Computer assisted retraining of attentional impairments in patients with multiple sclerosis

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Abstract

***Objective*—To evaluate the efficacy of a computer based retraining of specific impairments of four different attentional domains in patients with multiple sclerosis.**

***Methods*—Twenty two outpatients with multiple sclerosis received consecutively a specific training comprising 12 sessions in each of the two most impaired attention functions. The baseline of attentional deficits, the performance after each training period, and the course of performance in the next nine weeks was assessed by a computerised attention test battery. Additionally, the impact of the training on daily functioning was evaluated with a self rating inventory.**

***Results*—Subgroups of patients with multiple sclerosis showing different patterns of attentional impairment could be separated. Significant improvements of performance could almost exclusively be achieved by the specific training programmes. The increase of performance remained stable for at least nine weeks. For quality of life patients reported less attention related problems in everyday situations.**

***Conclusions*—In patients with multiple sclerosis it seems worthwhile to assess attentional functions in detail and to train specific attention impairments selectively.**

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Keywords: multiple sclerosis; attention; cognitive deficits; cognitive rehabilitation

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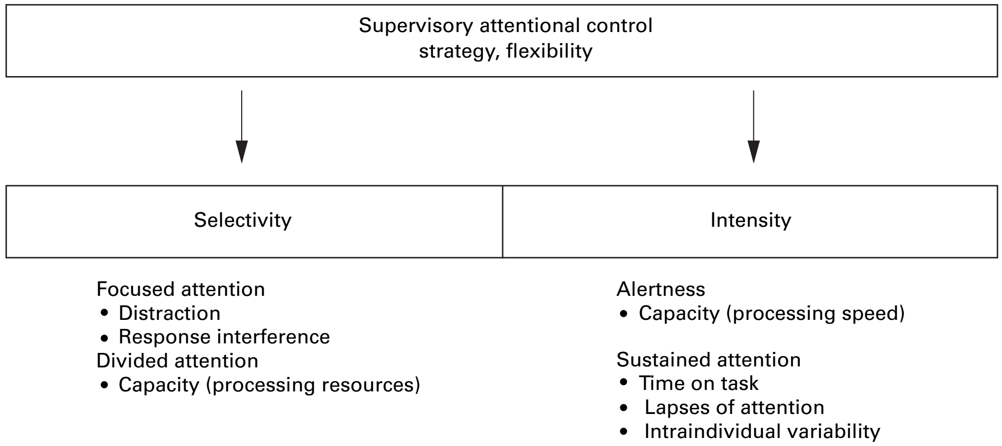
Neuropsychological investigations have shown that there is some degree of cognitive deterioration in 45%-65% of patients with multiple sclerosis.[1–4] These cognitive deficits seem to share numerous characteristics associated with the syndrome of "subcortical dementia".[5–9] The presumed mechanism underlying subcortical dementia is disconnection of pathways linking subcortical structures with cortical areas or the limbic system. The cardinal neurobehavioural features consist of a slowing of mental processing, forgetfulness (free recall memory tasks being more impaired than recognition tasks), impaired abstract reasoning, and changes in mood and personality in the context of relatively preserved intellectual and language functions.[10 11] Recent studies, however, disclose deficits related to multiple sclerosis on tasks of verbal fluency, verbal discourse, writing, and concept definition.[12 13]

Neuropsychological disturbances seem to have a major impact on the quality of life of patients with multiple sclerosis. As Rao *et al*[14] pointed out, cognitively impaired patients with multiple sclerosis, as opposed to merely physically disabled patients with the disease, were found to be less likely to be employed, engaged in fewer social and vocational activities, reported more sexual dysfunction, experienced greater difficulties in performing routine household tasks, and were more vulnerable in developing increased psychopathology.

Although the negative impact of neuropsychological deficits on social functioning is becoming more and more a focus of attention very few findings are available regarding treatment and rehabilitation of these deficits. As one of only a few studies Smits *et al*[15] found that 4-aminopyridine, a potassium channel blocker, had no effect on the performance of patients with multiple sclerosis in neuropsychological tests. Foley *et al*[16] have recently described a comprehensive psychological approach for managing the communication problems of cognitively impaired patients with multiple sclerosis. Jonsson *et al*[17] offered a specific cognitive treatment comprising cognitive training and neuropsychotherapy and compared this with a non-specific mental stimulation. They found an improvement of the total group of patients with multiple sclerosis on several cognitive factors and tests, which could be explained by a retest effect or a non-specific treatment effect. Interestingly, on the Beck depression inventory (BDI) the specific cognitive treatment group reported significantly less depression, whereas the non-specific treatment group rated themselves as significantly more depressed.

The present study aims at evaluating the effects of a specific computer based retraining of four attentional functions on cognitive measures in patients with multiple sclerosis with mild to moderate cognitive dysfunction. We have focused on attentional disorders as attention (or to use a more inclusive term, information processing) represents a controlling and integrating function with implications for nearly all other cognitive systems. Furthermore, attention has been recognised as possibly the most prominent aspect of cognition affected in some patients with multiple sclerosis. As shown in various studies attention is not a unitary phenomenon but has to be subdivided into at least four different components: on the one hand alertness and sustained attention (vigilance), both referring to the



Scheme of a theoretical framework of attention, adopted from Van Zomeren and Brouwer[32] .

intensity aspect of attention, on the other hand selective attention and divided attention as approaches to the selectivity aspect (fig 1).[18–20] According to Posner and Rafal[20] *alertness* refers to a generalised physical and mental state of arousal preparedness to respond. Alertness can be subdivided into two different types: *tonic alertness*, which refers to the diurnal fluctuation in wakefulness and performance and *phasic alertness*, the sudden increased attentiveness which immediately follows a warning signal which the organism knows will soon require a rapid response. *Selective attention* represents the ability to focus on one source or type of information to the exclusion of others.

Table 1 Descriptive statistics of the patient sample

	No of patients	*Mean (SD)*	*Range*
Total	22		
Age (y)		44.6 (11.4)	25–70
Education (y)		13.0 (2.0)	10–18
clinical indices:			
Multiple sclerosis course (n):			
Primary chronic progressive	1		
Secondary chronic progressive	5		
Relapsing-remitting	16		
Duration of disease (y)		16.6 (9.1)	4–40
Kurtzke EDSS		3.8 (1.8)	2–8

Tasks involving *divided attention* require attention to be divided or shared between two or more sources or kinds of information, or two or more mental operations.[21] *Sustained attention* or *vigilance* refers to the ability to attend over long and generally unbroken periods of time for the purpose of detecting and responding to relevant stimuli.

Although studies on the efficacy of rather non-specific attention retraining for patients with diffuse brain damage (patients with head trauma) showed effects on different attention and even intellectual functions,[22 23] corresponding studies concerning patients with more localised lesions such as some patients with stroke or head trauma disclosed that it might be advantageous to train different attention functions specifically.[24 25] For these reasons we used a computer assisted attention training software (AIXTENT) designed by Sturm *et al*,[26] which contains programmes for each of the four attention domains mentioned before. The programmes were constructed like computer games and aimed to represent daily attention situations. They have proved to be an effective tool in rehabilitation of attentional impairments in patients with stroke.[27]

Table 2 Median (range) before (T_{1-3}; baseline) and after (T_4) the first training

		Training group							
		Alertness (n=7)		*Divided attention (n=8)*		*Selective attention (n=6)*		*Vigilance (n=2)*	
Control test (TAP)		T_{1-3}	T_4	T_{1-3}	T_4	T_{1-3}	T_4	T_{1-3}	T_4
Alertness:									
Simple	RT	33 (27–37)	44 (33–55)*	46 (41–61)	45 (35–57)	48 (40–70)	57 (43–64)	53 (49–57)	57.5 (54–61)
Cued	RT	37 (28–45)	43 (32–52)	50.5 (38–60)	48.5 (39–61)	47 (37–66)	56 (47–62)	51.5 (49–54)	54 (54–54)
Divided attention	RT	43 (32–47)	43 (30–56)	41.5 (30–48)	45.5 (32–56)*	37.5 (30–46)	44 (35–60)	45.5 (43–48)	42.5 (41–44)
	Errors	1 (1–3)	2 (0–2)	1 (0–3)	0.5 (0–2)	0.5 (0–2)	0.5 (0–2)	0 (0–0)	0.5 (0–1)
	Omissions	3 (1–8)	3 (1–7)	2.5 (0–9)	2.5 (0–6)	2 (0–6)	1 (0–6)	1.5 (0–2)	0 (0–0)
Selective attention:									
Go/no-go	RT	42 (27–53)	45 (30–66)	45.5 (20–60)	46.5 (20–72)	41 (20–56)	51.5 (43–70)*	49.5 (42–57)	47.5 (35–60)
	Errors	0 (0–0)	0 (0–2)	0 (0–1)	0 (0–1)	0.5 (0–2)	0 (0–1)	0 (0–0)	0 (0–0)
Incompatibility	RT	31 (20–42)	36 (20–48)*	45 (20–63)	45 (20–63)	26.5 (20–58)	37.5 (30–66)*	58 (57–59)	60.5 (56–65)
	Errors	3 (2–6)	3 (1–6)	2.5 (0–10)	1 (0–3)	3 (1–7)	3.5 (0–12)	1 (1–1)	2 (0–4)
Flexibility	RT	42 (34–54)	44 (36–60)*	50 (29–64)	56.5 (34–72)*	44.5 (20–56)	52.5 (28–70)*	54.5 (49–60)	56 (51–61)
	Errors	4 (1–8)	3 (0–12)	2.5 (0–20)	2 (0–13)	5 (1–18)	2.5 (0–4)	3 (1–5)	1 (0–2)
Vigilance	RT	48 (42–57)	52 (39–61)	52 (40–63)	50 (39–61)	50.5 (46–64)	56 (45–66)	51.5 (48–55)	54.5 (51–58)
	Errors	1 (0–2)	2 (0–3)	1 (0–8)	1.5 (0–11)	0.5 (0–9)	0 (0–3)	0.5 (0–1)	0 (0–0)
	Omissions	1 (0–10)	5 (0–10)	3 (0–13)	2 (0–15)	1.5 (1–4)	1.5 (0–3)	7 (4–11)	2 (2–2)

*$p<0.05$; t_{1-3} *v* t_4, Wilcoxon signed ranks test.
Values for reaction time (RT) are T scores based on a normative sample (n=200 healthy subjects).
t_{1-3}=Median of t_1, t_2, and t_3.

Table 3 Changes of performance after the first training

Control test (TAP)		Training group p values: Alertness	Divided attention	Selective attention
Alertness:				
Simple	RT	0.018*	0.127	0.225
Cued	RT	0.09	0.671	0.172
Divided attention	RT	0.834	0.028*	0.068
	Errors	0.655	0.163	0.783
	Omissions	1.0	0.739	0.578
Selective attention:				
Go/no-go	RT	0.309	0.115	0.028*
	Errors	0.317	0.564	0.157
Incompatibility	RT	0.041*	0.753	0.046*
	Errors	0.683	0.206	0.588
Flexibility	RT	0.017*	0.012*	0.028*
	Errors	0.751	0.206	0.140
Vigilance	RT	0.446	0.672	0.249
	Errors	0.198	0.462	1.0
	Omissions	0.518	0.491	0.480

Because of the small sample size, no statistical analysis was done for the vigilance group.
p Values are differences between t_{1-3} and t_4 (Wilcoxon matched pairs test).
*Significant differences.

Methods

PATIENTS

Outpatients with multiple sclerosis who complained of cognitive disturbances were selected according to the following criteria: clinically definite multiple sclerosis,[28] stable phase of the disease for three months before inclusion (no relapse in this period), no steroid treatment in the four weeks before inclusion, and no change in immunosuppressive or immunomodulating treatment for the past six months. To avoid interference of visual deficits, visual acuity, visual fields and eye movement disorders were tested in the frame of a standardised neurological assessment. If deficits concerning visual acuity or visual fields were suspected, patients were referred for a comprehensive ophthalmological investigation including Goldman perimetry. Patients with interfering visual disturbances or severe motor disorders of the arms, hearing loss, psychiatric history, drug or alcohol misuse, or nervous system disorders other than multiple sclerosis were excluded from the study.

For neuropsychological deficits, only patients showing a percentile score<25 (with respect to reaction times) or exceeding the cut off point (of errors or omissions) in at least two of the four attention functions were referred for the training.

TESTS APPLIED

The main outcome criterion was a selection of seven subtests derived from the attention test battery (TAP-1.02c)[29] :

Tonic and phasic alertness

The examination includes a simple and a cued reaction time task with a visual test stimulus and an acoustic cue. The simple reaction time has been shown to be a valid measure of processing speed.[30 31] A phasic change of alertness can be assessed by comparing reaction time with (cued RT) and without (simple RT) a warning signal.[20 32 33] The present test consists of four trials in an ABBA design each containing 20 presentations (A=without cue, B=with cue).

Divided attention

Divided attention can be operationally defined by combining two or more tasks in one test.[32] For this it should be clear that the multiple tasks evoke no structural interference.[34] In this subtest a visual and an acoustic task are presented simultaneously. The visual task consists of crosses that appear in a random configuration in a 4×4 matrix. The subject has to detect whether the crosses form the corners of a square. In the acoustic task the subject has to detect an irregularity in a regular sequence of high and low beeps.

Go/no-go

Focused attention involves selectivity in perceiving and responding and is commonly referred to as concentration. The present task was designed to assess response inhibition to irrelevant stimuli as well as reaction time in response selection paradigms (choice reaction time). Five stimuli (squares filled in with different patterns) are employed in this task, two of them being critical. They have to be responded to by pushing a switch.

Incompatibility

The aim of this examination is an assessment of the capacity of focused attention—that is, to reject irrelevant, automatically processed infor-

Table 4 Median (range) before (T_4) and after (T_5) the second training

Control test (TAP)		Alertness (n=4) T_4	Alertness (n=4) T_5	Divided attention (n=10) T_4	Divided attention (n=10) T_5	Selective attention (n=7) T_4	Selective attention (n=7) T_5	Vigilance (n=1) T_4	Vigilance (n=1) T_5
Alertness:									
Simple	RT	44 (35–64)	55 (40–59)	51 (33–62)	48.5 (34–70)	55 (34–61)	58 (34–86)	47	43
Cued	RT	43 (39–61)	53 (42–59)	48.5 (32–62)	47.5 (30–67)	52 (37–61)	56 (44–93)	48	50
Divided attention	RT	47 (39–60)	44 (42–80)	43.5 (30–53)	41.5 (31–51)	43 (32–56)	44 (27–56)	47	32
	Errors	0 (0–2)	0 (0–2)	1 (0–2)	0.5 (0–2)	1 (0–2)	1 (0–2)	0	1
	Omissions	3 (0–6)	1.5 (0–2)	2.5 (0–7)	1 (0–7)	1 (0–4)	1 (0–11)	3	3
Selective attention:									
Go/no-go	RT	44 (32–70)	53 (20–70)	47 (30–60)	41 (30–64)	66 (20–72)	65 (29–98)	40	44
	Errors	0 (0–1)	0 (0–1)	0 (0–2)	0 (0–2)	0 (0–1)	0 (0–1)	0	0
Incompatibility	RT	39 (37–63)	36 (20–66)	36 (20–66)	36.5 (20–64)	48 (20–65)	47 (20–67)	33	31
	Errors	1 (0–4)	3 (1–12)	3 (0–12)	1.5 (0–8)	3 (1–6)	3 (1–6)	2	4
Flexibility	RT	57 (46–70)	48 (28–66)	48 (28–66)	48.5 (28–61)	56 (34–72)	57 (34–99)	53	51
	Errors	2 (0–5)	2 (0–5)	2 (0–5)	1.5 (0–5)	3 (0–13)	1 (0–9)	1	0
Vigilance	RT	53 (41–66)	54 (44–63)	56 (39–64)	53 (42–80)	51 (39–56)	48 (24–66)	56	64
	Errors	3 (0–11)	2.5 (1–4)	0 (0–3)	1 (0–2)	1 (0–3)	0 (0–0)	2	0
	Omissions	2 (1–4)	1.5 (0–7)	1.5 (0–10)	2.5 (0–11)	2 (0–15)	2 (0–19)	9	2

Values for reaction time (RT) are T scores based on a normative sample (n=200 healthy subjects).

Table 5 Changes of performance after the second training

Control test (TAP)		Training group p values: Alertness	Divided attention	Selective attention
Alertness:				
Simple	RT	0.414	0.382	0.059
Cued	RT	0.462	0.777	0.062
Divided attention	RT	1.0	0.799	0.753
	Errors	0.655	0.180	0.578
	Omissions	0.257	0.206	0.395
Selective attention:				
Go/no-go	RT	0.465	0.332	0.089
	Errors	1.0	0.564	0.564
Incompatibility	RT	0.655	0.888	0.599
	Errors	0.180	0.642	0.462
Flexibility	RT	0.414	0.339	0.173
	Errors	0.198	0.798	0.173
Vigilance	RT	0.144	0.541	0.499
	Errors	0.198	0.914	0.066
	Omissions	1.0	0.574	0.136

Because of the small sample size, no statistical analysis was done for the vigilance group.
p Values are differences between T_4 and T_5.

mation ("focused attention deficit" according to Shiffrin and Schneider[35]). The interference tendency is tested by a stimulus-response incompatibility. Arrows pointing to the left or the right are presented on the left or the right of a fixed point. The subject is required to press a key on the left or the right, depending on the direction of the arrow—irrespective of the side of presentation. If the side of presentation and the side of response are in accordance, the condition is classified as compatible, otherwise incompatible.

Flexibility

Selective attention presupposes both the capacity of focusing on one aspect of a situation and the ability to change the focus of attention.[19 36] In this examination the flexibility of focused attention is tested by mental alternation between two sets of targets (letters or numbers). Therefore a letter and a number are presented simultaneously. Between trials the position of the letter and the number varies randomly. From one presentation to the next, the target changes from letter to number and vice versa. The subject has to push the button on the side of the target.

Vigilance

Vigilance tests examine the ability to sustain and focus attention in itself.[33] The relevant aspects are time on task effects, lapses of attention, and intraindividual variability.[32] In the present examination a thick vertical line swings up and down with a varying amplitude. The subject has to detect a clearly larger swing upwards. The task is run with a low event rate of critical stimuli (by contrast with monitoring tests with high frequency of targets).

All the tasks consist of simple and easily distinguishable stimuli that the patients react to by a simple motor response. Thus the interference of other neurological impairments such as hemiparesis, ataxia, and visual disorders is very limited.

Evaluation of everyday attentional problems was done with the FEDA,[37] a self rating inventory assessing three factors disclosed by factor analysis: distractibility and slowing of mental processes (scale 1, 13 items), fatigue and slowing concerning practical activities (scale 2, eight items), and decrease of drive (scale 3, six items).

Table 6 Performance changes after the first (T_4–T_{1-3}) training, separated for patients with specific and non-specific training

	Alertness		Divided attention			Selective attention: Go/no-go		Incompatibility	
	Simple RT	Cued RT	RT	Errors	Omissions	RT	Errors	RT	Errors
Specific trained patients:									
Mean (s)	9.86 (9.41)	6.71 (9.12)	4.63 (4.14)	−0.63 (1.3)	−0.5 (2)	11.83 (7.73)	−0.33 (0.52)	9.5 (6.29)	1 (3.41)
Median	10	4	5	−0.5	0	12	0	10.5	0.5
Range	1 to 28	−5 to 24	−1 to 11	−2 to 1	−5 to 1	3 to 23	−1 to 0	−1 to 16	−3 to 7
Non-specific trained patients:									
Mean (s)	1.13 (6.84)	1.63 (5.28)	2.07 (7.46)	0.2 (1.08)	−0.33 (1.84)	4.35 (9.25)	0.18 (0.64)	2.06 (4.68)	−0.71 (2.52)
Median	0	1	1	0	0	2	0	1	−1
Range	−8 to 15	−6 to 15	−10 to 14	−2 to 2	−4 to 3	−8 to 24	−1 to 2	−6 to 11	−7 to 3
p Values	0.027*	0.07	0.40	0.14	0.82	0.0495*	0.069	0.022*	0.32

Values for reaction time (RT) are T scores.
Because of the small sample size, no statistical analysis was done for the vigilance group.
*Significant.

Table 7 Performance changes after the second (T_5–T_4) training, separated for patients with specific and non-specific training

	Alertness		Divided attention			Selective attention: Go/no-go		Incompatibility	
	Simple RT	Cued RT	RT	Errors	Omissions	RT	Errors	RT	Errors
Specific trained patients:									
Mean (s)	3.0 (7.26)	3.25 (5.5)	−0.2 (9.51)	−0.3 (.68)	−0.9 (2.13)	8.43 (10.18)	0.14 (0.69)	0.286 (5.62)	0.43 (1.5)
Median	2.5	3.5	2	0	−0.5	4	0	−1	0
Range	−5 to 12	−2 to 8	−19 to 12	−2 to 0	−5 to 3	−5 to 26	−1 to 1	−4 to 12	−2 to 3
Non-specific trained patients:									
Mean (s)	3.0 (7.32)	2.6 (8.03)	−1.8 (12.4)	−0.15 (1.14)	−0.08 (2.93)	−3.07 (10.54)	0.06 (0.44)	0 (5.96)	−0.563 (3)
Median	1.5	1.5	−0.5	0	0	−4	0	0	0
Range	−4 to 29	−5 to 32	−27 to 20	−2 to 2	−6 to 7	−24 to 16	−1 to 1	−15 to 8	−10 to 4
p Values	0.97	0.61	0.64	0.72	0.45	0.04*	0.69	0.67	0.47

Values for reaction time (RT) are T scores.
Because of the small sample size, no statistical analysis was done for the vigilance group.
*Significant.

TREATMENT/TRAINING PROGRAMMES

Training of alertness

This task requires the patient to control the speed of a car driving along a variable track, tracking as fast as possible, but coping with various dangerous situations such as stopping in front of obstacles or at crossroads.

Training of divided attention

In this programme a cockpit is simulated, in which the patient has to monitor two independent stimulus sequences simultaneously. He has to respond to critical stimuli or sequences of stimuli in either or both of two independent stimulus "channels" (visual-auditive or visual-visual).

Training of selective attention

This exercise resembles trap shooting and requires rapid responses to critical stimuli moving across the monitor screen.

Training of vigilance

In this task the patient has to monitor a radar screen and detect the appearance of objects or the changing of speed of objects already present.

In all the programmes the difficulty of the task is adapted automatically to the performance of the patient. The level of difficulty may, however, also be regulated by the trainer or the trainee himself. After each training session the patients can get feedback about reaction times, number and type of errors, and the achieved level of difficulty. For each task the patients have to press one or two big response buttons, thus avoiding more complex motor actions—for example, those required by a joystick or a keyboard. The response buttons used are the same as in the attention test battery (TAP).

STUDY DESIGN

According to Sturm[38] studies that evaluate the efficacy of neuropsychological treatment procedures should allow the separation of treatment effects from spontaneous remission and practice effects. Therefore in the present study the patients were tested with the TAP three times (T_1-T_3) at three-week intervals (multiple baseline testing) before the start of treatment. Regardless of how many functions were impaired, we decided to offer a training in only two of them—namely, in those that were affected most. As we were interested in specific effects of the four attention training programmes in a first treatment period each patient was trained in only one of the two most deteriorated attention domains. The first period of training included 12 sessions each lasting 40 minutes over three weeks. Immediately after the control tests with the TAP (T_4) were performed, the second attention function was trained for the same duration and intensity as the first one. Thus in each treatment period there was one attention domain trained specifically and at least one more function that was treated in a non-specific manner. After the second training period another testing with the TAP (T_5) followed. To obtain information about the stability of possible increases in performance due to the training two more examinations with the TAP (T_6, T_7) were done every three weeks. In all, the control tests were administered seven times. All the patients were tested and trained individually in a quiet room. Test order was the same in all sessions.

Additionally all patients underwent a comprehensive neuropsychological test battery including the Beck depression inventory (data are not shown in this presentation) before and after the two training periods to determine generalisation to other cognitive functions.

STATISTICAL ANALYSIS

For each training programme and for each subtest of the TAP the Wilcoxon signed ranks test was used to look for significant changes between baseline testing (median of performance T_1-T_3) and first control testing (T_4) as well as between first (T_4) and second control testing (T_5) (comparison within groups). A more direct examination of specific training effects was done as follows: for each control test the changes of performance of those patients who were trained specifically in the attentional domain in question were compared with the change of performance of all other groups as a whole (comparison between groups). For this kind of analysis the Mann-Whitney U test was used. Friedman two way analysis of variance (ANOVA) was computed to check whether performance after completion of the first training (t_4) remained stable until the last follow up testing (T_7). Differences in the mean BDI[39] as well as FEDA scores before and after treatment

Table 6 Continued

Flexibility		*Vigilance*		
RT	*Errors*	*RT*	*Errors*	*Omissions*
10.67 (9.37)	−4 (6.42)	3 (0)	−0.5 (0.71)	−5.0 (7.07)
7.5	−1.5		−0.5	−5
2 to 28	−16 to 2	3	−1 to 0	−10 to 0
4.88 (3.14)	−0.82 (4.61)	1.43 (5.43)	0.52 (3.68)	0.05 (2.58)
4	0	0	0	0
1 to 12	−8 to 8	−7 to 12	−9 to 10	−5 to 7
0.11	0.32			

Table 7 Continued

Flexibility		*Vigilance*		
RT	*Errors*	*RT*	*Errors*	*Omissions*
5.29 (10.23)	−2.86 (4.9)	8	−2	−7
2	−2			
−4 to 27	−11 to 4	8	−2	−7
0.33 (3.74)	0.38 (2.34)	−0.33 (9.37)	−0.96 (2.2)	0.77 (3.66)
0	0	−2	0	0
−6 to 7	−3 to 5	−15 to 24	−7 to 2	−8 to 10
0.2	0.09			

were analysed for significance using the Wilcoxon signed ranks test.

Results

A total of 22 outpatients with multiple sclerosis aged between 25 and 70 years completed the study (table 1 shows their details). As proposed, subgroups of patients with multiple sclerosis showing different patterns of attentional impairment could be separated. Originally we aimed to balance the order of the training programmes—that is, each kind of training should be at the first and second place with the same frequency. For that reason the attentional function trained first is not automatically identical with the worst or weakest function. Because of the combination of the impairments found in our patients (the affected dimensions were not distributed equally) a balanced order of the training programmes was not possible. In the end only nine of the 12 possible combinations occurred. Therefore we were not able to examine directly any kind of transfer (positive or negative) from the first to the second training period. Because the patients entered the study consecutively this unbalanced distribution was not anticipated. This resulted in different sample sizes in the two training periods.

Tables 2 and 3 show the performance of the different training groups in each of the control tests before and after the first training period. Significant improvements of performance for the domains alertness and divided attention as well as an increased performance in the go/no-go paradigm as an aspect of selective attention could only be achieved by the respective training programmes and not by the others. For selective attention, performance in all the subtests of function could only be improved by the specific training also. In the subtest Incompatibility reaction times could also be improved by an alertness training, which aims at increasing the speed of reaction. As a non-specific effect a better performance in the subtest flexibility was achieved by all of the training programmes.

Tables 4 and 5 summarise the results of the second training period. No additional improvement of performance could be shown.

Tables 6 and 7 show the comparison of the change of performance between the specifically trained and all the other patients for the first and second training period (comparison between groups). As the results of the corresponding *U* tests for the first training show, for the domains alertness and selective attention the specifically trained patients showed a significantly higher increase of performance in the respective control tests (tonic alertness, go/no-go, incompatibility) compared with the non-specific group. After the second training period only the "selective attention" group turned the training to its advantage. This led to significantly greater change of performance in the subtest go/ no-go.

Comparing the performance in the specifically trained attention domain after completion of the first training with the performance in the follow up examinations (T_5-T_7) disclosed no

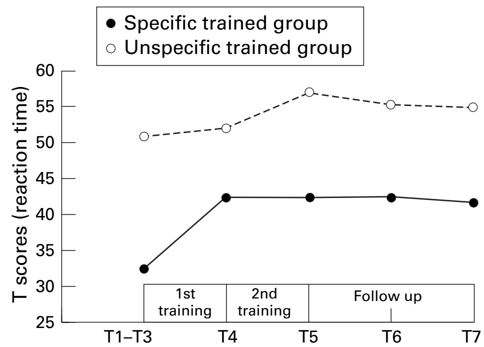


Figure 2 TAP: tonic alertness. Effects of first training (mean scores).

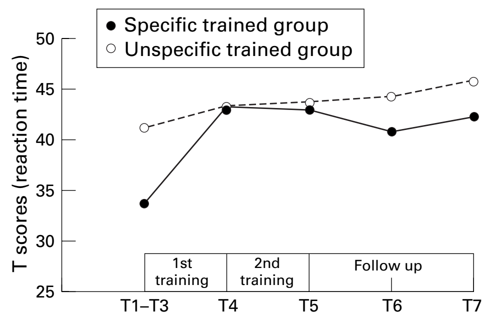


Figure 3 TAP: incompatibility. Effects of first training (mean scores).

significant differences (Friedman two way ANOVA), indicating stable treatment effects for at least nine weeks (figs 2 and 3).

Concerning the impact of this stimulation training on daily functioning there are significant differences in FEDA scores between baseline and post-treatment assessment. Patients reported less fatigue and slowing of physical activities (p=0.03) as well as decreased distractibility and a lower degree of slowing of mental processes (p=0.04, Wilcoxon signed ranks test).

The mean BDI score (8.33) of the total sample before the start of treatment was not in the range of clinically relevant depression and did not differ statistically from the mean values after completion of the training (Wilcoxon signed ranks test).

In almost all patients EDSS scores remained stable during the observation period. In one patient the EDSS score changed from 4.0 at baseline to 3.0 during training and follow up. Disability scores of another patient changed from 2.5 to 3.5, respectively.

Discussion

Different aspects of attention such as alertness, divided attention, selective attention, and sustained attention had been assessed in patients with multiple sclerosis. Most of the patients did not show a generalised decrease of performance, but a rather selective impairment of one or more of these attentional domains. As several authors stated[40–43] these results might reflect factors other than attention deficits, as for example, oculomotor, visual, or motor impairments. The influence of such confounding variables on the results of our study seems to be limited for several reasons. Firstly, as could be seen in stable EDSS scores in our sample, there was no significant change of physical impairment and disability during the study period. Furthermore, the tasks of the TAP do not place heavy demands on fine visual acuity, motor speed, or coordination. All the tasks require the same simple motor action such as pressing a big button. Therefore the fact of selectively reduced performance in different attention tasks should indicate real and specific impairments of attentional domains—that is, alertness, and divided and selective attention.

The aim of this study was to evaluate the efficacy of a stimulation therapy—namely, specific computer based retraining of the four attention domains described above. Therefore, dependent on the pattern of attentional impairment, patients were assigned to specific treatments. The results support the claim that different aspects of attentional impairment should be treated specifically. This applies at least to the domains alertness and selective attention and probably to divided attention as well. In view of the small sample size for the domain vigilance no statement was possible. Our results confirm the findings of Sturm *et al*,[27] who applied the same specific treatment to a group of patients with stroke and were also able to detect selective effects of this training.

In the present study significant reduction of reaction time in the domain selective attention was also seen after non-specific training—that is, training of alertness—which aims at an increase of reaction speed. These findings indicate that complex attentional demands contain aspects of basic attention functions in addition to specific components. These can be trained by programmes that try to improve general activation. Coping with a task assessing tendencies of interference and focused attention requires a sufficient degree of activation (tonic alertness). Analysis of the results concerning alertness discloses significant improvement in trials without a warning signal compared with trials with a warning signal. This suggests that especially the aspect of tonic alertness can be influenced by a specific training.

Interestingly, the described improvements translate exclusively in shorter reaction times. Qualitative aspects of performance remained stable during the study period. From the beginning most of the subjects showed only few omissions and rather low error rates, possibly the result of a strategy which in the face of limited attentional capacity might force reduction of processing speed. Therefore, another effect of training could be seen in the fact that the patients kept their high number of correct responses despite a significant increase of speed. In conclusion, a specific training seems to improve intensity and selectivity aspects of attention.

In the second training period a significant improvement could only be shown for the domain selective attention. As our patient sample had rather mild cognitive impairment a ceiling effect cannot be excluded as a result of a non-specific effect (general activation, increased motivation and mood, etc) of the first training. This finding would imply that only one training period would suffice, at least for patients with mild attention deficits, in which the most deteriorated function is trained. The limited effect of the second training could be also explained by the lack of re-evaluation of indication. The decision as to which function should be trained next was taken before the start of treatment. To be able to take into account some non-specific effects of the first training resulting in an increase of performance in different attention domains this decision should have been revised after the end of the first training period. Another explanation for the lack of significant improvement in the second training cycle may be that patients with multiple sclerosis only have a limited ability to learn.

As Van Zomeren and Brouwer[32] noted, the effect of such a computer based retraining of attention functions can be measured in three ways: at the task level, at the level of task related psychometric tests, and at the level of daily functioning. As in most of the studies that systematically measured improvement on trained tasks, in the present study patients also showed progress. This was evident in an increasing level of difficulty or gradual increase in the number of correct responses. As this could be interpreted as a trivial practice effect, indicating that patients can learn to carry out specific tasks, progress on trained tasks remains unsatisfactory. Therefore psychometric tests have to be used to determine generalisation. In this study the specific training programmes and control tests followed the same paradigm; however, the tasks were different. Because significant improvement can be selectively seen in the specifically trained functions, the increase of performance cannot be due to practice effects, spontaneous recovery, or improved mood, because these should have led to visible improvement in all of the impaired attentional functions.

To determine generalisation to other cognitive functions we additionally used a comprehensive neuropsychological test battery before and after the training period. The preliminary results suggest an increase of performance in tests of reasoning and abstraction (data not shown).

Undoubtedly, the most important question is whether the presented stimulation training has an impact on daily functioning. The analysis of the self rating inventory for every day attentional problems (FEDA) disclosed less distractibility and fatigue as well as a lower degree of slowing of both mental processes and physical activities. Furthermore, in a final interview, many of the patients pointed out that the experience of improving cognitive performance (based on both the trainer's feedback and their own perceptions) was important for their sense of self esteem, especially with respect to their progressive disease, involving mostly deterioration and rarely improvement of physical and mental functions.

In conclusion, our results underline the importance of a detailed assessment of attention functions in patients with multiple sclerosis to identify specific deficits in the attention domains described. Such an evaluation allows us to target the neuropsychological intervention—for example, to administer a specific computer assisted retraining that has shown efficacy in this study. In general, the training tasks should resemble daily attention situations as closely as possible. In this context the prospects of virtual reality offer interesting possibilities. To optimise rehabilitation outcome a combination with strategy training[44–47] would be useful.

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