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Case study

Effects of TENS and methylphenidate in tuberculous meningo-encephalitis

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Primary objective: Beneficial effects of transcutaneous electrical nerve stimulation (TENS) on cognition and behaviour were observed in a child with probable Herpes Simplex Encephalitis. Based on these positive findings, it was examined in the present case study whether a child who had been diagnosed to suffer from tuberculous meningitis would benefit from TENS. Furthermore, as aggression and over-active behaviour were also prominent clinical symptoms, the effects of methylphenidate were investigated.

Methods and Procedures: Neuropsychological tests were used to assess attention/concentration and visuospatial and visuoconstructive memory. Behaviour, including the level of activity during 24 hours, was assessed by one observation scale and actigraphy.

Experimental interventions: TENS and methylphenidate.

Main outcomes and results: TENS particularly improved overall affective behaviour. Methylphenidate appeared to have the opposite effect on cognition and hardly any effect on patient's behaviour.

Conclusions: TENS might improve the patient's behavioural functioning. Pros and cons for treatment effects are discussed.

Introduction

In a series of studies, patients with probable Alzheimer's disease (AD) were treated with Transcutaneous Electrical Nerve Stimulation (TENS) [1–6]. The results show that non-verbal short-term memory and non-verbal and verbal long-term (recognition) memory, as well as verbal fluency, improved by TENS. Moreover, stimulated AD patients showed an improvement in independent functioning, affective behaviour, and the sleep–wake rhythm. The rationale underlying these studies was that TENS could activate the septo-hippocampal region and the hypothalamus through direct spinoseptal and spinohypothalamic pathways [7–9] and, indirectly, through the locus coeruleus (LC) and nucleus raphe dorsalis (NRD) [7–13]. The septo-hippocampal region and the hypothalamus play a role in long-term (recognition) memory and affective behaviour, respectively [14–17] and are affected in AD [17–19]. The deterioration in the sleep–wake rhythm is associated with neuropathology in the hypothalamic nucleus suprachiasmaticus [17, 20]. In addition,

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the LC and NRD form part of the ascending reticular activating system (ARAS) [21] which terminates, among others, in the pre-frontal cortex [22]. The pre-frontal cortex plays an important role in response inhibition [23, 24], which might enhance 'executive functions' like attention and improve behavioural control [14, 25].

Interestingly, damage of the temporal lobe and limbic system primarily determines the clinical profile of Herpes Simplex Encephalitis (HSE) [26]. A strong association between a deterioration in the hippocampus and a decline in memory has been found in patients with HSE [27]. Another structure involved in HSE is the mamillary complex of the hypothalamus [27]. Considering the overlap in affected areas between AD and HSE and the effectiveness of TENS in AD, TENS was applied to a 9-year-old girl who, 2 years earlier, had been diagnosed to suffer from probable HSE [28]. The results of that study showed that TENS improved the patient's Verbal and Performance IQ and reduced her overactive and aggressive behaviour.

Compared to HSE, tuberculous meningitis (TBM) produces an even more generalized and severe neurological pattern, mostly related to hydrocephalus, followed by infarction in preferably the right basal ganglia and in the areas innervated often by the right middle cerebral artery [29]. More specifically, in several cases, CT demonstrated abnormalities in the right frontal lobe, right or bilateral temporal lobes and right or bilateral basal ganglia [30]. Considering the apparent similarities in affected areas between AD, HSE and TBM, and encouraged by the positive effects of TENS on cognition, independent functioning, overactive behaviour and the sleep–wake rhythm in AD and HSE, it was hypothesized in the present study that a 45 minute-a-day treatment with TENS could improve cognition and aggressive and overactive behaviour in a child who suffered from TBM 18 months earlier. Furthermore, as the patient's aggression and overactive behaviour were also prominent clinical symptoms, the effects of methylphenidate, a drug mainly prescribed to children with Attention-Deficit Hyperactivity Disorder (ADHD) [31] were examined in the present study.

Case history

In July 1996, an 11-year-old boy became ill, with fever, dizziness and headache, and, on suspect of meningitis, was hospitalized. After 12 days, the patient became increasingly confused, with an intermittent level of consciousness and dysarthria. On suspect of a viral encephalitis, acryclovir was administered. After the following 3 days, analysis of cerebrospinal fluid (CSF) appeared to be positive for TBM, and showed a high cell count, a low glucose and a high protein concentration. Chest radiograph showed a consolidation in the right lower lobe. Considering the presence of TBM, antituberculous therapy consisted of isoniazide, rifampicine, pyrazinamide, ethambutol, and dexamethason. As the tubercular bacillus appeared to be unsensitive to INH, this drug was replaced by ciprofloxacin. The presence of candidiasis required nystatine. About 2 weeks later, the patient showed an acute impairment of consciousness, with a slowly reactive left pupil and hyperthermia ($>42^{\circ}$C). On suspect of acute cerebral oedema, the patient was intubated and hyperventilated in combination with mannitol. Computed tomography scan (CT-scan) revealed three hypodense lesions in the right basal ganglia and the left frontal lobe with mild surrounding oedema. A follow-up CT scan, 1 week later, showed a reduction of the existing lesions but new lesions with oedema in the left

basal ganglia, a new lesion in the left putamen, bilateral dilatation of the ventricles, a widened third ventricle, and widened extracerebral spaces. Two weeks later, the next CT scan revealed a hypodense enhancement in the left and right basal ganglia as well as in the right internal capsule, probably consistent with infarctions. The hypodense lesions in the left frontal lobe were suspected of an increase in encephalitis. EEG appeared to be asymmetrical, with focal abnormalities in the frontal areas of the right hemisphere.

Two months after disease onset, neurological examination revealed widespread neurological deficits, i.e., spastic tetraparesis, most pronounced at the left side, prohibiting the patient to walk and to stand without aid. In addition, the patient remained confused and hallucinatory at times, which could be related to the cerebral damage and the underlying hydrocephalus. Moreover, the psychiatrist confirmed an organic psychosyndrome with anxieties for which haloperidol was advised but never taken. The patient was willing to drink and to eat only by inciting constantly. The level of consciousness still varied, his speech was slow and dysarthric, and his emotional behaviour appeared to be labile.

During the following year of rehabilitation, i.e., the period before starting the first TENS and methylphenidate treatment, the patient's physical condition further improved, i.e., from the spastic tetraparesis a left hemiparesis remained. However, particularly during walking, the left hemiparesis continued to deteriorate. The patient began to eat and to drink more independently. Nightly restlessness occurred frequently, for which temazepam was successfully prescribed. Of note is that the patient's behavioural problems remained level. When demands were placed, the patient reacted aggressively and ran away. Furthermore, the child was overactive, acted verbally and behaviourally aggressive and, in particular, sexually disinhibited. By the administration of amantadine, his verbal but not his behavioural expressions diminished. Importantly, the behavioural disturbances complicated his rehabilitation and, instead of making progress, the patient rather deteriorated. More specifically, the patient became more anxious, sad, and gloomy, and showed an increase in motor restlessness. Administration of pipamperon and paroxetine appeared to have no effect.

It is important to note that the patient's cognitive and behavioural functioning showed this clinical pattern during a long period preceding the first treatment-period with TENS, which was ~18 months after onset of the disease.

Materials and procedure

Measurements

Considering the left hemiparesis, tests were included which appealed to functions of the right hemisphere, i.e., visuospatial and visuoconstructive memory. In addition, tests were administered which focused on the patient's attention/concentration. The disturbances in behaviour, e.g., aggression, overactivity and a depressed mood, were evaluated by an observation scale. Patient's rest–activity rhythm was measured by actigraphy. The various neuropsychological tests, the observation scale and actigraphy were applied before and after each treatment period and again after each period without intervention.

Neuropsychological tests

Attention/concentration

The subtests *Calculation, Substitution and Digit Span* from the *Wechsler Intelligence Scale for Children-Revised* (WISC-R) [32] can be combined into one separate IQ factor, called Freedom of Distractibility (FD) [33]. The subtest *Calculation* implies that the children have to solve sums for which fundamental arithmetical skills are required (e.g., subtracting) ($M = 10$) [34]. With the subtest *Substitution*, the subject is asked to associate a specific number or picture with a specific symbol ($M = 10$) [34]. With the subtest *Digit Span*, the subject has to repeat a number of digits in the same or in a reversed sequence. Besides a variety of cognitive functions, all three subtests appeal specifically to one common cognitive function, i.e., attention/concentration ($M = 10$) [34].

The *Bourdon-Vos* [35] is a task which requires sustained attention. The test consists of a sheet of paper with groups of dots printed on it. However, each group has a varying number of dots, i.e., 3, 4, or 5 dots and, moreover, the dots are differently situated in each group. The subject is asked to cross out as quickly and accurately as possible the groups with 4 dots. Administration of the Bourdon-Vos results in two scores: (1) the mean time in seconds per line ($M = 10$), and (2) the total number of omissions ($M = 15$) [36]. Test–retest reliability for the mean time per line appeared to be 0.87, interrater-reliability was 0.91 [36].

Visuospatial and visuoconstructive memory

The *Rey Complex Figure* [37, 38]. The subject has to copy and, after a delay, draw from memory a complex geometrical figure. Copying the figure requires planning and strategy whereas, in the second part, the test appeals to the subject's visual memory [39]. Scoring: to each separate element of the figure points are attached, with a maximum score of 36. Internal consistency (Cronbach's α) for the subtest Copy was 0.60 and for the Delayed Reproduction from memory 0.82 [39].

The *Benton Visual Retention Test, version A* [40]. This test includes 10 pictures, each picture consisting of one or more abstract figures. Version A implies that each picture is presented to the subject during 10 seconds; directly after the presentation, the subject must draw the picture from memory. Scoring: 1 point for a correct reproduction, whereas an inappropriate reproduction, irrespective of type of error, receives no points (maximum score: 10). The highest interrater-reliability for Number Correct was 0.96 and for Error scores 0.97 [41]. Test–retest reliability coefficients were reported at 0.57 for Number Correct and 0.53 for Error scores [41].

The *Raven Progressive Matrices* [42]. This test appeals to the subject's reasoning by analogy and abstract thinking [39]. A booklet is presented to the subject, each page containing an abstract pattern with one part left out. At the bottom of the page, several bits are printed with various patterns and only one bit is the right one to complete the pattern of the upper figure. Scoring: the total number of correct answers (maximum score: 60). The reliability coefficient by means of Cronbach's α ('internal consistency') appeared to be 0.90 [41].

Observation scale

The *Revised Conners Parent and Teacher Rating Scale* [43] was used to rate the various behavioural symptoms and to evaluate possible treatment effects. The scale includes

seven subscales, i.e., conduct problem I (max score: 30), learning problem (max score: 12), psychosomatic (max score: 15), impulsive-hyperactive (max score: 12), conduct problem II (max score: 9), anxiety (max score: 12), and other items (max score: 54). A lowering of the score implies an improvement in behaviour.

Actigraphy

The rest–activity rhythm was assessed using actigraphy [6] on several occasions, i.e. before and after each treatment (free) period. On each occasion, the patient wore an actigraph around the right, non-paretic wrist, for an average of 7 days. From the resulting rest–activity rhythms, several non-parametric variables can be calculated, as described in detail previously [6]. For the purpose of the present study, two variables were of importance, i.e., (1) L5, which represents the subject's five least active hours, and (2) M10, which includes 10 hours of the subject's maximum activity, both within 24 hours.

Intervention

The patient was treated either with TENS or with methylphenidate.

TENS

Frequency and intensity. The patient was treated with an electro-stimulator, type Premier 10s. This stimulator generates transcutaneous electro-stimulation which consists of asymmetric biphasic square impulses, applied in bursts of trains, nine pulses per train, with an internal frequency of 160 Hz, a repetition rate of 2 Hz, and a pulse width of 100 μseconds. This type of TENS is known as BURST-TENS [44]. The intensity of the stimulation triggered visible muscular twitches, which were painless. A flickering green light placed on the electro-stimulator indicated stimulation.

Location. Two 2×3 cm $(h \times w)$ self-adhesive carbon rubber electrodes were fixed on the patient's back between Th1 and Th5, each on one side of the spinal column.

Duration. The patient was offered a stimulation time of 45 minutes per day, between 16:00 and 19.00 h, for 7 days a week, during a period of ~3 months.

Methylphenidate

The patient took methylphenidate three times a day, i.e., 8 am, around 12 and at 4 pm. To determine the most optimal treatment, methylphenidate was first administered at a low dose, which was raised in the following way. During the first week, the patient took 5 milligrams of methylphenidate at each point of time. The next week, the patient took a tablet of 10 milligrams at 8 am and around 12, and a tablet of 5 milligrams at 4 pm. This procedure was maintained during the third week, whereas in the fourth week the dose was raised up to 15 milligrams (one and a half tablets) for the medication at 8 am and around 12, whereas the medication at 4 pm remained level (5 milligrams). These different dosages were maintained during the following 2 months of treatment.

During the total treatment period of 3 months, blood pressure, pulse, and body weight were frequently checked, i.e., during the first month, once a week and, subsequently, once a month.

Table 1. Mean standard scores[a]; mean scores[b]; maximum scores[c]. A'dine = Amantadine; WISC-R: Wechsler Intelligence Scale for Children, Revised. Freedom of Distract.: Freedom of Distraction. Methyl: methylphenidate

	Mean + Max. score	Pre1 start TENS	Post1 stop TENS	Delay1	Delay2 no A'dine	Delay3= Pre2 start methyl	Post2 stop methyl	Delay4 = Pre3 start TENS	Post3 stop TENS	Delay5
Tests										
WISC-R										
Freed. of Distract.	100[a]	84	90	88	84	99	77	66	86	88
Calculation	10[a]	9	10	10	8	11	4	6	11	10
Substitution	10[a]	1	2	3	1	5	2	2	1	1
Digit Span	10[a]	12	14	12	13	14	14	12	12	14
Bourdon-Vos										
Seconds per line	10[b]	40.3	26	28.9	34.4	26.4	26.9	28.9	27.18	21.09
Omissions	15[b]	34	29	2	2	2	5	7	3	3
Rey Figure										
Copy	36[c]	26.5	32	33	33	36	29	32	30	36
Memory	36[c]	15	18	21	24	22	23	19	23.5	26
Benton A version	10[c]									
Hits		5	6	2	5	7	5	7	5	5
Failures		5	4	8	5	3	5	3	5	5
Raven matrices	60[c]									
Hits		35	39	39	40	38	31	37	35	44
Failures		25	21	21	20	22	29	23	25	16
Conners Scale										
Totalscore	144[c]	45	18	16	25	23	21	28	14	18

Amantadine

The patient took amantadine since the onset of the disease. Amantadine was administered to enhance, among others, attention/concentration, arousal, processing time and psychomotor speed and to reduce agitation and anxiety [45]. However, to exclude possible side-effects, e.g., confusion and nightmares [46] which might be mixed up with the other clinical symptoms, it was decided to stop the administration of amantadine (Delay2; table 1).

Design

First, the patient was treated by TENS during 3 months (Post1), followed by a treatment-free period of 2 months (Delay1). At that moment, the administration of amantadine was stopped and the patient was tested again 2 months later (Delay2). Because of the summer holidays, the patient was tested again 2 months later, just before methylphenidate was administered (Delay3 = Pre2). The possible effects of methylphenidate were evaluated 3 months later (Post2), followed by a treatment-free period of 2 months, after which the patient was tested again (Delay4 = Pre3). At that moment, TENS was applied again for 3 months (Post3), followed by a treatment-free period of 6 weeks (Delay5). The various treatment (free)-periods are presented in figure 1.

Data-presentation

The results of the various neuropsychological tests and Conners Scale are presented in table 1, with mean (standard) scores and maximum scores.

For each of the two variables, i.e., L5 and M10, describing the rest-activity rhythm, two-tailed paired *t*-tests at a 0.05 significance level were performed on

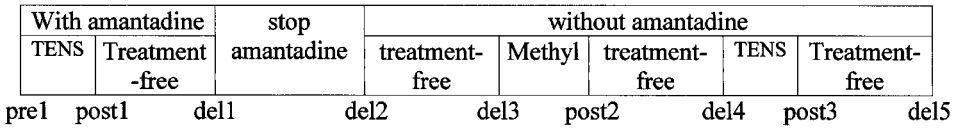

Figure 1. The various treatment(free) periods. Methyl: methylphenidate; aman: amantadine.

two orthogonal contrasts [47]; baseline 1 versus baseline 2 and experimental versus pooled baseline. Baseline levels were pooled in order to reduce the repeated measurement within-subject variability. The use of this procedure is appropriate when a lack of difference between two levels (baseline 1 and 2) can be demonstrated. If *t*-tests indicated no differences between baseline 1 and 2, *F* statistics on the contrast of the experimental versus pooled baseline levels are justified. If baseline 1 and 2 differ significantly, *F* statistics should be performed on the contrast of baseline 1 versus experimental baseline, and experimental baseline versus baseline 2. The results of the actigraphy are presented in figure 2.

Results and discussion

The results will be presented and discussed per separate treatment(free) period.

Pre1–Post1–Delay 1 (first TENS treatment)

After the first treatment period with TENS, the patient showed higher scores on the WISC-R/FD, the Bourdon-Vos, the Rey Complex Figure, the Benton Visual Retention Test and the Raven Progressive Matrices. These cognitive improvements coincided with an improvement in overall behaviour (lower score on the Conners Scale).

After the first treatment-free period, the scores on the WISC-R/FD slightly decreased. It should be noted, however, that, although speed of processing of the Bourdon-Vos slowed down somewhat, the number of omissions with the Bourdon-Vos decreased remarkably. Patient's performance on the visuospatial and visuoconstructive memory tests showed conflicting results. The score on the Benton Visual Retention Test declined, on the Raven Progressive Matrices remained level and on the subtest Memory of the Rey Complex Figure further improved. In addition, the score on the Conners Scale lowered just a little.

As for the actigraphy variables L5 and M10, *t*-tests indicated no differences between baseline 1 and 2. Consequently, *F*-statistic on the contrast of the experimental versus pooled baseline levels was performed, which showed that M10 directly following TENS treatment (mean $\pm$ SD) (32 415.75 $\pm$ 1516.43) was significantly decreased ($p = 0.001$) over-pooled baseline values (49 749.25 $\pm$ 2069.60), whereas L5 directly following TENS (970 $\pm$ 101.34) did not significantly decrease ($p = 0.23$) over-pooled baseline values (1083.12 $\pm$ 52.25).

The improvements in the neuropsychological tests and the Conners Scale after the treatment period, the decline and stability in the majority of the tests and Conners Scale after the treatment free period, together with the significant effect on the M10 rest–activity variable support a real treatment effect of TENS.

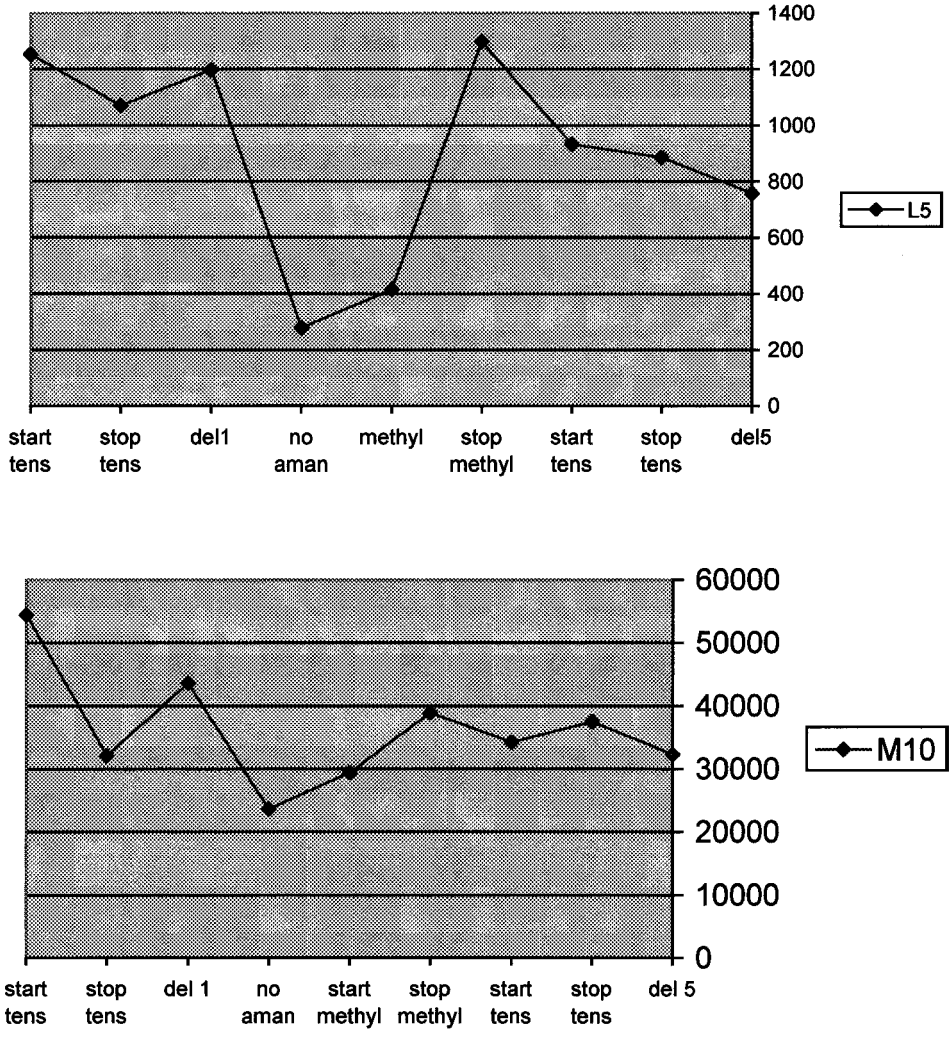

Figure 2. Scores on the actigraphy variables L5 and M10 (nightly restlessness and activity by day, respectively) at various moments of measurement. Aman: amantadine; methyl: methylphenidate; del: delayed measurement.

Delay 1–Delay 2–Delay 3 (period without amantadine)

After the next period, in which the patient stopped taking amantadine, patient's performance on the WISC-R/FD and speed of processing of the Bourdon-Vos further declined. In contrast, the scores on the Memory subtest of the Rey Figure, the Benton and the Raven Matrices showed some improvement. Importantly, the patient's behaviour deteriorated during this period (higher score on the Conners Scale).

After the next treatment-free period, up to the start of methylphenidate, the patient showed enhanced scores on all tests, except for the scores on the subtest Memory of the Rey Complex Figure and the Raven Progressive Matrices which hardly declined. Also, the patient's behaviour (Conners Scale) improved slightly.

As for the actigraphy variables L5 and M10, *t*-tests indicated significant differences between baseline 1 and 2. Therefore, for both variables, F statistic was performed on the contrast of baseline 1 versus experimental baseline and experimental baseline versus baseline 2. The results show that M10 directly following the period without amantadine ($24\,677.50 \pm 1443.45$) significantly decreased ($p = 0.03$) over baseline 1 ($42\,213.75 \pm 5302.67$), but did not significantly increase ($p = 0.14$) over baseline 2 ($28\,792.25 \pm 2005.06$). Similar results were observed for L5, i.e. L5 directly following the period without amantadine (223 ± 21.14) significantly decreased ($p = 0.003$) over baseline 1 (976 ± 114.64), but showed no significant increase ($p = 0.43$) over baseline 2 (236.25 ± 47.37).

These results are consistent with expectations. Amantadine is prescribed to enhance attention/concentration and psychomotor speed and to reduce agitation and anxiety [45]. Consequently, cessation of amantadine should produce the opposite pattern, which indeed was observed, i.e., a decrease in attention/concentration and an increase in behavioural disturbances. Moreover, confusion and nightmares are known side-effects of amantadine [46]. Of note is that L5 and M10 showed lower values after the taking of amantadine had stopped. These findings strengthen the reliability of the applied measurements and weaken the possible influence of test–retest effects.

Delay 3–Post2–Delay 4 (methylphenidate treatment)

Unexpectedly, after the treatment with methylphenidate, the scores on the WISC-R/FD, the subtest Omissions of the Bourdon-Vos, the subtest Copy of the Rey Figure, the Benton and the Raven Matrices declined. Only the performance on the subtest Memory of the Rey Figure slightly improved. In addition, the score on the Conners Scale decreased. Such an adverse effect of methylphenidate on cognition has, as far as the authors know, only been observed when it was combined with imipramine [48].

In the treatment-free period, the performance on the WISC-R/FD and the Bourdon-Vos further decreased. In contrast, the performance on all other tests—except for the subtest Memory of the Rey Complex Figure—recovered. Furthermore, the patient's overall behaviour deteriorated again.

Only for the actigraphy variable M10, *t*-tests indicated no differences between baseline 1 and 2. Consequently, the F-statistic on the contrast of the experimental versus pooled baseline levels was performed, which showed that M10 directly following methylphenidate ($40\,899.50 \pm 1203.21$) significantly increased ($p = 0.009$) over pooled baseline values ($31\,744.25 \pm 973.97$). For L5, the F-statistic was performed on the contrast of baseline 1 versus experimental baseline and experimental baseline versus baseline 2. The results show that L5 directly following methylphenidate (1252.50 ± 58.67) significantly increased ($p = 0.0005$) over baseline 1 (236.25 ± 47.37), but did not significantly decrease ($p = 0.10$) over baseline 2 (890.00 ± 225.20). The increase in nightly restlessness, measured by actigraphy, is a more common adverse effect of methylphenidate [31]. Importantly, this latter finding supports the reliability of the actigraphy-registration in the present case study.

The varying performance on the neuropsychological tests and the increase in behavioural disturbances are not easy to interpret. One plausible reason might be that in this period the patient was told that his schoolteacher, who was a great

support for him during his illness and in whom he had a lot of confident, would leave the school. Possibly, the forthcoming departure of the schoolteacher might have influenced the patient's cognitive and behavioural functioning. Considering the effect of methylphenidate on L5 and M10 in the former period, a decrease in both rest–activity variables was expected to occur after cessation of methylphenidate.

Pre3–Post3–Delay 5 (second TENS treatment)

After this second treatment with TENS, the scores on the WISC-R/FD and the Bourdon-Vos improved considerably. However, the performance on the majority of the visuospatial and visuoconstructive memory tests declined somewhat, i.e., only the performance on the subtest Memory of the Rey Complex Figure enhanced. Another remarkable improvement was observed in the patient's overall behaviour (Conners Scale).

After the treatment-free period, the data show that not only the patient's performance on the WISC-R/FD and the speed of processing of the Bourdon-Vos further improved, but also that the performance on the Rey Figure and Raven Matrices, which declined somewhat in the former period, was better. However, after stopping TENS, a decline in the patient's performance on the various tests was expected. Only patient's behaviour worsened (Conners Scale) after the treatment-free period.

As for the actigraphy variables L5 and M10, *t*-tests indicated significant differences between baseline 1 and 2. Therefore, for both variables, the *F*-statistic was performed on the contrast of baseline 1 versus experimental baseline and experimental baseline versus baseline 2. The results show that M10 directly following TENS ($38\,200.50 \pm 3098.21$) did not significantly increase ($p = 0.20$) over baseline 1 ($34\,696.25 \pm 2510$) and did not significantly decrease ($p = 0.08$) over baseline 2 ($32\,246.50 \pm 3730.12$). Similar results were observed for L5, i.e. L5 directly following the period with TENS (799 ± 119.92) did not significantly change ($p = 0.41$) over baseline 1 (890 ± 225.20), and over baseline 2 (757.75 ± 58.34) ($p = 0.40$).

In sum, the majority of these findings could be considered as a con for real treatment effects of TENS. On the other hand, the patient does not suffer from a progressive disease, and it might be just as realistic to expect a prolonged effect after a second application of a particular type of stimulation. In other words, one could speculate that after a period of 3 months with TENS, certain brain areas may continue to show improved functioning and, possibly, may also exert a beneficial influence on other brain areas.

Conclusions and limitations

TENS

On the basis of the results of each separate treatment(free) period, it is hard to make firm conclusions about the influence of TENS on patient's cognitive functioning. Although the enhanced performance on the Bourdon-Vos after TENS might suggest improved attention/concentration, this finding is not supported by the scores on the WISC-R/FD. Indeed, the subtests of the FD were included in the present

study specifically to evaluate attention/concentration. However, attention/concentration can be measured by the FD only under the condition that its three subtests will obtain about the same mean. This appeared not to be the case in the present study. During all treatment(free) periods, Digit Span remained well above the average level, whereas only very low scores were observed for Substitution. In other words, in the present study the WISC-R/FD may not be considered as a reliable measure for attention and concentration.

It is noteworthy, though, that the patient's behavioural functioning (Conners Scale) improved considerably after each TENS-application and declined or remained level after cessation of TENS. Only these latter findings support the hypothesis on the effects of TENS in TBM.

Cessation of amantadine and administration of methylphenidate

The most constant pattern in clinical symptoms was observed after the patient stopped taking amantadine and after administration of methylphenidate. The clinical profile which resulted after cessation of amantadine met the expectations and matched perfectly the outcome of the selected measurements, i.e. the neuropsychological tests, the Conners Scale and the actigraphy. The effects of methylphenidate were not anticipated, but the clinical findings appeared to be all in the same direction.

Overall evaluation

So far, the results of each separate treatment (free) period, with and without amantadine, were reviewed. Obviously, during these periods all kinds of transient positive and negative influences which could not be prevented might have played a role. Therefore, irrespective of type of intervention, it would also be worthwhile to evaluate the level of patient's cognitive and behavioural functioning over the *whole* period from Pre1 (start TENS) up to Delay 5, a period which took up 1.5 years. The data in table 1 suggest that, except for the scores on the Benton Visual Retention Test which did not change, patient's performance on all neuropsychological tests improved. Moreover, patient's overall behaviour enhanced dramatically (Conners Scale) as well as nightly restlessness (L5) and overactivity by day (M10) (figure 2). Of course, these improvements could be the result of 'natural' recovery processes, but it is emphasized that there was no such recovery—rather a decline—during a long period preceding the first TENS-treatment (Pre1–Post1).

Limitations

The present study also has some specific caveats. In the first place, the study coincided with the construction of an extensive medical team which provided, among other things, a strong social support for the patient and his mother. These social changes might have positively influenced the effects of TENS, but the question why methylphenidate was counterproductive remains unanswered. Moreover, TENS was applied by the parent at home under normal circumstances, i.e., in the absence of the investigator who could have been viewed as an additional source of stimulation. In the second place, in a study with multiple measurements, test–retest effects do play a role. On the other hand, during the 18 months of treatment in the present

study, the patient showed lower scores on the majority of the tests at several occasions, i.e., after the first treatment-free period (Delay1), after the period without amantadine (Delay2), and after methylphenidate (Post2). More specifically, compared to the cognitive scores after TENS-treatment (Post1), the patient performed worse on the majority of the tests after methylphenidate (Post2), whereas all tests were administered again three times following Post1. In the third place, the results of the present study do not provide direct evidence that the pre-frontal cortex, the septo-hippocampal region, and the hypothalamus are indeed activated by TENS.

Finally, although the present results should be considered with great caution, they are challenging enough to warrant further research.

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