

Electrical treatment of reduced consciousness: Experience with coma and Alzheimer's disease

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The right median nerve can be stimulated electrically to help arouse the central nervous system for persons with reduced levels of consciousness. The mechanisms of central action include increased cerebral blood flow and raised levels of dopamine. There is 11 years of experience in the USA of using nerve stimulation for acute coma after traumatic brain injury. There is a much longer period of experience by neurosurgeons in Japan with implanted electrodes on the cervical spinal cord for persons in the persistent vegetative state (PVS). But the use of right median nerve electrical stimulation (RMNS) for patients in the *subacute* and *chronic* phases of coma is relatively new. Surface electrical stimulation to treat anoxic brain injury as well as traumatic brain injury is evolving.

Novel applications of electrical stimulation in Amsterdam have produced cognitive behavioural effects in persons with early and mid-stage Alzheimer's disease employing transcutaneous electrical nerve stimulation (TENS). Improvements in short-term memory and speech fluency have also been noted.

Regardless of the aetiology of the coma or reduced level of awareness, electrical stimulation may serve as a catalyst to enhance central nervous system functions. It remains for the standard treatments and modalities to retrain the injured brain emerging from reduced levels of consciousness.

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INTRODUCTION

The right median nerve is a peripheral portal to the central nervous system. The sensory representation of the hand in the cortex is disproportionately large compared to other parts of the body. In the brain stem the ascending reticular activating system (ARAS) maintains the state of wakefulness. The spinoreticular component of the median nerve pathway synapses with neurons of the ARAS (Parent, 1996). Improvement of level of consciousness, whether in persons in acute coma, or those in a chronic vegetative or minimally conscious state, is driven by the electrically induced elevation of dopamine and norepinephrine (Hayashi, 1997; Moriya et al., 2000). Increase in cerebral blood flow, which is measurable shortly after starting the median nerve stimulation (MNS), is another important factor in neurostimulation for re-awakening (Liu et al., 2003).

The right median nerve was chosen as a portal to stimulate the brain stem and cerebrum because increased awareness and a better pattern of speech and abilities to calculate have been observed after right median nerve electrical stimulation (RMNS) (Cooper & Cooper, 2003; Cooper, Jane, Alves, & Cooper, 1999). In the majority of individuals, whether right handed or left handed, Broca's motor/speech planning area is in the left frontotemporal region. Broca's area has been shown to become more active in positron emission tomography (PET) when a subject moves his/her hand, or even contemplates speaking or moving the hand (Montgomery, 1989). This process is also artificially driven by RMNS (Cooper & Cooper, 2003; Spiegel et al., 1999).

EXPERIENCE WITH MEDIAN NERVE ELECTRICAL STIMULATION IN THE USA

Implantation of lower extremity nerve electrodes for treatment of spinal cord injury began in 1972 at the University of Virginia (Cooper, Bunch, & Campa, 1973). In the late 1980s, individuals with quadriplegia triggered their paralysed forearm and hand muscles through voice-activated computerised electrical stimulation (Gersh, 1992). This technique resulted in voluntary hand opening and closing at the Department of Biomedical Engineering at Duke University in Durham, North Carolina. Significant improvement was noted in distal motor abilities in direct response to electrical stimulation (Cooper, Han, & McElhaney, 1988). Proximal voluntary muscle strength in the stimulated arm also improved. But an unexpected result was a crossover effect causing improvement in the strength of the proximal muscles of the unstimulated arm. This observation about intra-cerebral transfer led to the development of median nerve electrical stimulation for coma arousal (Cooper et al., 1999).

Almost two decades ago at Caswell Center in Kinston, North Carolina, a non-ambulatory adult male received surface electrical stimulation to his right

forearm for reducing flexor muscle spasticity. The electrical stimulation was performed daily for a period of weeks. Progressive improvements in mental awareness and non-verbal interaction were observed on serial videotapes. There was better postural control of the head and trunk. This unexpected finding of generalised bodily motor improvement after right forearm electrical stimulation for a period of weeks, plus the crossover effect in the quadriplegic population with motor improvement in the non-stimulated upper extremity, led to the postulation that electrical stimulation of the right median nerve causes central nervous system arousal. This theory generated the right median nerve coma stimulation projects at East Carolina University and the University of Virginia in the early 1990s.

Observations have been made in the USA and in Japan in projects for patients with acute and long-term coma states. Progressive improvements that are somewhat predictable regarding eye co-ordination followed by facial, peripheral motor and speech function after several weeks of electrical stimulation have been seen in studies in the USA (Cooper, Jane, Alves, & Cooper, 1999) and Japan (Moriya et al., 1999).

MATERIALS AND METHODS

Multiple MNS studies have been done in the USA at the University of Virginia (Cooper et al., 1999; Peri et al., 2001) and East Carolina University (Cooper & Cooper, 2003). Similar studies have been initiated by neurosurgeons in Japan (Yokoyama, Kamei, & Kanno, 1996) and Taiwan (Liu et al., 2003). Two models of portable battery powered electrical neuromuscular simulators have been utilised (Respond Select and Focus, manufactured by the Empi Corporation). Similar electrical parameters have been standardised for the various studies. These electrical devices provided trains of asymmetric biphasic pulses at an amplitude of 15–20 milliamps with a pulse width of 300 microseconds at 40 Hz for 20 sec/min. The electrical treatment was delivered for 8–12 hours daily with a pair of lubricated one-inch square rubber electrodes placed on the skin over the median nerve. The location was on the palmar side of the right wrist in almost all cases. The number of weeks, or months, of electrical stimulation corresponded directly with the length of time since brain injury to the startup of the electrical treatment.

In acute trauma patients with severe brain injuries producing coma, the electrical stimulation was usually started less than one month post-injury, often in the first week. Glasgow Coma Scales (GCS) scores were 4–8, usually 4–5. In this group of acute patients, usually 2–3 weeks of electrical treatment would be needed. For traumatic brain injury (TBI) coma patients in which the electrical stimulation was started more than one month post-injury, stimulation duration varied widely. Usually a period of several weeks would be needed.

The newer experience of using RMNS in the treatment of patients in the persistent vegetative state or minimally conscious state, shows that longer periods of electrical stimulation measured in months or years would be needed for these more difficult cases.

For children and small adults, a setting of up to 15 milliamps is recommended. Electrical stimulation as high as 20 milliamps has been used in adults in deep coma. This level of stimulation is not usually tolerated by conscious or semi-conscious patients due to the strong tingling and the muscular contraction produced in the right hand. The RMNS is approximately 1.5 times the motor threshold. It produces right thenar apposition and flexion plus flexion of the index and middle fingers. Effects on vital signs are mild. Intracranial pressures usually remain stable. There have been no major complications induced by the peripheral electrical stimulation (Cooper & Kanno, in press).

RESULTS OF ELECTRICAL TREATMENT

Acute stage of TBI coma

In the 1990s, 38 comatose patients with severe closed head injury received right median nerve electrical (or sham) stimulation in a series of pilot studies at the University of Virginia in Charlottesville, Virginia (Cooper et al., 1999; Peri et al., 2001) and the East Carolina University in Greenville, North Carolina (Cooper et al., 1999). Similar RMNS protocols were used at both university medical centres.

There were two pilot studies at the University of Virginia (1994–1995 and 1998–1999). In both studies comatose trauma patients were randomly assigned into electrical treatment or sham treatment groups. The neurobehavioural raters were blinded to the treatment conditions. There were six patients in the first study and 10 patients in the second study. In the earlier study the electrical treatment group had a shorter time in the intensive care unit (Cooper et al., 1999). In the second study the electrically treated comatose patients had a shorter time of endotracheal intubation (Peri et al., 2001).

Coma patients with GCS scores near 8 on the day of injury can be expected to make very functional recoveries with standard treatment. In those cases where the GCS score is 4–5 with decerebrate/decorticate posturing, few can be expected to make good recoveries (Marshall & Marshall, 1996). But with median nerve electrical stimulation, if the patient survives the initial brain injury and other multi-system injuries, the time for awakening from coma is shorter in the electrically stimulated group than in the non-stimulated group. Gradual progress to a functional level is almost twice as frequent in the electrically stimulated group as in the non-stimulated group (Cooper & Kanno, in press).

There were 22 comatose patients treated with electrical stimulation at the medical centre at East Carolina University from 1993 to 1999. Twelve of the

TABLE 1
Twelve GCS-4 Survivor patients treated with early RMNS at ECU

<i>Initials</i>	<i>Age</i>	<i>Sex</i>	<i>Injury year</i>	<i>Glasgow Outcome Scale at ≤ 1 year*</i>
1. C	16	F	1993	Good recovery
2. P	21	M	1994	Severe disability
3. M	22	M	1994	Severe disability
4. C	16	F	1994	Moderate disability
5. A	15	F	1995	Good recovery
6. A	17	F	1995	Good recovery
7. M	26	F	1996	Moderate disability
8. K	19	F	1996	Good recovery
9. K	7	M	1997	Severe disability
10. R	14	M	1997	Severe disability
11. D	21	M	1997	Severe disability
12. E	15	F	1999	Moderate disability

*Cooper and Kanno, in press.

patients were in the Glasgow Coma Scale 4 category. They exhibited decerebrate posturing. These patients were in deep coma for more than a week. It is known that GCS 4 patients have a very poor prognosis (Cooper & Kanno, in press, Marshall & Marshall, 1996).

Therefore in the 12 young deeply comatose patients treated with early RMNS, almost 60% made a satisfactory recovery by one year post-injury (see Table 1).

SELECTED AMERICAN CASES

Two examples of adolescents with very severe traumatic brain injury with diffuse injury and no large haematomas are presented. In both cases, functional neurological survival was not expected.

C, a 16-year-old female, was involved in a motor vehicle accident and sustained a severe closed head injury in 1994. She suffered a basilar skull fracture, cerebrospinal fluid otorrhoea, left facial fracture, and left pelvic fracture. Computerised tomography (CT) scan revealed a left internal capsule contusion, right cerebellar subarachnoid haemorrhage, and blood in the fourth ventricle. Decerebrate posturing was observed and she received a GCS score of 4. She was briefly given electrical stimulation to the right median nerve but intracranial pressures continued to rise. With her extremely poor prognosis, she was expected to die. C was extubated, less than two weeks post-injury. She breathed spontaneously and electrical stimulation was resumed to the right median nerve. Within one week of restarting the electrical neuro-stimulation, she exhibited semi-purposeful movements of her right arm and leg and scored 7 on the GCS.

After a total of two weeks of stimulation, she was out of coma. One month after the injury, C followed simple commands. At two months post-injury C could walk with assistance and could read aloud. Two years later, C talked and walked well. She resumed dancing and driving and graduated from college. For a period of four years, C has been working as a recreation director in a nursing home and most recently at a retirement home (Cooper & Cooper, 2003).

In 2000, a 12-year-old boy, K suffered severe multi-system injuries. A van ran over his body and rested on his head producing severe brain trauma, intra-abdominal injury and multiple extremity fractures plus a compound fracture of the pelvis. On his initial CT scan there was a left frontal contusion, a small amount of subarachnoid haemorrhage in the interpeduncular cistern, and a non-depressed skull fracture of the left parietal bone. There was also a fracture of the left temporal bone. On the follow-up scan two days later, there were several contusions (right frontal and left temporal), increased cerebral oedema with marked effacement of the cortical sulci, and intraventricular haemorrhage. The scan one week post-injury demonstrated diffuse brain swelling and multiple haemorrhagic shear injuries. Haemorrhagic contusions of the left frontal lobe extending into the temporal lobe worsened the prognosis for the return of verbal function. K underwent several abdominal and orthopaedic operations early in his complex hospital course. He remained comatose with elevated intracranial pressures (over 70 mmHg) in spite of two courses of barbiturate therapy. His pupils remained unequal. K's survival was doubtful (Cooper & Cooper, 2003).

Surface electrical stimulation to the left median nerve (his right forearm was in a cast) in the 15 milliamps range was commenced two weeks post-injury. After two weeks of eight hours of daily median nerve stimulation, K began to emerge from his coma. He progressively improved and regained his ability to speak. He could use both of his hands in spite of a right hemiparesis which persisted. Two months post-injury, he was transferred to a rehabilitation centre. Electrical stimulation was resumed, but was switched to the right median nerve to help reduce the right hemiparesis. He continued to improve and was discharged home six weeks later. In schoolwork, he made good grades. Less than three years after the severe TBI system and multi-system injuries, K maintained a "B" average in junior high school. Additionally, he was able to resume some athletic activities, including swimming and ball sports (Cooper & Cooper, in press).

Subacute stage of TBI

J demonstrates the advantage of beginning median nerve electrical stimulation in the first month of coma. J was a 16-year-old girl from southern California whose car was T-boned (side impact) by a truck in 2002. At the scene she had agonal respiration and was unresponsive at GCS 3. In the emergency room at a large community hospital her post-intubation coma score was GCS 4 on the

day of the injury. The CT scan showed a large right putaminal haemorrhage and a small amount of blood in the mesencephalon. There was extensive shear injury in left fronto-temporal lobe and corpus callosum. Elevated intracranial pressure (ICP) was treated with mannitol and hyperventilation.

Operations included exploratory laparotomy, splenectomy, and ventriculostomy with monitoring of intracranial pressure, and later tracheostomy and feeding tube insertion. Follow-up brain CT scans on a daily basis showed progressive cerebral oedema and increasing haemorrhage. Two days after the injury there was a 7 mm midline shift. The small haemorrhage in the central mesencephalon was still present. By a week and a half post-injury the swelling and haemorrhage stabilised and gradually decreased. A week later cortical atrophy was observed.

J remained in coma and was decerebrate/decorticate at four weeks post-injury. Bilateral median nerve electrical stimulation (six hours per day for each wrist median nerve stimulation site) was started at five weeks post-injury. She remained in the intensive care unit for her entire two-month hospitalisation. Two weeks after the electrical stimulation was started, she remained left hemiplegic, but could follow commands. After three weeks of electrical treatment she could write, but could not speak. She was transferred to a rehabilitation unit eight weeks post-injury.

Next, J was able to speak in short sentences and communicate by writing. Six weeks post-injury she was able to walk with maximum support but remained left hemiplegic. Three months post-injury she had voluntary control of her left leg when walking. After three months of rehabilitation, she was transferred to a residential rehabilitation facility for an additional three months. She was discharged home to the care of her family in early 2003, eight and a half months post brain injury. She continued to receive outpatient therapies.

Later in the spring of 2003 she graduated from high school on schedule with her class, less than one year post-injury. In the fall of 2003 she was in college taking three courses, achieving "B" grades. She used a manual wheelchair but was able to walk with help and a brace on her left leg. Her left hand remained nonfunctional, flexed at the wrist. She regained good speech, conversing in normal sentences, although her vocal tone was somewhat flat with mild dysarthria (Cooper & Cooper, in press).

Chronic stage of brain injury

Kanno and Okuma, from the Department of Neurosurgery, Fujita Health University, Japan, have reported on the subacute and chronic stages of coma resulting from traumatic and vascular causes (Okuma et al., 2001). The Japanese neurosurgeons were concerned that during the acute and subacute stages that brain atrophy was in progress after the initial brain injury, whether from trauma or anoxic injury. They suggested that even if the aggressive

rehabilitation is started at the chronic stage it may be too late to achieve a recovery of brain function because of brain atrophy. Kanno stressed the importance of establishing a new treatment system for patients in the subacute stage (Kanno, 2000; Yamamoto et al., 1997; Yokoyama et al., 1996). Kanno and Okuma discussed median nerve stimulation (MNS) and dorsal column stimulation (DCS) for persistent vegetative state (PVS) produced by trauma, anoxia or other causes. It was their hope that electrical stimulation might stop the progress of the atrophy. (Kanno, 2000; Kanno, Kamei, Yokoyama, 1992).

Kanno and associates have described DCS in Japan. For almost two decades, electrodes have been implanted on the cervical spinal cord of patients in the PVS. All cases were in PVS and had been unconscious for a period of three months or more. In patients who had been in a vegetative state for over a year, improvement was still possible.

Numerous articles in Japan have referred to these patients. There has been a consistent observation of 42% showing clinical improvements (Kanno, Kamei, Yokoyama, 1989). Usually the improvement was in terms of interaction of the patient with the family, the ability to follow simple commands and self-feeding. But PVS adults who were electrically treated with the spinal cord stimulation, did not, in general, regain the ability to walk or talk. In half of the cases the regional blood flow improved. In general, the patients in PVS who showed a positive response to the DCS treatment were younger victims, less than age 40. They were in a vegetative state because of head trauma and not from anoxic injury. The prognosis was better when there was a relatively shorter period of coma prior to therapy. Their CT scans did not show severe damage to the thalamus and did not reveal marked cerebral atrophy. Of the patients who improved, the aetiology of the initial coma was trauma in 75% of the cases. Almost 90% of the improved patients were under age 30. Those over age 50 did not show improvement with the DCS therapy. Kanno observed that cases due to vascular or hypoxic injury rarely improved with the electrical treatment (Kanno et al., 1992).

In northern California, a current case (2004) with anoxic brain injury from cardiac arrest resulting in the persistent vegetative state lasting six months, has commenced daily RMNS. There have been some positive responses noted within the first three months of electrical treatment: better head and trunk posture, tracking with definite eye contact, swallowing (able to take yogurt), and, recently, phonation. K, an adult female, will be the subject of a future article (Davey, 2004).

The relationship between rehabilitation therapy and functional outcomes

In a large multi-centre study in the USA of 491 patients who were enrolled at three major medical centres, brain injury patients who had received acute care

and inpatient rehabilitation were analysed regarding outcomes relative to the intensity of rehabilitation therapies. Total therapy hours per day, usually involving speech, occupational, psychological and physical therapy, were calculated. The Functional Independence Measure (FIM) scores were analysed at admission and discharge from the rehabilitation hospitals. Regarding the cognitive outcome, the authors noted, "Examination of cognitive outcomes indicates that therapeutic intensity did not contribute to gains in cognitive ability" (Cifu et al., 2003). Longer length of stay and rehabilitation significantly predicted better motor potential achievement. A better motor score was achieved by greater therapy intensity. The authors concluded, "A multitude of additional treatment factors may be of benefit to outcomes, and additional research is needed to identify those factors. Rehabilitation outcomes research should help guide the development of evidence-based guidelines for rehabilitation" (Cifu et al., 2003).

OBSERVATIONS ABOUT RESPONSES TO RMNS

In the first few days of treatment, mirror movements of the unstimulated left hand may occur. This dynamic crossover effect heralds reactivation of the cerebral hemispheres through the corpus callosum in the electrically stimulated comatose patient. Usually the first simple command that the patient will respond to after one or two weeks of RMNS is a sluggish apposition of the right thumb and index finger. This purposeful right hand response while the brain injured patient still appears to be semi-comatose, demonstrates that the five million electrical pulses delivered to the nervous system in the first 10 days of treatment have been copied and stored in the hard drive of the brain (Cooper & Kanno, in press).

There is a predictable sequence of events that indicates positive response to the median nerve stimulation techniques, both for acute coma patients and long-term patients in the vegetative or minimally conscious state. There should be involuntary contraction of the median innervated muscles of the hand receiving the electrical stimulation. This would include abduction/flexion of the thumb and flexion of mainly the index and middle fingers and slight flexion of the wrist. Depending on the depth of the coma there may be some involuntary or semi-voluntary withdrawal of the whole upper extremity, plus other bodily movements.

The early positive changes observed clinically in electrically stimulated coma and PVS patients would be increased eye movements, followed shortly by some head movements to either side. As the depth of coma/vegetative state lightens, head control and trunk control should improve. Generalised improved skin circulation and increased salivation usually are noted in the first week or two of treatment. Mirror movements may be noted in the unstimulated

contralateral hand with slight contractions of that thumb or other hand muscles.

After some basic muscular functions have resumed, there may be changes in facial expression indicating discomfort or attempts to smile. This is followed shortly by groans or phonation. Semi-purposeful hand movements would usually be the next stage. Finally the full awakening to a conscious level may occur. After that there would be considerable variability in the return of cognitive, speech and ambulatory functions. Usually the reawakened coma/PVS patient would be able to eat, but not always able to feed him or herself. In cases that achieve higher neurological function, the ability to talk and walk would be expected to follow.

In previous studies, it was noted that the slope of the timeline of partial neurological recovery is inversely related to the interval of time from the injury to the startup of RMNS. The quality of the functional outcome is influenced by the severity of neurotrauma as diagnosed on early CT scans (Blackman et al., 2003; Eisenberg et al., 1990; Kampfl et al., 1998; Kido et al., 1992; Marshall et al., 1991; Toutant et al., 1984). In severe neurotrauma where the prognosis for brain survival in a functional state is approaching zero, any novel therapeutic intervention that produces better than expected results can be judged by the unexpected change in recovery slope. Professor John Jane (Chairman, Department of Neurological Surgery, University of Virginia), with a long time wealth of neurotrauma research, summarised the challenge of exploring median nerve stimulation: "Very few things do work in this situation and if your techniques make any difference whatsoever, I think it would be well worth it." (J. Jane, 1995, personal communication).

The coma cases presented anecdotally in this paper are examples of electrical treatment where medical expectations for a functional survival had vanished. The improvements noted are doubly validated by the unexpected change in clinical course and the similarity of observations reported from widely separated locations in the USA and Asia. Rigorous proof of the theory that peripheral nerve stimulation influences the function of the injured brain demands larger series of treated/sham treatment comatose subjects. The purpose of this overview is to stimulate such worldwide research.

TENS IN ALZHEIMER'S DISEASE AND ENCEPHALITIS

In a number of studies, transcutaneous electrical nerve stimulation (TENS) was applied to patients in a relatively early stage of Alzheimer's disease (AD) (Scherder, Bouma, & Steen, 1992; 1995; 1998; Scherder & Bouma, 1999; van Dijk, Scherder, Scheltens, & Sergeant, 2002). In those studies, the electric current was applied through two electrodes attached to the trapezius muscle, one electrode on each side of the spinal column, at the level of the first thoracic

vertebra. The 30-minutes-a-day application took place during six weeks, followed by a treatment-free period of six weeks. In all studies a control group was included; participants of this group received sham stimulation with the same treatment frequency and treatment time, during the same treatment period. In one recent study, AD patients received RMNS with exactly the same stimulation parameters as described above (Scherder & Van Someren, 2004).

A blinded investigator who did not know whether the patient belonged to the experimental group or the control group, administered a comprehensive neuropsychological test battery, including tests for various memory processes and verbal fluency. In addition, the nursing staff was asked to fill in observation scales and the rest-activity rhythm was measured by means of actigraphy.

Overall, the results indicate that patients who received real TENS treatment showed a statistically significant improvement with respect to nonverbal short-term memory, verbal and nonverbal long-term (recognition) memory, and verbal fluency. Affective behaviour showed *clinically* relevant effects, i.e., patients who were treated with TENS became less depressed, less anxious, and less irritated. Of note is that in two studies the rest-activity rhythm of AD patients, measured by actigraphy, improved. This improvement was reflected in among other things a decrease in nightly restlessness (Scherder, Van Someren, & Swaab, 1999b; Van Someren, Scherder, & Swaab, 1998). Based on data from animal experimental studies (Scherder, Luijpen, & Van Dijk, 2003) the stimulation-parameters frequency, intensity and pulse width were selected in such a way that an optimal activation of the locus coeruleus (LC) and dorsal raphe nucleus (DRN)—brain stem areas which project to the hippocampus (Ezrokhi, Zosimovskii, Korshunov, & Markevich, 1999) and the hypothalamic suprachiasmatic nucleus (SCN) (Legoratti-Sanchez, Guevara-Guzman, & Solano-Flores, 1989)—could be obtained. The biological clock, important for our 24-hour circadian rhythm, is situated in the hypothalamic SCN (Swaab, 2004). Please see next section for more details about possible underlying mechanisms.

The positive effects of TENS in AD patients should be considered with caution. In the first place, the studies were single blind, implying that the person who performed the treatment knew which patients belonged to the experimental group and which patients to the control group; this might have created a bias. Second, the number of participating patients was relatively small in each study, i.e., 8 to 10 patients in each group. In a recent study, a much larger number of AD patients participated (approximately 30 patients in each group) and only a treatment effect on the rest-activity rhythm was observed for those patients who did not take cholinesterase inhibitors (unpublished results). This finding might imply that previous results are based on chance instead of real TENS effects. On the other hand, the group of AD patients in this latter study was quite heterogeneous with respect to the stage of the disease, ranging from relatively early to advanced, and the onset of the disease, much earlier in the

latter study compared to the previous studies. Severity and early onset of the disease are two conditions that might reduce treatment efficacy (Cedazo-Minguez & Cowburn, 2001; Ho et al., 2002; Le Bars et al., 2002).

Particularly, the finding that in AD too much activity, for example, during the night, could be inhibited by TENS, was the main reason to apply TENS to two children who showed severe behavioural disinhibition after suffering from herpes simplex encephalitis (HSE). In a 9-year-old girl (Scherder, 1996) and an 11-year-old boy (Scherder et al., 2001), overall affective behaviour as well as nightly restlessness and over-activity by day decreased significantly with the use of TENS. These findings might be less surprising considering that HSE is strongly related to damage of the hippocampus and mamillary complex of the hypothalamus (Kapur et al., 1994), structures that are also affected in AD (Scheltens et al., 1992; Swaab, 2004).

Possible mechanisms underlying the effects of RMNS/TENS

The effects of RMNS in comatose patients and AD patients and the effects of peripheral electrical stimulation applied to the trapezius muscle in AD patients might have two similar mechanisms in which the basal forebrain nucleus basalis of Meynert (NBM) plays a crucial role. The NBM is the origin of the cortical cholinergic system and is important for the level of cortical activity (Dringenberg & Olmstead, 2003) and cognitive processes such as memory (Shinotoh et al., 2003).

The first mechanism concerns the ARAS. The ARAS originates in the brain stem reticular formation, more specifically the LC and the DRN, origins of the noradrenergic and serotonergic neurotransmitter systems, respectively (Kayama & Koyama, 1998). With respect to arousal, the brain stem reticular formation is functionally related to the NBM/cholinergic system (Sauvage & Steckler, 2001). Another area directly connected with the NBM and involved in arousal and attention (Critchley et al., 2003), is the anterior cingulate cortex (ACC). Interestingly, a recent functional magnetic resonance imaging (fMRI) study showed that the ACC is activated by RMNS applied with a painful intensity (Kwan, Crawley, Mikulis, & Davis, 2000). In the studies with comatose patients and patients with AD, the intensity of the stimulation was not nociceptive but high enough to provoke muscular twitches; fMRI studies are needed to examine whether this level of intensity is sufficient to stimulate areas such as the ACC.

A second mechanism that might underlie the effects of peripheral electrical nerve stimulation in coma and AD is related to neurotrophic factors, among which are nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). Neurotrophic factors play an important role in neuroplasticity by, among other things, transforming silent synapses into functional ones (Klintsova &

Greenough, 1999). AD is characterised by a reduction of NGF in the NBM whereas the level of NGF in the cerebral cortex is unchanged (Salehi & Swaab, 1999). Interestingly, it has been observed that by exposure to an enriched environment, cerebral NGF is retrogradely transported to the basal forebrain, enhancing its cholinergic activity (Salehi & Swaab 1999). With respect to coma, BDNF might enhance survival of neurons after a hypoglycaemic coma of a short duration (Kokaia, Othberg, Kokaia, & Lindvall, 1994). Interestingly, rats with a transient global ischaemia that were housed in an enriched environment showed increased BDNF levels (Gobbo & O'Mara, 2004). We argue that peripheral electrical stimulation could be considered as a type of enriched environment and could initiate a similar sequence of events (Luijpen et al., 2003).

The juxtaposition of neurological conditions of different aetiologies— young people with traumatic brain injury yielding the spectrum of coma, PVS and the minimally conscious state, next to the progressively plaqued and tangled elderly AD brains—at first does not seem logical. But the final events of cytotoxic concentrations of glutamate released by damaged neurons are reputed to be enemies of both sets of patients who exhibit decreased levels of consciousness (Clausen & Bullock, 2001; Cooper, 1996; Doraiswamy, 2003; Faden, 1996; Greenamyre et al., 1988; Hynd, Scott, & Dodd, 2004). Based on our clinical success with RMNS in some acute coma cases (albeit temporary in mid-stage Alzheimer's disease), we seek a physically effective treatment for the stabilisation of glutamate while increasing the dopamine levels to awaken the damaged brains. Encouraged by unexpected neuroprotective/glutamate results of median nerve stimulation in a new hypoxic rat brain study in Germany (Buitrago et al., 2004), we recommend that future projects explore the commonality of the two neurological maladies of TBI and AD. We hope that common patterns of electrical treatment may ameliorate similar physiological pathways that lead to neural death of the young and old.

CONCLUSION

Over the past two decades independent research projects have focused on electrical treatment of acute coma, persistent vegetative state, Alzheimer's disease and encephalitis. These investigations from the USA, Japan and Europe have yielded unifying theories of cerebral hypo-function that are amenable to novel treatments. Peripheral, spinal and direct brain stimulation improve long-term outcomes of individuals suffering from diffuse neuronal injury.

We present this series of experiences in acute, subacute and chronic coma along with data from Alzheimer's treatment to point out the efficacy of non-invasive peripheral electrical stimulation. The same methodology may be applied to multiple disabling conditions and diseases.

It is encouraging to observe positive effects through peripheral stimulation across three continents with hundreds of varied patients. Right median nerve electrical stimulation remains a simple and effective way to improve the long-term outcomes of patients affected by coma. The same treatment has a positive effect on patients with Alzheimer's disease.

Peripheral electrical stimulation is sufficient to cause clinical improvement. This suggests that neural plasticity is positively influenced by an electrical treatment via an external, non-invasive portal.

We believe that more widespread use of this technique and further investigations will prove beneficial. Improved behavioural and cognitive outcomes have been observed across a wide array of electrical stimulation techniques. Utilisation of inexpensive, safe, and non-invasive techniques such as peripheral electrical stimulation will prove invaluable in the coming years.

REFERENCES

- Blackman, J. A., Rice, S. A., Matsumoto, J. A., Conaway, M. R., Elgin, K. M., Patrick, P. D., Farrell, J., Allaire, J. H., & Willson, D. F. (2003). Brain imaging as a predictor of early functional outcome following traumatic brain injury in children, adolescents, and young adults. *Journal of Head Trauma Rehabilitation, 18*, 493–503.
- Buitrago, M., Luft, A., Thakor, N., Blue, M., & Hanley, D. (2004). Effects of somatosensory electrical stimulation on neuronal injury after global hypoxia-ischemia. *Experimental Brain Research, 158*, 336–344.
- Cedazo-Minguez, A., & Cowburn, R. F. (2001). Apolipoprotein E: A major piece in the Alzheimer's disease puzzle. *Journal of Cellular & Molecular Medicine, 5*, 254–266.
- Cifu, D., Kreutzer, J., Kolakowsky-Hayner, S., Marwitz, J., & Englander, J. (2003). The relationship between therapy intensity and rehabilitative outcomes after traumatic brain injury: A multicenter analysis. *Archives of Physical Medicine & Rehabilitation, 84*, 1441–1448.
- Clausen, T., & Bullock, T. (2001). Medical treatment and neuroprotection in traumatic brain injury. *Current Pharmaceutical Design, 7*, 1517–1532.
- Cooper, J. (1996). Actin is a PKC, anchoring protein: Role of this cytoskeletal signaling complex in actin organization, PKC, activation, and intracellular membrane trafficking. *Master's thesis*. East Carolina University Department of Biology, Greenville, NC, USA.
- Cooper, E., Bunch, W., & Campa, J. (1973). Effects of chronic human neuromuscular stimulation. *Surgical Forum, 24*, 477–479.
- Cooper, E., & Cooper, J. (2003). Electrical treatment of coma via the median nerve. *Acta Neurochirurgica Supplement, 87*, 7–10.
- Cooper, E., & Cooper, J. (in press). Electrical treatment of comatose teenagers via the median nerve.
- Cooper, E., Cooper, J., Alves, W., & Jane, J. (1996). Right median nerve electrical stimulation of comatose patients. *The Society for Treatment of Coma*, unpublished lecture.
- Cooper, E., Han, D., & McElhaney, J. (1988). A voice controlled computer system for restoring limited hand functions in quadriplegics. *Proceedings of the American Input Output Systems Applications Conference*, San Francisco, CA.
- Cooper, J., Jane, J., Alves, W., & Cooper, E. (1999). Right median nerve electrical stimulation to hasten awakening from coma. *Brain Injury, 13*, 261–267.
- Cooper, E., & Kanno, T. (in press). Electrical treatment of coma.

- Critchley, H. D., Mathias, C. J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B. K., Cipolotti, L., Shallice, T., & Dolan, R. J. (2003). Human cingulate cortex and autonomic control: Converging neuroimaging and clinical relevance. *Brain*, *126*, 2139–2152.
- Davey, M. (2004). personal communication and patient's website: <http://www.saratogahigh.org/shs/departments/staffpages/kabe/kathleenupdate.htm>
- Doraiswamy, M. (2003). Alzheimer's disease and the glutamate NMDA receptor. *Psychopharmacology Bulletin*, *37*, 41–49.
- Dringenberg, H. C., & Olmstead, M. C. (2003). Integrated contributions of basal forebrain and thalamus to neocortical activation elicited by pedunculopontine tegmental stimulation in urethane-anesthetized rats. *Neuroscience*, *119*, 839–853.
- Eisenberg, H., Gary, H., Aldrich, E., Saydjari, C., Turner, B., Foulkes, M., et al. (1990). Initial CT findings in 753 patients with severe head injury. NIH Traumatic Coma Data Bank Report. *Journal of Neurosurgery*, *73*, 688–698.
- Ezrokhi, V. L., Zosimovskii, V. A., Korshunov, V. A., & Markevich, V. A. (1999). Restoration of decaying long-term potentiation in the hippocampal formation by stimulation of neuromodulatory nuclei in freely moving rats. *Neuroscience*, *88*, 741–753.
- Faden, A. I. (1996). Pharmacological treatment of central nervous system trauma. *Pharmacology and Toxicology*, *78*, 12–17.
- Gersh, M. R. (1992). Neuromuscular electrical stimulation in rehabilitation. In S. L. Wolf (Ed.), *Electrotherapy in rehabilitation* (p. 260). Philadelphia, PA: Davis Co.
- Gobbo, O. L., & O'Mara, S. M. (2004). Impact of enriched-environment housing on brain-derived neurotrophic factor and on cognitive performance after a transient global ischemia. *Behavioural Brain Research*, *152*, 231–241.
- Greenamyre, J. T., Maragos, W. F., Albin, R. L., Penney, J. B., & Young, A. B. (1988). Glutamate transmission and toxicity in Alzheimer's disease. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *12*, 421–430.
- Hayashi, N. (1997). Prevention of hyperthermia after severe head trauma and stroke by combination therapy of cerebral hypothermia and activation of immune-dopaminergic nervous system. *Society for Treatment of Coma*, *6*, 133–147.
- Ho, G. J., Hansen, L. A., Alford, M. F., Foster, K., Salmon, D. P., Galasko, D. et al., (2002). Age at onset is associated with disease severity in Lewy body variant and Alzheimer's disease. *Neuroreport*, *13*, 1825–1828.
- Hynd, M. R., Scott, H. L., & Dodd, P. R. (2004). Glutamate-mediated excitotoxicity and neurodegeneration in Alzheimer's disease. *Neurochemistry International*, *45*, 583–595.
- Kampfl, A., Schmutzhard, E., Franz, G., Pfausier, B., Haring, H. P., Ulmer, H., Felber, S., Golaszewski, S., & Alchner, F. (1998). Prediction of recovery from post-traumatic vegetative state with cerebral magnetic-resonance imaging. *Lancet*, *351*, 1763–1767.
- Kanno, T. (1995). *Dorsal column stimulation for the persistent vegetative state*. University of Virginia neurosurgery lecture, unpublished.
- Kanno, T. (2000). Development of surgical neurorehabilitation. *Society for Treatment of Coma*, *9*, 23–24.
- Kanno, T., Kamei, Y., & Yokoyama, T. (1989). Effects of dorsal spinal cord stimulation (DCS) on reversibility of neuronal function—experience of treatment for vegetative states. *Pace*, *12*, 733–738.
- Kanno, T., Kamei, Y., & Yokoyama, T. (1992). Treating the vegetative state with dorsal column stimulation. *Society for Treatment of Coma*, *1*, 67–75.
- Kapur, N., Barker, S., Burrows, E. H., Ellison, D., Brice, J., Illis, L. S., Scholey, K., Colbourn, C., Wilson, B., & Loates, M. (1994). Herpes simplex encephalitis: Long term magnetic resonance imaging and neuropsychological profile. *Journal of Neurology, Neurosurgery & Psychiatry*, *57*, 1334–1342.
- Kayama, Y., & Koyama, Y. (1998). Brainstem neural mechanisms of sleep and wakefulness. *European Urology*, *33*, 12–15.

- Kido, D., Cox, C., Hamill, R., Rothenberg, B., & Woolf, P. (1992). Traumatic brain injuries: Predictive usefulness of CT. *Radiology*, *182*, 777–781.
- Klintonova, A. Y., & Greenough, W. T. (1999). Synaptic plasticity in cortical systems. *Current Opinions in Neurobiology*, *9*, 203–208.
- Kokaia, Z., Othberg, A., Kokaia, M., & Lindvall, O. (1994). BDNF makes cultured dentate granule cells more resistant to hypoglycaemic damage. *Neuroreport*, *5*, 1241–1244.
- Kwan, C. L., Crawley, A. P., Mikulis, D. J., & Davis, K. D. (2000). An fMRI study of the anterior cingulate cortex and surrounding medial wall activations evoked by noxious cutaneous heat and cold stimuli. *Pain*, *85*, 359–374.
- Le Bars, P. L., Velasco, F. M., Ferguson, J. M., Dessain, E. C., Kieser, M., & Hoerr, R. (2002). Influence of the severity of cognitive impairment on the effect of the Ginkgo biloba extract EGb 761 in Alzheimer's disease. *Neuropsychobiology*, *45*, 19–26.
- Legoratti-Sanchez, M. O., Guevara-Guzman, R., & Solano-Flores, L. P. (1989). Electrophysiological evidences of bidirectional communication between the locus coeruleus and the suprachiasmatic nucleus. *Brain Research Bulletin*, *23*, 283–288.
- Liu, J. T., Wang, C. H., Chou, I. C., Sun, S. S., Koa, C. H., & Cooper, E. (2003). Regaining consciousness for prolonged comatose patients with right median nerve stimulation. *Acta Neurochir Suppl*, *87*, 11–14.
- Luijpen, M. W., Scherder, E. J. A., Van Someren, E. J. W., Swaab, D. F., & Sergeant, J. A. (2003). Non-pharmacological interventions in cognitively impaired and demented patients—a comparison with cholinesterase inhibitors. *Reviews in the Neurosciences*, *14*, 343–368.
- Marshall, L., Marshall, S., Klauber, M., Eisenberg, H., & Jane, J. (1991). A new classification of head injury based on computerized tomography. *Journal of Neurosurgery*, *75*, S14–S20.
- Marshall, F., & Marshall, S. (1996). Outcome prediction in severe head injury. In R. Wilkins & S., Rengachary, (Eds.), *Neurosurgery* (pp. 2717–2722). New York: McGraw-Hill.
- Montgomery, G. (1989). The mind in motion. *Discover*, *10*, 58–68.
- Moriya, T., Hayashi, N., Sakurai, A., Utagawa, A., Kobayashi, Y., Yajima, K. et al. (2000). Usefulness of median nerve stimulation in patients with severe traumatic brain injury determined on the basis of changes in cerebrospinal fluid dopamine. *Society for Treatment of Coma*, *9*, 159–161.
- Moriya, T., Hayashi, N., Utagawa, A. et al. (1999). Median nerve stimulation method for severe brain damage, with its clinical improvement. *Society for Treatment of Coma*, *8*, 111–114.
- Okuma, I., Kaitou, T., Hayashi, J., Funahashi, M., & Kanno, T. (2001). Electrical stimulation therapy for prolonged consciousness disturbance. *Society for Treatment of Coma*, *10*, 67–71.
- Parent, A. (1996). Spinal cords: Fiber tracts; Medulla. In P. Coryell, L. Napor, & R. Adin (Eds.), *Carpenter's human neuroanatomy* (pp. 381–383, 435). Baltimore, MD: Williams & Wilkins.
- Peri, C., Shaffrey, M., Farace, E., Cooper, E., Cooper, J., & Jane, J. (2001). Pilot study of electrical stimulation on median nerve in comatose severe brain injured patients 3-months outcome. *Brain Injury*, *15*, 903–910.
- Salehi, A., & Swaab, D. F. (1999). Diminished neuronal metabolic activity in Alzheimer's disease. *Journal of Neural Transmission*, *106*, 955–986.
- Sauvage, M., & Steckler, T. (2001). Detection of corticotrophin-releasing hormone receptor 1 immunoreactivity in cholinergic, dopaminergic and noradrenergic neurons of the murine basal forebrain and brainstem nuclei—potential implication for arousal and attention. *Neuroscience*, *104*, 643–652.
- Scheltens, P. H., Leys, D., Barkhof, F., Huglo, D., Weinstein, H. C., Vermersch, P., Kuiper, M., Steinling, M., Wolters E. C. H., & Valk, J. (1992). Atrophy of medial temporal lobes on MRI in 'probable' Alzheimer's disease and normal ageing: Diagnostic value and neuropsychological correlates. *Journal of Neurology, Neurosurgery & Psychiatry*, *55*, 967–972.
- Scherder, E. J. A. (1996). Transcutaneous electrical nerve stimulation in severe viral encephalitis. A case study. *Children's Hospital Quarterly*, *8*(4), 187–191.

- Scherder, E. J. A., & Bouma, A. (1999). Effects of transcutaneous electrical nerve stimulation on memory and behaviour may be stage-dependent. *Biological Psychiatry*, *45*, 743–749.
- Scherder, E. J. A., Bouma, A., & Steen, L. (1992). Influence of transcutaneous electrical nerve stimulation on memory in patients with dementia of the Alzheimer type. *Journal of Clinical & Experimental Neuropsychology*, *14*, 951–960.
- Scherder, E. J. A., Bouma, A., & Steen, A. M. (1995). Effects of short-term transcutaneous electrical nerve stimulation on memory and affective behaviour in patients with probable Alzheimer's disease. *Behavioural Brain Research*, *67*, 211–219.
- Scherder, E. J. A., Bouma, A., & Steen, A. M. (1998). Effects of 'isolated' transcutaneous electrical nerve stimulation on memory and affective behaviour in patients with probable Alzheimer's disease. *Biological Psychiatry*, *43*, 417–424.
- Scherder, E. J. A., Luijpen, M. W., & van Dijk, K. R. A. (2003). Activation of the dorsal raphe nucleus and locus coeruleus by transcutaneous electrical nerve stimulation in Alzheimer's disease: A reconsideration of stimulation-parameters derived from animal studies. *Chinese Journal of Physiology*, *46*, 143–150.
- Scherder, E. J. A., Van Deursen, S., Van Manen, S. R., Ferenschild, K., Simis, R., & Vuijk, P. J. (2001). Effects of TENS and methylphenidate in tuberculous meningo-encephalitis. *Brain Injury*, *15*, 545–558.
- Scherder, E. J. A., & Van Someren, E. J. W. (2004). *Effects of right median nerve stimulation on memory in Alzheimer's disease. A randomized controlled intervention study*. Manuscript submitted for publication.
- Scherder, E. J. A., Van Someren, E. J. W., & Swaab, D. F. (1999). Transcutaneous electrical nerve stimulation (TENS) improves the rest-activity rhythm in midstage Alzheimer's disease. *Behavioural Brain Research*, *101*, 105–107.
- Shinotoh, H., Fukushi, K., Nagatsuka, S., Tanaka, N., Aotsuka, A., Ota, T., Namba, H., Tanada, S., & Irie, T. (2003). The amygdala and Alzheimer's disease: Positron emission tomography study of the cholinergic system. *Annals of the New York Academy of Sciences*, *985*, 411–419.
- Spiegel, J., Tintera, J., Gawehn, J., Stoeter, P., & Treede, R. (1999). Functional MRI of human primary somatosensory and motor cortex during median nerve stimulation. *Clinical Neurophysiology*, *110*, 47–52.
- Swaab, D. F. (2004). Neuropathology of the human hypothalamus and adjacent structures. Part 2. In M. J. Aminoss, S. Boller, & D. F. Swaab (Eds.), *Handbook of clinical neurology* (Vol. 80). Amsterdam: Elsevier Science.
- Toutant, S., Klauber, M., Marshall, L., Toole, B., Bowers, S., Seeling, J. et al. (1984). Absent or compressed basal cisterns on first CT scan: Ominous predictors of outcome in severe head injury. *Journal of Neurosurgery*, *61*, 691–694.
- van Dijk, K. R. A., Scherder, E. J. A., Scheltens, P., & Sergeant, J. A. (2002). Effects of transcutaneous electrical nerve stimulation (TENS) on non-pain related cognitive and behavioural functioning. *Reviews in the Neurosciences*, *13*, 257–270.
- Van Someren, E. J. W., Scherder, E. J., & Swaab, D. F. (1998). Transcutaneous electrical nerve stimulation (TENS) improves circadian rhythm disturbances in Alzheimer disease. *Alzheimer's Disease & Associated Disorders*, *12*, 114–118.
- Yamamoto, K., Sugita, S., Ishikawa, K., Morimitsu, H., Shimamoto, H., & Shigemori, M. (1997). A case of persistent vegetative state treated with median nerve stimulation. *Society for Treatment of Coma*, *6*, 117–121.
- Yokoyama, T., Kamei, Y., & Kanno, T. (1996). Right median nerve stimulation for comatose patients. *Society for Treatment of Coma*, *5*, 117–125.