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A systematic review of the effects of early onset cognitive rehabilitation on acquired brain injury patients from a neural perspective

Review

Cognitive impairments – a frequent consequence of acquired brain injury (ABI) – are currently addressed by compensatory approaches within cognitive rehabilitation. However, several studies support a restorative approach, because a period of increased neural plasticity is seen in the first three months after ABI. Starting neuropsychological rehabilitation within this period could maximize functional improvement. To examine this hypothesis, a systematic review of randomized controlled trials on early onset cognitive rehabilitation programmes for ABI patients was executed. A total of thirty studies were included studying 1988 patients. Thirty-seven per cent was found to be effective in restoring (partly) multiple domains of cognitive functioning, especially visuospatial functioning and awareness. The influence of intervention onset on cognitive functioning was evaluated by comparing the effectiveness of early and late onset rehabilitation programmes. A new theoretical model, the Interplay Model, and guidelines for a more restorative approach in clinical practice and future research are discussed.
Keywords: Acquired Brain Injury (ABI), cognitive neuropsychological rehabilitation, systematic review, restorative approach.

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INTRODUCTION

Cognitive impairments are a frequent consequence of acquired brain injury (ABI). ABI can be subdivided in cerebrovascular accident (CVA) and traumatic brain injury (TBI). A CVA or stroke is the loss of brain function due to ischemia or haemorrhage (van den Berg & van Zandvoort, 2012). Ischemia, lack of blood flow, arises when a blood vessel is blocked while haemorrhage, loss of blood, arises due to a tear in the blood vessel. A CVA causes the loss of brain functionality which could comprise multiple cognitive functions. More than 50% of the CVA patients experience cognitive function disorders (Bots et al., 2009). Cognitive impairments can also be a consequence of TBI, which is brain damage due to an external force on the skull (Stapert & Spikman, 2012). The prevalence of ABI, especially CVA, is high and will increase enormously over the following decades due to the aging population and lower mortality rates (Koek et al., 2005). Which cognitive impairments are commonly seen after ABI are dependent on the locus and severity of the brain damage.

Commonly seen affected cognitive functions are attention (e.g. loss of ability to concentrate), memory (mostly anterograde), mental speed (e.g. slowness), social cognition (e.g. loss of empathy), executive functions (e.g. inability to plan, be cognitively flexible and regulate behaviour) and language (e.g. inability to speak). Cognitive rehabilitation tries to address these impairments and their enormous interferences with daily life activities and participation in society.

According to many national clinical guidelines cognitive rehabilitation is a standard component of rehabilitation programmes for ABI patients (van Heugten et al., 2012). The effectiveness of different cognitive rehabilitation programmes is well established by Cicerone et al. (2000, 2005, 2011). Especially, attention training after TBI and language and visuospatial training for respectively aphasia and neglect syndromes after stroke are found to be effective. Another conclusion by Cicerone et al. (2000, 2005, 2011) is that the current approach of cognitive rehabilitation is mostly compensatory, meaning that the patient is taught to compensate for their impaired functions with their intact functions (e.g. an agenda for memory problems). According Krakauer et al. (2012) this is a consequence of the proven effectiveness of compensatory interventions on functional outcomes. However, improving the impaired function itself and therefore minimalizing the interference with daily life activities would be a tremendous improvement for the patient, the patient's surroundings and the therapist.

Lately a new view towards neural plasticity of the adult brain has been extensively investigated in animal studies, which supports the possibility of improving impaired cognitive functions due to ABI. Neural plasticity is the possibility of neurons to structurally and functionally adapt.

In animal models it is found that after acquired brain injury heightened plasticity occurs in the residual neural circuits. This means that there is a higher possibility that other intact neurons could replace the damaged neurons and take over their original function and therefore restore the cognitive functioning of the patient. This plasticity is found on the level of cortical activation maps, neurotransmission, dendritic spine structures and axonal connections.

Dijkhuizen et al. (2003) found that cortical sensory maps are highly plastic within the first two weeks after a stroke. Directly after a stroke, unilateral sensory stimulation leads to activation of the ipsilateral cortex instead of the contralateral cortex. However, after two weeks the same sensory stimulation leads to activation of the contralateral cortex. The shift of an abnormal activity response to a normal activity response is correlated with level of sensory recovery. On a cellular level, Clarkson et al. (2010) found that in the first weeks after a stroke motor neurons are hypo-excitable due to diminished re-uptake of the inhibitory neurotransmitter GABA. This diminished re-uptake leads to more GABA in the synaptic cleft, which leads to less signal transduction. Fortunately, the excitability of the motor neurons is restored within two weeks and remaps limb functioning. Formation of new axonal connections, also known as axonal sprouting, and reorganization of dendritic spines, also known as dendritic spine morphogenesis, accompany this process (Brown et al., 2009).

An extensive amount of research has shown that the neurophysiological processes causing the plasticity in a human brain are comparable to the described neurophysiological changes in a rodent brain (Grossman et al., 2002; Sadato et al., 1996). This is highly influenced by the common role of the brain-derived neurotropic factor (BDNF) in rodents and humans. BDNF enables the structural changes needed for plasticity (Murphy & Corbett, 2009).

This heightened plasticity is the underlying mechanism for relearning the impaired function driven by brain injury and learning in the intact brain driven by behavioural experiences (Kleim, 2011; Krakauer et al., 2012). In the intact brain the amount of plasticity is negatively related to age, meaning that plasticity is very high in the immature brain and gradually diminishes after maturing (Eriksson et al., 1998). A short window of increased plasticity is seen in the first three months after acquired brain injury to provide rearrangement of impaired functions to different intact brain regions by several structural changes. This is the so-called intrinsic repair/learn capacity of the brain (Krakauer et al., 2012).

There is a possibility that rehabilitation enhances this intrinsic repair capacity of the brain, so that there is interplay between the two causal factors of neuroplasticity: injury and experience. In other words, rehabilitation could optimize the neural plasticity and therefore the functional improvement. Importantly, in the phase of heightened plasticity, the first four weeks after ABI in rodents and the first three months after ABI in humans, the brain can maximally recover and maximal functional improvement can take place (Kleim et al., 2008; Krakauer et al., 2012; Murphy & Corbett, 2009). Biernaskie et al. (2004) reported that rats exposed to rehabilitation initiated within the period of heightened plasticity (5 days after stroke) experienced a significantly greater recovery than rats exposed to rehabilitation which was not initiated within the period of heightened plasticity (30 days after stroke). This finding and comparable findings by Chikahisa et al. (2006) and Kim et al. (2006) support the possibility that rehabilitation enhances this intrinsic repair capacity of the brain. However, implementing rehabilitation or training in the first days, could have the opposite effect, namely worsening of the impairment, due to overuse effects (Kleim et al., 2008; Krakauer et al., 2012; Murphy & Corbett, 2009).

Translating these findings to humans and clinical practice would imply to start interventions for cognitive impairments within these three months, because these interventions could benefit from the restorative ability of the brain. So, if heightened neural plasticity is a requirement for maximal effectiveness of cognitive rehabilitation, which implies a more restorative approach, this should be shown in a greater effect of early onset cognitive rehabilitation on cognitive functions than late onset cognitive rehabilitation measured by the same outcome measures.

To examine the possibility and evidence for this restorative approach in a clinical setting, randomized controlled trials evaluating the effectiveness of cognitive rehabilitation programmes for ABI patients, starting within three months after the injury will be reviewed. Content and effects of these programmes will be evaluated. Furthermore, a comparison between early onset cognitive rehabilitation programmes and late onset cognitive rehabilitation programmes is made. Implications for clinical settings and future research are discussed according the Interplay Model.

METHODS

The following method was used to identify randomized controlled trials (RCTs) evaluating early onset interventions targeted at cognitive impairments as a consequence of acquired brain injury, published within the period from January 1970 until August 2010.

The database created by van Heugten et al. (2012) was filtered by an eight exclusion criterion concerning early onset interventions, because their systematic literature search identified randomized controlled trials (RCT's) evaluating both early onset and late onset interventions targeted at cognitive impairments as a consequence of acquired brain injury, published within the period from January 1970 until August 2010.

The systematic literature search, which was executed by van Heugten et al. (2012), used PubMed and PsycINFO and was based on the articles found by Cicerone et al. (2000, 2005). For an overview of the search terms, see table 1. This process yielded 1963 published articles in PubMed and 959 in PsycINFO. In total 2832 articles were found after exclusion of duplicates.

Studies were only included if they addressed the effect of a cognitive rehabilitation programme in a randomized controlled trial with a non-progressive human adult ABI sample, which was defined operationally in the search terms. Only randomized controlled trials were included because of their high validity.

Further study selection was done on the basis of the following seven exclusion criteria: (1) no intervention; (2) other design than RCT; (3) reports without explicit description of randomization of patients; (4) subjects did not have acquired brain injury; (5) pharmacological interventions; (6) aim of intervention was not cognitive impairments; (7) language was not English. An article could be excluded based on title, abstract or full paper.

As already mentioned, for the purpose of this article an eight exclusion criteria was needed, namely that the intervention started later than three months after acquired brain injury (time since injury was longer than 91 days).

All included RCTs were identified by extracting the early onset interventions from the database created by van Heugten et al. (2012). Their database included 95 articles of which 30 articles started their intervention within three months after acquired brain injury. These 30 articles were included. See figure 1 for an overview of the selection process.

After study selection the articles were assigned to categories according to their primary area of intervention as was done in the previous reviews of van Heugten et al. (2012) and Cicerone et al. (2000, 2005, 2011): awareness, visuospatial functioning, memory, attention, executive functioning, apraxia, language and communication and multi-domain studies. The investigated domains of the selected 30 studies were awareness, visuospatial functioning, attention and language and communication. The following data was extracted: (1) intervention characteristics (duration, intensity, form); (2) patient characteristics (number of patients, type of injury, time since injury); (3) treatment outcome; (4) content of effective treatment.

Table 1. Search terms used for the period from January 1970 till August 2010 (van Heugten et al., 2012)

	Search Terms
Cognitive domain	Attention/concentration, information processing/slowness, awareness/insight, cognition, communication, executive/planning/organisation/regulation, language/aphasia, memory, perception/perceptual/agnosia/neglect/visual, problem solving, reasoning, apraxia/dyspraxia
Rehabilitation	Rehabilitation, remediation, education, training, retraining, paging system, treatment, treatments, therapy
Acquired brain injury	Stroke, brain injuries/brain-injuries/brain injury/brain-injury/brain injured/brain-injured, head injuries/head-injuries/head injury/head-injury/head injured/head-injured, brain damage/brain damaged, tbi/head trauma/traumatic, cerebrovascular disorders/cerebrovascular accident/cerebrovascular accidents/cva/stroke/poststroke/post-stroke/post stroke, chronic aphasia

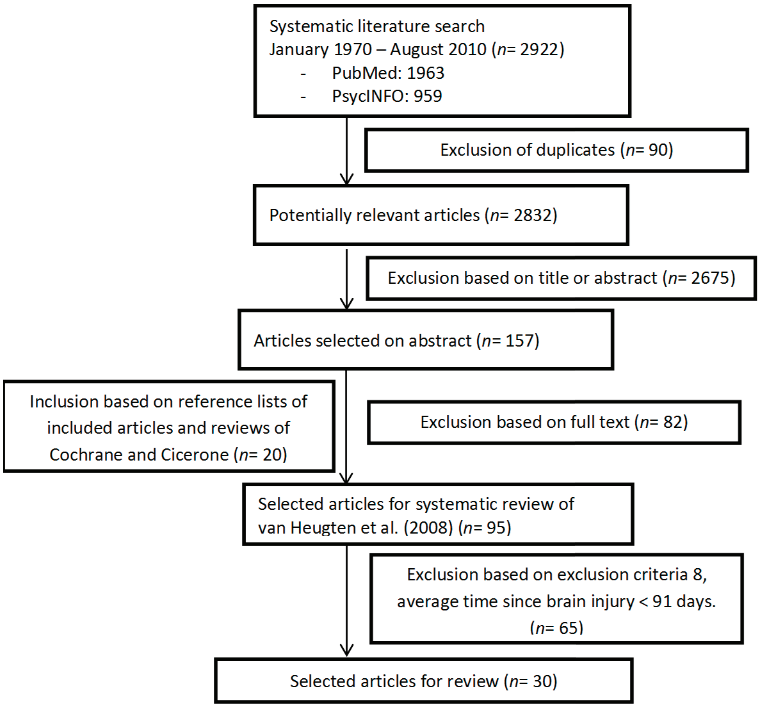

Figure 1. Flow-chart

RESULTS

The frequency of studies per domain (including all references) is shown in table 2. Most studies were conducted in the area of visuospatial functioning (n= 16). This is in line with the extensive amount of neglect rehabilitation research, which contains one of the oldest rehabilitation RCTs, namely the RCT conducted by Weinberg et al. (1977).

Table 2. Study Domains

Domain	n	%	Author, year of publishing
Awareness	5	17	Carter et al., 1983 Salazar et al., 2000 Sarkamo et al., 2008 Soderback, 1988 Vanderploeg et al., 2008
Visuospatial Functioning	16	53	Antonucci et al., 1995 Cherney et al., 2003 Edmans et al., 2000 Fanthome et al., 1995 Kalra et al., 1997 Katz et al., 2005 Lincoln et al., 1985 Luukkainen et al., 2009 Rossi et al., 1990 Rusconi et al., 2002 Si Hyun et al., 2009 Taylor et al., 1971 Tsang et al., 2009 Weinberg et al., 1977 Weinberg et al., 1979 Wiart et al., 1997
Memory			
Attention	4	13	Barker-Collo et al., 2009 Malec et al., 1984 Mazer et al., 2003 Novack et al., 1996
Executive Functioning			
Apraxia			
Language and communication	5	17	Bakheit et al., 2007 David et al., 1982 Lincoln et al., 1984 Wertz et al., 1981 Wertz et al., 1986
Multi-domain			
Total	30	100	

Treatment characteristics.

Type of therapy was not reported in seven studies. The other 23 studies provided individual therapy.

Frequency, duration and intensity were not always described in the original papers, for this reason the following data is based on 24 studies which did report these treatment characteristics. Frequency, duration and intensity are summarized in table 3. On average patients received 4.0 hours therapy per week for 8.7 weeks.

Table 3. Frequency, duration and intensity

	Mean	Standard Deviation
Hours	40.0	70.8
Week	8.7	9.1
Hours/Week	4.0	2.6

Patient characteristics.

In the included 30 studies 1988 patients were studied. The mean (SD) number of patients per study was 70.3 (66.3) ranging from 4 to 360. The largest study by Vanderploeg et al. (2008), for instance, included 360 adult veterans or active duty military service members with moderate to severe traumatic brain injury. Eight studies have included a sample of 20 participants or less, indicating a small sample size, which could influence interpretation of results.

The mean age of the patients was 59.9 years (SD = 13.9), ranging from 25.5 to 77.0. Most of the studies which included younger subjects assessed traumatic brain injury patients, while most of the studies which included older subjects assessed CVA patients.

The time since the acquired brain injury was described in all studies, which was also necessary for inclusion in this review. The intervention started on average 44.1 days after the injury (*SD* = 24.4, with a minimum of 4.7 days and a maximum of 88.3 days).

The most studied diagnosis was stroke, which was studied in 23 articles (76.7%). Other studied diagnoses were traumatic brain injury (*n*= 5, 16.7%) or heterogeneous populations (*n*= 2, 6.7%).

Treatment Outcome.

In 11 of the 30 studies the experimental treatment was found to be beneficial (*n*= 11; 36.7%), meaning that the improvements in the impaired cognitive functions were significantly higher in the treatment group compared to the control group. These improvements were measured by various outcome measures, like the line bisection task and letter cancellation test for visuospatial functioning. The other 19 studies concluded with no differences between experimental and control treatment (*n*= 13; 43.3%) or ambiguous results (*n*= 6; 20.0%). Ambiguous results consisted primarily of various effects on different domains.

Content of effective early onset interventions.

An overview of the characteristics of the included studies which examined effective early onset interventions can be found in table 4. Sample size, time since injury, content of interventions, outcome measures and results are mentioned.

Table 4. Characteristics of included RCTs which examined effective early onset interventions.

Domain	Study	N tot	N exp	N cntrl	Diag-nosis	Time since injury (days)	Intervention Experimental group	Intervention Control group	Mean hours a week (weeks)	Results	P
Visuospatial functioning	Antonucci et al., 1995	20	10	10	Stroke	79	Neglect rehabilitation training, which consisted of visuo-scanning training, reading and copying training, copying of line drawings on a matrix and giving a description of a figure.	General cognitive stimulation.	Exp: 5 (8) Control: 3 (8)	The experimental group showed significantly greater improvement on standard neglect tests, like the letter cancellation test, compared to the control group. These improvements were generalizable to daily life activities as measured by the Functional Scale for the Evaluation of Neglect.	<0.05
	Kalra et al., 1997 Full text unavailable	47	24	23	Stroke	6	Spatial-motor cueing based intervention with emphasis on restoration of functioning.	Conventional therapy, which concentrated on movement pattern, motor activity and restoration of tone.	Exp: 2.8 (12) Control: 3.3 (12)	- The experimental condition significantly outperformed the control condition on the letter cancellation subtest. Due to the movements of the affected limb, summation of brain activation will arise which will cause improvements in attentional skills and spatial exploration. - The experimental group stayed significantly shorter at the hospital than the control group.	0.01 0.001
	Katz et al., 2005	19	11	8	Stroke	41	Virtual reality based street crossing training.	Computer based visual scanning tasks.	Exp: 9 (4) Control: 9 (4)	- During virtual street crossing the experimental group made significantly fewer accidents than the control group. - The experimental group looked more to the left during virtual street crossing than the control group.	<0.04 NS

Weinberg et al., 1977 Full text unavailable	57	25	32	Stroke	70	Visual training (VT) + occupational therapy.	Occupational therapy, but no visual training (VT).	Exp: VT 5 (4) Control: VT 0 (4)	After one month the experimental group significantly outperformed the control group on different specific scanning tasks (e.g. letter cancellation task) and academic reading tasks which were hypothesized to depend on intact visual scanning.	<0.05
Weinberg et al., 1979 Full text unavailable	53	30	23	Stroke	42	Visuo-perceptual remediation with emphasis on sensory awareness and spatial organization.	Standard rehabilitation.	Exp: 5 (4) Control: 5 (4)	After one month the treatment group showed a significant greater improvement on visuospatial and academic tasks than the control group, which was most apparent in subjects with more severe perceptual impairments.	<0.05
Wiart et al., 1997	22	11	11	Stroke	33	The Bon Saint Come method (BSC), during which the patient wears a thoraco-lumbar vest with a metal pointer above his head in order to point to targets, while receiving visual and auditory feedback. In addition the patient received additional physiotherapy (PT) and occupational therapy (OT).	Standard rehabilitation.	Exp: BSC 5 (4) PT 10 (4) OT 1 (4) Control: 17 (4)	Scores on the assessments of neglect (e.g. line bisection) and ADL function (activities of daily living), measured by the Functional Independence Measure (FIM), showed a significant higher improvement in the experimental group than in the control group.	<0.05

Language & Communi-cation	Wertz et al., 1986 Full text unavailable	121	A: 43 B: 38	40	Stroke	36	A: First twelve weeks stimulus-response treatment by speech pathologist in clinic (SP), then twelve weeks no treatment (NT). B: First twelve weeks stimulus-response treatment by trained volunteers at home (VOL), then twelve weeks no treatment (NT).	First twelve weeks no treatment (NT), then twelve weeks stimulus-response treatment by speech pathologist in clinic (SP).	ExpA: SP 9 (12) NT 0 (12) ExpB: VOL 9 (12) NT 0 (12) Control: NT 0 (12) SP 9 (12)	After twelve weeks the two treatment groups performed comparable and significantly better than the control group on communicative ability measured with various language tests.	<0.05
Attention	Barker-Collo et al., 2009	78	38	40	Stroke	19	Standard care + Attention Process Training (APT).	Standard Care.	Exp: APT 5 (4) Control: APT 0 (4)	After five weeks the experimental group outperformed the control group as measured by the Integrated Visual Auditory Continuous Performance Test (IVA-CPT) indicating that APT had a significant positive effect on attention	0.01
Awareness	Carter, Howard & O'Neil, 1983	33	16	17	Stroke	5	Conventional therapy + cognitive skill remediation training. This training involved numerous elements, like paper and pencil tasks, positive reinforcement and immediate feedback.	Conventional therapy.	Exp: 1.5 (3) Control: 0 (3)	The treatment group showed a significantly higher improvement than the control group within three skill areas: visual scanning, visual-spatial orientation and line judgment measured by exercises of the Thinking Skills Workbook.	0.00

Sarkamo et al., 2008	55	A: 19 B: 19	17	Stroke	9	A: The music group listened for two months every day to music + standard rehabilitation. B: The language group listened for two months every day to audio books + standard rehabilitation.	Standard rehabilitation.	ExpA: 11.2 (8) ExpB: 9.1 (8) Control: 0 (8)	- After three months verbal memory, measured by the story recall subtest of the RBMT, improved significantly more in the music group than in the other groups. - After six months focused attention recovery, measured by summed reaction times during the Stroop task, was significantly higher in the music group than in the other groups.	<0.05 <0.02
Soderback, 1988. Full text unavailable	67	A: 15 B: 19 C: 15	18	Stroke	68	A: Intellectual function Training (IFT) plus standard rehabilitation. B: Intellectual Housework Training (IHT) plus standard rehabilitation. C: IFT + IHT + standard rehabilitation.	Standard rehabilitation.	ExpA: 3 (12) ExpB: 3 (12) ExpC: 2 (16) Control: 0 (11)	The three experimental groups were significantly more effective on intellectual functioning than the control group, measured by the Intellectual Function Assessment (IFA) and the Intellectual Housework Assessment (IHA).	<0.05

*Effect sizes are not mentioned because they were not reported or unavailable to the author.

DISCUSSION

Several studies showed the existence of a time window of heightened plasticity in the first three months after acquired brain injury (Kleim et al., 2008; Krakauer et al., 2012; Murphy & Corbett, 2009). Due to this finding it was hypothesized that early onset interventions would be more effective in enhancing cognitive functioning of ABI patients compared to late onset interventions, by benefiting from this intrinsic neural repair capacity. In order to examine this hypothesis, early onset interventions (time since injury <3 months) targeted at cognitive impairments as a consequence of acquired brain injuries (ABI) were identified by performing a systematic literature search. It is important to note that identification of some RCTs may have failed, although the used strategy identified those found in other systematic reviews (Bowen & Lincoln, 2008; Greener et al., 2008).

Thirty randomized controlled trials have been identified of which eleven found beneficial effects for stroke patients. Out of these eleven studies six studies were primarily aimed at treating spatial neglect and therefore improving visuospatial functions. More research on TBI patients is needed to generalize these results to TBI patients.

To investigate the cause of the effectiveness of the eleven studies and provide guidelines for clinical practice and research, therapy elements that the effective treatments have in common were identified per domain. In order to identify common therapy elements, content of the treatment programmes and hypothesized underlying mechanism were evaluated.

Extraction of communal treatment elements in the 'Visuospatial functioning' domain leads to the two conclusions. Firstly, Wiart et al. (1997) and Karla et al. (1997) assessed an effective training for spatial neglect which both comprises motor activation. A possible theory for this effectiveness could be that motor activation leads to a change in brain activity in networks which are linked with networks controlling visuospatial functioning. Through this indirect route, the increased activation will draw awareness to the neglected contra-lateral visual field and therefore, treating spatial neglect. However, this conclusion should be interpreted with caution. These findings are based on a relatively small sample size and assume a similar effect of brain activity and localization on this activity, which may not be valid. Secondly, Antonucci et al. (1995) and Weinberg et al. (1977, 1979) have shown that visual scanning training and other forms of visual trainings are a beneficial addition to standard rehabilitation for neglect patients. However, it remains unclear if the improvements on the specific tasks also generalize to the daily live activities of these patients. Katz et al. (2005) did show that virtual reality training could be beneficial for neglect patients and that these effects generalize to daily life activities. However, the programme should be further developed before application in clinical practice and future research is needed for replication of these results and further investigation of the causes of the effectiveness of these interventions. Overall, it can be concluded that the addition of motor training or visual scanning training is beneficial for treating neglect patients in the early stage of recovery. Motor training is often already part of the rehabilitation programme because of motor impairments. Further research into motor rehabilitation programmes with a 'side'-effect on cognitive impairments is necessary, while this could be a very effective, cost and time efficient standard rehabilitation programme for stroke patients.

Extraction of communal treatment elements in the 'Awareness' domain leads to the conclusion that awareness could be improved significantly in stroke patients by intensive training as an addition to the standard cognitive rehabilitation programmes. The discussed studies examined three different kinds of training, but all required an active role of the patient, which could be (part of) the reason for the effectiveness. Translation of these findings to traumatic brain injury patients should be studied more extensively, since these discussed studies included only stroke patients.

Extraction of communal treatment elements is not possible for the domain 'Language & Communication' and 'Attention', because there is only one effective study within these domains.

Another possible reason for the effectiveness of the eleven studies could be the interplay between cognitive rehabilitation and the heightened neural plasticity during the first three months after ABI (Chikahisa et al., 2006; Kim et al., 2006; Kleim, 2011; Sarkamo et al., 2008). If this neural plasticity is indeed a requirement for maximal effectiveness of cognitive rehabilitation, this should be shown in greater effect of early onset cognitive rehabilitation on cognitive functions than late onset cognitive rehabilitation measured by the same outcome measures.

To examine if the onset of the intervention has an influence on its effectiveness the results of early onset rehabilitation programmes (intervention onset < 3 months) were compared with the results of effectiveness of late onset rehabilitation programmes (intervention onset > 3 months), acquired by filtering the database of van Heugten et al. (2012). The proportion of studies that found a positive effect in cognitive functioning is higher in the late onset rehabilitation programmes than in the early onset rehabilitation programmes. Regarding late onset rehabilitation, more than half of the studies, 42 out of the 64 studies (65%), found beneficial effects of the intervention. Regarding early onset rehabilitation, only 11 out of 30 studies (36.7%) found beneficial effects of the intervention. These findings suggest that starting earlier with the rehabilitation programme does not increase the beneficial influence of the programme on improving cognitive functions due to ABI.

However, this conclusion should be carefully interpreted, because this is a rough comparison. The homogeneity of groups is restricted due to the difference in the distribution of the amount of studies in all the different domains and the difference in participant characteristics (only stroke patients vs. mixed patients) and outcome measures.

More importantly, the characteristics of the interventions differ between the early onset group and the late onset group. In the early onset group, interventions are primarily aimed at restoring the cognitive function. However, in the late onset group, interventions are primarily aimed at compensating for the cognitive impairment with intact cognitive functions. When the same outcome measures are used, measuring cognitive functioning, the same level of improvement could be found between the two groups. However, in the early onset group this could be the consequence of actual improvement of the cognitive function, while in the late onset group this could be the consequence of the compensating behaviour. For example, when a patient has memory impairments, due to early onset interventions the actual memory function will improve and therefore the patient reports less forgetting. In contrast, due to late onset interventions the patient learns to compensate for his memory loss by using a pager and therefore the patients reports less forgetting. The outcome is the same, but the underlying mechanism is different and therefore limits comparability.

The above mentioned reasons made clear why comparison between these two groups, early onset rehabilitation programmes and late onset rehabilitation programmes, is invalid. Therefore, no direct conclusions about the effect of onset on the effectiveness of cognitive rehabilitation can be made based on this comparison.

However, Antonucci et al. (2008) executed a RCT with onset of intervention as independent variable to examine if onset of rehabilitation had an effect. There were two groups of stroke patients, one group received the neglect rehabilitation training immediately after admission to the clinic and the other one received the same training after two months. They found that both groups obtained similar improvement which implies that the moment of onset of intervention had no influence on the effectiveness, which is in accordance with the results of this review.

Controversially, Horn et al. (2005) and Salter et al. (2005) reported in their reviews, which included 830 and 435 post stroke patients respectively, that earlier initiation of rehabilitation is preferred for stroke patients. For instance, Salter et al. (2005) reported that interventions started within 30 days result in greater functional gains than interventions started beyond 30 days. This means that there is a significant difference in functional outcome between interventions started within one month after brain injury and interventions started more than one month after injury. Yet, there are no differences in functional outcomes between interventions started one month after brain injury and interventions started two or more months after brain injury. This implies that a functional improvement window of one month appears after a stroke. Applying this to the results of Antonucci et al. (2008), the conclusion that the moment of onset of intervention has no influence on the effectiveness is invalid, since it is based on the comparison of interventions both started beyond 30 days, namely 79 days. These results imply that the hypothesized critical period of the first three months after brain injury seems to be too liberal and should be restricted to only the first month, which also limit interpretation of the current results of the review because the liberal 3 months criteria for early onset interventions was used.

Combining the discussed neural findings and clinical findings, a new theoretical model is suggested, named the Interplay model. This model states that maximal effect of a rehabilitation programme on cognitive impairments due to ABI can be achieved by initiating the intervention within the first month instead of the hypothesized three months. The first month forms the so-called window of opportunities, where the amount of neural plasticity exceeds the threshold for interplay between neural plasticity and rehabilitation. Furthermore, the model states that neural plasticity is enhanced in the first three months after brain injury, but that this enhancement gradually decreases after the first month till the premorbid level of neural plasticity is reached after three months. According to Wade et al. (1985) a similar course of recovery is seen in motor functioning of stroke patients. So only within the first month, the amount of neural plasticity is high enough for the possibility that rehabilitation enhances the intrinsic repair capacity of the brain, so that there is interplay between the two causal factors of neuroplasticity: injury and experience. In other words, only when a rehabilitation programme is implemented during a specific time window, where neural plasticity is above a certain level, it will cause a significantly greater effect on cognitive impairments than implemented beyond this time window. This model states that there is an effect of onset on the effectiveness of cognitive rehabilitation. So to maximize the effect of a rehabilitation programme on cognitive impairments due to ABI, the intervention should be initiated within the first month, the so-called window of opportunities. However, as mentioned before, implementing rehabilitation or training in the first days, could have the opposite effects due to overuse effects. This is included in the model, since the amount of neural plasticity does not exceed the threshold for interplay during the first week (Kleim et al., 2008; Krakauer et al., 2012; Murphy & Corbett, 2009). See figure 2 for a clarification of this model.

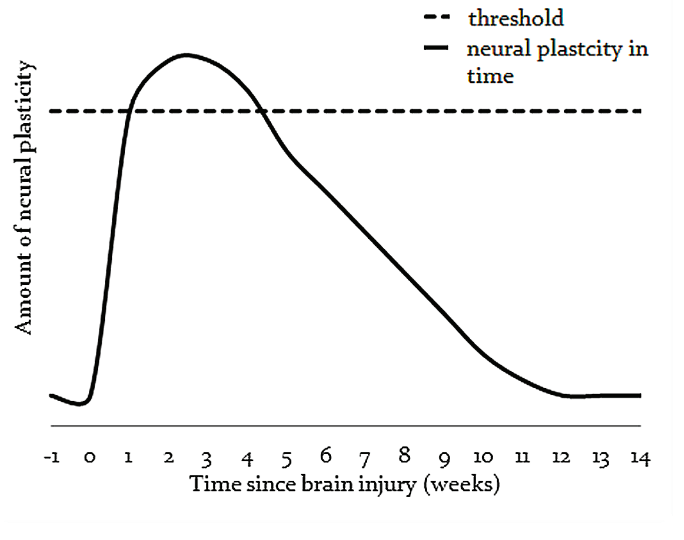

Figure 2. The Interplay Model. The black line displays the time course of the amount of neural plasticity, based on discussed neural findings from human and animal studies. Zero on the X-axis represents the moment of injury. The dotted line displays the hypothesized threshold for interplay between neural plasticity and rehabilitation. In the time window where neural plasticity exceeds this threshold, effect of the cognitive intervention will be maximized, the so-called window of opportunities. Note that there is always neural plasticity, but that this neural plasticity is increased during the first 12 weeks and only exceeds the threshold between one and four weeks after brain injury.

Future research is needed to validate the accuracy and application of this model. This research could consist of multiple randomized controlled trials on cognitive rehabilitation for ABI patients with onset of intervention as independent variable. So ideally, two randomly formed groups consisting of ABI patients receive the same intervention aimed at restoration of the cognitive function, but initiate at different moments regarding their time since injury. The interplay model suggests that the early onset group should start their intervention after one week and the late onset group after more than one month.

Moreover, limitations of the Interplay Model are that the time course of neural plasticity is primarily based on animal studies. More research is needed to investigate the generalizability of the findings of neural plasticity in rodents to the human brain. Furthermore, the findings supporting the existence of a time window of interplay were solely based on stroke patients. Therefore, more research validating translation of these findings to other acquired brain injuries is needed due to their difference in type of injury. TBI is most often diffuse, whereas brain injuries due to stroke are most often local.

Despite these limitations, the Interplay Model is in line with the findings of all discussed studies and the results of the discussed systematic review. Therefore, the main implications for clinical practice are to shift from a compensatory approach to a restorative approach, where treatment of cognitive impairments should already start in the first month after ABI. This is even earlier than the current view of early cognitive rehabilitation of the first three months suggests. So, it is important to start within this first month with cognitive rehabilitation in order to utilize the natural brain recovery mechanism of heightened plasticity and therefore maximize the possibility of restoration of the impaired cognitive function. Compensatory approaches can always be offered, their effectiveness is, unlike the restorative approach, not dependent of a level of neural plasticity exceeding the interplay threshold. So ABI patients should receive earlier rehabilitation than the current standard compensatory rehabilitation, namely within the first month after brain injury, the window of opportunities. Use it or lose it.

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