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Efficacy of alertness training in a case of brainstem encephalitis: Clinical and theoretical implications

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Although attention functions are often impaired after stroke, traumatic brain injury or inflammatory diseases, little is known about the time course and the long-term efficacy of training-induced improvement. The present single case study evaluates the time course and longitudinal stability of attention improvement after alertness training by repeatedly testing the subject between individual training sessions as well as one and seven months after the end of the training. The outpatient (M.P.) trained developed severe alertness deficits following brainstem encephalitis in 2003 without signs of cortical damage, and since then had not achieved full recovery. In 2008, M.P. participated in 15 treatment sessions on 15 separate working days over a period of three weeks. In each session a 45-minute alertness training task was administered, using the CogniPlus ALERT computer training program. Attention performance was assessed by neuropsychological tests four years, one year, and immediately before the therapy after every third training session and three times after the termination of therapy. Furthermore, a self-report questionnaire measured subjective experience of attention in everyday life situations. In order to compare the performance between training sessions, a procedure specialised for psychometric single-case diagnosis was used to analyse the data. Surprisingly, even after three consecutive training sessions, M.P. showed immense improvement in alertness. Furthermore, after two weeks she felt more energetic and more able to concentrate. Six months after the end of the training the improvement remained stable. The unexpectedly fast time course of recovery
induced by the training, as well as the stable long-term effects, probably depend on intact cortical structures. In M.P. it appeared that top-down control of the alertness network on impaired brainstem arousal structures had been re-activated by the training procedure and had remained stable across a long time period.

**Keywords**: Arousal deficit; Alertness training; Improvement of attention functions; Long-term effects.

**INTRODUCTION**

It is impossible to read a newspaper, watch television or to have a proper conversation without attention. This renders attention one of the most important cognitive functions. A lot of research has been conducted in order to elucidate attention deficits and their rehabilitation. However, it is not clear how attention can be trained in the most efficient way to achieve good and long-lasting effects. This study aims to shed light on the time course of attention improvement and how to retrain it.

In order to train attention deficits properly, deficits in specific domains of attention need to be elaborated (Sturm, Willmes, Orgass, & Hartje, 1997). With the variety of attention deficits caused by traumatic brain injury (TBI), stroke and other brain lesions, it became evident that Posner’s well-known three-fold attention system (the orienting network, the executive network, and the alerting network: Fernandez-Duque & Posner, 2001; Posner & Peterson, 1990; Posner & Raichle, 1997) needs to be further differentiated into subsystems (Cicerone et al., 2005; Mathias & Wheaton, 2007). The attention taxonomy proposed by Sturm (2008) which, in its core functions, refers to the taxonomy system of van Zomeren and Brouwer (1994), proposes three main domains of attention: intensity, spatial attention, and selectivity. According to this taxonomy, energetic (intensity) aspects of attention can be further subdivided into three subgroups: intrinsic (or tonic) and phasic alertness, sustained attention, and vigilance. Intrinsic alertness is thought to function as a top-down control of the arousal system without the influence of external stimuli. Tonic changes of (intrinsic) alertness are mostly attributed to physiological, diurnal changes in the organism. Phasic alertness is “the capability to enhance response readiness following a warning stimulus” (Sturm et al., 1997, p. 82).

In PET-activation studies, Sturm and colleagues (1999, 2004) showed that intrinsic alertness is controlled by a widespread right hemisphere network. Inferences from these studies lend support to the assumption that the right anterior cingulate cortex (ACC) modulates intrinsic alertness via the thalamus (Mottaghy et al., 2006). The reticular nucleus of the thalamus acts as a gating system. The nucleus under “frontal control” allows noradrenergic activation
to spread to the inferior parietal lobe and to the middle frontal gyrus (Sturm et al., 1999).

Sustained attention encompasses the detection of changes over a long-lasting period with a high rate of relevant stimuli. Vigilance, on the other hand, is defined as “a state of sustained alertness”, when only a low rate of relevant stimuli exists. Both intensity functions also rely on a right hemisphere fronto-parietal network (Pardo, Fox, & Raichle, 1990; Paus et al., 1997).

The intensity category as a whole seems to have an important impact on attention rehabilitation (Robertson, Tegnér, Tham, Lo, & Nimmo-Smith, 1995; Sturm et al., 1997; 2004; Sturm, Thimm, Küst, Karbe, & Fink, 2006; Thimm, Fink, Küst, Karbe, & Sturm, 2006; Thimm et al., 2009). The positive effects of alertness retraining are evident in behavioural and functional analyses. Sturm and co-workers (1997, 2004) developed a computerised alertness training procedure (AIXTENT) during which the patient has to watch a car (motorcycle) driving along a winding road. The patient’s task is to drive the vehicle as fast as possible but to stop just in time in front of obstacles on the road. These obstacles are announced (depending on the difficulty level) by blinking traffic signs, by non-blinking traffic signs, or not at all. Patients have to learn to adapt their speed to the specific needs of the task and to use warning signals as alerting means for optimal reactions. At the highest difficulty level the warning signal is omitted and trainees must take their information regarding the possible appearance of obstacles from other cues in the program. The training led to a significant improvement in a control test (subtest “Alertness” from the Test of Attentional Performance – TAP; Zimmermann & Fimm, 2007) and to an improvement in the self-evaluation of fatigue in the Attention Questionnaire (FEDA) also applied in the present study (Plohmann et al., 1998). In a PET/fMRI study patients with alertness deficits after right frontal vascular lesions who behaviourally responded positively to the AIXTENT alertness training revealed a perilesional right frontal reactivation of the alertness network (Sturm et al., 2006).

Sturm and colleagues (1997) describe a hierarchical system for attention processes. According to their assumption, alertness and sustained attention are the most basic attention functions needed for all attention processes. Thus, if training improves the alertness system, other attention processes might also improve. However, the most important implication of their study was that attention deficits in the intensity domain must be specifically trained in order to improve. Hence, if a patient suffers from problems in alertness, the training should focus principally on this particular function. Nonspecific attention training may even lead to deterioration in the intensity attention domain (Plohmann et al., 1998; Sturm et al., 1997, 2003).

This study aims to clarify how training of attention intensity (alertness training) affects different forms of attention and what the implications for
clinical practice are. Furthermore, the time course of training-induced attention improvements is largely unknown. Up until now, researchers in this field took approximately 14 training sessions to detect significant improvements (Engelberts et al., 2002; Plohmann et al., 1998; Sturm et al., 1997; 2003). However, under specific conditions improvement might be seen much earlier. This study aims to investigate the progress of attention functions during alertness training longitudinally. This is of special importance in planning intensity and frequency of training sessions.

The outpatient (M.P.) receiving alertness training in this study was primarily suffering from general fatigue. M.P. sustained a brainstem encephalitis in 2003 and never fully recovered. She was no longer able to work under pressure, quickly lost concentration during meetings at work, and was unable to follow conversations. She had had to cut her working time to half normal hours and decided to work at home for a few months in 2004. Even everyday tasks such as driving and talking to people exhausted her.

METHOD

Participant

M.P. was a 43-year-old right-handed woman who was an outpatient at the University Hospital in Aachen. In 2003, she sustained brainstem encephalitis. Initial symptoms were imposture, emesis and blurred vision. A neurological assessment revealed oculomotor dysfunction to the right, a right facial paresis and hypaesthesia of the right half of the body. These symptoms rapidly regressed after intravenous antibiotic therapy. A cranial MRT as well as a control MRT scan were normal. Nevertheless, M.P. had since then been complaining of attention deficits, fatigue and memory impairment. She underwent neuropsychological assessment in 2004 and 2008. Test results from May 2008 showed average performance in logical thinking (subtest “reasoning” of the German LPS, a test battery representing Thurstone’s primary mental abilities; Horn, 1983), word fluency (subtest “formal lexical fluency” from the LPS) and spatial orientation (subtest “mental rotation” from the LPS). Severe deficits were evident in the attention domains. Phasic and intrinsic (unwarned) alertness were well below average. When the intrinsic alertness test was administered again two hours after the first test with other neuropsychological testing in between, further deterioration was evident. These results are clear evidence that M.P. could not maintain an average level of alertness, especially after working for a prolonged time. Recent research indicates that goal maintenance may be especially challenged under “simple” conditions with no interference, conflict, or dual-task demands, as is characteristic of simple reaction time (SRT) tasks used to assess intrinsic alertness (Dreisbach
& Haider, 2007; Goschke & Dreisbach, 2008; Kane & Engle, 2003). There, individuals are assumed to need more effortful control to “stay on the job”, which would render SRT tasks even more susceptible to fatigue (cf. Walker, Muth, Odle-Dusseau, Moore, & Pilcher, 2009). Vigilance appeared to be average in the first part of the test. However, the second half of the 30 minute assessment revealed extreme deterioration. Focused and divided attention capacities were also well below average. Similar test results in May 2004, too, had shown that intrinsic alertness was the most affected attention domain. M.P. did not suffer from any psychiatric disorder as evidenced by self-reports (Freiburg Personality Inventory, Beck Depression Inventory) which were administered in 2004 as well as at the beginning and end of the training period. Neither during baseline nor during the training phase did M.P. receive any medication that might have affected attention performance. M.P. was informed about the procedure and the aims of the training and gave oral informed consent.

Design and treatment

M.P. participated in 15 treatment sessions on 15 consecutive working days (Monday to Friday) over a three week period. Treatment consisted of a 45 minute alertness training task, using the CogniPlus program (Version 2.01; Sturm 2007). During the training period M.P. was excused from her normal half-time working routine.

The effectiveness of the treatment was assessed using the WAF subtests from the Vienna Test System (Version 22.00; Sturm, 2007) and the Test of Attentional Performance (TAP; Zimmermann & Fimm, 2007) one day before the start of treatment (pretest) and after 3, 6, 9, 12, and 15 treatment sessions (T1–T5, respectively). Four weeks and six months after the end of the training two further test sessions were carried out (January 2009 and June 2009, respectively). Between May 2008 and the actual intervention in November 2008 a baseline period was established for the above-mentioned attention domains. The alertness data from 2004 are included as an additional long-term baseline. In order to measure subjective complaints, the FEDA (Fragebogen erlebter Defizite der Aufmerksamkeit: Questionnaire of experienced attention deficits; Sturm 2005), a self-report questionnaire, was administered before the first training session, after the 8th and the 15th training sessions and at the post-tests four weeks and six months after the end of the training. This questionnaire aimed to measure M.P.’s subjectively experienced changes in the attention domains “Distractibility and slowing of mental processes”, “Fatigue and slowing concerning practical aspects”, and “Decrease of drive”.

Procedure

M.P. was not allowed to take any medication during the training and test periods. Testing was always carried out at the same time of the day (9:00
a.m.) in order to avoid tonic changes of arousal. An overview of the test and training procedure is given in Table 1.

M.P. carried out the attention test battery as described below. Every test, except for the intrinsic alertness test, was administered once. Intrinsic alertness had to be accomplished at the beginning (alertness I) and at the very end of each test session (alertness II). All sessions encompassed the same test battery.

### Alertness training

The alertness training consisted of a subprogram of the Attention Training Program CogniPlus (Version 2.01; Sturm 2007) and was developed from the AIXTENT alertness training described in the introduction. The patient sees a motorcycle from a driver’s viewpoint, in motion, in a realistic scene. Sudden events, such as falling trees or rocks, cars crossing the street, traffic lights changing to red, and animals crossing have to be responded to as fast as possible. There are two different modes of the training: (1) Training of phasic alertness: In order to evoke phasic alerting, the participant hears a warning signal and sees a traffic sign announcing possible target situations before the actual event happens. Feedback is given visually if an obstacle is overlooked or if the response was too slow. This feedback ensures that participants know when they have made an error so that they can work on improving their performance. (2) Training of intrinsic alertness: Under this training condition, no warning signals are given in order to provoke an improvement of intrinsic, top-down controlled alertness. Furthermore, under the intrinsic alertness condition the whole scene is fogged in order to prevent phasic alerting signals being evoked by the surroundings.
Under both conditions, the difficulty level is regulated by the average speed of the motorcycle. To reach a specific level, a minimum response time is necessary, ranging from 1.8 s at the lowest to 0.3 s at the highest level. Depending on the subject’s mean response time the difficulty level is adapted automatically by the computer program. If, on a specific level, for 10 consecutive “response situations” the maximal response time for this level is maintained in 80% of the situations, there will be a change to the next higher level. If responses are slower than the maximal response time in ≥50% of 10 consecutive situations, there will be a decline to the next lower level. Before starting the training, during an instruction and practice period, the mean response time of the patient is assessed, which, in turn, defines the initial difficulty level for the next training period.

**ASSESSMENT**

**Attention tests**

Neuropsychological attention testing was carried out with the WAF subtests of the Vienna Test System (Version 22.00; Sturm, 2007) and with the Test of Attentional Performance (TAP; Zimmermann & Fimm, 2007); both are computerised attention test batteries.

The applied test batteries (WAF subtests of the Vienna Test System and TAP) encompass phasic and intrinsic alertness tests, vigilance, and focused and divided attention. Phasic and intrinsic alertness tests, vigilance and focused attention tests are part of the WAF subtests of the Vienna Test System (Sturm, 2007). The divided attention task belongs to the TAP (Zimmermann & Fimm, 2007).

During the intrinsic alertness test, the participant has to press a button as fast as possible whenever a black circle (diameter 30 mm on a 17” screen) appears in the centre of the screen. The circle appears for 1500 ms and disappears if no response is given within this time interval. Interstimulus intervals (ISI) vary between 3–5 s. In order to test phasic alertness, an acoustic warning signal (400 Hz tone signal; duration 200 ms) precedes the target symbol (time between warning and target: 400–1000 ms). The intrinsic and phasic alertness tests take four minutes each. The intrinsic alertness task was administered once at the beginning (alertness I) and once at the end (alertness II) of each test session. Hence, the same test was administered twice in order to measure a possible decrease in alertness over time (see above). The tests used are standardized and scores are adjusted according to age and education. Thus, raw scores (ms) and standard scores can be used to describe changes in performance.

In all test and training sessions, the participant was instructed to do her best and to pay attention to the computer screen. Each test was preceded by a short
instruction and practice session. M.P. was aware of the purpose of the training. The whole test battery took about 80 minutes.

Self-report questionnaire

Additionally, a self-report questionnaire referring to subjectively experienced attention deficits (Fragebogen erlebter Defizite der Aufmerksamkeit, FEDA, Zimmermann and Fimm, 1997) was administered in order to explore daily functioning (Sturm, 2005). This questionnaire has three domains assessing different aspects of attention: (I) Distractibility and slowing of mental processes, (II) Fatigue and slowing concerning practical activities, and (III) Decrease of drive. The questionnaire is based on a Likert scale (1–5) ranging from very often to never. An example of the statements is: “I lose track of a conversation if too many things happen around me.”

Statistical analysis

In order to compare the performance between test sessions, critical differences (dcrit, α = .05) according to the methods of psychometric single case studies were used. Since for all reaction time parameters of the control tests standard norms (T-scores) as well as reliability estimates are available, critical differences according to the methods of psychometric single case analysis (Huber, 1973; Willmes, 1990) were computed. If the critical difference is surpassed by the observed difference between two test occasions, this change in performance cannot be attributed to measurement errors alone. Therefore, with the determination of a critical difference for repetitions of individual tests, significant changes between test occasions can be documented in the single case. This was done for the mean reaction time for all attention tasks and for the intra-individual differences between alertness I and alertness II per test session. See Table 2 for an overview of critical differences (T-scores) for the different tests.

Moreover, the scores of the FEDA questionnaire administered at different time points can be compared with each other. However, these scores remain

<table>
<thead>
<tr>
<th>Attention test</th>
<th>Critical difference (dcrit): T-scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alertness</td>
<td>≥ 7 (response time)</td>
</tr>
<tr>
<td></td>
<td>≥ 8 (standard deviation)</td>
</tr>
<tr>
<td>Focused attention</td>
<td>≥ 5</td>
</tr>
<tr>
<td>Vigilance</td>
<td>≥ 6</td>
</tr>
<tr>
<td>Divided attention, visual or auditory</td>
<td>≥ 4</td>
</tr>
</tbody>
</table>
The FEDA scores are given as percentile ranks and represent the probability with which a specific attribute can be expected in the healthy population.

RESULTS

Alertness

Critical differences between baseline 1 (BL1) in May 2004, baseline 2 (BL2) in May 2008, and pretest immediately before the start of the training in November 2008 show that for both alertness I and alertness II there is no significant change of performance across these test sessions (d_crit < 7). However, in BL1, BL2 and in the pretest, the performance for alertness II is significantly worse than for alertness I (d_crit ≥ 7). This means that deterioration in performance between the beginning and the end of each individual test session is evident and does not change during this time period.

A comparison between pretest and T1 performance (three days after starting the training) reveals significant improvement both in intrinsic alertness I (T = 38 vs. T = 52) and intrinsic alertness II (T = 20 vs. T = 42). There is further significant improvement for Alertness II between T1 and T2. All further tests show that the performance from then on remains stable for both alertness tasks, and that the difference between Alertness I and II (except for T5) disappears. This holds true even for the two post-test trials 4 weeks (January 2009) and 7 months (June 2009) after the end of the training. In June 2009 there is a somewhat steeper improvement for alertness I compared to alertness II. Thus, at this test occasion there is again a (just) significant difference between the two alertness tasks (Figure 1).

Standard deviations

Training-induced progress in alertness should go in parallel with stable reaction time and less fluctuation. Therefore, it is essential to examine intra-individual variability of reaction times. All intra-individual standard deviations are given as T-scores. Significant changes of standard deviations over time were calculated by using the critical differences approach (d_crit ≥ 8).

Intra-individual variability of reaction times stabilised during the alertness training. There was, however, significant spontaneous improvement of variability up to a T-score of 49 (normal range) already between baseline 2 and pretest immediately before the training started. In T5 and in the post-test, stability of reaction times was above average (T-score of 61 and 64, respectively). This represents further significant improvement in the stability of reaction times. Variability for intrinsic alertness II started below average at a T-score of 38. M.P. was able to improve performance to a T-score of 47
Figure 1. Intrinsic alertness (reaction time without warning) performance over time. Vertical dotted lines show significant differences (difference > dcrit, $\alpha = .05$) between alertness I and alertness II. Horizontal dashed lines show significant differences between two test occasions. BL = Baseline; Pretest = alertness test immediately before starting the training in November 2008; T1–T5 = alertness tests during training, three training sessions between each test session; January 2009 = alertness test four weeks after the end of the training; June 2009 = alertness test seven months after the end of the training.

Figure 2. Time course of intra-individual variability ($T$-scores for standard deviation) of alertness I and II. Vertical dotted lines show significant differences (difference > dcrit, $\alpha = .05$) between alertness I and alertness II. Horizontal dashed lines show significant differences between two test occasions.
There was no significant difference between variability for alertness I compared to alertness II only at T2, T4 and during the two post-test sessions. Figure 2 summarises the results for the standard deviations.

Non-trained attention domains

M.P. showed spontaneous recovery between May and November 2008 in the attention domains focused and divided attention and vigilance. Therefore, the pretest administered in November 2008 served as initial score and not the one administered in May 2008.

Critical differences for T-scores referring to response time show that the performance in all attention domains improved. This improvement perpetuated up to the second test session during the training (T2). From then on test performance remained stable and M.P. reached an average or even above average level of performance in all attention domains. Data are given in Figure 3.

FEDA and subjective experiences in everyday life

Subjective experience of attention deficits was assessed using the self-report FEDA questionnaire.

Figure 4 shows that M.P. reported subjective reduction of her attention complaints addressed in the questionnaire. The scores show that she started
below average in the FS (fatigue and slowing in practical aspects) and DS (distractibility and slowing of mental processes) scales. After eight training sessions she achieved average results in DS; results in DD (decrease of drive) rose to the upper average level. However, the FS domain stayed below average although it improved compared to the pretest. All scores remained stable from then on.

As described in the introduction, before the start of the training M.P. primarily suffered from fatigue and distractibility. Since test performance uncovered severe deficits in the alertness task, this domain was trained. Following the final training session, M.P. additionally reported that she was feeling less tired during activities of daily living, for example, unlike in previous years, she did not feel exhausted after a meeting at work. Rather, she felt excited, just as she had at similar occasions before the illness. Furthermore, prior to the training, she felt pain all over her body when she was tired and when she had to focus on a particular task. These symptoms ceased after the third week of training. Four weeks later M.P. was able to concentrate during a long work meeting for the first time for years and did not experience the usual exhaustion afterwards.

**Time course of difficulty levels achieved during the training**

M.P. started the phasic alertness training (warning cues preceding critical situation) on difficulty level 11 (maximum response time 0.65 s) and reached level 12 after three training sessions, from where she gradually increased her performance up to level 16 (0.40 s) after seven training sessions. The intrinsic alertness training period (training sessions 11–15) started at level 17 and this level was maintained (except for session three when it
dropped to level 16) for the next seven sessions up to the end of the training. Thus, the time course of difficulty levels achieved roughly follows the time course of alertness test performance.

**DISCUSSION**

The aim of this study was to investigate the impact of alertness training on intensity aspects of attention and other attention domains such as divided and focused attention in a patient suffering from isolated damage to the brainstem. Furthermore, since little is known about the time-course of training-related attention improvements, this time course also was of specific interest in our study. For years M.P. had presented with severe deficits in alertness which were prominent since she had suffered from brainstem encephalitis. Thus we chose the alertness domain for attention retraining for a total of 15 training sessions. Test sessions took place after three consecutive training sessions. Post-tests were administered four weeks and six months after the final training session. The present design enabled us to use the patient as her own control subject.

It was continuously possible to assess the specific attention domains and, by means of standardised test procedures, the change of the inspected capacities could be explored and evaluated for significant changes by measures of psychometric single case analysis, making use of reliability-related critical difference values. The intrinsic alertness performance measured by the alertness test described above was crucial to this study. The test was administered twice at each test occasion: once at the beginning of each test session (alertness I) and once at the very end (alertness II). This enabled us to see whether M.P. improved in maintaining the same alertness level over time after prolonged working periods which had proved to be one of her main deficits. Baseline and pretest performance showed that alertness II always differed significantly from alertness I and was always in a range far below average.

The results of the alertness training were surprising in that significant improvement could already be seen in T1 after just three consecutive training sessions. Alertness I (the intrinsic alertness task administered at the beginning of each test session) changed from below average to average performance. Performance stayed on an average level for the whole testing procedure and M.P. achieved long-term stability of her alertness performance even for six months after the end of the training. Since M.P. performed below average in the baseline tests as well as in the pretest immediately before the training started, without signs of any changes in performance for years, it is most likely that the improvement in alertness was caused by the training procedure. The same holds true for alertness II. After six training sessions,
improvement of alertness II clearly showed that M.P. was able to hold attention for a longer period of time reflected by comparable performance for alertness I and alertness II. Here, the progression was even more pronounced. As already pointed out, M.P. performed well below average for alertness II in the baseline tests and the pretest, and stabilised over the training period to average performance. It is noteworthy that already during T1 the difference in performance between alertness I and alertness II diminished, and it completely disappeared at T2. This demonstrates that the trained intensity domain benefited immensely from the exercises (although at the end of the training, alertness II, while still in the normal range, tended to deteriorate again).

Alertness was the attention domain that was specifically trained. In accordance with the results shown in earlier studies (Plohmann et al., 1998; Sturm et al., 1997; 2003) our data revealed the most prominent improvements in this particular attention domain. Since performance in other attention functions also showed some improvement, it may be that the positive effects of the alertness training spread to other domains as well. However, it is difficult to disentangle effects of training and spontaneous recovery for the other attention domains, since they already showed significant improvements between the baseline and pretest phases. The same holds true for changes of intra-individual variability of reaction times in the alertness task, although, in accordance with other studies (O’Connell et al., 2008; Sturm et al., 1997), there seemed to be some specific benefit from the training: During the two post-test occasions and one and seven months after the training the difference of intra-individual variability between alertness I and II disappeared.

The rather rapid progress in the alertness task might be explained by the specific lesion features of our patient. As mentioned before, M.P. sustained brainstem encephalitis in 2003. The brainstem is known to be involved in arousal processes and in bottom-up energetic aspects of attention (Sturm et al., 1999, Sturm & Willmes, 2001). Sturm et al. (1999) showed that the top-down control of alertness (intrinsic alertness) depends on a right-hemispheric network consisting of cortical structures, such as the anterior cingulate cortex (ACC), the middle frontal gyrus, and the brainstem reticular formation. Path analyses of these results revealed that the ACC activates the thalamic gates in order to allow the distribution of the neurotransmitter noradrenalin (NA) to cortical sites involved in a specific task (Mottaghy et al., 2006). The crucial agent, NA, originates from the locus coeruleus (LC) in the brainstem (Aston-Jones, Rajkowsk, & Cohen, 1999). NA is heavily involved in the sleep–wake cycle and therefore also in the function of alertness. Damage to reticular parts of the brainstem and especially to the LC may elicit states of drowsiness and reduced wakefulness (Pace-Schott & Hobson, 2002). Further evidence for the role of the LC in alertness comes from studies concerning sleep and arousal. In an aroused state, animals show enhanced LC activity whereas decreased activity is prevalent during drowsiness (Aston-
Jones et al., 1999). Furthermore, noradrenergic agonists and antagonists influence alertness in animals (Berridge & Waterhouse, 2003). A study conducted by Witte and Marrocco (1997) showed that administering the α2 adrenergic agonist clonidine slowed down response times in rhesus monkeys. Thus, an (artificially) impaired LC impedes cognitive velocity.

Probably, the brainstem encephalitis M.P. suffered in 2003 led to malfunctioning of the noradrenergic system. Before the training, she had an increased need for sleep and often felt tired and unable to work under pressure. The main deficits were reflected in slowed reaction time and increased response time variability and were less pronounced for error rates in the attention tasks representing attention selectivity. Obviously, there had been no spontaneous recovery from this deficit for many years. On the other hand, a training-induced recovery of this deficit was possible since crucial cortical areas enabling top-down control on the arousal system were still intact in our patient. This top-down control of the noradrenergic system was addressed by the alertness training programme; functional changes may have taken place and the system may have recovered and/or reorganised (Sturm et al., 2004). In summary, it appeared that M.P. had a disturbed arousal system caused by brainstem encephalitis. The training probably activated the frontal cortex, including the ACC, as has been shown in functional imaging studies (Sturm et al., 2004), and the activation of these structures improved the top-down control of subcortical arousal processes. Interestingly, this improvement in our case was achieved after only three 1-hour training sessions and remained stable for a very long time, while former studies with patients suffering from cortical lesions reported substantial improvement not earlier than after three weeks of intensive training. It seems that damage to cortical structures of the alerting systems calls for a much longer reorganisation process in order to regain at least near normal performance (Sturm et al., 1997; 2004; 2006). However, these results need to be re-examined and confirmed by further imaging studies.

The effects of the training were not only obvious in the test results but also in M.P.’s subjective experiences. She felt more vigorous and alert. Furthermore, the test results gave her the confidence to perform well in everyday tasks, without fear of exhaustion and tiredness. Two weeks after the beginning of the training programme, M.P. felt more energetic and more able to concentrate on tasks at hand. Four weeks after the final training session, she was able to attend meetings at work and felt less sleepy. These results are in line with the results of the FEDA questionnaire. M.P. showed a stable subjective improvement after eight training sessions, reflected in her responses on the FEDA assessment. The FEDA scores had a particular focus on improvement in the trained attention domain. The FEDA dimension “Distractibility and slowing of mental processes” represents arousal processes and showed the highest level of improvement.
However, there are some limitations to the present study. First, and most importantly, it is a single-case study. Therefore, generalisation to other patients has to be treated with extreme caution even though there are several examples in other studies that prove that alertness training is effective (Plohmann et al., 1998; Robertson et al., 1995; Sturm et al., 1997) and may lead to a functional reorganisation in the networks involved (Sturm et al., 2006; Thimm et al., 2006, 2009). However, since nobody so far has investigated the time-course of the improvement, it is not clear whether this quick change in performance is due to the specific brainstem lesion of M.P. without the involvement of cortical sites or whether this might be a more general time course of improvement that may be seen in other patients as well.

Secondly, the self-report method we administered to measure improvement in daily living might only have limited validity because there might be a strong tendency for patients to express compliance for a specific rehabilitation method by giving more positive self-evaluations in the course of the therapy. On the other hand, the fact that there was only improvement for the scales referring to fatigue indicates that M.P. at least did not develop a general tendency for “streamlined” subjective evaluations. Furthermore, the fact that four weeks after the final training session M.P. was able to attend meetings at work for the first time for four years and that she felt less tired while doing so can be taken as more objective evidence for improvement of alertness control.

Furthermore, one might argue that the progress in M.P’s performance was due to test repetition. M.P. herself did not report that she got used to the tasks, and the simple reaction time task used for assessment of alertness revealing the most prominent improvement is so easy that profit from test repetition is highly implausible. Furthermore, since the baseline of alertness was very stable for about five years, improvements in this specific attention domain after training cannot be attributed to learning effects. Alertness training seemed to affect primarily intensity aspects of attention. In the case of M.P. this concerned intrinsic alertness and vigilance. However, as described above, vigilance also improved between baseline and pretest and therefore further progress cannot be solely attributed to the training. Alertness improved after the very first training sessions, and performance remained stable from then on. The other two attention domains, focused and divided attention, seemed to improve more gradually following the intensity training. Performance kept improving until the final training session. However, in these attention domains there was also an improvement between baseline and pretest performance and therefore, again, progress cannot be purely attributed to training. However, intra-individual response stability also improved due to the training.

These results give further insight into the use of alertness training in clinical practice. A patient who suffers from alertness deficits should undergo a training programme tailored specifically to his or her condition. It is very
likely that other attention domains may benefit from this kind of training programme, too. Training is likely to be more effective if no or only a small area of the relevant cortical network is damaged. An intact frontal cortex is important, particularly for the alertness training, in order to establish and re-activate damaged subcortical arousal systems. Referring to this single-case study, it seems that if cortical areas are not affected, progress in the trained attention domain can be achieved in a relatively short time span. M.P. showed significant improvement after just three training sessions, which was entirely unexpected. After six training sessions, the performance further improved and then remained stable until the end of the training and test period. However, it seems reasonable to train patients for longer than three days since it is unlikely that long-term functional reorganisation can take place in such a short time. This especially holds true in cases of cortical damage to the alertness network. Non-trained attention domains seem to need longer until they improve. This study corroborates earlier findings that the trained attention domain benefits most from the training programme. Nevertheless, other attention domains may benefit in later stages. Intra-individual stability of response times is also achieved by the training. Prior to the treatment, M.P. showed immense fluctuations in reaction times within one test session.

To sum up, the present outcome fits with the literature concerned with alertness training after brain damage. M.P.’s recovery from alertness deficits induced by brainstem encephalitis revealed effectiveness of the training in a relatively short period of time. In contrast to patients who suffered cortical lesions, M.P., as well as showing fast progress, also showed long-term improvement (Sturm et al., 2006). Additionally, as has been shown, the training may also improve other impaired attention areas. However, the effectiveness of the training seems to depend on intact cortical structures. In the case of M.P., functional reorganisation, probably leading to improved top-down control on impaired brainstem arousal structures, was possible and therefore long-term beneficial effects were present.

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