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ACQUIRED BRAIN INJURY AND EVALUATION OF INTENSIVE TRAINING OF ATTENTION IN EARLY NEUROREHABILITATION

- STATISTICAL EVALUATION AND QUALITATIVE PERSPECTIVES

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Acquired brain injury and evaluation of intensive training of attention in early neurorehabilitation - statistical evaluation and qualitative perspectives

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Sapere aude

Dare to be wise

"Jag tackar Dig för att jag är danad så övermåttan underbart.
Ja, underbara är Dina verk, min själ vet det väl"
Psaltaren 139:14

ABSTRACT

Attention dysfunction is a cardinal symptom after an acquired brain injury (ABI) sometimes leading to life-long consequences that affect learning skills, daily functioning and social and emotional life. Attention may be successfully improved by structured training within rehabilitation programs, with the Attention Process Training (APT) as practice standard in the chronic stage after ABI. Practice recommendations in an earlier stage after ABI are less conclusive, possibly due to difficulties in distinguishing treatment effect from individual trajectories of spontaneous recovery.

A randomized controlled trial (RCT) was performed at a university department of rehabilitation medicine. Patients with attention dysfunction after stroke or traumatic brain injury received 20 hours of attention training added to their individual rehabilitation program. The patients were randomized to one of two interventions of attention training: APT or activity-based attention training. The thesis focuses on **the effect of attention training within four months post-injury**.

In **Study I**, the strict inclusion and exclusion criteria common to interventions trials in clinical research decimated patient recruitment, ultimately leading to an inclusion of < 10 % of admitted patients with stroke or TBI. Sampling bias was identified within the group of patients meeting all criteria. Eligible patients participating in the intervention study were more likely to be in a relationship and had a higher education. Strict inclusion and exclusion criteria prolonged data collection rendering the study group potentially less representative. We advocate the use of broader inclusion criteria and common data elements in future studies.

Study II evaluated the feasibility of time-series measurements using statistical process control (SPC) for detecting change in an evolving process. SPC identified if, and when change occurred and the results described three patterns of performance: rapid improvement, steady improvement and stationary performance showing no improvement. By providing information about when change occurs, SPC enables adjustment of individual treatment response in early cognitive rehabilitation.

In **Study III**, we applied SPC to explore the intervention effect of two methods of attention training: APT and activity-based attention training, within four months post injury. Although substantial improvement of attention was confirmed for both intervention groups, APT lead to an increased robustness of improvement, and resulted in a higher number of improved patients reaching change in performance at a faster rate.

Study IV explored the experience of managing attention difficulties in daily life 2-4 years after brain injury and APT. Fourteen interviews were analyzed according to grounded theory and lead to the development of a model of attention management. The attention management emerged as a dynamic process where adjustment and refinement of management strategies increased with awareness and deepened application of applied knowledge, regulated by situation-dependent factors. Self-awareness and the detailed identification of dysfunction derived problem areas, including tenacious self-training with specific goal-setting, were promoted by APT.

In **conclusion**, attention training is a promising intervention in the early stage after ABI with APT potentially boosting the improvement process as seen both during intervention and in the experience of attention management over time. SPC enables us to identify if, when and how change occurs in an evolving process. It may be used on both individual and group level.

LIST OF SCIENTIFIC PAPERS

I. Markovic G, Schult M-L & Bartfai A (2016): The effect of sampling bias on generalizability in intervention trials after brain injury, Brain Injury, DOI: 10.1080/02699052.2016.1206213

II. Markovic G, Schult M-L, Bartfai A, Elg M (2017): Statistical process control: a feasibility study of the application of time-series measurement in early neurorehabilitation after acquired brain injury. J Rehabil Med 2017; Jan 31;49(2):128-135, DOI: 10.2340/16501977-2172.

III. Markovic G, Schult M-L, Elg M, A Bartfai. Attention process training is beneficial during early intervention after acquired brain injury. A randomized controlled trial. Manuscript.

IV. Markovic G, Bartfai A, Ekholm J, Nilsson C, Schult M-L, Löfgren M. Daily management of attention dysfunction 2-4 years after brain injury and early cognitive rehabilitation with Attention Process Training. A qualitative study. Submitted to Neuropsychological Rehabilitation, Feb 2017.

INNEHÅLL

LIST OF ABBREVIATIONS

ABI	acquired brain injury
ABAT	activity-based attention training
ACRM	American Congress of Rehabilitation Medicine
APT	Attention Process Training
CFQ	Cognitive Failure Questionnaire
df	degrees of freedom
fMRI	functional magnetic resonance imaging
GCS	Glascow Coma Scale: a neurological scale based on eye opening, verbal performance and motor responsiveness. Low scores correlate to severity of injury.
HADS	Hospital Anxiety and Depression Scale
LCL	lower control limit
LOC	loss of consciousness: altered awareness at time of brain injury involving degree of responsiveness to environment and other people. Longer duration correlates to severity of injury.
MRI	magnetic resonance imaging
PASAT	Paced Auditory Serial Addition Test
PET	positron emission tomography
PTA	Post Traumatic Amnesia: state of confusion affecting memory of events occurring from the time of the injury. Longer duration correlates with severity of injury.
RBMT	Rivermead Behavioral Memory Test
RCT	randomized controlled trial
SPC	statistical process control
TBI	traumatic brain injury
TPM	Time Pressure Management
UCL	upper control limit
WAIS-III	Wechsler Adult Intelligence Scale – Third edition

1 BACKGROUND

1.1 ACQUIRED BRAIN INJURY

Acquired brain injury (ABI) is the result of physical trauma or medical illness that is unrelated to congenital disorders, developmental disabilities, or processes that progressively damage the brain. ABI leads to various symptoms depending on diagnosis and injury characteristics [1]. The two largest diagnostic groups with ABI are stroke [2] and traumatic brain injury (TBI) [3]. For stroke, the prevalence rate in Sweden has dropped with 19% for the past 20 years [4]. However, the incidence of stroke is rather high, affecting about 25 000 each year out of which 20% are in working age [5], and depending on factors such as general health, age and gender [6]. The prevalence for TBI worldwide is about one percent with some variations [7, 8]. In Sweden approximately 22 000 people each year suffer a TBI resulting in medical attention out of which half require hospitalization [9]. The incidence for TBI depends on factors such as age, gender and socioeconomic level [10, 11].

ABI is known as a highly disabling disease typically affecting cognitive, emotional, behavioral and motor functions [12-15]. Cognitive changes after ABI constitute a major challenge both for the survivor and to society with long-term consequences on the ability to work and perform activities in daily living; to fulfil a family role and to participate in community life [16-18]. Cardinal symptoms include decreased mental speed, memory impairments, attention deficits, executive dysfunctions and fatigue [19-22]. These cognitive functions are necessary for everyday abilities such as learning, goal-formulation, and planning [23]. Behavioural and emotional changes are common, including diminished self-awareness [24].

1.1.1 Stroke

Stroke includes several neurological events of circulatory failure causing a global or focal impairment of functions associated with the affected area [25, 26]. Damage to the brain is caused by ischemic stroke (brain infarct) where the blood supply to the brain is impaired due to cardiovascular infarction [27], and by haemorrhagic stroke [25] where blood vessels in the brain burst [27].

1.1.2 Traumatic brain injury

TBI is characterized by an external impact to the head and is classified in order of severity depending on level and duration of altered consciousness, including influence on memory function and other cognitive or motor problems at the time of injury [28]. The standard tools for assessing severity are the Glascow Coma Scale (GCS) [29], duration of loss of consciousness (LOC) [30] and post-traumatic amnesia (PTA) [31] (Table 1). Most common causes of TBI include transportation accidents, violence and recreation activities/sports.

However, the classification of mild and moderate TBI does not necessarily correspond to the degree of dysfunction as even a mild TBI may result in long-term cognitive impairments [32-34].

Table 1. TBI *injury severity as defined by Glascow Coma Scale (GCS), duration of loss of consciousness (LOC) and post-traumatic amnesia (PTA).*

	GCS	LOC	PTA
Mild	score 13-15	0-30 min	< 24 hours
Moderate	score 9-12	30 min-24 hours	> 24 hours
Severe	score 3-8	> 6 hours	1-7 days

1.1.3 The cognitive recovery process after stroke and TBI

Changes in the adult brain activity after an injury involve both degenerative and reparative processes over the following days, weeks and months [35]. A major driving force in cortical reorganization after brain injury and the very base for learning new skills, is neuroplasticity [36]. Neuroplasticity is the ability to adjust and modify the organization and structure of neural circuits, particularly in dendritic fields and synapses, in response to external and internal stimuli [27, 37]. The increased knowledge of the plasticity of the brain and the restorative ability of the nervous system is vital to cognitive rehabilitation directed at remediation and compensation of function after ABI [37, 38] and emphasizes the need for targeted goal-driven rehabilitation in the early phase post-injury [39]. Key findings provide evidence for reorganization of cortical maps [40] but also evidence of maladaptive plasticity in “self-taught” behavioral changes in the absence of specific professional interventions [41, 42]. Cognitive recovery following ABI encompasses a set of processes by which the person suffering from a brain injury learns compensatory behavior as a substitute of functions lost, and relearns functions impaired by injury. It does not entail the complete reversal to a premorbid state of function but rather an amelioration of functionality.

A great deal of the spontaneous recovery process following stroke happens within the first three to four months [43, 44]. For TBI, an initial period of six months bears a great amount of the recovery [45]. Although improvement continues up to five years post-injury [46], the recovery process does slow down leading to relatively small gains in function over time [47] where the rate of recovery decreases with increased complexity of function [46]. However, there is a great variability in the recovery process between individuals, where the degree of brain pathology does not necessarily correspond to symptoms and rate of cognitive recovery [48]. Demographic factors such as age [49] and gender [50], together with admission characteristics (diagnosis, injury severity, secondary insults) [51] and rehabilitation interventions [52] are known predictors of outcome [53, 54]. Cognitive reserve may also influence the impact of trauma on the brain [55]. Predicting responsiveness to cognitive rehabilitation or a specific intervention is important given the effort needed for successful outcome. Effectiveness of intervention could improve through personalized therapeutic interventions based on clinical evidence and predictive analysis of intervention response.

1.2 COGNITIVE REHABILITATION

Rehabilitation of ABI involves different types of interventions aiming to reduce the impact of functional deficits on activities in daily life and maximize recovery and participation [56]. Effective rehabilitation requires interdisciplinary teamwork [57], bringing together a wide range of professionals including medical staff, neuropsychologists, occupational therapists, physiotherapists, and speech and language therapists, to enable and facilitate the re-learning of skills and adjustment of behavior [58]. There is successively increasing evidence for intensive individual interventions specific to function deficit [59] with good potential to improve performance, decrease activity limitations and thus reach potential gains for both the individual and society [57, 59, 60].

Cognitive rehabilitation is a concept that refers to systematic therapeutic interventions and efforts aiming at improving cognitive functions, information processing and the injured person's well-being [52, 59, 61]. Depending on the function impaired, cognitive interventions are either restorative of function (direct training of function), or compensatory for loss of function with the establishment of strategies (indirect training of function) [39]. Central to cognitive interventions are metacognitive approaches involving self-monitoring, emotional regulation, and consideration of subjective beliefs and experiences [62]. An important aspect is the generalization of skills and strategies achieved in rehabilitation to functioning in daily life [39]. Cognitive rehabilitation needs to emphasize the individual characteristics of the injured and include the influence of social [63], personal [64] and emotional [65] contextual variables, to evaluate the impact of the brain injury [52, 66]. The outcome of different cognitive interventions depends on etiology of the injury and the cognitive function(s) affected [59, 67, 68]. This is confirmed by a meta-analysis [60] that includes time post injury and age as moderators of treatment effect decisive for the choice of cognitive intervention. Furthermore, the brain's plasticity and thus the effects of direct training are modulated by the participant's motivation and level of attention [36]. Thus, a fundamental assumption in cognitive rehabilitation is that cognition cannot be isolated concerning function or effective management of symptoms seeing that ABI affects the complete range of functions: motor, cognitive, social, behavioral, and emotional [69-71].

Many researchers within the discipline of cognitive rehabilitation [58, 69, 72, 73] discuss the general framework and basic principles for cognitive training. The need for a theoretical model is emphasized, ensuring a rationale for the treatment being used. Cognitive rehabilitation relies on three principles [58, 62, 73]: 1) restorative training directed at a specific function [74], 2) training of metacognitive strategies emphasizing continuous and detailed feedback of performance that provides the therapists with tools of how to proceed with the treatment [58, 75] and, 3) promoting generalization of learned strategies into real-world activities, including strategies for emotional control, effort, and motivation [52]. This perspective implies that training *specific* cognitive skills may contribute to alleviating the effects of ABI, in contrast to models assuming that general stimulation of any ability is to the overall benefit of the patient [59].

Restorative approaches are impairment-based and attempt to decrease cognitive dysfunction by tapping into the underlying cognitive function [58]. The restorative approach presupposes that the underlying impaired cognitive function can, in fact, improve on a functional level [76] through intensive, repetitive and structured practice on tasks with a progressive level of difficulty. However, a compensatory approach that includes performance-driven strategy training is also proven to lead to functional improvement [77], suggesting restorative properties also within the compensatory approach.

Compensatory cognitive training focuses on practicing and improving performance in activities in daily life with the help of internal and external strategies [73, 78]. Interventions are designed to increase occupational performance for experienced problems related to daily activities [79]. The aim is to optimize performance through strategies leading to improved skills, and through the identification and ultimately avoidance of situations that could lead to failure in performance. External strategies are directly linked to the environment and comprise support to the person affected by the modification of the environment, e. g. using planners and electronic devices [80]. Internal strategies, such as association techniques, rehearsal, cuing and verbalization comprise the mental support needed to facilitate performance [52]. Modifications to the environment, implementation of strategies, provision of emotional support, and the introduction of external supports/aids are important parts of a rehabilitation program, especially as the client returns to their home environment and work.

Metacognitive training is an umbrella term for several interventions with a top-down organisation aiming to re-establish patients’ ability to exert control over behaviour and underlying supportive or inhibiting cognitive functions [81, 82]. Metacognitive processes are decisive for *self-directed* complex behaviour through the employment of skills such as goal setting and anticipating task demands; for *self-monitoring* through comparing outcome on performance with goals; for *decision making* whether it concerns changing or alternating strategies in a situation; and for accomplishing a *change of behaviour*. The severity of cognitive deficits and exact nature of injury determine rehabilitation. To illustrate, mildly injured patients may have difficulties understanding the need to utilise compensatory strategies, whereby moderately injured patients may be the most likely to engage in compensation. Severely injured patients may lack the skills necessary to engage in compensation without support and training [39].

Attention has been found to be one of the cognitive functions that successfully improves through systematic training and through applying metacognitive strategies in everyday activities in the chronic phase after ABI [31, 59, 83, 84].

1.3 ATTENTION

Attention difficulties are among the most common cognitive sequelae after ABI [31, 45, 85]. It is a cognitive function supporting other cognitive functions and is a core component of activity and participation. Relatively small changes in the function of attention might, therefore, have a large impact on a person's daily life by affecting learning skills and daily functioning, and perturb participation in social and emotional life. Attention serves cognition and behaviour by several means and may be understood from different perspectives. It functions as a filter for selecting relevant cues for sustained cognitive processing, and when alternating between different tasks. In a sense, it can function as a gateway for information flow into the brain and as such facilitate behaviour by directing it in relation to time and space [86]. Attention processes frame the constant inflow of information from both external sensory input and internal sources, directing the selection of salient information and allocating cognitive resources for adequate processing. It may be argued that the overarching function of attention is to prepare the individual for optimal sensory intake, analysis, and integration.

The construct of attention is the product of multiple interacting neural sub processes requiring different resources depending on the target of focus [35, 87, 88]. Attention processes rely on separate as well as shared neural networks and are modulated by specific situational demands. Lesions affecting these networks also affect our ability for intentional behaviour and thereby our ability to engage in a functional way in human relations, work, studies and leisure time.

To better understand attentional components a description of its recognized manifestations is helpful.

- *Focused* attention, as the most basic component of attention, refers to the ability to recognize and act on specific sensory information [58] such as finding a telephone number in a directory and searching for a friend in a crowd of people.
- *Sustained* attention comprises keeping focus during a continuous activity, and includes working memory and mental control at its highest level [58]. It is employed in activities such as reading and watching a movie. Sustained attention in demanding tasks is dependent on vigilance and the ability to withstand both boredom and fatigue. Affecting the temporal distribution of attention, sustained attention is considered a factor separate from other aspects of attention [86].
- *Selective* attention is closely related to focused attention and is involved in processes that select or prioritize some stimuli over others while inhibiting non-target

information, such as when reading in a public place and working in open-space offices.

- A*lternating* attention refers to the ability to shift focus between tasks that demand different cognitive skills without losing focus at the task at hand. Typical household activities would include cooking dinner while helping your child with homework.
- *Divided* attention refers to the ability to simultaneously respond to two or more stimuli, such as driving in urban areas while engaging in a conversation. However, there is a debate as to whether mental processes underlying different tasks are performed simultaneously or in a quick, alternating fashion [74].

Several theoretical models deriving from applied research and clinical observations have been developed to describe and understand the different components of attention and their interaction with one another. Approaches within cognitive psychology were based on the control or automatization of cognitive processing [89]. In neuropsychology, the neuroanatomical analysis of attention and the identification of attention networks [88] is dominating. The neurophysiology approach is based on factor analytic understanding of attention and the identification of the basic neural subcomponents of attention [90]. The common denominator for the different models is the selectivity in attention.

The understanding of attention has evolved from identifying activated brain areas to describing attention regarding integrated activity of *large-scale networks* of brain regions along which attention can vary [87, 91]. Posner's and Petersen's influential network model [88, 92] differentiates attention into subcomponents whose activation depend on task situations and engages networks of different anatomical areas. The subcomponents are independently engaged and can be specified in cognitive terms: 1) alertness and sensory selection; 2) orienting and directing attention to the stimulus, and 3) conscious processing of stimuli (executive control).

An equally influential model describes a *dual-network approach*, with neural systems directing attention in a goal-directed top-down or stimulus-driven bottom-up manner [93]. This substantiates that a fundamental principle of attention is a continuous selectivity of the target of focus.

A recently identified brain network describes a third dimension along which attention can vary, concerning *internal and external attention processes* [94]. Internal processes, activated during rest, are dependent on the default mode network. They refer to successful sustained attention, self-reflection, and mind wandering [95, 96], while external processes are activated during task performance and further described within the two models described above.

The ability to respond to shifting demands and prioritize selected information is closely related to the concept of executive functions [81]. Mental operations of an executive nature are dependent on a complex interplay between several cerebral areas through neural circuitry running across multiple regions, including those of attention. A study on the relationship between working memory and attention [97] highlighted the co-dependency on neural networks of different cortical localities, and the overlap in activity in areas associated with working memory and controlled attention. The similarities of characteristics of working memory and attention, as well as the neural relationship, have caused some scholars to view these constructs as synonymous [86]. The three functions (attention, working memory, executive function) are partially interdependent, both regarding underlying neurocircuitry and function, and are affected by emotional, behavioral and physical difficulties [52, 69, 70].

1.3.1 Remediation of attention after ABI

There are two main approaches to attention training: *structured* training with repeated exercises, assuming isolated components of attention [98]; and *metacognitive* training including the practice of strategies critical for transfer and generalization of skills acquired in rehabilitation [98].

The structured training aims at a specific attentional deficit, or with a more comprehensive perspective, it targets a range of attentional functions [98]. Structured training of attention usually comprises performance of progressively challenging attentional exercises, and assumes that recurrent activation and stimulation of the attention system will strengthen and widen the cognitive ability [39]. Structured training has support in the evidence-based literature recommending it being combined with the training of metacognitive strategies targeting inability or deficits in self-monitoring of thoughts and behaviour.

It is argued that *metacognitive* training is a much-needed addition to direct training rehabilitation programmes such as APT, as well as for programmes of more comprehensive nature [59]. Rehabilitation of attention integrates thus a structured direct training of the components of impaired attention, with elements used in the treatment of executive dysfunctions and memory impairment.

Three specific interventions of attention are recommended [59, 67, 99]: The Attention Process Training (APT) program developed by Sohlberg and Mateer (1987) [83, 100], Time Pressure Management (TPM) focusing on metacognitive strategies and executive skills to avoid attention overload [101], and the *n-back* procedure addressing underlying problems with working memory [102]. Computer-based interventions are recommended adjunct to clinician-guided treatment providing feedback and strategy training [74, 76].

Remediation of attention is recommended in the *post-acute* phase after TBI [60] as the evidence for earlier provided attention training is insufficient in distinguishing training effect from natural recovery or more general cognitive interventions [59, 60]. Literature provides inconclusive support for attention training early after ABI, whether referring to the insufficient amount of high-quality studies permitting conclusions to be drawn [103], or to methodological issues in separating intervention outcome from the spontaneous recovery that is expected early after ABI [104].

1.3.2 Attention Process Training (APT)

The APT was found to be a successful restorative method during the late phase after ABI for both adults [59, 83, 105] and children [106]. Meta-analytic reviews [107] found an effect size of 35-38% for domain specific training of attention in adults. Sustainable effects up to six months after treatment were found in children with a training method (Amat-C) [108] based on the model of Sohlberg and Mateer differentiating attention to different levels [109]. The intervention of Attention Process Training (APT) is considered as the golden standard for treatment of attention deficits in the post-acute stage after TBI [59] and endorsed to be standard practice in cognitive rehabilitation by the American Congress of Rehabilitation Medicine [73]. It is recommended that APT should include metacognitive training to establish compensatory strategies and achieve generalizations to everyday life [59]. Results are however more conflicting when the APT program is in the early and sub-acute phases after ABI. Once accounting for the effect of spontaneous recovery, differences in treatment effect between two intervention groups remained stable in two studies [105, 110] and were rendered insignificant in two other studies [111, 112] including showing little or no generalization of treatment effect to related cognitive functions, e.g. executive functions and memory.

The APT [83] is a theoretically based structured training program of attention providing a hierarchy for task administrations in such a way that basic abilities are used throughout the program, but more complex ones are added as the program moves forward. The program is administered individually with assignments organized after five types of attention: focused, sustained, selective, alternating and divided. The APT program is designed to remediate attention deficits [52] by stimulating the underlying process through intensive and repetitive exercises in a structured manner. APT includes structured questionnaires and attention rating scales focusing on perceived attention difficulties in everyday life; and a brief test of attention, the Attention Process Training Test, useful for identification of the type of attention impairment [113]. The program focuses on the generalization of treatment by emphasizing transfer of strategies learned in a clinical setting to novel contexts [52, 100]. It is individually adjusted allowing intensive training to facilitate the establishment of neural connections [83, 113-115] and relies on ongoing feedback on progress: quantitative regarding accuracy and speed, and qualitative regarding error profiles and effort. Finally, the program puts an emphasis on using meta-cognitive strategies promoting motivation and insight [113].

1.4 EVALUATING THE EFFECT OF COGNITIVE TRAINING

Intervention studies can be approached by using different designs depending on the research question - whether the primary goal is to evaluate and scientifically advance (evaluative and effectiveness studies), or to secure change and improve care (qualitative improvement studies) [116]. Outcome in brain injury rehabilitation is usually evaluated with various imaging techniques, or behavioral measures such as psychometrical testing and observation, and evaluation of activity and participation in standardized procedures. Assessment and evaluation of treatment progress might be limited by methodological problems e. g. in the selection of assessment instrument and in the emphasis on endpoint measures. [117]. An identified variability in results could be due to factors such as fluctuations in the patients' biological processes and error variance in the measure itself [118]. Repeated measures of the same parameter may also yield different results even though no real change has occurred [119]. These limitations could be subdued by increasing the number of measurement points permitting a more detailed analysis of behaviour and higher confidence in the results of the described intervention or process.

A typical design comprises measurements pre- and post-intervention and preferentially at follow-up. In rehabilitation research the therapeutic efficiency of interventions is demonstrated by randomized controlled trials, RCTs' - considered the golden standard of research design [120], and by single case studies [121]. Although demanding strict control in recruitment, RCT's have high validity with organizational and economic gains and are especially suitable for larger populations and whenever the intervention is being considered for widespread use [122]. The strict enrollment criteria could however bias patient recruitment leading to an increased cost in time, size and effort in the data collection [123]. RCT's are also concurrent with potential confounding effect such as test-retest effect, initial severity of the deficit and individual differences in recovery rate. Repeated measurements with detailed analyses of recovery and the treatment process have been used in single-case studies as a purposeful tool for developing rehabilitation techniques and for examining individual effects [69, 119, 124]. They are however insufficient for describing effects of rehabilitation at group level [119, 125]. To understand the natural recovery pattern and the effects of *early* intervention after acquired brain injury, repeated measurements are necessary. Basic pre- and post-measures, such as RCT's, could prove to be somewhat insufficient in reflecting the full spectrum of changes in the most critical phases of the recovery process [62, 126]. In the early stage after ABI the recovery process is in an evolving state, thus when measuring the effects of rehabilitation one needs to consider the impact of both natural recovery and treatment effects on outcome.

Process analysis with time-series measurements and statistical process control (SPC) offers an advancement to the single-case design, on two accounts by presenting: 1) statistical criteria regarding control limits when assessing the effects of an intervention, and 2) specific rules confirming a statistical change in a process. Qualitative research methods permit an exploration from the perspective of the informants regarding components of rehabilitation less known. Findings ultimately advance the theoretical understanding of the rehabilitation process and support the improvement of interventions.

Studies establishing the value of early cognitive rehabilitation and specifying the conditions where the highest efficiency is achieved, would strongly contribute to the much-needed detailed information on recovery and on restorative interventions.

1.4.1 Statistical Process Control (SPC)

The SPC is a method that considers the inherent variability in a process and was developed in the 1920s by Walter Shewart for improving processes in industrial manufacturing [118, 127-129]. The underlying assumption is that a certain degree of variation is inherent in every process [118, 127, 129] and that by controlling for variations the method permits an effective management of the process [119]. The key technique of SPC is the use of control charts visually displaying time-ordered performance while considering variability and stability of the process at hand [130]. The purpose of the control chart is to detect significant changes. SPC distinguishes between two types of variation: common cause variation and special cause variation [118, 130, 131]. Common cause variation is influenced by random factors and is considered to derive from the inherent nature of the process. Common cause variation cannot be changed without some form of active intervention. Within the context of clinical research, random factors would include time of day or physical predisposition to treatment response. Special cause variation represents variation due to unusual disruptions in the process, and could within the context of clinical research signal an important improvement or deterioration in performance [131]. Recognizing true special cause variation would highlight *when* variation should be interpreted as a *change in the process*, thus enabling a deeper inspection of different aspects of the process [119].

Control charts include a plot of data with time represented on the horizontal (x) axis and outcome measurement values on the vertical (y) axis. The graph displays a centerline representing the mean of measurements and an upper (UCL) and lower (LCL) control limit, calculated from the variation in data, thus representing the limits of random variability. The center line and control limits of the chart allow the inspection of different aspects of the process by indicating special cause variation. The limits are set to three standard deviations from the mean, establishing margins where data will be found approximately 99.7% of the time. They are based on the underlying probability distribution and are used as a means for repeated-hypothesis testing. For instance, the normally distributed Xbar-S chart relays information about the central tendency of the data collected, thus showing variation between measurements over time; while the S chart relays information about the variation in the process. The process variation must be in control to correctly interpret the Xbar chart. The Xbar-S charts are thus displayed and interpreted together. Data points outside the control limits are considered markers of special causes of variation.

SPC considers statistically derived interpretation rules when examining the data more rigorously for systematic variations [118, 130, 132, 133]. The most fundamental rule for special-cause variation, thus supporting the interpretation of a defined change in the process, is one point falling outside the control limits of three standard deviation [119, 134]. By using supplementary rules of interpretation, although increasing the risk of Type I error, the SPC improves the sensitivity to detect special causes of variation, changes that would not occur by natural variability in a process.

1.4.2 Qualitative research

The outcome and the consequences of ABI are determined by the complex interaction of many biological, psychological and social factors, requiring an integrated approach to rehabilitation [135]. When exploring the experience and the views of the participants, the use of qualitative methods is appropriate. Grounded theory is a suitable method for exploring human experience of social phenomena from the perspective of the informants and as such, for understanding the complexities of participants' experience of rehabilitation and the APT treatment approach [136, 137].

1.4.2.1 Grounded theory

The aim of grounded theory is to describe a studied field while developing new theoretical models. Grounded theory distinguishes itself on three levels: 1) the concepts and hypothesis underlying the emerging theory derive from the data collection as opposed to being chosen beforehand; 2) collection and analysis of data is an ongoing continuous process; and 3) emerging models are contrasted to existing models and theories ultimately leading to the development of a theory [138]. The method allows for systematic analyses of an individual's narrative, where the essence of an experience is extracted through coding and categorization. Various data collection methods can be used: individual interviews or in groups, observations, records, and diaries. Data is analyzed by constant comparison, i.e. breaking down data into meaningful units that are mutually compared for similarities and differences [138]. Data referring to the same concept are grouped together, and concepts are further grouped into categories or themes. Abstraction of data continues until the researcher develops a theory based on the data derived categories. Variation in data is valued, rather than consistency.

1.4.2.2 The process of analysis in qualitative research and grounded theory

The analysis in qualitative research is a process of simultaneous inductive and deductive reasoning [136] that has reality (a phenomenon, an experience) as a starting point. Hypothesis and models derive from collected data while interacting with the interpretation of data. To reach an abstraction of collected data, a coding process in three steps is initiated (Fig 1): *open* coding aiming to identify important pieces of information in the material together with axial coding aiming to explore relationships between categories, *selective* coding aiming to cluster important codes into categories, identify properties and refine the emerging theory, and *theoretical* integration aiming for the construction of concepts and hypothesis [136]. Several analytical strategies are useful in the coding process. Open-ended questions and making comparisons (both constant comparison and theoretical) are standard features of the analysis process [138]. Other strategies include using the flip-flop technique (exploring a concept in reverse perspective), reflecting on various meanings of words, expressed emotions, and time indicators, as well as looking for negative cases (a case that does not fit the pattern) [138].

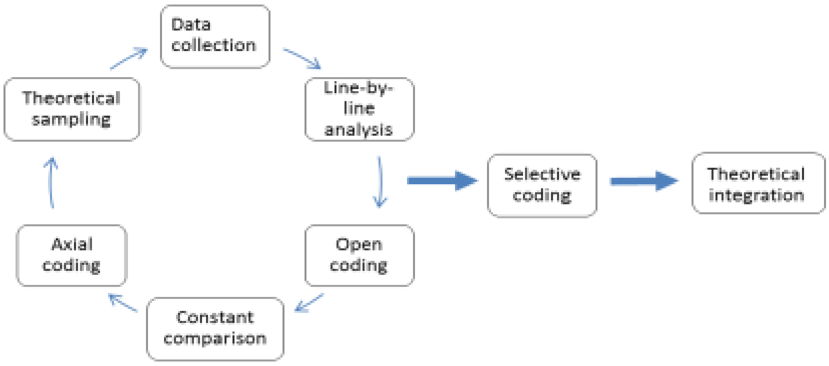


Figure 1. *Data analysis according to grounded theory (Corbin & Strauss 2012).*

1.4.2.3 Trustworthiness in grounded theory

To ensure trustworthiness, triangulation of data collection and interpretations is recommended [138] as well as an explicit grounding in formal theory supporting a deeper understanding of how an intervention is expected to make a difference [136]. Trustworthiness in grounded theory is discussed in terms of credibility, transferability, dependability and confirmability [136, 139].

Credibility refers to the ability to capture and establish confidence in the “truth" concerning the accurate identification and description of a phenomenon. Credibility is ensured through triangulation, e. g. that the evaluation of an issue is coming from different angles. Triangulation can occur with different data sources, data collection methods, researchers with different backgrounds and different methods for analyzing data. Other methods include presenting preliminary findings to colleagues (peer-debriefing), prolonged engagement and conscious search for data that do not fit (negative case analysis) [138].

Transferability refers to the degree to which the findings can be applied or generalized to other contexts. Transferability includes analytical and naturalistic generalization. Both depend on the reader’s judgment, the former based on logical reasoning, the latter based on being familiar with the context. A “thick description” should be provided, with enough details describing the research context and pre-assumptions to allow informed choices about transferability to be made [136].

Dependability refers to the ability to account for the complexity of the situation or the people studied in a consistent manner. Evaluation through audit trails focusing on the process is recommended, e. g. thorough description of the research process including decisions made and personal notes.

Confirmability refers to the degree to which the findings can be corroborated by others. The researcher aims for neutrality of the data by being as detached an observer as possible, all the while being aware of personal bias. A good means in achieving neutrality is to conduct audit trails focusing on the end-product. This facilitates checking and re-checking the data, thus ensuring that results and conclusions are grounded in data.

2 AIMS OF THE THESIS

2.1 GENERAL AIM

The thesis aims to evaluate the effects of Attention Process Training in the early stage after mild to moderate ABI, and how patients handle attention deficits in daily life.

2.2 SPECIFIC AIMS

Specific aims were:

- to explore the effect of strict inclusion and exclusion criteria on patient recruitment in cognitive rehabilitation and to analyze the representativeness of study patients for all eligible TBI and stroke patients referred during the data collection period (Study I);

- to evaluate the feasibility of using a time-series method, statistical process control, in early cognitive rehabilitation (Study II);

- to examine the efficacy of Attention Process Training for attention dysfunction after ABI with statistical process control (Study III);

- to explore and obtain further knowledge of the patients' perspective of the management of attention deficits in daily life after ABI, rehabilitation and attention process training (Study IV).

3 METHODS

3.1 OVERVIEW OF METHODS

Table 2. *Overview of research questions, study design, methods of data collection, assessment and analysis used in the four studies.*

Study	**I**	**II**	**III**	**IV**
Research question	What are the effects of strict inclusion- and exclusion criteria on study flow and patient selection in an intervention trial?	What is the feasibility of using a time-series method, statistical process control, in early cognitive rehabilitation?	What is the effect of attention process training early after acquired brain injury?	How do people with attention dysfunction after an acquired brain injury manage attention deficits in daily life?
Study design	Descriptive study	Feasibility study	Randomized controlled intervention trial.	Exploratory and analytical, emergent design.
Participants	626 patients with stroke or TBI < 4 months post injury. 60 patients included in the study.	27 participants with attention dysfunction receiving activity-based attention training (ABAT)	59 participants randomized to attention process training (APT) or activity-based attention training (ABAT)	14 informants with attention dysfunction 2-4 years after ABI and early attention process training (APT).
Data collection and assessment	Medical records, attention process training test (APT-test), Matrix reasoning (WAIS-III), Rivermead Behavioral Memory test (RBMT), Albert's test, Barthel ADL-index, Hospital Anxiety and Depression Scale (HADS)	Paced Auditory Serial Addition test (PASAT), version A	Paced Auditory Serial Addition test (PASAT), version A	Semi-structured individual interviews.
Methods of data analysis	Chi-square test, parametric t-test, Spearman's rank order correlation, Levene's test of homogeneity of variance; descriptive statistics	Statistical process control (SPC), descriptive statistics	Statistical process control (SPC), descriptive statistics	Constant comparisons according to grounded theory

3.2 INTERVENTION TRIAL

3.2.1 Study setting

The study was carried out at a university department of rehabilitation medicine for patients with acquired brain injury, with an urban catchment area of 1.5 million inhabitants. All patients participated in an interdisciplinary rehabilitation program and were enrolled from the inpatient and outpatient wards depending on symptom complexity. Multiple professions in teams specialized in rehabilitation medicine were responsible for the outline of an individualized rehabilitation plan and the administration of rehabilitation interventions. The two different attention interventions were provided in addition to the multi-professional rehabilitation program.

3.2.2 Procedure

The participants were recruited between September 2011 and January 2014 to a randomized controlled trial on cognitive rehabilitation within the first year after ABI [140]. The study was registered at ClinicalTrials.gov.trial registration: NCT02091453, 19 March 2014. The inclusion process for the four studies in the thesis is shown in Fig 2. During the intervention period the participants were not allowed to engage in other process-dependent cognitive training such as training of working memory with CogMed QM (http://www.cogmed.com/qm). They were however offered the possibility to proceed with CogMed QM after participation in the study.

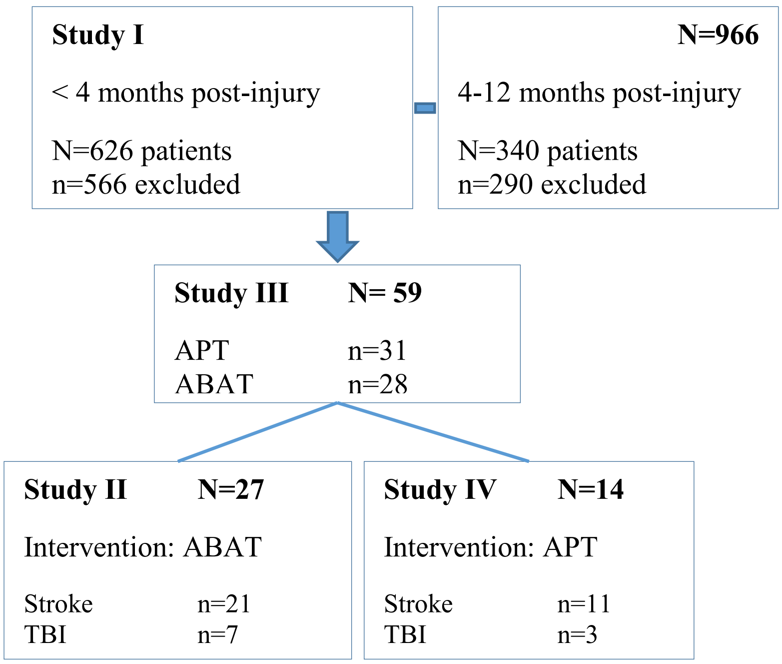


Figure 2. *An overview of the inclusion process for each study respectively.*

3.2.2.1 Study I

Computerized screening logs were used to follow patients during recruitment. Medical records were screened, in- and outpatient teams were visited weekly by research team members to identify potential study participants. Patient recruitment followed two steps: 1) screening of medical records and 2) clinical assessment to verify inclusion and exclusion criteria [140, 141].

3.2.2.2 Study II and Study III

After baseline assessment, the participants were randomly assigned to one of the two intervention programs. Treatment started approximately 60 days post-injury (SD=26 days; min=16; max=105); the participants received 20 hours of attention training, three to five days a week, for a period of five to six weeks. Repeated assessment by the primary outcome measure at baseline and after every third hour of intervention was used to monitor and evaluate the treatment process. Due to the nature of the rehabilitation procedures, neither patients nor rehabilitation professionals were blinded as to intervention. Different neuropsychologists and occupational therapists conducted assessments and training. Interrater reliability and conformance to data collection were secured by following an assessment protocol and individual training for each instrument.

Individual APT sessions were administered by a clinical neuropsychologist/the author of this thesis and lasted 30-90 minutes. An occupational therapist was responsible for the content and implementation of attention training in attention demanding activities. Types of training and time devoted to a specific training procedure were individually registered. Training sessions lasted 60-120 minutes.

3.2.2.3 Study IV

Patients participating in the RCT study [140] and included in the APT intervention group were re-invited by letter for participation in the qualitative interview study. The letter comprised information about the interview study. The patients were subsequently contacted by telephone within a week to ascertain interest to participation and degree of occupation in work and/or study. The interviews were conducted in a quiet room at the hospital by a research clinician not involved in the informant's rehabilitation team. Two interviews were conducted at the informants' workplace and at their home respectively. The interviews were recorded with a smartphone and lasted on average 51 minutes (range: 32-92 minutes).

3.2.3 Intervention programs

Two interventions for remediation of attention were compared: intensive area-specific cognitive training with the Attention Process Training (APT I [142]; APT II [143], and training in attention demanding activities.

3.2.3.1 Attention Process Training (APT)

APT exercises have a common structure based on visual and auditory activities, typically taking 3 to 5 minutes to complete, and include two speed levels. Task difficulty is set at a performance success rate of 50%. Repetition of various exercises continues until the patient performs at 85% of a specific task or reduces task execution time by 35%. See Table 3 for examples of exercises. Progress is based on intensity of training, continuous feedback promoting motivation and on successful use of metacognitive strategies. Feedback regarding endurance, speed of performance, accuracy, and pattern of errors is provided by the therapist and is discussed after each exercise. APT in this study included psychoeducation, training of metacognitive and emotional strategies, and training for generalization.

Table 3. *Examples of exercises for the separate attention levels from the APT-material.*

	Low complexity	Moderate complexity	High complexity
Focused attention	Listen to a series of letters. Press the button each time you the letter K.	Listen to a short recital. Answer multiple-choice questions.	Listen to a list of words. Press the button each time you hear a 3-letter word.
Sustained attention	Listen to a series of digits. Press the button each time number 8 is followed by number 3.	Listen to a recital of months. Press the button for each month that comes chronologically before the previously mentioned month.	Listen to a list of words. Press the button for each word that constitutes another word if spelled in reversed order.
Selective attention*	Low volume of auditory background distractor e. g. soft music, mumbling, while engaging in a task of sustained attention.	Moderate volume of auditory background distractor e. g. noise from a coffee shop while engaging in a task of sustained attention.	Moderate volume or, competing auditory background distractors e. g. recital of numbers, recital of news at high speed while engaging in a task of sustained attention.
Divided attention	Sort cards according to color. Turn king of hearts and king of spade upside down.	Work with semantic categorization and identify the word that does not belong. Press the button every 60 seconds.	Read a script. Mark all words spelled with three letters and words with the ending '-ing'. Answer questions about the content.
Alternating attention	Listen to a series of digits. Press the button for odd numbers. After the signal, press the button for even numbers. Continue alternating focus for each signal.	Listen to a series a 5-word sentences. Alternate between reciting the words in the sentence in reverse order and alphabetically.	Headcount: start with the number 99 and continue counting in the following order: 3 +4 6. Ex 99-96-100-94-91-…

*same tasks as in training of sustained attention, albeit with various levels of distractors.

3.2.3.2 Activity-based attention training (ABAT)

Attention-specific activity limitations identified by an occupational therapist during evaluation formed the basis for the ABAT. Attention deficits have a general overall impact on both activity and participation which leads to the possibility of training attention in many different situations. Training involved attention-demanding everyday activities such as personal care, household activities, work, leisure and social activities and focused on adjustment and management of observed difficulties. The aim of ABAT was to optimize occupational performance. One of the investigators in the research team provided the occupational therapists with examples of suitable activities for attention training (Table 4). Training sessions could be individual or group-based depending on the aim. Compensatory strategies used for all activities were, among others: taking frequent breaks, verbal self-guidance, using notebooks and keeping a structured daily schedule. The selected activities and strategies were considered as treatment as usual at the rehabilitation clinic.

Table 4. *Examples of activities proposed for optimizing performance in attention-demanding situations.*

Training tasks for attention training in activities		
Cook/bake	Participate in a meeting	Read/listen to books
Vacuum-clean	Prepare a presentation	Cross-words
Pay bills	Take notes during a lecture	Socialize in a cafeteria
Grocery shopping	Commute	Handwork e. g. carpentry

3.2.4 Participants

A consecutive series of patients with mild-to-moderate stroke or traumatic brain injury (TBI) (18% scored GCS <13) participating in an interdisciplinary rehabilitation program within four months after the brain injury and fulfilling criteria for participation were included in the study. An ample majority of the included participants suffered from stroke with thrombosis accounting for fifty-one percent of stroke occurrence. TBI was a result of traffic accidents (n=7), winter sports (n=3), falls from heights (n=3) and assault of person (n=1).

3.2.4.1 Inclusion and exclusion criteria

Inclusion criteria were: deficits in attention as defined by the APT test (< 70% correct answers after correcting for late responses and false positives on at least two of five subtests) [83], scores on the lower average and above for reasoning skills and abstract thinking (Matrices (WAIS-III): standard score ≤ 7) [144], age range 18–60 years and a good understanding of the Swedish language.

Co-morbid factors potentially influencing performance on psychometric testing formed the basis for choice of exclusion criteria: neglect or visual field defects (Albert's test: ≥ 3 uncrossed lines) [145], motor disability interfering with participation (Barthel Index: score < 50) [146], severe memory disorders (RBMT: profile score at ≤ 7 points) [147], ongoing psychiatric illness including depression and anxiety (HADS: ≥ 10 on any of two sub-scales) [148], moderate to severe aphasia (the major part of test and training material were verbal), a history of severe somatic disorder causing anoxic periods, ongoing substance abuse, and severe pain. Patients with symptoms of severe depression or anxiety were offered pharmacological treatment and were included in the study when fulfilling inclusion criteria on HADS, usually after three weeks.

3.2.4.2 Power calculations

The sample size calculation for the primary endpoint variable was based upon the estimate of 1 SD improvement after 20 hours of attention training. A sample size of 19 completed data sets was needed to detect a statistically significant difference between treatment arms, with power 0.85 and alpha set at 0.05. Supplementary data sets were added to account for an expected statistical loss of at least 25%. For time-series measurements with statistical process control a sample of 10 subjects/observations per subgroup is sufficient for statistical significance [130, 132]. The statistical software IBM SPSS version 22 was used for power calculations.

3.2.4.3 Study I

Consecutive patients with stroke or TBI referred to the rehabilitation clinic at Danderyd hospital, during the period September 2011 and November 2014 were included in Study I. The patients were further divided into two groups according to time since injury: early phase after ABI (≤ 4 months) and sub-acute phase after ABI (4-12 months).
Thirty-eight patients declined participation and twelve of the ultimately included participants discontinued the intervention study, four due to health-related issues and eight due to personal reasons.

3.2.4.4 Study II

Patients receiving interdisciplinary brain injury rehabilitation and ABAT were included in study II within 12 weeks after injury (mean=8; SD=4) and completed the intervention program within 20 weeks after injury (mean=14; SD=5). The sample comprising a full set of process measures consisted of 27 patients (75% stroke, 75% male, 71% had higher education, and 82% lived in a relationship). Mean age was 45 years (SD=10). The overall performance level of attention, as defined by the Attention Process Test [83] was between 27% and 61% (minimum 6%, maximum 64%) of an expected 80–100% in a healthy population, and affected sustained, selective and alternating attention.

3.2.4.5 Study III

Sixty patients, fulfilling the inclusions and exclusion criteria [140] randomized to APT (n=31), and ABAT were included. Most participants suffered a stroke (80%), were male (64%), in a relationship (81%) and had a higher education (73%). Brain injury was localized as follows: anterior (34%), subcortical (42%) and posterior lesions (15%). Unilateral brain damage accounted for 76% (left hemisphere, n=25; right hemisphere, n=20). Participants were enlisted in the study within 13 weeks after injury (mean=9; SD=4) and completed the intervention program within 20 weeks after injury (mean=15; SD=5) with a median of five weeks for APT and six weeks for ABAT. The attention deficit as defined by the APT test [83] affected sustained, selective and alternating attention.

Due to an incomplete set of process measures, the results from one participant were excluded from process analysis. Eight participants (four from each intervention group) failed to participate at follow-up. Follow-up took place approximately 6 months after the intervention (mean=27; SD=2).

3.2.4.6 Study IV

Sixteen men and women receiving APT in the intervention study were invited between June 2014 and March 2015. An additional inclusion criterion for this study was currently working or studying at ≥25%. The informants were chosen through purposive sampling to obtain a representative sample of patients with different age, gender, the cause of brain injury and level of attention dysfunction.

Most informants suffered a stroke (n=11). The three remaining had suffered a traumatic brain injury in traffic-, ice skating- and skiing casualties. The attention dysfunction at the time of training was moderate-to-severe as defined by the APT test [83] for all participants except for one whose dysfunction was estimated as mild. All informants had completed high school. Nine informants had tertiary education. Everyone had worked full time before the brain injury, except for one who had just graduated from high school. At the date of the interviews, seven informants were working or studying full time. The remaining worked or studied part-time (25% to 80%). Nine informants lived in a relationship. The gender ratio was equal. The informants were interviewed two to four years after completing APT.

Fourteen informants were ultimately included (median=50 years; range 23-63 years): one informant declined for personal reasons, one agreed to participate but was not included due to saturation in data from informants with similar characteristics.

3.3 METHODS AND ANALYSIS

3.3.1 Primary outcome variable

The *Paced Auditory Serial Addition Test (PASAT)* [149] was selected as the primary outcome measure due to its sensitivity in detecting subtle attention deficits [144, 150]. The test is presumed to measure working memory, speed of information processing and sustained and divided attention [144, 151]. The procedure includes 60 one-figure additions, presented at set intervals ranging from 0.8 sec to 2.4 sec, and last for 15-20 minutes. Scoring is based on the number of correct answers produced within the time-frame [152]. The participants were presented with a practice trial of eleven numbers before each assessment. In study II and III results for the slow-paced interval condition (2.4 s) are presented.

3.3.2 Other neuropsychological tests

Attention process training test, APT test [83] is a screening instrument serving as an indicator for level and degree of attention dysfunction. It consists of five subtests corresponding to the five clinically derived attention levels: focused, sustained, selective, divided and alternating attention. A visual scanning task complements the subtest of divided attention. Performance calculations are based on number of correct, omitted and incorrect responses within the time-frame. The APT test was used as a test of inclusion and served to evaluate level of attention dysfunction and to develop a treatment plan with the APT material.

Matrices (WAIS-III) [144] is a test of abstract thinking and reasoning skills consisting of a series of increasingly difficult visual patterns that need to be completed by choosing from a multiple-choice array. It was used as a test of inclusion to ensure a minimum limit of reasoning skills and abstract thinking during intervention.

Albert's test [145] is a test of perceptual neglect and visual field disorders in which the participant must cross out randomly oriented lines on a paper. Lines left uncrossed, with more than 70% of uncrossed lines on the same side as the motor deficit indicates unilateral spatial neglect. The test is also sensitive to hemianopia and was used as an exclusion test.

Barthel Index [146] is a tool to measure a person's independence in activities of daily living regarding personal care (feeding, grooming, bathing, dressing, bowel and bladder care, toilet use) and mobility (transfers, ambulation, stair climbing). Scoring varies from unable or dependent to independent. Barthel Index was used as an exclusion test to identify motor disability that would interfere with participation.

Rivermead Behavioral Memory Test (RBMT) [147] is a measure of memory used to predict everyday memory problems after ABI. The RBMT comprises task that are similar to situations appearing troublesome to the patient aiming at visual, verbal and spatial memory. Two parallel versions equivalent in difficulty were used to monitor change over time and to minimize re-test effect. The RBMT was used as an exclusion test to indicate degree of memory impairment.

The Hospital Anxiety and Depression Scale (HADS) [148] was used as an exclusion test to indicate the degree of depression and anxiety. A score of < 7 on the respective subscale indicates no signs of depression or anxiety, a score of 8–10 indicates mild signs and scores > 10 points indicate that the participant suffers from depression and anxiety that is expected to have an impact on attention.

3.3.3 Interviews (Study IV)

Semi-structured thematised interviews were conducted to gain access to the experience of the participants. A thematic interview guide was developed and adjusted during data collection, covering both pre-defined and emerging themes during the interviews. We used a flexible interview style focusing on comparing, and contrasting ideas to test emerging hypothesis. Our aim was to describe variances and nuances in the daily management of attention deficits. The questions were open-ended in the sense that simple yes-or-no answers were made impossible. Follow-up questions were interpretative and ideal [136] in the sense of referring to previous answers and clarifying what has been said during the interview. Capturing as many aspects as possible was important to ensure credibility and data with high quality [153]. Interviews were added until saturation in the main themes was reached, i.e. no further information was generated by the added interviews [136, 153]. See Fig 3 for the sampling of interviews.

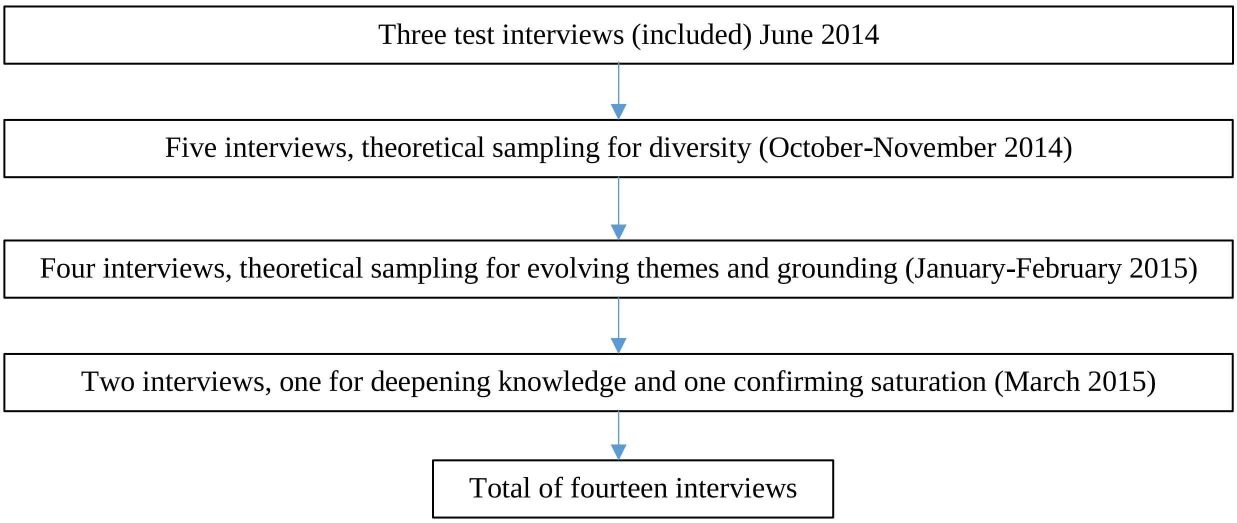


Figure 3. *Details on a purposive and theoretical sampling of interviews.*

3.4 DATA ANALYSIS

3.4.1 Statistical analyses in Study I-III

In Study I-III parametric and non-parametric statistical methods were used for demographic, clinical and injury-related data. Data were checked for skewness and kurtosis. Demographic and injury-related nominal data such as diagnosis, gender, marital status, education level, employment status, and localization of injury were investigated using the chi-square test. The parametric t-test was used to compare groups on age, the Glasgow Coma Scale, length and timing of intervention, the level of attention dysfunction and results on psychometric tests. Ordinal data included in the HADS were investigated using the non-parametric Spearman's rank-order correlation. Levene's test of homogeneity of variance was used to investigate within-group variances at each trial between the intervention groups. The statistical software used was: IBM SPSS Statistics v. 22, and MS Excel. Statistical significance level was set at $p<0.05$ 2-tailed for all analyses.

3.4.2 Time-series measurement with SPC: Study II and Study III

Statistical control limits and variability in improvement were explored with SPC with the underlying assumption that data plots within the control limit indicate a process in stable statistical control. Data points outside control limits were considered related to special causes of variation, such as an effect of treatment. Xbar charts (based on the mean) and S-charts (based on SD) (Fig 4) were used to follow the process on group level. Individual processes were monitored by I-diagrams.

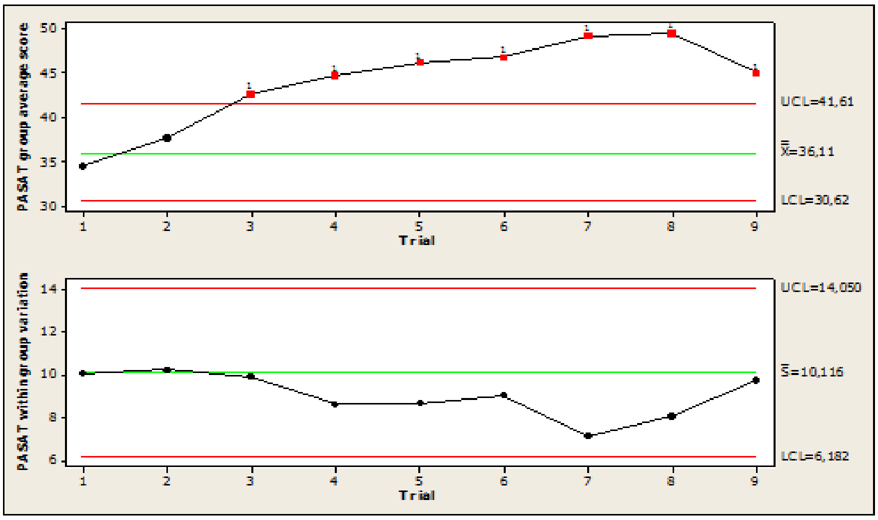


Figure 4. *Xbar-S chart plotting the process mean in Xbar chart (upper control chart) and process standard deviation S chart (lower control chart) over time for variables in subgroups. Control limits are calculated considering both process center and spread.*

The control charts included three additional lines: the center line (based on the mean of baseline measures) and an upper (UCL) and lower control limit (LCL) set at ±3 standard deviations from the mean respectively [134]. Patterns were analyzed through run analysis and following specific rules for statistical change (Table 3) [129]. The statistical software used was: MINITAB 16 and MS Excel.

Table 5. *Primary and supplementary rules for statistical control applicable for Study II and Study III.*

1. One point >3 SD or more from centerline
2. Eight consecutive points on the same side of the centerline
3. Seven or more consecutive points exhibiting an increasing or decreasing trend
4. Six-to-seven or more consecutive points move up or down bisecting the centerline
5. Two of three consecutive points fall >2 SD from the centerline, on the same side
6. Four of five consecutive points fall >1 SD from the centerline, on the same side

3.4.3 Qualitative analysis

3.4.3.1 Constant comparison

Data was analyzed by means of constant comparison. Audio recordings of the interviews were listened to several times to get an overview of themes before being transcribed verbatim by the author. The transcripts were imported to the computer program Open Code 4.0 to facilitate sorting of the text information (http://opencode.software.informer.com/4.0/). Each interview was followed by a preliminary analysis including memos by the interviewer; each transcription was followed by an independent survey of the data by the interviewer and the first author, before initiating open coding of the text, i.e. a line-by-line analysis of meaningful units initiating abstraction of data into codes. Interviews and transcriptions were discussed and analyzed several times for substance. With each new interview, all aspects of previously identified themes were sought as well as observing new emerging themes and strategies. Insights gained were discussed after every third interview with a third researcher, an experienced qualitative researcher. The interviews and the analysis continued and developed in parallel as described by Strauss and Corbin (2012) [138]. Further abstraction of data was initiated after the third interview. Codes were compared for similarities and differences, and clustered together into sub-categories [138]. Properties and dimensions of emerging categories were explored. Relations between the categories were linked based on shared characteristics. See Table 6 for an example of data interpretation. A first preliminary model was formed and the interview guide was subsequently refined. With the emerging model in mind, additional reviews of the transcripts, re-listening of the recordings and to interviews were considered and analyzed afresh leading to an adjustment of the preliminary model. Results were discussed and analyzed by all authors regularly during the whole process.

3.4.3.2 Trustworthiness

Triangulation in researchers was used. Three researchers with different backgrounds and professions collaborated on the analysis: brain injury rehabilitation based on neuropsychology and occupational therapy, and physiotherapy with a reference to pain rehabilitation. Peer-debriefing was initiated continuously with senior researchers in the field of rehabilitation medicine and neurological conditions, as well as doctoral students at the clinic.
Triangulation in analysis comprised grounded theory and content analysis. A thick description was kept throughout the data collection and analysis.

As a neuropsychologist with many years' experience of rehabilitation after ABI and being the therapist administering the 20 hours of APT to each informant, the author had prolonged involvement in the field. Although prolonged involvement is considered important to understand the field, preconceptions could have prevented the understanding of other perspectives. To avoid answers adjusted to the interviewer's expectations, a clinician with no previous relation to the informant conducted the interviews. To increase awareness of personal bias, analysis and emerging hypothesis were continuously discussed in the research group. Audit trails were kept in laboratory journals covering memos, transcripts, and details of the analysis process.

3.5 ETHICAL CONSIDERATIONS

The Karolinska Institutet Ethical Committee (Registration no. 2007/1363-31) approved the study protocol. Patients received written and oral information, and they all gave written consent. Participation in the training was quite demanding as to intensity and length of training. The continuous assessment could be experienced as cumbersome for the patient. Qualitative research through interviews may cause discomfort. The interviewer with extensive knowledge and professional experience of this patient group was experienced in qualitative research and adjusted the interviews at signs of discomfort. Also, the informants were given the possibility to see a psychologist after the interview.

Table 6. *An example of levels of abstraction in data interpretation for the main category Awareness during the analysis process in grounded theory.*

Interview quotation (concrete level)	**Open coding** (descriptive level)	**Categories** (abstract level)	**Generated model** (generalized level)
We have reached a period where we won't be bothered by the symptoms and the therapies anymore **-** *I'm not getting any better.*	permanent damage	acceptance (process)	
I need more help from others to stay independent…and that could be complicated.	independence through strategies	acceptance (process)	
I depend on others and I believe I earned the right to get help from others.	dependence	acceptance	
I have more time to do other things in life than work…others also need to be given the possibility to feel responsible at work (laughs).	attitude	insight	AWARENESS
I can't do as my much as before, I'm tired. But that has nothing to do with the brain injury **-** *I'm getting older!*	justification	comparison to self	
I don't have the same capacity as before. It took time to come to terms with that.	acceptance (attitude)	comparison to self	
It took time to recuperate from the brain injury. I thought I would regain my capacity, but I stopped improving about a year ago.	improvement ends	acceptance (process)	

4 RESULTS

4.1 STUDY I

4.1.1 Inclusion process

Approximately one third (n=302) of patients eligible in terms of diagnosis and time since injury met the criteria for inclusion- and exclusion and were thus formally qualified for participating in the RCT study [140]. An additional 63% were excluded for administrative reasons, such as shortage of staff, early discharge, conflicting staff decisions, and aborting participation.

The inclusion process for participants in Study I is presented in Fig 5: 10% were ultimately included in early rehabilitation (within 4 months post-injury), and 15% were enrolled in the sub-acute phase (4-12 months post-injury).

Exclusion in the early phase was mostly due to complexity of brain injury symptomatology (63%). These exclusion criteria were also applicable for 35% of the patients in the sub-acute phase. Another 31% of patients in the sub-acute phase failed to meet the criteria of time since injury.

Exclusion of potential participants regardless of time since injury were age (24%), aphasia (13%) and not matching the requirement of attention impairment (10%) as stated in the APT-test guidelines for the RCT-study. The complexity of brain injury symptomatology as defined by exclusion tests answered for 17% of excluded potential participants, out of which the lion’s share (93%) were in the early phase after brain injury.

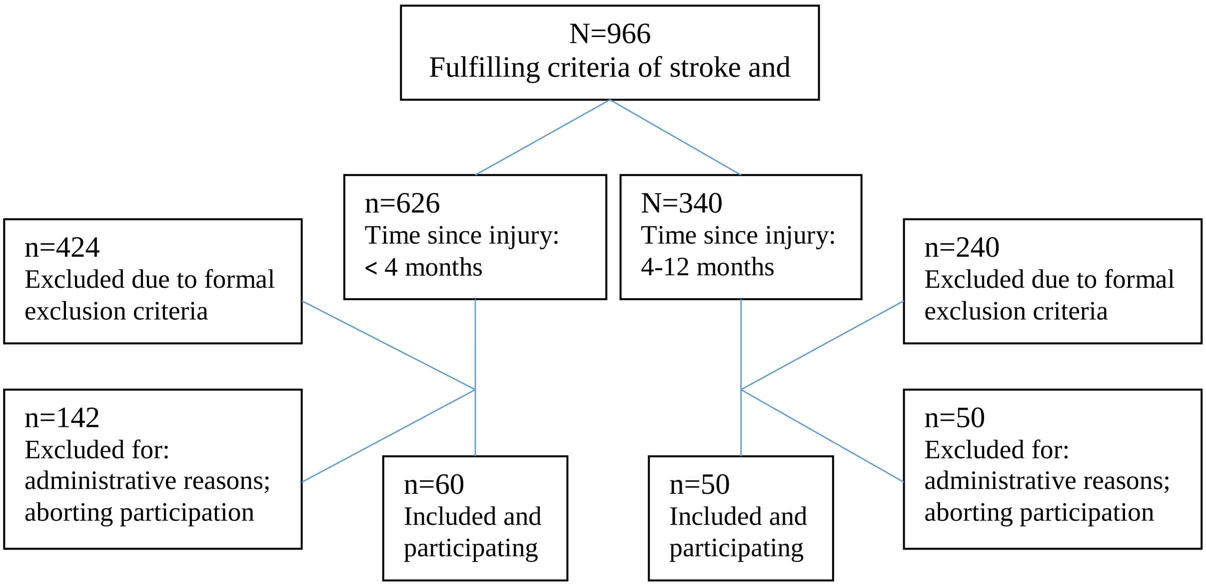


Figure 5. *Inclusion process for all patients considered in the RCT study (Bartfai et al 2014).*

4.1.2 Differences between eligible patients ultimately participating in the intervention study and those not participating

Eligible patients in the *early* phase (< 4 months; n=202) differed significantly for diagnosis (p=0.047) with a predominance of stroke survivors among non-participants (78.3%) who also had suffered a more severe brain injury (p=0.005) as expressed in GCS scores. The majority of eligible patients were married or in a relationship, and had a higher educational degree. They differed however for relationship status (p=0.002) and education level (p < 0.001) with significantly more singles and low educated among non-participants. No significant differences regarding age, gender or country of origin, or in clinical features such as depression, anxiety, mental fatigue and reasoning skills, were found.

Eligible patients in the *sub-acute* phase (4-12 months; n=100) also differed significantly for gender (p=0.025) and education level (p=0.029). Women and patients with high education were more likely to participate in the intervention study. There were no significant differences in the sub-acute phase regarding diagnosis, age at onset, and severity of injury expressed in GCS, marital status or employment, nor were there any significant differences regarding any of the clinical variables, such as depression, anxiety, mental fatigue and reasoning skills.

4.2 STUDY II

A variable degree of spontaneous recovery was expected for all patients. The SPC method was modified to capture variation in an evolving process: on group level the mean of the first two measures of the PASAT was used as baseline providing an initial value from which we wished to detect changes. Estimation of the standard deviation was used through a pooled standard deviation measure based on the first two trials. A similar approach was used for construction of I-diagrams, with an individual baseline per participant [154]. Estimation of the standard deviation was made by calculating the average of the moving range between the two first trials (n=27) [155] (see Appendix 1 in Study II) [156]. For this study we used a total number of eight measurement points.

4.2.1 Group level

The X-bar chart showed an upward slope beyond control limits fulfilling multiple rules for special-cause variation, allowing the conclusion that an improvement had occurred at group level. The S-chart, representing group variation, indicated no special cause of variation within the group; variation over time during the sampling period was considered stable. Mean values and standard deviations for PASAT with control limits at three standard deviations for statistical control are presented in Fig 6.

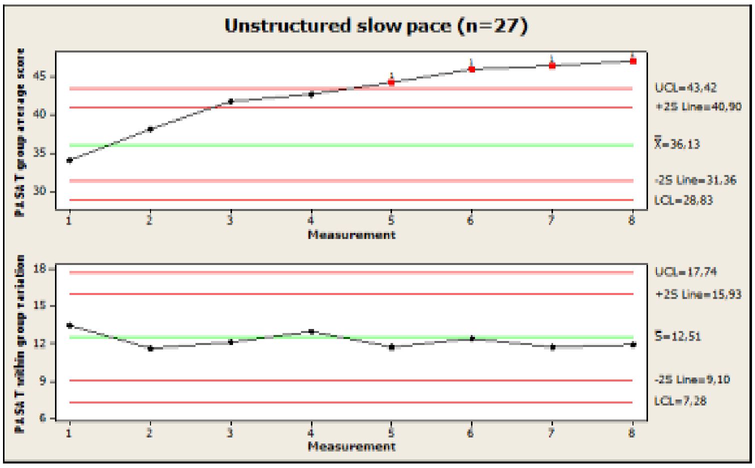
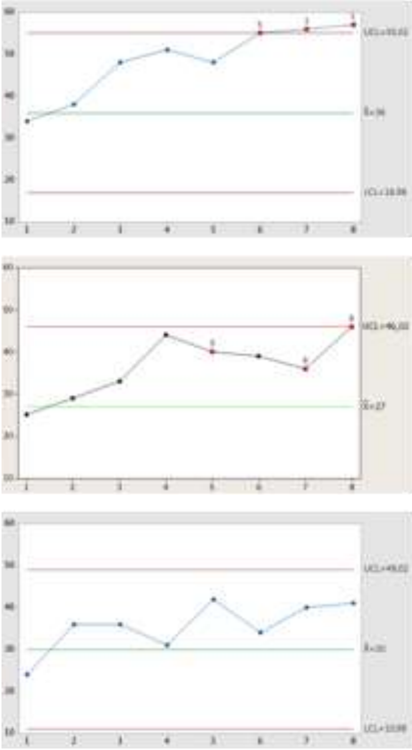


Figure 6. *Xbar-S chart at group level with 3-sigma control limits for each intervention. The average is presented in the upper chart (Xbar); within-group variation is presented in the lower chart (S-chart). Measurements one through eight illustrate variations in the process during interventions.*

4.2.2 Individual level

I-diagrams were examined to identify special-cause variation indicating a statistical change in 15 out of 27 individual processes. Data was further examined for the time-point for special-cause variation defining the pattern of improvement in the three subgroups: rapid improvers, steady improvers, and stationary performers. Rapid improvers were defined as fulfilling the criteria for special-cause variation within five measurement points, corresponding to a maximum of 12 hours of attention training; steady performers were defined as fulfilling the criteria for special-cause variation between six and eight measurement points, corresponding to 15-20 hours of attention training. The pattern of a stationary performer, displaying only random variation, fulfilled no criteria of special-cause variation (Fig 7).



Patient 2 was at the age of 27 involved in a car accident leaving him with a mild traumatic brain injury consisting of deep axonal injuries and contusions in the anterior parts of his brain. He has a high school degree and works as a construction worker. At inclusion, his level of attention impairment was 53% of an expected 80-100%. Patient 2 is considered to follow a **steady pattern of improvement** (+23 range of variation at PASAT).

Patient 15 survived a car accident at the age of 19 years. As for patient 2, she received injuries at deep axonal level and haemorrhages mainly in the frontal lobes. She had just fished her high school degree and started working as a hairdresser. At inclusion, her level of attention impairment was 26% of an expected 80-100%. Patient 15 illustrates a **rapid pattern of improvement** (+19 range of variation at PASAT) 6

At the age of 40 years, **patient 1** survived a fall leaving him with bilateral multifocal contusions, mainly in the frontal lobes. He works as a stage technician, and is married with two children. His level of attention impairment was at 45% of an expected 80-100%. The pattern of improvement of patient 1, illustrates a **stationary performer** (+18 range of variation at PASAT).

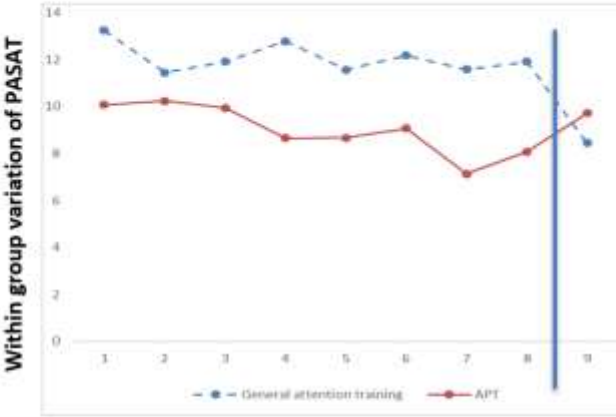
Figure 7. *I-diagrams illustrating patterns of improvement with SPC.*

4.3 STUDY III

In this study, we evaluated differences between the two intervention groups using SPC and further analyzed the results according to previously identified patterns of change (Study II). APT patients improved significantly both in number and timing of achieved improvement.

Analysis of individual processes for all patients showed that improvement occurred for 71% of the participants regardless of type of intervention. The majority (60%) reached improvement after 15-20 hours of treatment. The within-group variation as shown in S-charts was stable, thus confirming the results in the Xbar charts. Within the group of stationary performers (showing no pattern of improvement), six participants presented high scores at the PASAT (>50) at each measurement, thus preventing the possibility of monitoring improvement. Approximately two-thirds of the participants (63%) retained their improved level in performance at the 6-months follow-up. Only 10% of the patients showed decreased performance at follow up.

The effect of the interventions was examined for the two groups separately. There were no differences between treatment conditions in group average performance. There was however a significant decrease of the within-group variation for APT at measurement point four, and sustained decrease in within-group variation from measurement point six (Fig 8).



Measurement	Levene Statistic	df (1)	df (2)	*p (Sig)*
1	3,627	1	57	0,062
2	0,693	1	57	0,409
3	1,894	1	57	0,174
4	5,045	1	57	0,029
5	2,337	1	57	0,132
6	4,924	1	57	0,03
7	7,972	1	57	0,007
8	5,163	1	57	0,027
9	2,059	1	57	0,157

Figure 8. *Differences in within-group variation during intervention (n=8 measurement points). Measurement (9) corresponds to six-month follow-up of PASAT performance. P-value for within-group variability is computed with Leven's test for homogeneity in variance, Sig. (2-tailed).*

APT patients improved significantly in several aspects: the proportion of improved patients was higher (84% APT group and 56% ABAT group, $\chi2$ (1, N = 59) = 5,93, p=.015); the pattern of improvement differed between treatment conditions ($\chi2$ (1, N = 59) = 7,411, p=.025) with improvement occurring earlier in the process. The improved performance was maintained at the 6-months follow-up as indicated by decreased within-group variability. Performance at follow-up differed between treatment conditions ($\chi2$ (1, N = 51) = 6,847, p=.033) favoring APT. ABAT was presented in 71% of stationary performers. See Fig 9 for details regarding distribution of performance patterns within the treatment groups.

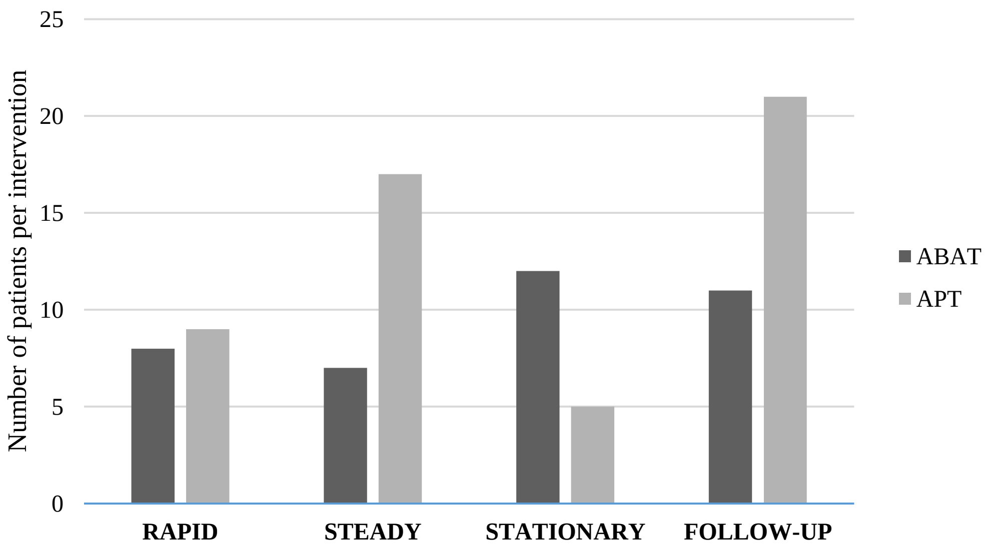


Figure 9. *Distribution of patients per identified improvement patterns, including number of patients with maintained improvement at six months follow-up.*

4.4 STUDY IV

The qualitative analysis of fourteen interviews resulted in a theory illustrating a dynamic management of attention dysfunction regarding a suitable and flexible use of action plans and strategies (Fig 10). The theory includes three main categories and eleven subcategories. Categories are described in terms of properties and dimensions, see Table 7.

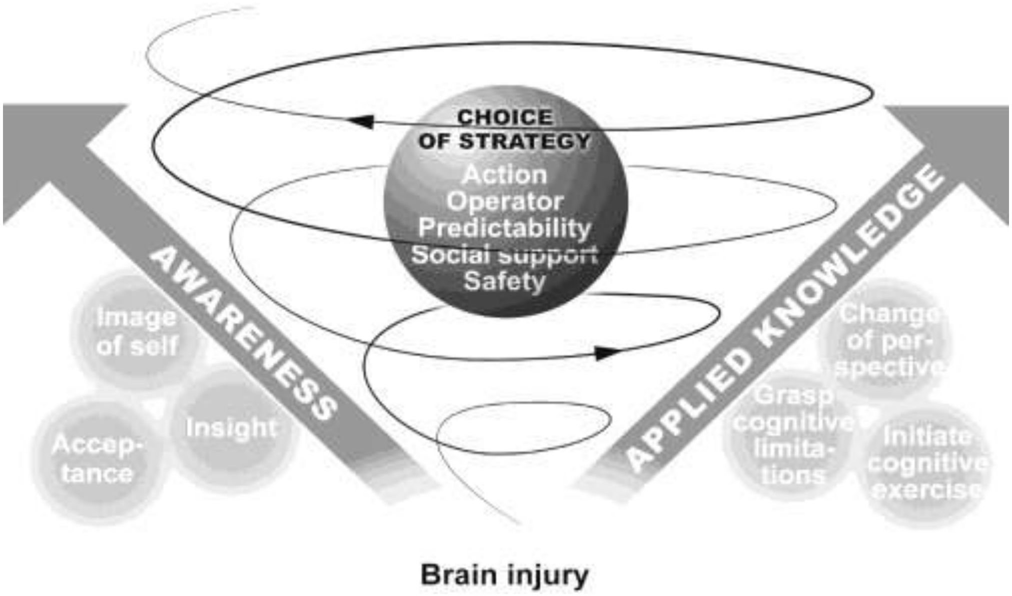


Figure 10. *A dynamic model illustrating the long-term management of ABI-based attention dysfunctions after early attention process training (APT).*

The long-term management of ABI-based attention dysfunction was dynamic and adjusted to fit each situation to the current level of knowledge regarding the cognitive dysfunction and the attitude towards it. The management of a problem in a given situation was pursued concerning the choice of strategy and was influenced by context, such as level of awareness and readiness to adjustment. When a specific strategy was insufficient, the need to experiment with other strategies emerged. Increasing knowledge supported the generalization of strategies, and readiness to apply this knowledge.

The core category "*Choice of strategy*" describes action plans comprising what to do in a given situation and, when needed, who would carry out the plan if the informant could not. Influenced by the degree of predictability, the level of dependence on social support and the sense of security in each situation, a need for adjustment of the chosen strategy during action were also described. Depending on the nature and severity of the dysfunction, pronounced routines or pre-defined time-schedules could help to guide the behavior to a favorable outcome. Reflective processes encompassed meta-cognitive strategies and were used for fine-tuning both strategies and behavior in specific situations. A flexible approach to the choice of strategy was necessary to handle diverse situations throughout a day.

“*Awareness*” includes the person’s insight, level of acceptance and an exploration of self-image in each situation. The informants described growing awareness of the consequences of ABI as a process driven by grasping the implications of limitations in daily living. The experience emerged in situations where the informants faced cognitive limitations contrary to their self-image and expectations regarding capacity. Insight was described as continuous and part of a process leading to a point where change in adjustment was possible. The long-term consequences of ABI were subdued by a stepwise acceptance. The informants described that only when realizing that no further functional improvement for a specific situation was likely, were they able to initiate change in behavior and establish new and attainable goals for future life. Awareness promoted dealing with problems related to attention impairment in daily living.

The third main category, “*Applied knowledge*” refers to grasping cognitive limitations, initiating continuous cognitive self-training, and to the change of perspective towards problem solving. The informants described understanding the implications of the brain injury and the individual change in capacity resulting from it, including what specific aspect of a dysfunction to work harder with, why continuous training was necessary, how to plan training on their own and how to work around some of the consequences of cognitive delimitations. Only after applying that knowledge in real-life situations after discharge from rehabilitation were the informants able to comprehend the scope and nature of their limitations in different situations. This process took time and effort. New habits were developed regarding deliberate maintenance of cognitive capacity. The informants expressed that the understanding of how they function in different settings, and what they could do to influence this, ultimately led to a change in perspective when considering their difficulties and their improvement. Obstacles were not necessarily perceived as limitations.

Table 7. *The three main categories with their subcategories and related properties and dimensions*

Main category	*Subcategories*	*Properties*	*Dimensions*		
AWARENESS	insight	emotional reaction	breakdown	↔	triggers change
		frequency	few/zero	↔	frequent
	acceptance	independence	depending on others	↔	independent by using strategies
		attitude to adjustment	feeling of loss	↔	actively letting go
		justification of new behavior	considered unrelated to ABI	↔	considered related to ABI
	image of self	comparing to former self	as before	↔	adjusted or changed
		comparing to healthy others	identifying with	↔	different
		comparing to other with ABI	better off	↔	identifying with
		hidden dysfunction	relief	↔	frustration
APPLIED KNOWLEDGE	grasping cognitive limitations	selection of situation for training	general	↔	specific
		choice of target for training	general	↔	specific
		change in priorities based on limitations	same	↔	changed
	initiation of cognitive exercise	cognitive maintenance	maintain level	↔	push limits
		level of priority	taking breaks	↔	persevering
		choice of goal	easily attainable	↔	stepping stone to next goal
		longterm commitment	experience based	↔	knowledge based
	change of perspective	orientation towards problem solving	passive	↔	active
		empowerment	weak	↔	powerful
CHOICE of STRATEGY	action (what)	type of strategy	automatized	↔	reflective
		identified problem area	general	↔	situation specific
	operator (who)	performer	self	↔	other
		attitude towards responsibility	passive	↔	active
	predictability	level of predictability	high	↔	low
	social support	need of social support	dependance	↔	independance
		identified situation (when)	general	↔	specific
	security	sense of security	insufficient	↔	pronounced
		dealing with hidden dysfunction	masking	↔	revealing
		behavior	withdrawal	↔	pro-active change

5 DISCUSSION

5.1 COMMENTS ON MAIN FINDINGS

Intervention studies in the early stage after ABI is a challenging matter as one needs to distinguish treatment effect from a natural and highly individual evolving recovery process. There is a controversy regarding early brain injury rehabilitation concerning the role of cognitive therapy, efficacy, optimal timing and the specific needs of different subpopulations of ABI [157]. Several factors need to be addressed when evaluating intervention outcomes such as generalizability and robustness of the findings; explanatory confounding factors; and in what way the intervention has a long-lasting effect for the patient. The four papers address some of these challenges.

The question of outcome of intervention early after brain injury has been approached from complementary perspectives, including quantitative and qualitative approaches at level of outcome interpretation [158]. Through process analysis with time-series and statistical control we have investigated the outcome of both interventions in detail and through interviews and qualitative analysis with emergent design, we have explored the patients' long-term perspective of the intervention. Based on our findings we argue that attention process training and metacognitive strategies early after ABI are highly beneficial for functional improvement of attention deficits and for the long-term management of experienced difficulties in daily life due to attention impairment. We argue also that time-series measurements with SPC provide a more sensitive analysis of robustness and distribution of performance within subgroups during intervention.

5.2 THE EFFECT OF SAMPLING BIAS ON GENERALIZABILITY IN INTERVENTION TRIALS AFTER ABI (STUDY I)

Passing through the needle's eye.

In the present RCT study [140] the number of potential participants were significantly reduced due the strict criteria and prognostic targeting recommended for strengthening generalizability of RCT results. This study followed the recommendation in the CONSORT statement [159, 160] emphasizing the disclosure of eligibility criteria for participants, including the quantity of eligible patients and reasons for exclusion. The use of strict selection criteria decreased the representativeness of the patient group and prolonged data collection, and thus increased the risk of dropouts for administrative and organizational reasons as found in other studies [161].

Methodological challenges related to heterogeneity has been addressed in numerous studies [162-167] suggesting strategies such as adopting *strict enrollment criteria* in RCT studies

[168, 169], various *statistical approaches* [170] and the use of *common data elements, CDE's* [171, 172].

The purpose of *strict enrollment and prognostic targeting* is to obtain a relatively homogeneous study group with comparable conditions at baseline [59, 173, 174]. Inclusion and exclusion criteria in our study were based on earlier research and clinical experience to reduce systematic confounding factors, such as cognitive conditions interfering with baseline testing (aphasia, age, visual or motor impairment) [144]; or conditions interfering with interpretation (premorbid attention problems) [162, 169, 175]. However, most of these conditions in brain injury patients have been shown to benefit from attention training including aphasia [176, 177], elderly subjects [178, 179], and subjects with developmental attention impairment [60, 76].

A *statistical* strategy to issues dealing with heterogeneity in RCT's such as recruitment, randomization, measurement and retention [180, 181], is to investigate the statistical power and efficiency per baseline characteristics (e. g. inclusion and exclusion criteria), prognostic targeting (e. g. excluding those with relatively extreme prognosis) and covariate-adjusted analysis (e. g. adjusting for a baseline covariates) [170]. These strategies have the potential to reduce sample size but could have a negative impact on study duration (apart from covariate-adjusted analysis not affecting recruitment) [170, 182].

The *CDE* technique, e.g. the choice and coding of common data elements, could be used to pool data or share them in different trials, allowing larger samples and thus stronger results [172]. A collection of CDE has been developed for TBI in adults [183] and children [184], as well as for cognitive dysfunction following TBI [18]. However, the collection of CDE's specific to stroke is still incomplete [185]. Several studies have demonstrated the relative independency of cognitive domains, such as the relative independency between linguistic and non-linguistic skills in aphasia [186] and between verbal intelligence and neglect after stroke [187]. Hence, the CDE technique could be applied to these patients in future studies instead of excluding them thus allowing a more efficient data collection.

So, where do strict enrollment criteria leave us regarding generalization of results, study efficiency and cost-effectiveness? We advocate the use of broad inclusion criteria in line with Maas [171] and re-emphasize the need to report data from the total patient population in intervention studies. The results indicate the need for closer links between selection of exclusion criteria and study aims. In our case, data collection could have been significantly faster and more cost-effective, with a higher number of eligible patients enabling subgrouping and the use of CDEs [188].

5.3 SPC: A FEASIBILITY STUDY OF THE APPLICATION OF TIME-SERIES MEASUREMENT IN EARLY NEUROREHABILITATION (STUDY II)

Distinguishing significant variation in an evolving process.

SPC provided data concerning *when* special cause variation occurred within the recovery process for each patient. We found that by using the SPC method, one may approach the extent and timing of changes in performance at both group and individual levels.

The challenge in early intervention research is to find a method both sensitive and specific to change in an evolving process where individual differences in the recovery process could lead to confounding results. Special-cause variation in SPC signaling change in performance, is identified by using statistically sound rules for change also providing data concerning the sustainability of change. Our studies have advanced SPC as a feasible method for distinguishing significant variation in individual processes.

We identified three different *patterns of change* depending on timing i. e. when the change occurred expressed in the amount of training hours, and sustainability of observed change: rapid and steady improvers, and stationary performers indicating no improvement in performance during the intervention period. The finding of different improvement patterns indicates that even within this relatively well-defined homogeneous group there are discernible subgroups responding differently to rehabilitation implying systematic heterogeneity in treatment response. This has not been described earlier within the context of brain injury recovery. The identification of specific patterns of recovery is of high importance for rehabilitation planning e.g. real-time clinical decision making, and for prognosis e.g. included as a predictive factor.

In SPC, assessment relies on one single outcome measure, thus caution must be taken to choose a measure that fits the purpose of the study. The primary outcome variable, the PASAT, is an objective neuropsychological attention test independent of the intervention and sensitive to attention dysfunction [140, 144]. The test is psychometrically sound with a documented test-retest effect for two administrations [150, 189] implying an expected initial improvement of results. Therefore, the lack of test-retest effect and the lack of improvement for some patients were both interesting and clinically disturbing. Furthermore, participants were included due to attention dysfunction, as registered on several tests [150]. Nevertheless, some patients reached high scores at PASAT, consequently preventing the registration of potential functional improvement due to ceiling effects of the test.

The use of SPC charts provides statistically based feedback on the process at hand, and could support clinical decision-making [130] and adjustments of the intervention process. Real-time feedback would enable a closer examination of the underlying factors for variation, sustainability of observed change, and lack of variation, and as such provide a powerful tool for clinical rehabilitation management [69]. SPC reaches the requirements for statistical significance in group-sizes as small as ten participants [130, 132].

5.4 APT IS BENEFICIAL DURING EARLY INTERVENTION (STUDY III)

Within-group differences in outcome

Attention dysfunction can be improved with early cognitive rehabilitation as illustrated in Study III. Although both groups, APT and ABAT, improved in performance the use of SPC allowed the observation that on a subgroup level there were several significant differences regarding the *robustness* and *distribution* of results between the interventions, favoring APT. The group receiving APT presented a more *robust* outcome of intervention as defined by decreased within-group variability during the intervention. This finding prompts the hypothesis that structured attention training in early neurorehabilitation might affect the organization of cognitive processes, probably through mechanisms of Hebbian plasticity – ”cells that fire together, wire together” [190]. Data examined regarding within-group variability in earlier studies of structured attention training [104, 111] indicated a tendency to decreased within-group variability. Conflicting results in earlier studies using traditional pre- and post-evaluation statistics might be due to a neglected consideration for the impact of differences in within-group variability [173].

The *distribution* of patterns of improvement also differed between the intervention groups in terms of number of improved patients after intervention and at follow-up favoring APT. It is noteworthy that significantly fewer patients receiving APT failed to show improvement in PASAT performance as compared to ABAT. The length of intervention could contribute to conflicting results on the effect of attention training in early rehabilitation. We found that after twelve hours of intervention, the ratio of improved versus non-improved performances was the same between the two groups and that it was during the subsequent eight hours of training that the major difference in outcome unfolded. Studies finding inconclusive evidence for early structured attention training [104, 111] offered less than 15 hours of training, whereas studies offering up to thirty hours found conclusive evidence for the benefit of APT [105]. The lesser treatment dosage could have contributed to the inconclusive results.

In conclusion, the present results endorse the advantage of implementing process measures in early cognitive rehabilitation seeing that it enables an identification of differences in robustness of an intervention, in the distribution of performance patterns within the subgroups, and of timing of change. In Study III, we demonstrate that SPC in general using patterns of recovery, and control charts as indicators of statistical change in performance provide substantial and detailed information about the improvement process while allowing comparison of two interventions. Thus, control charts could support clinical decision-making in early neurorehabilitation. Furthermore, the findings allow for targeted research hypothesis.

5.5 DAILY MANAGEMENT OF ATTENTION DYSFUNCTION 2-4 YEARS AFTER INJURY (STUDY IV)

Development of strategies fit for purpose

Although APT has been accepted as golden standard in post-acute ABI rehabilitation [62, 73], its influence on the daily attention management as experienced by patients was yet to be investigated. By applying grounded theory with an emergent design on interviews of patient experience, we found that the daily management of attention dysfunction was a dynamic process resulting in strategies both refined and flexible to common and demanding situations. The management was promoted by several inter-related factors: increased self-awareness including detailed apprehension of resources and obstacles; deepened application of metacognitive strategies generalized to new situations including self-training with an elaborate goal-setting; and a problem-solving approach to perceived dysfunction. Our findings emphasize the role of early cognitive rehabilitation as a tool to raise awareness and to develop strategies fit for purpose. The APT seems to endorse the adjustment of strategies and the dynamics of the management process. Most informants in Study IV engaged in continuous self-training and refined goal-setting through self-evaluation based on internal and external feedback on performance and high personal motivation. This has been found to be an important prerequisite for long-term success of rehabilitation [62, 191-193] and reinforced through self-awareness [193], participation in some form of rehabilitation and life-experience [193-196].

In our study as in others [197] awareness of the consequences after ABI emerges in the experienced discrepancy between expected and actual outcome in a situation. Awareness-gaining is described as a time-consuming, continuous process, elsewhere confirmed [194, 198]. The process was found to be driven by comparisons for self-evaluation to self and other [199, 200]; by understanding cognitive limitations including practical and emotional consequences thereof [195, 201]; and by a stepwise acceptance specific to situation or task that builds on metacognitive knowledge, goal-setting and beliefs of own capacity [202, 203]. This process resulted in the development of practical solutions, counteracting passive resignation to a state of disability. Our model links elements both from Toglia and Kirk’s multidimensional model of awareness [195], and from Fleming and Strong’s conceptualization of self-awareness (1995) [204]. The dynamics of knowledge, metacognition and awareness influences the management of task demands [195] but the ability to set realistic goals and know how to pursue them, constitutes the driving force for functional improvement [204] as illustrated for example in the informants’ self-training habits.

The informants viewed themselves as ultimately responsible for managing the situation and adjusting strategies accordingly. This finding provides a complementary perspective on the altered responsibility after ABI experienced by the caregiver in terms of increased burden and change of roles [205-208]. The description of an emerging dynamic mind-set that is self-supportive in problem-solving seems to extend the capacity to manage attention deficits caused by ABI, as confirmed in other studies [203, 209]. The own responsibility is a necessary component in compensatory strategies [124, 210] and in the acceptance process [211] and ultimately for successful rehabilitation. A combination of three determinants seems to regulate the choice and adjustment of strategy: level of predictability, degree of external support, and sense of security. Each determinant per se e. g. predictable situations are less challenging to handle [212, 213]; security found in routines [58, 214] and in relying on assistance [205, 206], have been previously discussed. However, the influence of these three determinants combined has not been presented in earlier studies.

Cognitive rehabilitation provides a tool for raising awareness and strategy development when dealing with practical and psychological consequences after ABI [196, 215]. APT appears to assist in developing tools to increase real-world outcome after ABI. This has been found also in other protocols for functional improvement, such as constraint induced rehabilitation protocol for motor dysfunction [216] and aphasia [217]. As for APT, the protocols rely on two components: 1) remediation of dysfunction through intensive repetitive tasks with increased difficulty; and 2) adaptation to consequences of deficit through mastering metacognitive strategies, developing techniques for transfer of skills and knowledge to daily activities, and promoting self-training [113, 216]. APT contributed to the daily management of attention dysfunction in three aspects: 1) a sense of control when managing situations, 2) the increasing knowledge about the consequences of their brain injury and how to make use of strategies, and 3) the tenacity in training. The prolonged and continuous self-training including goal-setting has not been described in earlier APT studies [45, 83, 113]. Our results support that the specific steps of APT training describe and teach the necessary elements in self-training, and as such enhances motivation and promotes a sense of ‘ownership’ necessary for a successful outcome [71, 203, 210]. The process of using cognitive tools tally with earlier studies [58, 214], and are in our study described in greater detail.

Our findings indicate that functional improvement is consolidated with the application of metacognitive strategies through self-awareness, refinement of goal-setting and a problem-solving perspective. Metacognitive strategies promote generalization of skills, and as such independent improvement in performance. The daily management of the attention dysfunction, while life-long may thus continue to improve albeit in a different manner than prior to the brain injury.

5.6 METHODOLOGICAL CONSIDERATIONS

Limitations of alternative and supplementary approaches to evaluate intervention outcome found in this project could help improve the design of future studies. In-depth description and discussion of the different methods used in this thesis are given in the four papers.

Limitations as to *recruitment* when launching RCTs in multi-professional rehabilitation settings, has been discussed in other studies [161] where clinical priorities along with factors such as institutional constraints on admission and scheduling regulation, and caregiver protectiveness impede full engagement in research participation. The large drop-out rate for organizational reasons found in Study I, reflected decisions in treatment priorities in conflict with the study protocol. Practical solutions comprised cultivating collaborative relationships between researchers and clinicians and capitalizing on benefits of the research project for the participants, the clinician and the research team, as well as for the clinic. An example from our study was to continuously provide repeated information about the study to all clinicians involved during data collection to maintain compliance with study procedures.

Sample size calculation was based on an estimated improvement in performance ensuring statistical power. However, with a larger sample, division into groups on variables such as educational level, complexity of work and injury characteristics (aetiology, localization and distribution of injury, cognitive dysfunction) could offer a more nuanced picture of the efficacy of rehabilitation using APT. Statistical analysis of sub-groups would be beneficial in this respect, as would multivariate prognostic models.

Although the participants were included both from in- and outpatient units, the data collection was limited to one, single rehabilitation clinic. Study I should not be regarded as a population study since the participants had been referred from other units and thus already selected. Data regarding referral practice of the other units, is lacking.

A limitation as to *data collection* is that the first author was responsible for both managing the data collection and studying intervention effect of her own patients. However, assessment at all levels for Study II and Study III was blinded and randomization was delegated to a supervisor not involved in the data collection. Neutrality in Study IV was ensured through frequent discussions with the research team and by deploying an interviewer unknown to the informants.

Limitations to *generalization* of results have been discussed in Study I and Study III regarding the effect of strict enrollment criteria on recruitment. The strife in RCT's for homogeneity in participants potentially creates groups with lower ecological validity that disregard clinically important issues. Although APT proved to be beneficial in Study III, a broader generalization to other patient groups must proceed with caution. With regards to the results in Study IV it is however reasonable that the experiences described by the informants are not unique and that similar results can be attained in other remediating cognitive rehabilitation interventions with similar composition as the APT program.

Limitations in choice of *outcome measure* have been discussed in Study II and Study III where we identified several participants reaching scores too high for the test to measure. Ceiling effect on the primary outcome variable potentially limited the ability to detect change in the improvement process.

The *design of the study* meant that all patients received some form of attention intervention, additional to the rehabilitation offered. Thus, this study compares two interventions without assuming, that one should be equivalent to placebo or considered a control group. From a clinical perspective, it would have been unethical to withhold treatment for a control group, given the positive evidence for rehabilitation of cognitive dysfunctions post brain injury [57]. In our study, we deployed an active control group with training procedures equating level of challenge and engagement as argued for in other studies [218]. The best current training procedure would thus yield the most informative control.

6 CONCLUSIONS

6.1 GENERAL CONCLUSIONS

- Process measures with SPC provide a detailed analysis of performance in real-time, and is sensitive to variations in performance in the early stage after ABI.
- Three subgroups were identified following different patterns of improvement based on time of confirmed change in performance, where one group showed no improvement during intervention.
- SPC differentiated effect of intervention on group level in terms of robustness and number of improved patients.
- APT and the use of metacognitive strategies is beneficial in the early stage after ABI as evaluated with process measures and confirmed through interviews with informants.

6.2 CLINICAL IMPLICATIONS

An important area of application of the process method for clinical purposes is the individual, real-time monitoring of treatment. Variability in performance during rehabilitation is common, and the rules of detecting a systematic change can supply vital information for rehabilitation professionals for decision-making. This information can also be used to track treatment changes, discuss these changes with the patients, optimize improvement and register potentially adverse changes in patients' status, e.g. due to hydrocephalus or other medical complications. In Study IV the importance of ownership of the rehabilitation process was highlighted, with the management of flexible metacognitive strategies and tenacity in continuous self-training as two major factors. The application of this finding would be beneficial when outlining rehabilitation programs.

6.3 FUTURE STUDIES

In general, there is a marked need to develop multivariate prognostic models for recovery after brain injury both for individuals and on a group level. Prognostic models could increase the sensitivity to special cause variation by using biological and psychological predictors in the context of process measures. The finding of three subgroups indicating different patterns of improvement during intervention is of great prognostic value. Earlier findings regarding prognostic variables need to be integrated along with future studies to identify relevant criteria for developing such models. In further studies, it is also of interest to establish the generalizability of this finding to the recovery of cognitive functions other than attention and to identify possible biological and psychological parameters with predictive value.

7 SVENSK SAMMANFATTNING

Förvärvade hjärnskador resulterar ofta i kognitiva funktionsnedsättningar av varierande grad. Ett av de vanligaste symtomen är uppmärksamhetsnedsättning med vanligtvis livslång påverkan på inlärning, minne, dagliga aktiviteter och delaktighet i samhället. Uppmärksamhet går att träna upp med intensiv strukturerad träning inom ramen för hjärnskaderehabilitering. Attention Process Training (APT) är ett träningsprogram med hög evidens i det kroniska tillståndet efter hjärnskada. Behandlingsrekommendationer för kognitiv träning i tidigare skeden efter skada är inte lika tydliga, bland annat på grund av metodologiska svårigheter att särskilja träningseffekt från spontanläkning.

Målet med studien var att utvärdera effekten av APT i tidigt skede efter mild till måttlig stroke eller traumatisk hjärnskada, samt utforska hanteringen av uppmärksamhetsnedsättningar i vardagen och APT-behandlingens eventuella påverkan på detta.

En randomiserad kontrollerad studie genomfördes vid en större rehabiliteringsklinik. Patienter med stroke eller traumatisk hjärnskada erhöll tjugo timmar uppmärksamhetsträning utöver det ordinarie rehabiliteringsprogram. Patienterna fördelades slumpmässigt till process-inriktad uppmärksamhetsträning med APT, vilket inkluderar träning av metakognitiva strategier; eller till aktivitetsbaserad träning med mål att optimera utförande i uppmärksamhetskrävande aktiviteter. Behandlingen genomfördes inom de första fyra månaderna efter insjuknandet/skadetillfället.

I **Studie I** utvärderade vi vilken påverkan strikta urvalskriterier kan ha på patient-rekrytering i forskning. Med knappt 10% inkluderade patienter i tidigt skede, exkluderas lejonparten av patienterna med stroke eller traumatiska hjärnskador under datainsamlingen. De patienter som uppfyllde samtliga kriterier men som exkluderades av andra skäl, hade i högre utsträckning lägre utbildning och levde ensamma än de som i slutändan medverkade i studien. Våra urvalskriterier, som baserades på tidigare forskning och kliniska erfarenheter, ledde till förlängd datainsamling och resulterade i en potentiellt mindre representativ grupp. Baserat på vår analys av flödesprocessen bör det finnas stora fördelar med bredare och färre urvalskriterier, samt användandet av redan fastlagda gemensamma datapunkter (common data elements) och statistiska justeringar, i utformandet av framtida studier.

En metodologisk svårighet i tidigt skede efter förvärvad hjärnskada är att särskilja statistiskt signifikanta förändringar i den rörliga process som pågår parallellt med behandlingen – individens naturliga läkningsprocess. I **Studie II** har vi utvärderat möjligheten att använda tidsserieanalyser med statistisk processkontroll (SPC) för att fånga signifikanta förändringar i individuella rehabiliteringsprocesser och på gruppnivå. Med SPC kunde vi identifiera *om* och *när* förändring i processen skedde, samt förekomsten av tre förbättringsmönster: snabb eller stadig förbättring i utförande, samt avsaknad av förbättring. Detta fynd har stort värde för prognos av behandlingsutfall. SPC är en användbar utvärderingsmetod inom tidig hjärnskaderehabilitering och har stor potential för kliniskt beslutsfattande.

I **Studie III** använde vi SPC metoden för att närmare analysera och jämföra effekten på grupp- och individnivå av de två träningsmetoderna, APT och aktivitetsbaserad träning för uppmärksamhetsnedsättning. Signifikanta förbättringar i prestation uppnåddes i båda behandlingsgrupperna, emellertid skildes resultaten åt inom grupperna. APT hade större effekt på såväl antal förbättrade individer som i stabilitet avseende förbättring över tid.

För att bättre förstå hanteringen av uppmärksamhetsnedsättning i vardagen 2–4 år efter att ha genomgått APT behandlingen, har vi i **Studie IV** analyserat fjorton intervjuer med en kvalitativ, framväxande design enligt den grundande teorins metod. Upplevda brister i uppmärksamheten hanterades på ett högst dynamiskt sätt. Anpassning och finjustering av strategier ökade med växande självmedvetenhet och med en fördjupad kunskap i identifieringen av problemområden och tillämpningen av metakognitiva strategier. APT-träningen främjade den utökade självmedvetenheten och gav verktyg för tydlig avgränsad målformulering vilket ökade motivation och en ihärdighet i kontinuerlig självträning.
De sammanlagda slutsatserna från denna doktorsavhandling kan få betydande implikationer för utformningen av rehabilitering. En samstämmig bild från både processanalysen och intervjuer i den kvalitativa studien visar att APT är en lovande behandling i tidigt skede efter förvärvad hjärnskada. Förbättrad prestation under behandlingen uppnåddes i högre grad för den grupp som tränade med APT. Strategier för tanke och träning som lärts in under APT-träningen användes i hög utsträckning av patienterna även långt efter avslutad rehabilitering. Den individuella realtidsmätningen av behandlingen som SPC medger tillhandahåller rehabiliteringspersonalen samt patienten med kritisk information. Denna information visar på om patienten förbättras eller försämras och möjliggör att träningen kan skräddarsys efter varje patients behov. För patienten kan det bidra till att öka delaktighet och ägarskap för rehabiliteringsprocessen, vilket också kan stimulera flexibelt användande av utvalda strategier och fortsatt självträning – faktorer avgörande för en effektiv rehabilitering.

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