal Task	Stop signal reaction time (ms)
Information processing	Baseline Speed	Simple reaction time (ms)
Motor skills	Finger Tapping	Number of taps
Fluency	Category Fluency	Number of correct animals and professions

Statistical analysis

To determine if performance on the computerized EF tests was related to basic psychomotor functions, Pearson correlation coefficients were calculated between performance measures derived from the EF tasks and basic information processing and motor function. Differences between groups were determined in analyses of variance

(ANOVAs) or, if appropriate, in analyses of covariance (ANCOVAs), with one-sided tests. To compensate for the use of multiple comparisons, a level of significance of .01 was applied and an alpha from .01 to .05 was considered a trend. Partial eta squared effects sizes were calculated and characterized as small, medium or large when corresponding with .01, .06 and .14, respectively (Cohen 1977). If a score of a participant was missing on a particular variable, the individual was excluded from analysis regarding that variable. SPSS Base for Windows Version 12.0 was used for all analyses.

Results

Pearson correlation coefficients indicated that slower information processing speed was significantly associated with lower scores on measures of working memory (r = -.40, p < .05) and inhibition (r = .41, p < .05). Therefore, information processing speed was entered as covariate in all analyses of the computerized EF measures to ensure that group differences were not due to slowed information processing. In addition, there appeared to be a significant association between information processing and motor skills on one hand and the fluency score on the other hand (r = -.51, p < .01, r = .39, p < .05, respectively) and therefore, information processing speed and motor skills were controlled for when analyzing differences between groups on the fluency task. Averages and statistics of the computerized EF measures and control measures are given in Table 6.2.

Group differences on computerized EF measures

Planning

The AD patients needed significantly more moves above the minimum necessary to solve the problems. In addition, there was a near significant difference between groups on the number of problems solved in minimum moves, with lower scores for the AD patients. The effect sizes for these differences were both very large. The two groups did not differ on mean initial thinking time.

Table 6.2 Group means and standard deviations of the neuropsychological measures

	group							
	AD		NC		ANOVA / ANCOVA			
	M	***SD***	***M***	***SD***	***F***	***df***	***p***	η^2
Planning (Stockings of Cambridge)								
Number of problems solved in minimum moves	4.3	1.5	6.4	2.1	6.4	1,24	.01*	.21
Mean number of moves above minimum	2.0	.8	1.3	.6	8.9	1,24	.003**	.27
Mean initial thinking time (s)	17.4	12.2	16.4	12.6	.0	1,24	.50	.00
Working memory (Spatial Span)								
Span length	3.8	1.0	4.3	.9	1.0	1,24	.17	.04
Number of errors (boxes not in sequence)	12.3	5.6	12.5	5.6	.2	1,24	.33	.01
Attention (Focused Attention)								
Number of hits of relevant targets	19.1	1.3	19.9	.3	3.8	1,26	.03*	.13
Inhibition (Stop Signal Task)								
Stop signal reaction time (ms)	377.6	281.3	266.9	187.5	.6	1,26	.22	.02
Information processing (Baseline Speed)								
Simple reaction time (ms)	649.2	355.2	456.7	129.5	4.1	1,29	.05	.13
Motor skills (Finger Tapping)								
Number of taps	28.7	12.5	27.6	12.6	.1	1,29	.81	.00
Fluency (Category Fluency)								
Number of correct animals and professions	17.8	5.0	27.8	8.2	10.9	1,20	.003**	.33

*η^2 = (partial) eta squared effect size, ** = statistically significance ($p < .01$), * = statistical trend ($.01 \leq p < .05$)*

Working memory

No significant differences between the groups were found.

Attention

There was a trend for the difference between groups in the number of hits of relevant targets with slightly more correct hits for the non-demented elderly. The effect size was medium to large.

Inhibition

The two groups did not differ significantly on the stop-signal reaction time, the measure of latency of the inhibition process.

Group differences on the control measures

Information processing

Simple reaction times were near significantly slower in the AD group when compared with the control group.

Motor skills

No significant differences between the groups were observed.

Fluency

The correct number of words generated by the normal elderly controls was significantly higher and showed a very large effect size.

Discussion

The goal of the present study was to administer computerized EF tests in AD which are comparable to the tests used by Swainson et al. (2001) and Amieva et al. (2002) in order to assess planning and inhibition. In addition, the battery was extended with computerized tests of working memory and attention and a group of normal elderly controls was included for comparison.

The difference between the two groups on one of the three measures of the planning task (mean number of moves above the minimum) was significant and near significant on another (number of problems solved in minimum moves). In addition, the difference between groups on the attention test showed a trend with better scores for the normal controls. Group differences on the tests of working memory and inhibition were not significant.

Swainson et al. (2001) used a modified version of the Stockings of Cambridge, in which the participants were asked to calculate how many moves were required to match two sets of colored balls and to respond by touching the corresponding number on the screen. Their main index of performance (number of attempts to select the correct number of moves needed at the 5-move level) is related to the planning measures which showed (near) significant differences in the present study. Therefore, our results seem to support earlier findings of impaired planning in AD using this task.

Normative data of a group of 222 persons between the ages 50 and 69, on the same version of the planning task as used in the present study, show slightly higher scores (number of problems solved in minimum moves: $M = 7.5$, $SEM = 0.2$) when compared to our control group, a difference that may be explained by the fact that the average age of our control group was much higher. The third measure from the Stockings of Cambridge (mean initial thinking time) did not differ between groups and we are not aware of any other study reporting this index for AD patients and elderly controls. In a study in which frontal lobe patients and normal controls were subject to the same test, thinking times did not differ between groups either (Owen et al. 1990). The 26 normal controls in that study were much younger (age: $M = 44.6$, $SD = 3.5$) and showed shorter thinking times (ranging from 3.12 to 11.54 s). The longer thinking times in the present study in both the AD group and the control group can very likely be explained by the general cognitive slowing which is typical for AD patients as well as for normal elderly controls (Salthouse 2000; Storandt & Beaudreau 2004).

One study that used a Stop-Signal Task in AD patients reported that the AD group did not show significant differences on their main index (number of errors on stop-trials) when compared with normal controls (Amieva et al. 2002). However, the number of subjects in that study that committed at least one error was significantly higher in the AD group and therefore, offers limited evidence that AD patients in an early stage of the disease (MMSE: $M = 24.6$, $SD = 1.9$) have more problems stopping an ongoing motor response than normal elderly controls. Unfortunately, the authors did not calculate the stop-signal reaction time, which is the primary measure of the inhibition process from the stop-signal paradigm (Logan 1994; Logan & Cowan 1984). In the present study we used a version of the Stop-Signal Task with a tracking mechanism which allows the participant a 50% chance of successful inhibition on stop trials and consequently, makes error analysis unsuitable for group comparisons. Instead, we used the stop-signal reaction time, representing the latency of the inhibition process. Although we did not detect statistically significant differences between groups, it is interesting to note that the mean stop-signal reaction time of the AD group was much longer. The absence of group differences could likely be attributed to the large variance within the AD group. Whether the Stop-Signal Task can significantly differentiate between AD patients and normal controls, awaits investigation with larger groups.

Group differences on the measure of focused attention showed a trend and a medium to large effect size. Although not significant, this finding is in the same direction as reported in the comprehensive review by Perry and Hodges (1999) which states that aspects of selective attention (similar to our measure of focused attention) are vulnerable to AD. The present findings are in contrast with Nebes and Brady (1989) and Lafleche and Albert (1995), however, who reported sparing of focused attention in AD. It is noteworthy that the AD patients in the later study were an earlier stage of the

disease (MMSE: *M* = 25.1, *SD* = 2.4) (Lafleche & Albert 1995) which might explain this discrepancy.

Scores on the working memory measure did not differ between groups in the present study. A study in which the same task from the CANTAB was administered showed similar scores (span length: *M* = 4.0, *SD* = .4) for 13 AD patients who were in a comparable stage of the disease (MMSE: *M* = 19.2, *SD* = 1.6) (Lange et al. 1995). Normative data from 19 healthy elderly controls show somewhat higher scores than our control group (span length: *M* = 5.0, *SD* = .9), but taking into account the fact that the group in that study was much younger (age: *M* = 55.9, *SD* = 5.3) (De Luca et al. 2003), we believe that our control group scored within normal limits. Since there is an abundance of literature reporting working memory deficits in AD (e.g., Baddeley et al. 1986; Collette et al. 1999; Collette et al. 1997; Waters & Caplan 2002; White & Murphy 1998), it can be argued that working memory is affected in our AD group but the task used in the present study is not suitable to detect this deficit.

The present study included a rather limited number of participants and therefore, additional replication is required. Nevertheless, the current study indicates that a battery of computerized EF tests can be used in healthy elderly persons and AD patients and partially differentiates between groups.

Chapter 7

Summary and conclusions

Summary

Chapter 1 provides an introduction into the prevalence and pathophysiology of Alzheimer's disease (AD). It is argued that decreased neuronal metabolism is the major pathological hallmark of AD. The theory of Swaab which states that neuronal stimulation may protect neurons against degenerative changes in aging and AD, is briefly introduced. One way to stimulate the central nervous system is using peripheral electrical nerve stimulation. Several previous studies have examined the effects of electrical stimulation in AD and found improvements on cognition, behavior, the rest-activity rhythm, and the pupillary light reflex. The present thesis examines the effects of peripheral electrical stimulation in a substantially larger group of AD patients than any other study on this topic to date.

For **Chapter 2**, an extensive literature search was performed in order to review the effects of Transcutaneous Electrical Nerve Stimulation (TENS) on non-pain related cognitive and behavioral functioning. Eight studies were identified on neglect due to stroke, six studies on AD, one study on aging, and two studies on coma due to traumatic brain injury. The results of the various studies revealed that TENS has a variety of effects. These effects consist of enhanced somatosensory functioning, visuospatial abilities, and postural control in neglect as well as improved memory, affective behavior, and rest-activity rhythm in AD, and acceleration of awakening in coma. Effectiveness of TENS is discussed in relation to various stimulation parameters: duration, frequency, pulse width, and intensity. It is argued that arousal may underlie the beneficial influence of TENS in various conditions. Finally, suggestions are offered for future research.

Chapter 3. Since 1990, a series of studies have examined the effects of TENS on cognition, behavior, and the rest-activity rhythm of patients suffering from AD. In these studies, TENS was aimed at stimulating the dorsal raphe nucleus (DRN) and the locus coeruleus (LC) with a combination of low- and high-frequency (2 Hz and 160 Hz, respectively), a pulse width of 0.1 ms, and an intensity that provoked muscular twitches. TENS was applied 30 minutes a day, five days per week, during a six-week period. For the purpose of reliable comparisons between studies, identical stimulation parameters

were used in all studies thus far, including the study presented in this thesis. In order to optimize TENS treatment in AD, chapter 3 is meant to reconsider the once selected stimulation parameters by reviewing the relevant literature published since 1991. The results derived from animal experimental studies show that for optimal stimulation of the LC and DRN, the pulse width should be more than 0.1 ms.

Chapter 4 presents a randomized, placebo-controlled, parallel-group clinical trial on the effects of peripheral electrical stimulation on cognition and behavior in a group of AD patients that is three times as large as the samples in any earlier study on this topic. Participating patients still lived at home and the treatment was applied by a family caregiver for 30 minutes a day during six weeks. The majority of the patients and the caregivers evaluated the treatment procedure positively and applying the daily treatment at home caused minimal burden. Repeated measures analyses of variance revealed no effects of the intervention in the experimental group (n = 32) compared with the placebo group (n = 30) on any of the cognitive and behavioral outcome measures.

In **Chapter 5** data are presented regarding the effects of peripheral electrical stimulation on the rest-activity rhythm from the same study as described in chapter 4. Effects on the rest-activity rhythm were assessed using actigraphy. Results show no significant effects of electrical stimulation when all participants were analyzed. Interestingly, however, post hoc analyses revealed significant effects in a subgroup of patients who were not using acetylcholinesterase inhibitors (AChEIs) concomitantly.

Chapter 6. Executive functions (EFs) are often impaired early in the course of AD. Since EFs play a crucial role in self-care, communicative functioning, and financial capacity, and because executive dysfunctions have been linked to increased neuropsychiatric symptomatology, evaluation of EFs is essential. In the past decades there has been a growing interest in computerized tests of cognitive functions but only a limited number of studies employed computerized tests of EFs in AD patients. The goal of the present study was to administer computerized EF tests of planning, inhibition, working memory, and attention in AD. Sixteen AD patients and seventeen healthy elderly controls participated in the study. Results show that the AD patients score significantly lower on tests of planning and near significantly lower on attention. Differences on the tests of working memory and inhibition were in the expected direction but not significant. Although replication with larger groups is required, the current study indicates that a battery of computerized EF tests can be used in AD patients and healthy elderly persons and partially differentiates between groups.

Conclusions

It is important to acknowledge that the results of this study do not lead to a simple general conclusion which states that peripheral electrical nerve stimulation is, or is not, an effective symptomatic treatment in AD. Given the complex nature of the disease and the restrictions of the present study setup, it would be presumptuous to assume that such a general conclusion can be drawn. Yet, the following, more modest, conclusions can be formulated:

1. The vast majority of the patients and the caregivers evaluated the treatment procedure positively. Applying the daily treatment at home caused minimal burden. This shows that an active role for the family caregiver is feasible in symptomatic treatment of a demented relative.
2. In the study reported in chapters 4 and 5 we did not find significant effects of electrical nerve stimulation on the main measures of cognition, behavior, and the rest-activity rhythm. The hypothesis that this type of treatment is beneficial in AD is not supported by our findings.
3. Patient characteristics (level of cognitive functioning and age of onset of AD) differed between this study and previous studies which could imply that the theory that stimulating the central nervous system improves metabolism and reactivates impaired neurons, does not hold for AD patients in a more advanced stage and/or patients with early-onset AD. Thus, heterogeneity of the present sample possibly masked significant treatment effects.
4. Near significant effects of electrical stimulation on the rest-activity rhythm were found, in conjunction with significant results in a subgroup of patients that was not using acetylcholinesterase inhibitors (AChEIs) concomitantly.

From these conclusions it is apparent that more research is needed before firm conclusions about the general effectiveness or ineffectiveness of peripheral electrical nerve stimulation in AD can be drawn. Three recommendations for future investigations are of particular importance:

i. Larger and more homogeneous groups of participants need to be included. In this way the issue of heterogeneity of patient groups can be dealt with in more detail.
ii. Refined stimulation parameters, such as a longer pulse width and prolonged duration of stimulation, should be applied. This will give more insight into effects of treatment with peripheral electrical nerve stimulation.
iii. More advanced methods, such as brain imaging techniques and computerized neuropsychological tests, should be used. Improved outcome measures may increase the sensitivity for treatment effects.

Nederlandse samenvatting

Inleiding

De ziekte van Alzheimer (Alzheimer's disease: AD) komt voor bij 1% van de mensen van 65 jaar en ouder en bij 22% van de mensen van 90 jaar en ouder en is daarmee de meest voorkomende oorzaak van dementie. Een steeds voortschrijdende verslechtering van de kwaliteit van het hersenweefsel (progressieve neurodegeneratie) veroorzaakt algehele achteruitgang van kennis (verminderde cognitie), problemen met activiteiten van het dagelijks leven, neuropsychiatrische symptomen, verstoring van het rust-activiteitritme en slaapproblemen. De zorg voor een patiënt met AD plaatst een enorme druk op familieleden en ook de kosten van de ziekte voor de samenleving zijn groot en zullen naar verwachting aanzienlijk stijgen ten gevolge van de vergrijzende populatie.

"Use it or lose it"

Onderzoek van de laatste decennia toont aan dat afsterven van hersencellen minder is dan men eerder aannam en dat niet celdood maar een verminderd functioneren van de cel door verlaagde stofwisseling, het cruciale kenmerk is van AD. Tevens zijn er aanwijzingen dat verhoogde activiteit van de hersenen – en dus een verhoogde stofwisseling – beschermend werkt tegen neurodegeneratie. Deze hypothese staat ook wel bekend als "Use it or lose it" (Swaab, 1991). Therapeutische strategieën bij een neurodegeneratieve ziekte als AD zouden zich kunnen richten op stimulatie van het centraal zenuwstelsel om verder verminderde stofwisseling tegen te gaan en om mogelijk gedeactiveerde cellen weer aan te sturen en te reactiveren.

Een aantal observaties biedt steun voor de theorie dat stimulatie van het brein een positieve werking heeft. Ten eerste blijkt een hogere opleiding en een baan die een groter beroep doet op de hersenen een zekere bescherming te bieden tegen de uiting van symptomen van de AD. Ten tweede blijken cognitief stimulerende activiteiten (zoals regelmatig lezen, spelletjes doen en museumbezoek) de ontwikkeling van dementie tegen te gaan. Ten slotte blijkt dat blootstelling aan extra helder licht een positieve uitwerking heeft op rust-activiteitritme, cognitie en stemming van ouderen met- en zonder dementie.

Elektrische zenuwstimulatie bij AD

Een andere manier om de hersenen te stimuleren is het toedienen van elektrische prikkels op de huid door middel van Transcutane Elektrische Neuro Stimulatie (TENS). Perifere zenuwbanen geleiden de prikkels naar de hersenen waar deze inactieve hersencellen mogelijk weer reactiveren. Eind jaren negentig zijn in een serie placebogecontroleerde studies positieve effecten van deze vorm van zenuwstimulatie gevonden bij AD patiënten. Er bleek onder andere verbetering van cognitieve functies (zoals het geheugen), het gedrag en het rust-activiteitritme. Hoewel deze bevindingen bemoedigend zijn, moeten ze met voorzichtigheid geïnterpreteerd worden omdat de groepen deelnemers aan deze studies relatief klein waren: variërend van 6 tot 18.

Doel van het proefschrift

Het doel van het huidige proefschrift was om de effecten van elektrische zenuwstimulatie te onderzoeken in een groep AD patiënten die aanzienlijk groter is dan in de studies tot nu toe.

Bevindingen

Hoofdstuk 2 is een literatuuroverzicht van zestien studies die de effecten van elektrische zenuwstimulatie op niet-pijngebonden cognitief en gedragsmatig functioneren hebben onderzocht. Acht studies worden besproken die de effecten van elektrostimulatie onderzochten bij een beroerte, zes studies bij AD en twee studies bij coma tengevolge van traumatisch hersenletsel. De studies toonden verscheidene effecten van elektrostimulatie. Somatosensorisch functioneren, visuospatiële functies en houdingscontrole verbeterden na een beroerte, aspecten van het geheugen, gedrag en rust-activiteitritme verbeterden bij AD en bovendien bleken comapatiënten sneller te ontwaken uit hun coma. De effectiviteit van TENS wordt in dit hoofdstuk bediscussieerd in relatie tot de stimulatieparameters: duur, frequentie, pulsbreedte en intensiteit. Wij beargumenteren dat een verhoogde prikkeling, of arousal, ten grondslag ligt aan de positieve effecten van TENS bij de verschillende condities.

Hoofdstuk 3. De studies die sinds 1990 zijn uitgevoerd waarin TENS werd toegepast bij AD hadden onder andere tot doel twee hersenkernen te stimuleren: de nucleus raphe dorsalis en de locus coeruleus. Dit zou bereikt kunnen worden door het toedienen van

een combinatie van een lage en een hoge frequentie (respectievelijk 2Hz en 160 Hz), een pulsbreedte van 0.1 ms en een intensiteit die kleine motorische contracties laat zien. TENS werd in die studies toegediend gedurende 30 minuten per dag, 5 dagen per week, 6 weken lang. Om de studies goed met elkaar te vergelijken was ervoor gekozen om identieke stimulatieparameters te gebruiken. Dit geldt tevens voor de klinische studie die in het huidige proefschrift wordt beschreven. Het doel van hoofdstuk 3 is om vast te stellen of, in het licht van dierexperimentele studies *vanaf* 1991, de eerder gekozen stimulatieparameters wel optimaal zijn. Resultaten van dierexperimenteel onderzoek laten zien dat voor een optimale stimulatie van de bovengenoemde hersenkernen de pulsbreedte waarschijnlijk meer dan 0.1 ms moet zijn.

Hoofdstuk 4 betreft een gerandomiseerd, placebogecontroleerd effectonderzoek, waarin de effecten van perifere elektrische zenuwstimulatie op cognitie en gedrag worden onderzocht bij een groep AD patiënten, die ten minste drie keer zo groot is als de eerdere studies op dit gebied. De deelnemers woonden thuis en de 30 minuten durende behandeling werd zes weken lang door de partner, of een ander familielid, thuis toegepast. De resultaten toonden geen effecten bij de 32 patiënten die behandeld werden met elektrische zenuwstimulatie, wanneer deze werden vergeleken met de 30 patiënten die een placebobehandeling hadden gekregen. Het is noemenswaardig dat de behandeling als positief werd geëvalueerd door het overgrote deel van de deelnemers en dat het uitvoeren van de dagelijkse behandeling geen extra belasting veroorzaakte.

In **hoofdstuk 5** worden de resultaten van perifere elektrische zenuwstimulatie op het rust-activiteitritme gepresenteerd verkregen uit dezelfde studie als beschreven in hoofdstuk 4. Effecten op het rust-activiteitritme werden bepaald door gebruik te maken van actigrafie (bewegingsmeting door middel van een polsbandje). Bij analyse van de gehele groep bleken geen significante resultaten van elektrische zenuwstimulatie. Echter, uit verdere analyses bleek dat er wel significante resultaten waren bij patiënten die niet tegelijk een acetylcholinesteraseremmer gebruikten (een klasse medicijnen die voorgeschreven wordt voor symptomatische behandeling van AD).

Hoofdstuk 6. Executieve functies zijn vaak aangedaan in een vroeg stadium van de AD. Omdat EFs een cruciale rol spelen bij zelfverzorging, communicatie en financiële vaardigheden en omdat stoornissen in executieve functies in eerdere onderzoeken geassocieerd bleken met meer neuropsychiatrische problematiek, is evaluatie van executieve functies bij AD patiënten essentieel. In de laatste decennia is er een groeiende interesse in gecomputeriseerde tests voor het meten van cognitieve functies, maar slechts weinig studies onderzochten de toepassing van gecomputeriseerde tests om executieve functies te meten bij AD patiënten. Het doel van het huidige hoofdstuk was om een aantal executieve functies (planning, inhibitie, werkgeheugen en aandacht) bij

AD patiënten in kaart te brengen gebruik makend van gecomputeriseerde tests. Zestien AD patiënten en zeventien gezonde ouderen werkten mee met deze studie. De resultaten lieten zien dat de AD patiënten significant slechter scoorden op de planningstaak en er bleek een statistische trend voor een groepsverschil op de aandachtstaak. De verschillen in werkgeheugen en inhibitie bleken in de verwachte richting, echter niet significant. Hoewel replicatie van deze bevindingen in een grotere groep nodig is, laat de huidige studie zien dat een batterij gecomputeriseerde tests voor executieve functies gebruikt kan worden bij AD patiënten en gezonde ouderen en dat deze batterij gedeeltelijk onderscheid kan maken tussen de groepen.

Conclusies

Het is van belang te erkennen dat op grond van de resultaten van dit proefschrift geen eenvoudige algemene conclusie getrokken kan worden zoals: “perifere zenuwstimulatie is wel (of niet) een effectieve symptomatische behandeling voor AD”. Gezien de complexe aard van de ziekte en de beperkingen van de huidige studie zou het aanmatigend zijn om te veronderstellen dat een dergelijk algemene conclusie nu getrokken kan worden. Vooralsnog kunnen de volgende meer bescheiden conclusies worden geformuleerd:

1. Het overgrote deel van de patiënten en hun partners, of andere familieleden, rapporteerden dat zij de behandeling als positief hebben ervaren. Dit toont aan dat een actieve begeleidende rol van de partner, of een ander persoon uit de directe omgeving van de patiënt, mogelijk is.
2. In de studies die in hoofdstuk 4 en 5 worden beschreven vonden wij geen significante resultaten van elektrische zenuwstimulatie op de maten van cognitie, gedrag en rust-activiteitritme. De hypothese dat deze vorm van behandeling effectief is bij AD wordt door onze bevindingen niet ondersteund.
3. Kenmerken van de onderzochte patiëntengroep (niveau van cognitief functioneren en leeftijd waarop de ziekte zich openbaarde) verschillen enigszins tussen de huidige studie en de eerdere studies. Dit zou kunnen betekenen dat de theorie die stelt dat stimulatie van het centrale zenuwstelsel metabolisme verhoogt en inactieve hersencellen reactiveert, niet geldt voor patiënten in een verder gevorderd stadium en/of in het geval dat de ziekte zich vroeg in het leven manifesteert. Kortom, heterogeniteit van de onderzochte groep kan mogelijk positieve effecten van de behandeling hebben versluierd.
4. Wij vonden wel effecten van elektrische zenuwstimulatie op het rust-activiteitritme die naar significantie neigen, evenals significante resultaten bij een groep patiënten die niet tegelijk een acetylcholinesteraseremmer gebruikte.

Op basis van deze conclusies is het duidelijk dat meer onderzoek nodig is voordat robuuste conclusies over de algemene effectiviteit, of ineffectiviteit, van perifere elektrische zenuwstimulatie bij AD getrokken kunnen worden. Drie aanbevelingen voor toekomstig onderzoek zijn van bijzonder belang:

i. Grotere en meer homogene subgroepen deelnemers dienen te worden onderzocht. Op deze mannier kan het probleem van heterogeniteit van de patiëntengroepen beter worden ondervangen.
ii. Verfijnde stimulatieparameters, zoals langere pulsbreedte en een langere duur van de behandeling, moeten worden toegepast. Dit zal meer inzicht geven in de effecten van een behandeling met elektrische zenuwstimulatie.
iii. Geavanceerde onderzoeksmethoden, zoals beeldvormende technieken en gecomputeriseerde neuropsychologische tests, moeten worden gebruikt omdat verfijnde diagnostiek de sensitiviteit voor behandeleffecten verbetert.

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