

# Anxiety and depression in people with acquired brain injury

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# Anxiety and depression in people with acquired brain injury

Acceptance and Commitment Therapy  
as a possible intervention



Johanne Rauwenhoff



# Anxiety and depression in people with acquired brain injury

Acceptance and Commitment Therapy as a possible intervention

Johanne Rauwenhoff



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# Anxiety and depression in people with acquired brain injury

## Acceptance and Commitment Therapy as a possible intervention

PROEFSCHRIFT

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kom gaan we rijden, pijn doet het toch wel  
waar je ook bent

Uit het lied *Soms breekt er een hart, soms blaft er een hond* van Spinvis





# CHAPTER 1

General introduction

## **Anxiety and depressive symptoms following acquired brain injury**

An acquired brain injury (ABI) can be defined as damage to the brain that occurs after birth and is not related to congenital disorders, developmental disabilities, or processes that progressively damage the brain (1). The National Institute for Public Health and the Environment estimated that approximately 650.000 people live with the consequences of an ABI in the Netherlands (2). An ABI can have different causes of which the most common are a stroke (caused by blood leakage in the brain or when blood supply is blocked) and trauma (caused by a fall or accident). Other causes can be hypoxia (due to for instance a heart attack) or a brain tumour. When ABI is mentioned in this thesis, it refers to traumatic brain injury (TBI) or brain injury caused by a stroke. An ABI can lead to a wide variety of consequences. People can experience physical consequences, such as (one sided) paralysis, muscle weakness, or changed sensory sensations. However, ABI can also lead to non-physical, 'invisible' consequences. These include fatigue, cognitive impairments such as memory, attention, and executive difficulties, and behavioural changes such as impulsivity, aggression, and irritability (5, 6).

People with ABI are at an increased risk of developing anxiety and depressive symptoms (7-9). The prevalence rates for anxiety symptoms following TBI vary from 21 to 37% and for depressive symptoms from 30 to 43% (10-13). The prevalence rates for anxiety symptoms following stroke vary from 20 to 29% and for depressive symptoms from 29 to 33% (8, 14-17). The varying prevalence rates are likely due to differences in study populations, time since injury, and outcomes used. Besides, depressive and anxiety symptoms often co-occur (8). The trajectories of these symptoms can vary. In the year following the ABI, symptoms can stay constant, increase, or decrease (18).

The pathophysiology of anxiety and depressive symptoms post-ABI is not yet clearly understood. However, it seems likely that there is a complex and multifactorial interplay between biological, psychological, and social processes, possibly depending on the time since injury. Possible biological mechanisms are related to oxidative stress, lipids, and inflammation (19-21). The results of studies on the potential association between lesion location, TBI severity, and anxiety and depressive symptoms are inconclusive (16, 22-24). Next to biological mechanisms, several psychological factors likely play a role in the development of ABI-related anxiety and depressive symptoms. An ABI is a life-changing event; people have to cope with a new way of life and are faced with many forms of loss. Feelings of grief often follow loss. People suffer from alterations or losses in health, independence, occupation, social roles, and social contacts. Furthermore, people with ABI can experience a loss regarding the subjective experience of who they are, their own identity or self. Their present self is often viewed negatively in comparison with the pre-injury self (25, 26). Previous studies have found that changes in self-identity are related to higher levels of depression and grief (26, 27). Additionally, various psychosocial risk factors for the development of ABI-related anxiety and depressive complaints have been identified. These include psychiatric history, neurotic personality traits, an avoidant coping style, impaired social functioning, and social isolation (28-31). Other general risk factors are sleep difficulties, gender, age, time since injury, cognitive and functional impairments, and insufficient rehabilitation (7, 22, 30). How these psychological and biological processes relate to each other is unclear.

However, Fang and Cheng (32) proposed that the biological mechanisms might be more prominent in the acute period following the stroke, whereas psychological and environmental factors start playing a more important role over time. This is likely comparable for other forms of ABI.

Anxiety and depressive symptoms can have a large impact on the well-being of patients with ABI and are negatively associated with quality of life (33, 34). Moreover, anxiety and depressive symptoms can lead to increased caregiver burden (35) and are associated with higher hospitalization costs and mortality (30, 36).

### *Treatment of anxiety and depressive symptoms*

Given their high prevalence and large impact on the lives of people with ABI, it is important to develop evidence-based prevention and treatment options for anxiety and depressive symptoms post-ABI. Unfortunately, it remains unclear what optimal strategies are for prevention and treatment (37). A Cochrane review concluded that the evidence-base for pharmacological interventions for post-stroke depressive symptoms was weak and stroke-survivors receiving a pharmacological intervention experienced more adverse events compared to placebo (38). Furthermore, pharmacological interventions do not offer people approaches on how to cope with the consequences of an ABI. Given the fact that psychological interventions have no neurological side effects, they might be preferred for people with ABI. However, several meta-analyses have concluded that the effect of psychotherapies is uncertain for people with ABI, with some reporting an effect that did not sustain at follow-up or rather small effect sizes (38-42). Most of these studies, furthermore, mentioned that there is a need for more high-quality studies investigating psychotherapies for ABI-related anxiety and depressive symptoms.

Next to deciding whether treatments are likely effective, it is important to know what the right treatment is for a particular patient, as there is individual variability in the effectiveness of psychotherapy (43). Currently, it is difficult for clinicians to decide what treatment option is most suitable or effective for a certain patient (44). It is therefore not clear what works for whom and models to predict treatment outcomes are lacking. New statistical analyses permit the development of prediction models utilizing machine learning techniques (45). These techniques are increasingly being used in the depression research field (46, 47), while applications to predict the outcome of psychotherapy for depressive symptoms following ABI are lacking.

In this thesis, it was investigated how to optimize the treatment of depressive symptoms by developing a clinical prediction tool for post-stroke depressive symptoms. Furthermore, we investigated if Acceptance and Commitment Therapy (ACT) would be a possible intervention for people with ABI-related anxiety and depressive symptoms.

## **Acceptance and Commitment Therapy for people with acquired brain injury**

An approach which may form an interesting perspective on how to treat patients with ABI-related anxiety and depressive symptoms is ACT (48, 49). Below the philosophical and theoretical underpinnings of ACT are explored, next to the applicability of ACT for people with ABI, and the evidence-base of ACT.

### *Theoretical foundations of Acceptance and Commitment Therapy*

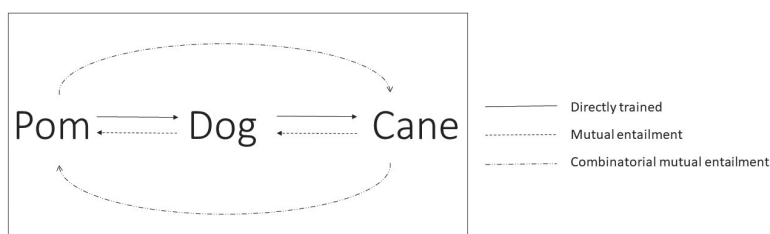
The philosophical view behind ACT is functional contextualism. The goal of functional contextualism is to predict and influence behaviour, accurately and effectively, using empirically supported principles. Events are viewed as ongoing actions; an act is always placed within a situational and historical context (50). From this point of view, thoughts, feelings, or memories are inherently not problematic, dysfunctional, or pathological. Therefore, merely analysing the behavioural symptoms, outside of the context in which the behaviour occurs, is thought to miss the essence of the problem and ways to reach a solution (51). The truth criterion of functional contextualism is ‘successful working’. This means working towards an explicitly stated behavioural goal, which has value or importance and is defined preceding the analysis (52).

The theoretical base of ACT is the relational frame theory (RFT), which is a behavioural model of language and cognition and builds upon operant learning theory (3, 53). It explains the concept of relational framing, which share three common properties; mutual entailment, combinatorial mutual entailment, and transformation of stimulus functions. Box 1 below illustrates these properties with an example.

#### **Box 1.** Mutual entailment, combinatorial mutual entailment, transformation of stimulus functions, and Pom

In the first corona lockdown, my partner and I adopted Pom. Pom is a dog. I just trained you in the relation between ‘Pom’ → ‘Dog’. If I now start to talk about my dog, you will assume this is Pom, while this association is not trained. This derived relation is called mutual entailment. We train one relation (‘Pom’ → ‘Dog’) between stimuli, and another relation (‘Dog’ → ‘Pom’) is entailed. You might feel this is obvious. It probably is obvious because this is something we (humans) are constantly doing and feels natural to us. Previous studies, however, have not convincingly shown that other species have this ability (3, 4). This summer we went to Italy and there a dog is called cane. When I now present you with the word ‘Pom’ and several Italian words such as ‘fiore’, ‘cane’, and ‘libro’, which word would you choose in relation to ‘Pom’? Most likely you chose ‘cane’. Assuming you do not speak Italian, a relation was derived between ‘Pom’ and ‘cane’, although they are not in a directly trained mutual relation. This derived relation is called combinatorial mutual entailment. The derived relations through mutual entailment and combinatorial mutual entailment can be seen in figure 1.

**Figure 1.** Mutual entailment and derived mutual entailment



These derived relations can include much more than three stimuli and there are multiple types of relations; causal relations (if/then), temporal relations (before/after), perspective (I/you/them), and so on. Moreover, most stimuli have various functions, based on the characteristics of the stimulus, previously established relations, and earlier history of relational framing of the individual. Now imagine that you had a very bad experience with a dog in the past and developed a fear of dogs. Me talking about Pom might therefore elicit a fear reaction, despite that you have never encountered a ‘Pom’ before. This is called transformation of stimulus function. The function of ‘Pom’ (formally presumably a quite neutral stimulus) was altered by the derived relation with ‘dog’. The function of a stimulus can be transferred to another stimulus in the same network.



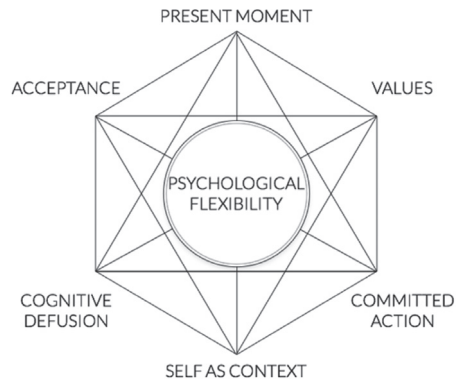
Due to relational framing humans can relate any sort of stimulus to another related stimulus and develop complex, uncontrollable, verbal networks of relations, called relational frames (3). Relational framing improves our ability to learn and take perspectives, which leads to the experience of self, and it can lead to rule-governed behaviour. Antecedents can lead to rule-governed behaviour, by functioning as an instruction or rule, without an actual intervention or contingency (54). For instance, the rule ‘don’t put your hand in an electrical socket or you will get electrocuted’ can shape your behaviour without directly experiencing the contingency (actually being electrocuted by putting your hand in a socket). While rule-governed behaviour gives us the ability to behave flexibly, it can also have highly negative consequences. Humans form rules on how to behave and live meaningful and good lives. We are often fused with our own language and tend to take our own thoughts very seriously. When private events obtain negative functions, we try to control or avoid them, which is called experiential avoidance (3).

For example: a man, who survived a stroke, lost his job due to the consequences of the stroke. He finds this very painful since he always had the belief ‘my job gives me purpose’. He starts to avoid things that remind him of his former job, as these make him feel sad and frustrated. He no longer talks to his ex-colleagues, avoids coming near his old office building, and eventually stops reading the newspaper afraid to read something that reminds him of his old job.

The avoidance of emotions, thoughts, and bodily sensations can be rewarding in the short term, however, in the long term, this will often be counterproductive. Given the nature of relational framing, thoughts and self-rules are difficult to change. ACT tries to decrease the influence of the verbal content of cognition that can cause avoidant behaviour and dismantle ineffective rule-governed behaviours (51).

### *The psychological flexibility model*

ACT is a third-wave cognitive behavioural therapy and given its pragmatic nature, the outcome of an intervention is always related to valued behaviour as opposed to symptom reduction. The main treatment aim of ACT is an increase in psychological flexibility (48), which is described as “the ability to contact the present moment more fully as a conscious human being and to change, or persist in, behaviour when doing so serves valued ends” (51). Psychological flexibility is established through the six core components of ACT: acceptance, cognitive defusion, self-as-context, mindfulness, values, and committed action. These core processes both overlap and interact with each other (55) as illustrated in figure 2. Patients are familiarized with these six core components using experiential therapeutic processes. Experiential exercises, behavioural change processes, and metaphors are used. Metaphors let the patient view their situation from a different perspective and facilitate a transfer of functions from one network to another (49). As a result, the abstract becomes concrete and implicit memory resources are engaged to support learning (56). In the remainder of this paragraph the core components of ACT will be further explained and discussed in the context of their potential therapeutic applicability for people with ABI.

**Figure 2.** The psychological flexibility model

*Acceptance.* ACT therapists will explore the different (ineffective) control strategies that their patients have used so far to avoid and control negative thoughts, feelings, or sensations. ACT suggests acceptance as an alternative approach to dealing with these phenomena. Acceptance is tolerating negative and positive thoughts and feelings related to events or circumstances that cannot be changed or one has no control over (51). For patients with ABI, this would imply accepting thoughts associated with the ABI and its consequences. For instance, patients are encouraged to make contact with feelings of pain or loss instead of avoiding them. In neuropsychological rehabilitation, acceptance is an important concept in the recovery of patients with ABI. Ben-Yishay and Diller (57) wrote in their handbook on holistic neuropsychological rehabilitation: “Acceptance of limitations is not so much an act of passive ‘surrender’ or defeat, but rather it is the result of an active process of psychological transformation, leading to the recognition that, despite limitations, one can find meaningful alternatives worth living for” (page 132). Furthermore, acceptance has been associated with better psychological outcomes and positive experiences of self-identity following ABI (58, 59).

*Cognitive Defusion.* Instead of altering the content, form, or frequency of thoughts, as is done in traditional cognitive therapies, ACT focuses on the function of thoughts. Patients are asked to perceive their thoughts more mindfully and to detach from these thoughts (49). This likely decreases the influence of relational frames and self-rules on behaviour. Therefore, implying that not the content of the brain injury-related thoughts but the response to these thoughts is the problem. The thought “I am not going to that party because I cannot follow the conversation” is not attacked in its validity or negativity but in its avoidant content. Cognitive defusion is likely a more suitable process for patients with cognitive deficits as opposed to cognitive restructuring techniques. For example, there is no need to detect thoughts and keep them in mind while looking for positive alternatives, which can be quite a cognitively demanding process. Furthermore, following a life-changing event, such as ABI, patients might have quite realistic worries and thoughts given the situation. Challenging these thoughts might therefore work counterproductive for the adaptation process (60).

*Self-as-context.* According to RFT, there are three senses of self. Firstly, the conceptualized self (self-as-content) entails the thoughts, social roles, and the image humans relate to and of themselves. We often

behave in accordance with our conceptualized self. Secondly, the experiential self (self-as-process) is the verbal awareness of ongoing psychological experiences and the ability to describe thoughts, feelings, and senses in light of the external context (49), for instance, “I feel energetic now”. Thirdly, the observing self (self-as-context) is a sense of perspective and a point of view that is unique. Being in contact with the observing self is seen as beneficial and associated with increased psychological flexibility. However, often the conceptualized self overshadows the observing self. As described above people with ABI can experience negative changes in self-identity. Myles (61) describes how an ABI can lead to a crisis in the conceptualized self as people might not be able to keep up with the thoughts, social roles, and images they have of themselves. This crisis in the conceptualized self often leads to emotional distress as patients might try to protect or sustain the pre-injury conceptualized self. Denial of injury-related changes can be seen as a coping mechanism to avoid emotional distress, though this is not sustainable in the long term (61). Moreover, it is also imaginable that a person with ABI becomes very fused with the idea of being an ABI-patient and that a large part of their identity is related to the ABI and its consequences.

During an ACT intervention, patients loosen their identification with the conceptualized self and increase contact with the observing self (49). This can lead to flexible and value-driven behaviour, rather than acting to keep up or protect the pre-injury conceptualized self. From the perspective of the observing self, patients can accept the post-injury changes (61) and experience that the story of the ABI is one of their stories.

*Mindfulness.* Mindfulness means being present in the moment and having full, non-judgemental attention to the here and now. Paying attention in this particular way will help to accept the reality of the present moment (62). During an ACT intervention, having attention to the present moment is trained with the help of mindfulness exercises. Mindfulness conforms with cognitive strategies such as doing activities or tasks with attention and just one at a time (63). Mindfulness has become increasingly popular and much research has been done on its effectiveness. Lawrence et al. (64) conducted a systematic review and concluded that mindfulness-based interventions can have a positive effect on anxiety, depression, fatigue, and quality of life in stroke survivors. Furthermore, mindfulness-based interventions have been found beneficial for people with different psychiatric diagnoses and multiple sclerosis (65, 66).

*Values.* Value exploration and clarification are an important part of ACT. During this process, the patient might be asked to identify values within different life domains such as family, health, and spirituality (51). Values and goals are closely related but are not the same. Goals can be completed. Values, on the contrary, can be used as an “inner compass”, guiding choice-making and goal-setting. Consequently, personal values can guide goal setting during rehabilitation. Limitations as a consequence of the ABI might prevent returning to the pre-injury lifestyle and activities. Whereas inquiry into values may help people to find new ways of living. Furthermore, people with a chronic illness can be quite narrowly focused on their illness. Thinking about values can help to take a step back and look at life from a broader perspective. Pais et al. (68) investigated the role of valued living on psychological and functional outcomes in patients with a TBI. They found that valued living was strongly related to functional outcome, positive outlook, and reduced depressive symptomatology. Furthermore, valued living has been found to be related to enhanced well-being and post-traumatic growth and negatively related to distress and post-traumatic stress symptoms in people with ABI (69).

*Committed action.* Once the patient has set their values, the next step is to commit to these values. To achieve behavioural change, ACT uses various techniques which stem from traditional behavioural therapies (51). These can include exposure and setting small, achievable goals. Traditionally goal setting is an essential component of neuropsychological rehabilitation (5). For instance, a patient can be narrowly focused on returning to work and as difficulties arise, the patient might struggle with coming to terms with the realization that returning to work might not be possible. Following the value exploration, the patient realizes that one of the core values behind their focus on going back to work is to contribute to society. The first step to living by this value could be to search for charity organizations that are looking for volunteers. Therapists can aid in formulating goals and help with finding creative ways for to engage in valued driven behaviour while keeping in mind cognitive and physical impairments.

### *Evidence for ACT*

Several meta-analyses have been conducted showing that ACT can be an effective treatment for anxiety and depressive symptoms, addiction, obsessive-compulsive disorder, and schizophrenia (70-72). Moreover, ACT is effective for people with various chronic health conditions and related mood complaints such as chronic pain and multiple sclerosis (66, 73).

At the start of this PhD trajectory, there was little evidence for the effectiveness of ACT for people with ABI-related mood symptoms. Kangas and McDonald (74) had published an article describing that ACT could be an interesting treatment option for people with ABI-related depression symptoms and Soo et al. (75) did this for ABI-related anxiety symptoms. Furthermore, Graham et al. (76) performed a case study in which a man with post-stroke depressive symptoms and medically unexplained symptoms benefited from an ACT intervention. Besides, Whiting (77) described the results of a pilot RCT in which they compared ACT ( $n = 10$ ) to befriending therapy ( $n = 9$ ) for people with severe TBI and psychological distress. The study had a follow-up period of one month. Despite the small sample size, a significant greater reduction in depressive and stress symptoms was found in the ACT group compared to the control group. However, no significant differences were found regarding ACT related processes such as psychological flexibility. Additionally, they described two cases who received ACT in a dyad. A therapeutic effect was found for one participant and the ACT intervention was acceptable to both participants (78, 79). Since then, the evidence-base of ACT for people with ABI has grown rapidly. Sander et al. (80) conducted a RCT comparing ACT ( $n = 49$ ) to devised usual care ( $n = 49$ ; this consisted of a referral to a psychological service, however, it is unclear whether participants received care) in a sample of people with a TBI. The study had a follow-up period of three months. They found a significantly greater reduction in depressive symptoms and a significant increase in psychological flexibility in the ACT group compared to the control group. Majumdar and Morris (81) conducted an RCT investigating the effectiveness of a didactic ACT group intervention ( $n = 26$ ) for stroke survivors compared to treatment as usual ( $n = 27$ ). The study had a follow-up period of two months. Significant improvements were found in depression, self-rated health status, and hopefulness. These studies have shown promising results. Nevertheless, they also concluded that more and larger scale studies with longer follow-up time and active control interventions are needed to confirm these findings.

## This thesis

Currently, it is not known how to best treat anxiety and depressive symptoms following ABI. There is a clear need to improve the care of people with ABI-related anxiety and depressive symptoms. To optimize treatment selection, we investigated if it was possible to develop a clinical prediction tool for post-stroke depressive symptoms. Additionally, we investigated a novel treatment option for people experiencing ABI-related anxiety and depressive symptoms. Philosophically and theoretically, ACT seems a fitting treatment option for people with ABI who experience anxiety and depressive symptoms. We started by investigating how to measure psychological flexibility and cognitive defusion in people with ABI. Hereafter, we developed the BrainACT treatment, an ACT treatment adapted for the needs and possible cognitive deficits of people with ABI. We consequently tested the effectiveness of the BrainACT intervention and examined its feasibility. The outline of the thesis is as follows:

### *Can we predict the outcome of an intervention for post-stroke depressive symptoms?*

In chapter 2 we developed a prognostic index model for treatment outcome in patients with post-stroke depressive symptoms who received cognitive behavioural therapy or computerized cognitive training.

### *How to measure cognitive defusion and psychological flexibility in people with ABI?*

In order to measure the effect of the BrainACT treatment, we investigated the validity of the Dutch versions of the Acceptance and Action Questionnaire for Acquired Brain Injury (AAQ-ABI; measuring psychological flexibility related to thoughts and feelings about ABI) and the Cognitive Fusion Questionnaire (CFQ-7; measuring cognitive defusion) in a population of people with ABI in Chapter 3.

### *How to adapt ACT for people with ABI?*

In chapter 4, the rationale and description of the BrainACT treatment protocol are presented. This is an ACT treatment adjusted to possible cognitive deficits and needs of people with ABI.

### *Is ACT effective and feasible for people with ABI?*

In chapter 5 we investigated the effectiveness of the BrainACT treatment in four people with ABI-related anxiety and/or depressive complaints using a single case experimental design. We described the protocol of the BrainACT randomized controlled trial in chapter 6, and in chapter 7 we performed a process evaluation of the BrainACT treatment in order to investigate the feasibility of ACT for people with ABI.

In the final chapter, all results are integrated and discussed, clinical implications are provided, and recommendations are made for future directions.

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## CHAPTER 2

Personalized predictions of treatment outcome in patients with post-stroke depressive symptoms

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## Abstract

*Objective.* Post-stroke depressive symptoms (PSDS) have a vast individual and societal impact. Studies on interventions for PSDS show contradictory results. It is unclear what works for whom and clinical prediction tools are lacking. This study aimed to develop a prognostic index (PI) model for treatment outcome in patients with PSDS.

*Methods.* Data from a randomized controlled trial ( $n = 61$ ) evaluating two interventions for PSDS were used to predict post-treatment PSDS and participation. From 18 pre-treatment variables of patients and caregivers, predictors were selected using elastic net regression. Based on this selection PI scores (i.e. predictions) for both outcomes were computed for each individual patient.

*Results.* The depression model included all pre-treatment variables, explaining 44% of the variance. The strongest predictors were: lesion location, employment, participation, comorbidities, mobility, sex, and pre-treatment depression. Six predictors of post-treatment participation were identified, explaining 51% of the variance: mobility, pre-treatment participation, age, satisfaction with participation, caregiver strain and psychological distress of the spouse. The cross-validated PI scores correlated highly with the actual outcome scores (depression:  $\text{corr.}=0.672$ ; participation:  $\text{corr.}=0.718$ ).

*Conclusions.* PSDS forms a complex and multifactorial problem. Treatment outcome is influenced by characteristics of the stroke, patient, and spouse. Results indicate that psychological distress is likely no obstacle when attempting to improve participation. The personalized predictions (PI scores) of treatment outcome show promising results which can, after replication and validation, aid clinicians with treatment selection.

## Introduction

Depressive symptoms are common following stroke and have a vast impact on functional and neurological outcome (1, 2), the rehabilitation process (3), and overall quality of life (4) of patients. Moreover, it places a high burden on society and the health care system (5). The treatment of post-stroke depressive symptoms (PSDS) has been proven challenging. In clinical practice, treatment selection is often based on trial and error with modest treatment efficacy. Furthermore, randomized controlled trials (RCTs) evaluating possible effective treatments, such as psychotherapy and pharmacological treatment, show contradictory results (6-8). A potential explanation is the heterogeneity and the multifactorial nature of the disorder (9). As a result, it is not clear what works for whom and clinical prediction tools for treatment outcome are currently lacking.

There is a growing interest in the development of clinical prediction tools utilizing machine learning techniques (10). One such approach is the use of a large pool of variables to develop predictive algorithms, which produce estimates of an individual's prognosis, otherwise known as prognostic index (PI) scores (11, 12). These predictive algorithms, or PI models, can predict the future symptom status of an individual patient, for instance following a certain therapy, to determine the level of care that is needed in the future and therefore aid treatment selection. This technique is used within medical decision making, for instance, to predict the effectiveness of different treatment options for breast cancer (13). Furthermore, the application is rapidly growing within the depression literature (11, 12). The current study aimed to develop a PI model to predict the post-treatment outcome scores for patients with PSDS. Pre-treatment variables (such as clinical and injury-related variables) of a RCT, investigating two treatments for PSDS, were used to develop the PI model. This PI model predicted post-treatment outcome scores of depression and experienced participation restrictions for each participant. These predicted values are referred to as "PI scores".

## Method

### The study

Data used in this study came from a multicentre RCT investigating the effectiveness of cognitive behavioural therapy (CBT) and computerized cognitive training for PSDS (6). CBT was adapted for people with a stroke; for instance, three sessions of occupational- or movement therapy were added to the treatment to enable the application of pleasurable activities. A detailed description of the intervention is published elsewhere (14). During computerized cognitive training, patients could select a combination of four cognitive domains, such as memory, for training. The program difficulty level was adjusted accordingly (6). Both interventions consisted of 13 to 16 sessions in a 4-month time period. Both interventions were effective in significantly improving depressive symptoms and quality of life. However, no significant differences between the interventions were found for any of the outcome measures. Further procedures of the study and efficacy results can be found elsewhere (6). The trial was approved by the Medical Ethical Committee of Nijmegen (the Netherlands).

## Participants

Participants met the following inclusion criteria: having sustained any type of clinically confirmed stroke at least 3 months earlier, scoring  $>7$  on the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D), being 18 years or older, having only mild cognitive impairments (Mini-Mental State Examination score (MMSE)  $>27$  out of 30), scoring positively on the communication-related items of the National Institutes of Health Stroke Scale, and mastering the Dutch language. Exclusion criteria were pre-stroke major depression requiring psychiatric care, premorbid disability as reflected in a Barthel Index (BI) score  $<19$  (out of 20), stay in an inpatient setting, severe comorbidity that might affect mood (eg, malignancies), and post-stroke major depression requiring treatment with antidepressants.

## Outcomes

Both depression and participation restriction scores, assessed immediately post-treatment, were used as primary outcome measures for the current analysis. Post-treatment depression scores were measured using the HADS-D. Scores on the depression subscale range from zero to 21, with higher scores indicating more depressive symptoms. Good internal consistency for the HADS-D (Cronbach's  $\alpha=0.81$ ) was found in a stroke population (15). In the current sample, patients showed a significant decrease in the HADS-D pre-treatment compared to post-treatment (mean difference, -4.6; 95% CI, -5.7 to -3.6) (6).

Participation restrictions were measured using the restrictions subscale of the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P). This scale measures the experienced restrictions regarding vocational, leisure, and social participation. The ten items are rated on a scale from zero to three or a "not applicable option". The sum score is converted to a 0-100 scale based on the items deemed applicable, with a higher score indicating fewer participation restrictions. It is a valid and reliable measure for former rehabilitation outpatients; the internal consistency of the restriction subscale was found to be good (Cronbach's  $\alpha=0.91$ ) (16). In the current sample, patients did not show a significant difference pre-treatment compared to post-treatment on the USER-P restriction scale (mean difference, 2.9; 95% CI, -0.4 to 6.2). Despite this overall non-significant difference, inspection of raw data showed vast differences in pre-post change scores between participants. Because of this high variability, it is interesting to predict individual post-treatment scores in order to identify who might benefit from the treatments.

## Pre-treatment variables

A correlation matrix was computed for all variables measured pre-treatment in the original study. Variables that were highly correlated ( $r \geq 0.60$ ) were discussed between co-authors (JR, SB, FP, and CvH) and based on previous research and consensus, the variable that was considered redundant was removed from the dataset (see supplemental material). As a result, the following 18 variables were selected as potential predictors in order to develop the PI model.

Demographic variables included sex, age, and employment status. Variables related to the stroke were: time since stroke, type of stroke (ischemic stroke, hemorrhagic stroke, subarachnoidal haemorrhage,



or combination), location (left hemisphere, right hemisphere, brainstem, subarachnoidal haemorrhage, or combination), cognitive impairments measured with the MMSE (17), activities of daily living measured with the BI (18), and stroke impact measured with the mobility subscale of the Stroke Impact Scale (SIS) (19). Variables related to the psychological characteristics of the patients were: symptoms of anxiety measured with the anxiety subscale of the HADS (HADS-A), depressive symptoms measured with the HADS-D, coping style measured with the Utrecht Proactive Coping Competency List (UPCC) (20), frequency of behaviour regarding social participation measured with the frequency subscale of the USER-P, participation restrictions measured with the restriction subscale of the USER-P, satisfactions regarding social participation measured with the satisfaction subscale of the USER-P, and comorbidities measured with the Cumulative Illness Rating Scale (CIRS) (21). Finally, since stroke places a high burden on the spouse, variables related to the psychological characteristics of the spouses were considered as possible predictors. These included symptoms of anxiety and depression measured with the HADS and caregiver strain measured with the Caregiver Strain Index (CSI) (22).

## Statistical analyses

### *Data pre-processing*

*Missing data.* Missing data (outcome variables and pre-treatment variables) were imputed using a non-parametric random forest approach (R-package “MissForest”, (23)). This imputation method has been proven to be accurate with lower imputation errors compared to other methods (23, 24). The following data was used to inform the imputation procedure: 1) non-missing outcome variables; 2) non-missing pre-treatment variables; 3) post-treatment measures of the pre-treatment variables (available for HADS-A, UPCC, the USER-P subscales, and the spouses’ HADS and CSI); and 4) treatment condition (CBT or computerized cognitive training). The imputation method was tested by producing missing data in the complete (non-missing) dataset and then comparing the imputed data values with the actual data values. This comparison was done using the normalized root mean squared error (NRMSE) for continuous data and the proportion of falsely classified entries (PFC) for categorical data (23).

*Variable transformation.* All continuous variables were standardized and categorical variables were mean-centred to prevent potential errors in statistical inference (25). Variables with skewed distributions were transformed using a log transformation or a square root transformation based on visual inspection and normality tests. For variables that contained categories with limited observations, these categories were merged, since previous research recommends at least 10% of the sample in each category (26).

### *Prognostic index*

*Building the PI model.* Two PI models were built to predict the study outcomes; one to predict post-treatment PSDS severity (HADS-D) and one to predict post-treatment participation restrictions (USER-P participation subscale). These PI models were constructed using elastic net regression (with R-package glmnet (27)). Elastic net regression is a combination of Lasso and Ridge regression. These are both linear regression models, which incorporate two penalty terms into the regression to prevent overfitting when

many variables are included (28). Both penalty terms work by shrinking the regression coefficients of these variables. The Lasso (L1) penalty term can exclude variables by shrinking coefficients to 0, however, has difficulties with handling highly correlated variables. The Ridge regression penalty (L2) is less affected by highly correlated variables, but shrinking coefficients to 0, and therefore selecting variables, is not allowed. Two tuning parameters are of importance in elastic net regression: 1) Alpha that regulates the ratio between the L1 and L2 penalty terms (range between 0-1; 0=Ridge/L2 penalty; 1=LASSO/L1 penalty). 2) Lambda that regulates the overall degree of penalization. To determine the optimal alpha parameter, 25 iterations of 10-fold cross-validation were run with alpha values between 0 and 1 with 0.05 intervals. The optimal alpha was defined as the alpha that had the lowest cross-validation prediction error. With the resulting optimal alpha parameter, we determined the optimal lambda parameter, using 1000 iterations of 10-fold cross-validation. The optimal lambda was defined as the lambda with the lowest cross-validation prediction error.

*Estimating the PI scores (i.e. predictions).* Post-treatment depression severity and post-treatment participation restrictions were estimated for each individual using the final PI models. These individual estimates are also referred to as scores on the PI (“PI scores”) since these predictions can be used to determine the level of future care that is needed (11, 12). To evaluate the predictive accuracy of the PI scores, the average difference between the actual outcomes and the PI scores was calculated, and the association between these scores was examined using a correlation analysis. Finally, we determined whether outcomes varied between the two treatments for different levels on the PI: i.e. did individuals with certain prognoses benefit more from one of the two therapies? To test this, we examined the interactions between the PI scores and treatment condition in the following multiple regression analyses:

$$Outcome = \beta_0 + \beta_1 * treatment + \beta_2 * PI + \beta_3 * treatment * PI + \varepsilon$$

*Evaluating the PI models.* Predictors that were included in the PI models were categorized important to less important depending on their parameters. The prediction accuracy of the PI models was evaluated using the adjusted R-square, i.e. the explained variance corrected for the number of included pre-treatment variables and the root mean squared error (RMSE), i.e. the root of the sum of the squared residuals, which are the observed values minus the model predictions. Furthermore, the model performance was assessed using a resampling technique, namely 5-fold cross-validation (26). Therefore, the sample was (randomly) split into five equal groups. Then, for each of these groups, the PI scores of the individuals were predicted using the regression model based on information from the other four groups (the “training dataset,” (29)). Model performance was then determined by evaluating the adjusted R-square, the RMSE, and the correlations between actual outcomes and PI scores.

## Results

### Sample description, imputation of missing variables, and variable transformation

In the original study, 62 patients were included. For the current analyses, one participant was excluded, due to drop-out before randomization. In total 52 patients completed the post-treatment assessment. Table I

shows the 18 pre-treatment variables grouped into four domains. No values were missing in the demographic variables. Of the injury-related variables, 18 values were missing (4.2%). Of the psychological variables of the patient, no values were missing. For the psychological variables of the spouse 24 values were missing (19.4%), this is due to the fact that not all spouses participated in the study (38 spouses did participate). The data imputation was tested to be successful with an estimated NRMSE of 0.27 and an estimated PFC of 0.26.

After standardization of the variables, two pre-treatment variables were not normally distributed (time since stroke and CIRS score). These variables were both log-transformed.

**Table 1.** Sample Description (n=62)

Demographic variables	Mean (SD) or n (%)	
Sex, n women (%)	23 (37.1)	
Age, median (range)	61 (25-79)	
Active employment, n (%)	10 (16.1)	
<b>Injury-related variables</b>		
Time (months) since stroke, mean (SD)	41.9 (46.5)	
Type of stroke		
Ischemic stroke, n (%)	45 (72.6)	
Hemorrhagic stroke, SAB, Combination, n (%)	11 (17.7)	
Unknown, n (%)	6 (9.7)	
Location of stroke		
Left, n (%)	24 (38.7)	
Right, n (%)	19 (30.6)	
Brainstem, cerebellum, combination, n (%)	11 (17.7)	
Unknown, n (%)	8 (12.9)	
MMSE score, mean (SD)	29.1 (1.4)	
BI, mean (SD)	19.5 (1.32)	
SIS score, mean (SD)	65.2 (20.6)	
<b>Psychological variables</b>	<b>Pre-treatment</b>	<b>Post-treatment</b>
HADS-D, mean (SD)	12.4 (3.3)	7.8 (3.6)
HADS-A, mean (SD)	9.9 (4.2)	7.4 (3.9)
UPCC, mean (SD)	2.5 (0.5)	2.5 (0.6)
USER-P frequency, mean (SD)	28.7 (9.9)	28.9 (9.2)
USER-P restriction, mean (SD)	72.2 (12.1)	75.3 (13.3)
USER-P satisfaction, mean (SD)	52.6 (16.9)	62.7 (16.8)
CIRS, mean (SD)	5 (3.9)	-
<b>Psychological variables spouse</b>		
HADS total score, mean (SD)	11.4 (6.6)	
CSI, mean (SD)	6.4 (3.1)	

SD, standard deviation; MMSE, Mini-Mental State Examination; BI, Barthel Index; SIS, Stroke Impact Scale; HADS, Hospital Anxiety and Depression Scale; UPCC, Utrecht Proactive Coping Competence Scale; USER-P, Utrecht Scale for Evaluation of Rehabilitation-Participation; CIRS, Cumulative Illness Rating Scale; CSI, Caregiver Strain Index

## Predictor selection

For the depression PI model the alpha was estimated to be zero, indicating that it is based on a pure Ridge regression (including all pre-treatment variables). Therefore, all 18 variables were included as predictors in the depression model (see Table II). The seven variables with the highest parameters (higher than 0.3) were a lesion in the left hemisphere, being employed, more social participation, fewer comorbidities, better mobility, male

sex, and less severe depressive symptomatology pre-treatment. These variables were all associated with a lower HADS-D score post-treatment. For the participation restrictions PI model, the alpha was estimated to be 0.95, indicating that it is a combination of Lasso and Ridge regression. In this model, a total of six predictors were selected (see Table III). These were better mobility, fewer pre-treatment participation restrictions, older age, less caregiver strain, less anxiety, and less depression of the spouse, and more satisfaction regarding participation pre-treatment. These variables were all associated with fewer participation restrictions post-treatment.

**Table 2.** Predictors Selected with Elastic Net Regression for the Depression Model

Predictor	Coefficient
Location of stroke (right vs left)	0.530
Active employment	-0.445
USER-P frequency	-0.442
CIRS	0.405
SIS score	-0.382
Sex	0.338
HADS-D	0.330
USER-P satisfaction	-0.296
MMSE score	0.203
UPCC	-0.198
CSI	0.171
HADS-A	-0.159
USER-P restriction	-0.153
Time since stroke	-0.121
Location of stroke (left vs brainstem, cerebellum, combination)	0.093
BI	-0.087
Type of stroke	-0.642
HADS spouse	-0.0004
Age	0.00002

USER-P, Utrecht Scale for Evaluation of Rehabilitation-Participation; CIRS, Cumulative Illness Rating Scale; SIS, Stroke Impact Scale; HADS, Hospital Anxiety and Depression Scale; MMSE, Mini-Mental State Examination; UPCC, Utrecht Proactive Coping Competence Scale; CSI, Caregiver Strain Index; BI, Barthel Index

**Table 3.** Predictors Selected with Elastic Net Regression for the Participation Restrictions Model

Predictor	Coefficient
SIS score	4.105
USER-P restriction	1.966
Age	1.946
CSI	1.491
HADS spouse	-0.430
USER-P satisfaction	0.049

SIS, Stroke Impact Scale; USER-P, Utrecht Scale for Evaluation of Rehabilitation-Participation; CSI, Caregiver Strain Index; HADS, Hospital Anxiety and Depression Scale

## Estimating and evaluating the PI models

Table IV shows the model performance of the PI models of Depression and Participation Restrictions based on the complete dataset and based on a hold-out dataset. The  $R^2$  of the depression model was 0.442, meaning that the model explains 44.2% of the variance. The mean difference between the actual post-treatment HADS-D scores and the PI scores was 2.162 (SD=1.562). The RMSE was 2.66, indicating that the average of the model residuals (actual scores minus the model predictions) was 2.66 points on the HADS depression scale. Furthermore, the correlation between the actual and predicted values was significant and strong (corr.=0.672,  $p < 0.001$ , see figure 1).

**Table 4.** Model performance of PI models of Depression and Participation Restrictions

	Depression PI Model	Participation Restrictions PI Model
Model performance based on models fitted on the complete dataset		
$R^2$	0.451	0.516
RMSE	2.660	8.927
Model performance based on models fitted on a hold-out dataset (5-fold cross-validation)		
$R^2$	0.134	0.316
RMSE	3.169	10.321

RMSE, root mean squared error

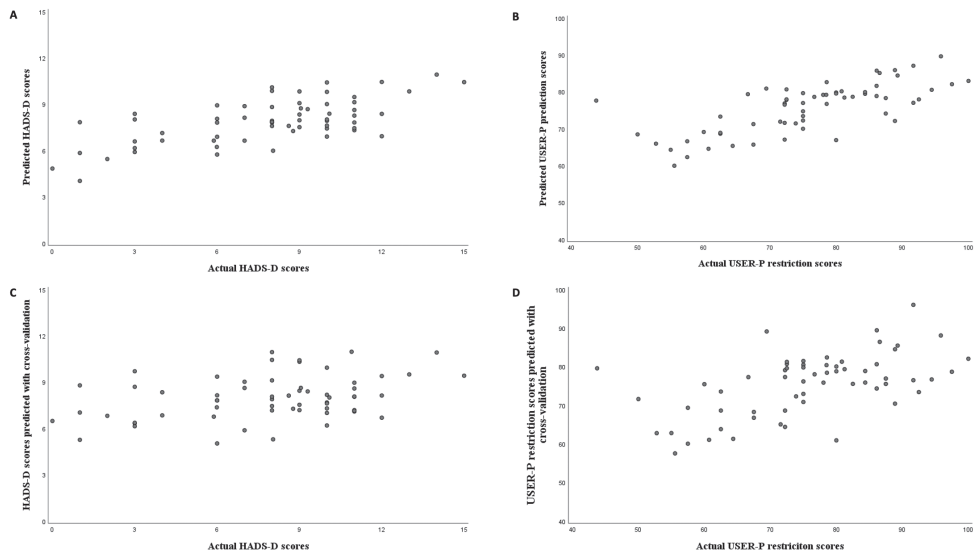
The  $R^2$  of the depression PI model that was developed and fitted on a hold-out dataset (5-fold cross-validation) was 0.134 and the RMSE was 3.17. When examining the association between actual post-treatment HADS-D scores and the PI scores based on this cross-validation model, a moderate and significant correlation was found (corr.=0.366,  $p = 0.004$ , see figure 1).

The  $R^2$  of the participation PI model was 0.507, meaning that the model explains 50.7% of the variance. The mean difference between the actual post-treatment USER-P restriction scores and the PI scores was 6.563 (SD=6.102). The RMSE was 8.93 indicating that the average of the model residuals (observed values minus the model predictions) was 8.93 points on the USER-P restriction scale. The correlation between the observed and predicted values was again strong and significant (corr.=0.718,  $p < 0.001$ , see figure 1).

For the participation PI model that was developed and fitted on a hold-out dataset (5-fold cross-validation), the  $R^2$  was 0.335 and the RMSE was 10.15. When examining the association between actual post-treatment USER-P restriction scores and the PI scores based on this cross-validation model, a moderate and significant correlation was found (corr.=0.562,  $p < 0.001$ , see figure 1).

Multiple regression analyses were carried out to test whether depression and restriction outcomes varied between the two treatments for different levels on the PI. The models indicated no distinct treatment effects on different PI levels.

**Figure 1.** Scatterplot of A. the actual and the predicted HADS-D scores; B. the actual and the predicted USER-P restriction scores; C. the actual HADS-D scores and the HADS-D scores predicted with cross-validation; and D. the actual USER-P restriction scores and the USER-P restriction scores predicted with cross-validation



HADS, Hospital Anxiety and Depression Scale; USER-P, Utrecht Scale for Evaluation of Rehabilitation-Participation

## Discussion

The goal of this study was to develop a PI model for treatment outcome in patients with PSDS. The post-treatment outcome scores for depression and experienced participation restrictions were predicted based on pre-treatment variables of both the patient and the spouse. The depression model explained 44.2% of the variance and the actual depression scores correlated highly with the predicted scores. The participation model explained 50.7% of the variance and predicted scores again correlated highly with actual scores.

The range of the HADS-D is 0-21. The RMSE, the squared root of the average of squared differences between predictions and actual outcomes, was 2.66 for the HADS-D, which is likely not a clinically significant difference (the minimum difference on the HADS-D to be a clinically significant difference ranges from 0.5 to 6 dependent on the population (30-32)). The range of the USER-P participation is 0-100. The RMSE was 8.927 for the USER-P, which is likely not a clinically significant difference either (although this has not been studied yet, in this situation Ringash et al. (33) advice that 10% of the instrument range can be considered the minimum important difference, which would be at least 10 points in this case).

Furthermore, the performance of both models was promising when assessed using a resampling technique. No interaction effect was found between predicted scores and the received intervention, meaning that there was not a group of patients with a certain (predicted) prognosis who benefited more from one of the two therapies.

A more favourable outcome of PSDS was predicted by a left-hemispheric lesion, sex, better mobility, less depressive symptoms pre-treatment, more social participation, fewer comorbidities, and being employed. These variables showed to be most predictive of PSDS post-treatment of the 18 variables included in the depression model.

A left hemispheric lesion was identified as an important predictor for less depressive symptoms post-treatment, which is somewhat surprising. To our knowledge, there is no earlier research on the association between lesion location and treatment outcome and studies identifying lesion laterality as a possible predictor related to post-stroke depression show inconsistent results (34, 35). Nevertheless, the meta-analyses of Wei et al. (36) did find an association between right-hemispheric lesion and risk of depression. However, this association was only apparent one to six months' post-stroke. The results are therefore likely not applicable to our sample, since there were only three patients who were less than six months post-stroke. Currently, the focus is shifting to damaged neuronal networks instead of brain regions as an underlying mechanism for PSDS (35), which, in future research, should also be considered in relation to treatment outcome for PSDS. The finding that pre-treatment depression severity is predictive of PSDS outcome, is in line with previous studies, which show that pre-treatment depression levels play an important role in treatment outcome in patients irrespective of the presence of acquired brain injury (11, 37, 38). Likewise, the finding that being employed is a predictive factor of a more favourable outcome is in line with earlier research in depressed patients without brain injury (11). The other predictors of post-treatment depression severity in our study (including male sex, better mobility, more social participation, and fewer comorbidities) are all known protective factors against the development of PSDS (39-41). It is feasible that most of these resilience factors can also provide opportunities to better use and apply the competencies obtained during therapy.

In this study, the potential predictors for fewer restrictions regarding participation scores post-treatment in patients with PSDS were better mobility, fewer pre-treatment participation restrictions, older age, less caregiver strain and psychological distress of the spouse, and more satisfaction regarding participation. The finding that mobility is the strongest predictive factor is not surprising. Social participation is associated with functional disability in the recovery process following a stroke (42). However, whereas one would hope that a treatment for stroke patients would decrease participation restrictions despite physical disabilities, the interventions in this study might not have achieved this. The finding that older age is predictive of a more favourable outcome is not in line with earlier research. Previous studies found that older age is often related to more experienced participation restrictions (43). However, in previous studies patients were relatively older and might experience, next to stroke-related restrictions, more restrictions due to older age. It seems probable that patients who are younger experience more participation restrictions because society expects a higher level of participation (i.e. going back to work, taking care of children). Furthermore, participation satisfaction and restrictions, but not participation frequency, were predictive factors. Earlier research found that change in frequency of vocational activities but not social and leisure activities are predictive of participation restrictions at six months post-stroke (44). Merely increasing participation frequency will, therefore, likely not lead to an improvement of participation restrictions and satisfaction.



Both the level of caregiver burden and psychological distress of the spouse were predictive of participation restrictions following the interventions. It seems plausible that spouses who are psychologically more resilient and experience less psychological distress and less caregiver strain can support and encourage their spouses better during treatment and help to change therapeutical intentions into practical therapeutic actions. Furthermore, earlier research found that spouses experience more participation restrictions themselves, when they have more depressive symptoms, are employed, have a younger age, and support a stroke patient with more disabilities and a lower participation levels (45). It seems that experienced participation restrictions reflect a close interplay between spouse and patient.

When comparing the two models in this study, it becomes apparent that improving PSDS and decreasing experienced participation restrictions might involve different processes. The treatment of depression seems complicated, with many factors influencing the outcome, while less factors are influencing the outcome when decreasing participation restrictions. The results highlight the complexity and multifactorial nature of treating depressive symptoms following a stroke. The outcome of treatment for PSDS is influenced by characteristics of the patient, stroke, and well-being of the spouse, which should all be considered when treating a patient with PSDS. The process of decreasing experienced participation restrictions is for a large part influenced by the physical characteristics of the patient and psychological characteristics of the spouse. Interestingly, the levels of anxiety and depression of the patient him/herself were not predictive of restriction, implying that the experienced participation restrictions can be decreased regardless of experienced psychological distress. This is in line with third-generation cognitive behavioural therapies, including Acceptance and Commitment Therapy (ACT). The goal of ACT is not to decrease symptomatology, but to increase psychological flexibility and behaviours based on values despite the presence of for instance depressive thoughts and feeling (46).

This study has several strengths. First, the state-of-the-art variable selection approach used (i.e. elastic net regression) combines multiple predictors instead of examining individual predictors separately. To our knowledge, this is the first study to incorporate multiple predictors to develop personalized predictions for the outcome of treatment for PSDS. Second, elastic net regression is able to minimize the number of predictors and to categorize predictors from important to less important. Third, we evaluated the performance of both PI models using a resampling technique (cross-validation). Fourth, this study included a broad range of possible predictors. For instance, characteristics of the spouse were considered as predictors of outcome which have not been included in earlier research. Fifth, this study predicted both depression and experienced participation restrictions and therefore was able to show the different nature of these two outcomes.

The results of the study should be considered in light of some limitations. The patients in this study were quite young compared to the average stroke population (median age 61 yrs). Furthermore, patients with severe cognitive impairments, communication problems, major depression, or who were in need of inpatient care were excluded. This resulted in a sample of patients with less severe complaints. Both considerations should be taken into account when interpreting the results. Furthermore, the small sample size can be seen as a limitation, which is a common problem in studies using data from RCT's to develop prediction models

(47). Due to the relatively small sample size, no separate training and testing datasets were used. This could have led to overfitting of the models to the current dataset, which decreases the external validity of the PI models (48). However, machine learning methods have many advantages compared to more traditional models (such as linear models), because they have an increased model prediction accuracy by reducing overfitting (49). The external validity of both PI models was assessed with a resampling technique on a hold-out dataset, which showed promising results. In addition, elastic net regression includes two penalty terms to the regression function to prevent overfitting (28). Furthermore, although we tested whether depression and participation outcomes varied between the two treatments for different levels on the PI, we were not able to investigate predictors of differential treatment effects (i.e. moderators) specifically. This was due to the small sample size. The results apply to both interventions which are very different in nature (i.e. behavioural therapy and cognitive training), although equally effective in the original RCT from which the data were drawn. It is clear that replication and external validation of the current results is needed.

In conclusion, this proof of concept study shows that machine learning techniques, such as elastic net regression, can be used to compute personalized predictions of outcome following treatment for PSDS. The models developed in this study are not yet ready for implementation in clinical practice. However, the results do demonstrate the complex and multifactorial nature of PSDS, which should be considered in treatment approaches. Furthermore, it was shown that psychological factors are likely no obstacles when improving restrictions regarding social participation. In order to realize the use of these models in clinical practice, future research should focus on their replication and external validation. PI models have a great potential to aid clinicians and their patients with treatment selection and therefore increase the effectiveness of treatments for PSDS.

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Supplementary material

Supplemental table 1. All pre-treatment variables measured in the original trial (1)

<b>Demographic variables</b>
Sex
Age
Active employment
<b>Injury-related variables</b>
Time since stroke
Type of stroke
Location of stroke
Mini-Mental State Examination
Barthel Index
Stroke impact scale
<b>Psychological variables</b>
Hospital Anxiety and Depression Scale – Depression Subscale
Hospital Anxiety and Depression Scale – Anxiety Scale
Post-stroke Depression Rating Scale
Short stroke specific Quality of Life scale
Utrecht Proactive Coping Competency List
Utrecht Scale for Evaluation of Rehabilitation Participation – Frequency subscale
Utrecht Scale for Evaluation of Rehabilitation Participation – Restriction subscale
Utrecht Scale for Evaluation of Rehabilitation-Participation – Satisfaction subscale
EQ5D
Life Satisfaction questions
Cumulative Illness Rating Scale
<b>Psychological variables spouse</b>
Hospital Anxiety and Depression Scale
Caregiver Strain Index
Involvement and Evaluation Questionnaire-Brain Injury

**Supplemental table 2.** Spearman Correlation Matrix of all variables included in the original trial (6)

Measure	MMSE	Barthel Index	CIRS	SIS score	HADS-D	HADS-A	PSDRS	SSQ	UPCC	USERP frequency	USERP restriction	USERP satisfaction	EQ5D	LS2	HADS spouse	CSI spouse	IEQ spouse
MMSE	-	.058	.087	.013	-.031	-.013	.204	-.004	.090	.090	.130	-.076	.059	-.053	.045	-.125	-.161
Barthel Index	.058	-	.127	.048	.043	-.098	-.055	.045	.020	.347**	-.013	.001	.126	-.008	-.054	-.205	.180
CIRS	.087	.127	-	-.408**	.160	.355**	.138	-.254*	-.018	-.025	-.180	-.183	-.280*	-.098	.040	.202	.406**
SIS score	.013	.048	-.408**	-	-.198	-.129	-.150	.419**	.261*	.198	.526**	.298*	.418**	.209	-.147	-.322*	-.314*
HADS-D	-.031	.043	.160	-.198	-	.430**	.431**	-.402**	-.152	-.253*	-.295*	-.451**	-.421**	-.359**	-.032	.044	.154
HADS-A	-.013	-.098	.355**	-.129	.430**	-	.504**	-.397**	.030	-.038	-.317*	-.363**	-.409**	-.241	.072	.260	.266
PSDRS	.204	-.055	.138	-.150	.431**	.504**	-	-.414**	-.113	-.160	-.245	-.371**	-.458**	-.517**	-.010	.025	.290
SSQ	-.004	.045	-.254*	.419**	-.402**	-.397**	-.414**	-	.330**	.154	.417**	.611**	.680**	.501**	-.168	-.285*	-.341*
UPCC	.090	.020	-.018	.261*	-.152	.030	-.113	.330**	-	.161	.299*	.274*	.322*	.353**	-.189	-.248	-.390**
USER-P frequency	.090	.347**	-.025	.198	-.253*	-.038	-.160	.154	.161	-	.130	.273*	.186	.236	-.208	-.167	-.314*
USER-P restriction	.130	-.013	-.180	.526**	-.295*	-.317*	-.245	.417**	.299*	.130	-	.524**	.509**	.313*	-.241	-.460**	-.434**
USER-P satisfaction	-.076	.001	-.183	.298*	-.451**	-.363**	-.371**	.611**	.274*	.273*	.524**	-	.697**	.532**	-.219	-.319*	-.391**
EQ5D	.059	.126	-.280*	.418**	-.421**	-.409**	-.458**	.680**	.322*	.186	.509**	.697**	-	.659**	-.083	-.273	-.424**
LS2	-.053	-.008	-.098	.209	-.359**	-.241	-.517**	.501**	.353**	.236	.313*	.532**	.659**	-	-.209	-.268	-.488**
HADS spouse	.045	-.054	.040	-.147	-.032	.072	-.010	-.168	-.189	-.208	-.241	-.219	-.083	-.209	-	.462**	.453**
CSI spouse	-.125	-.205	.202	-.322*	.044	.260	.025	-.285*	-.248	-.167	-.460**	-.319*	-.273	-.268	.462**	-	.637**
IEQ – BI spouse	-.161	.180	.406**	-.314*	.154	.266	.290	-.341*	-.390**	-.314*	-.434**	-.391**	-.424**	-.488**	.453**	.637**	-

MMSE, Mini-Mental State Examination; CIRS, Cumulative Illness Rating Scale; SIS, Stroke Impact Scale; HADS, Hospital Anxiety and Depression Scale; PSDRS, Post-stroke Depression Rating Scale; SSQ, Short stroke specific Quality of Life scale; UPCC, Utrecht Proactive Coping Competence Scale; USER-P, Utrecht Scale for Evaluation of Rehabilitation-Participation; LS2, Life Satisfaction questions; CSI, Caregiver Strain Index; IEQ-BI, Involvement and Evaluation Questionnaire-Brain Injury; \*p < .05; \*\*p < .01









## CHAPTER 3

Measuring psychological flexibility and cognitive defusion in individuals with acquired brain injury

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*Brain Injury, 2021*

## Abstract

*Purpose.* Acceptance and Commitment Therapy (ACT) is used increasingly for individuals with psychological distress following acquired brain injury (ABI) in different countries. However, questionnaires measuring ACT-processes are often not validated for this patient group and need cross-cultural validation. This study investigated the psychometric properties of the Acceptance and Action Questionnaire for Acquired Brain Injury (AAQ-ABI; measuring psychological flexibility related to thoughts and feelings about ABI) and the Cognitive Fusion Questionnaire (CFQ-7; measuring cognitive defusion).

*Materials and methods.* Score distribution, reliability, and convergent validity of the AAQ-ABI and the CFQ-7 were examined in Dutch individuals with ABI.

*Results.* Seventy-three patients with ABI were included. The AAQ-ABI showed good reliability (Cronbach's  $\alpha=0.87$ ) and the CFQ-7 excellent reliability (Cronbach's  $\alpha=0.97$ ). Both did not show a floor or ceiling effect, nor a skewed distribution. There were strong to moderate correlations between the questionnaires and measures of psychological flexibility, mood, quality of life, and value-driven behavior (AAQ-ABI:  $r = -0.70$ – $0.81$ ; CFQ-7:  $-0.67$ – $0.84$ ). Inter-item total correlations indicate that the questions within each questionnaire measured the same construct (AAQ-ABI:  $r=0.40$ – $0.78$ ; CFQ-7:  $r=0.84$ – $0.93$ ).

*Conclusions.* The current study shows that the Dutch AAQ-ABI and CFQ-7 have acceptable to good psychometric properties when measuring psychological flexibility and cognitive defusion in patients with ABI.

## Introduction

Acquired brain injury (ABI) is associated with an increased risk for the development of psychological distress (1, 2). The psychological flexibility model provides an interesting perspective on how to deal with psychological distress related to medical conditions (3). This model forms the basis of Acceptance and Commitment Therapy (ACT), a third-generation Cognitive Behavioral Therapy. Psychological flexibility is the ability to adjust or persist in behaviors based on chosen values while staying in contact with the present moment, regardless of unpleasant thoughts, feelings, and bodily sensations (4). The treatment goal of ACT is the improvement of psychological flexibility. This is achieved through several interacting processes such as acceptance, cognitive defusion, mindfulness, and value based living.

Psychological flexibility is associated with wellbeing and is suggested to be a fundamental aspect of mental health. Previous studies have found relationships between psychological flexibility and physical and mental health, life satisfaction, quality of life, and rehabilitation adherence (5-7). Psychological inflexibility (which is characterized by the avoidance of thoughts and feelings, also called experience avoidance) is associated with psychopathology. This is especially apparent in individuals suffering from anxiety and depressive disorders (8-10), which are also common following an ABI (11).

Patients with ABI often experience negative thoughts (for instance: “life will never be the same again” or “I cannot do what I used to do”). These thoughts can be upsetting and therefore patients will try to avoid these thoughts. Cognitive defusion is the disentanglement and the process of creating a distance from thoughts (4) which can be helpful in the adaptation process following ABI, since people often experience thoughts that hold some truth (12). For instance, if the patient learns to let a reoccurring thought (such as “I cannot do what I used to do”) come and go (defusion) instead of focusing on or trying to avoid this thought (fusion), the impact of these thoughts on the patient’s behavior will decrease and there is more room for valued driven behavior.

When applying and evaluating ACT, both psychological flexibility and cognitive defusion as core elements must be measured validly for treatment selection, monitoring of patients during rehabilitation and treatment, and the evaluation of interventions. Several questionnaires have been developed to measure psychological flexibility and cognitive defusion. The Acceptance and Action Questionnaire (AAQ-II) is a widely used questionnaire measuring experiential avoidance and psychological inflexibility (13). Since ACT is used for various disorders, the AAQ-II has been adapted for different patient populations, including patients with chronic pain (14), diabetes (15), and substance abuse (16). These population-specific measures are valuable since they measure experiential avoidance and psychological flexibility related to the problem area of interest. Consequently, they are thought to be more treatment-sensitive and measure psychological flexibility in a more content-valid manner compared to a generic measure (17). Sylvester (18) adapted the AAQ-II to measure both psychological inflexibility and avoidance of issues relating to ABI, namely the Acceptance and Action Questionnaire for Acquired Brain Injury (AAQ-ABI). The AAQ-ABI has only been validated within an Australian ABI population (19). Cross-cultural validation is needed, especially, since ACT is used frequently for patients with psychological distress following ABI in other countries as well (12).

To measure cognitive defusion, Gillanders et al. (20) developed the Cognitive Fusion Questionnaire (CFQ-7) which can be used for various patient populations. In patients with chronic pain (20), mental health problems, multiple sclerosis, and caregivers of people with dementia (21) it shows good psychometric properties. However, the psychometric properties have not yet been examined for patients with ABI.

Therefore, this study aimed to perform a cross-cultural validation of the Dutch AAQ-ABI and to validate the CFQ-7 for patients with ABI. The score distribution and reliability of the two questionnaires were examined. Convergent validity was established by comparing the questionnaires to measures of psychological flexibility, mood, quality of life, and value based living. We hypothesized that the correlations between the AAQ-ABI and CFQ-7 would correlate positively with the AAQ-II. We furthermore expected stronger correlations between the AAQ-II and AAQ-ABI (since they are both measures of psychological flexibility) than between the AAQ-II and the CFQ-7. Lastly, positive correlations were expected between measures of mood and negative correlations between measures of quality of life and value based living.

## Methods

### Participants

The inclusion criteria were: having sustained any type of acquired brain injury (such as a stroke, traumatic brain injury, or hypoxia), which is diagnostically confirmed by a neurologist; being 18 years or older; mastering the Dutch language sufficiently to fill in the questionnaires; and giving informed consent. The exclusion criteria were: the inability to complete the questionnaire because of cognitive impairment or communicative impairment based on the clinical judgment of a psychologist or inability to complete questionnaires in previous research.

### Measures

*Acceptance and Action Questionnaire Acquired Brain Injury (AAQ-ABI).* The AAQ-ABI measures psychological inflexibility regarding thoughts, feelings, and behaviors related to an ABI (19). The scale specifically focusses on identifying thoughts, feelings, and behaviors that may arise around functional disability occurring after an ABI. The AAQ-ABI relies on a 5-point Likert scale to reduce cognitive demand. Sylvester (18) initially developed a questionnaire consisting of 15 items. Whiting et al. (19) evaluated the psychological properties of the AAQ-ABI and concluded that, based on a factor analysis, a shorter (one-factor) version with nine items has good reliability across time, satisfactory internal consistency (Cronbach's  $\alpha = .89$ ), and associations with theoretically-relevant constructs. The scale includes items such as "I stop doing things when I feel scared about my brain injury" and "I need to get rid of my anxiety about my brain injury". The score ranges from 0 to 36 with higher scores indicating greater psychological inflexibility. The questionnaire was translated into Dutch using a forward and backwards-translation method. It was first translated into Dutch by the first author (JR); afterwards, it was translated back into English by a native English speaker who was blinded for the original version. Differences were discussed and a final version was agreed upon.

*Cognitive fusion Questionnaire (CFQ-7).* The CFQ-7 (20) consists of seven items and measures cognitive fusion on a 7-point Likert scale. Scores range from 7 to 49. The higher the score, the more fused one is with one's thoughts or identifies with one's thoughts. The English version of the CFQ-7 demonstrated excellent internal consistency (Cronbach's  $\alpha = .90$ ) and good test-retest reliability (20). The questionnaire was translated into Dutch by Batink and De Mey (22) and this version showed good psychometric properties. The English version had good psychometric properties in patients with chronic pain and multiple sclerosis (20, 21).

*Acceptance and Action Questionnaire II (AAQ-II).* The AAQ-II (23) is a seven-item questionnaire measuring experiential avoidance and psychological inflexibility. The items measure the negative evaluation of feelings, forms of cognitive entanglement, and the influence of thoughts and feelings (13, 24). The items are scored on a 7-point Likert scale and the total score ranges from 7 to 49 with a higher score indicating greater experiential avoidance and psychological inflexibility. The internal consistency of the AAQ-II is good (Cronbach's  $\alpha = .84$ ) (13). The questionnaire was translated into Dutch by Jacobs et al. (25) and showed good psychometric properties. In an Australian ABI sample, the questionnaire showed excellent internal consistency (Cronbach's  $\alpha = .90$ ) and good test-retest reliability (19).

*Hospital Anxiety and Depressive Scale (HADS).* The HADS was used to measure anxiety and depressive symptoms. The score ranges from 0 to 42 with higher scores indicating higher levels of depression or anxiety. The HADS was found to have good psychometric properties in patients with TBI and stroke (Cronbach's  $\alpha = 0.94$ ) (26, 27).

*Depression Anxiety Stress Scales-21 (DASS-21).* The DASS-21 was used to measure the levels of anxiety, depression, and stress of the participants. It consists of 21 items which are rated on a 4-point Likert-scale. The score ranges from 0 to 63 with higher scores indicating greater levels of depression, anxiety, or stress. The questionnaire has been validated and found to have good psychometric properties in a TBI sample (Cronbach's  $\alpha = 0.95$ ) (28). The DASS-21 was included next to the HADS because it includes a stress scale and includes items on devaluation of life, self-deprecation, and hopelessness which the HADS lacks (29).

*Short Form Survey (SF-12).* Quality of life was measured with the Short Form Survey (SF-12). The SF-12 was used to measure the health status of the participants, but it can also be described as a broad assessment of quality of life (30). The SF-12 has two subscales: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The total score of both scales ranges from 0 to 100, with a higher score indicating a better health status. The SF-12 demonstrates good psychometric properties in patients with stroke (Cronbach's  $\alpha$  PCS = 0.85 and MCS = 0.81) (31).

*Valued Living Questionnaire (VLQ).* The Valued Living Questionnaire (VLQ) is a two-part instrument that measures value based living (32). The participants rate the importance of ten value domains on a 10-point Likert scale. Subsequently, participants rate how consistently they have lived by their values within these domains. Scores from both parts are used to calculate a value based living component. The internal consistency of the valued living component is adequate (Cronbach's  $\alpha = 0.74$ ) (32). The VLQ has been used in earlier research to measure valued living in patients with TBI (33).

*Demographic questionnaire.* Participants filled in details on demographic characteristics, including age, sex, educational level, marital status, employment status, type of brain injury, and time since brain injury.

## Procedure

Individuals with ABI were recruited between October 2018 and May 2020 via databases of participants from previous studies investigating the consequences of an ABI (which matched the inclusion criteria of this study) for which medical ethics approval had been acquired. The participants had given written permission to be contacted for participation in future studies. If the participant agreed to participate and had given informed consent, they received a secure link to the questionnaires, which they could fill out at home. The participants filled in the questionnaires at one time point. A forced-choice response format was employed and thus there was no missing data. Additionally, part of the data was collected retrospectively. The data was drawn from an RCT examining the effect of ACT for patients with ABI for which the baseline measurement was used. The procedures for this study can be found elsewhere (34). Only these patients (N=33) filled in the HADS, DASS-21, SF-12, and VLQ. The current study was approved by the medical ethics committee of Maastricht University Medical Centre and Maastricht University (reference number 2018-0543).

## Statistical analyses

The score distribution of the AAQ-ABI and CFQ-7 was reported in terms of mean, SD, median, range, skewness, and floor and ceiling effects. Skewness values lower than -1.0 or higher than 1.0 were considered strong. Those between 0.5 and 1.0 and -0.5 and -1.0 were regarded as moderate (46). Floor and ceiling effects were interpreted as present if at least 15% of the participants obtained the highest or lowest score (35). Furthermore, to test the homogeneity of the scales the item-total correlations were computed (the correlation between one item and the rest of the items). Each item was required to have a correlation coefficient higher than 0.3 (36). Furthermore, internal consistency was assessed in terms of Cronbach's  $\alpha$  ( $>0.9$  = excellent;  $0.9 - 0.8$  = good;  $0.8 - 0.7$  = acceptable;  $0.7 - 0.6$  = questionable;  $0.6 - 0.5$  = poor) (36). Convergent validity was examined by calculating Spearman's rank correlation coefficients between the AAQ-ABI, CFQ-7, AAQ-II, HADS, DASS-21, SF-12, and VLQ. Correlations were interpreted as strong if higher than 0.6, moderate if between 0.3 and 0.6, and weak if smaller than 0.3. Data were analyzed using SPSS version 26.0 (37).

## Results

### Participants' characteristics

A total of 73 participants filled in the questionnaires. Participants' characteristics are shown in Table 1.

**Table 1.** Demographic characteristics

Demographic variables	Mean (SD) or n (%)
Sex, n women (%)	34 (46.6)
Age, mean (SD)	56.5 (11.47)
Marital Status, n (%)	
Unmarried	5 (6.8)
Married	48 (65.8)
Living together with partner	12 (16.4)
Divorced	5 (6.8)
Widowed	3 (4.1)
Education, n (%)	
Low (primary education and lower vocational education)	12 (16.4)
Medium (general secondary education and secondary vocational education)	24 (32.9)
High (pre-university education, higher professional education, and university education)	37 (50.7)
Employment, n (%)	
Employed	26 (35.6)
Incapacitated for work	24 (32.9)
Unemployed	4 (5.5)
Retired	11 (15.1)
Other	8 (10.9)
ABI-related variables	Mean (SD) or n(%)
Time (years) since ABI, mean (SD)	3.68 (5.39)
Type of ABI, n (%)	
Ischemic stroke	34 (46.6)
Hemorrhagic stroke	8 (10.9)
Traumatic brain injury	31 (42.5)

ABI, acquired brain injury

### Score distribution and reliability

Table 2 shows the score distributions of the AAQ-ABI and the CFQ-7. The mean score of the AAQ-ABI was 11.18 (SD = 8.40). 2.7% of the participants obtained the lowest score and no participants obtained the highest score. The skewness value was 0.28 and the Cronbach's  $\alpha$  was 0.87.

The mean score of the CFQ-7 was 22.73 (SD = 12.24). On the CFQ-7, 13.7% of the participants obtained the lowest score while no participants obtained the highest score. The skewness value was 0.18 and the Cronbach's  $\alpha$  was 0.97.

**Table 2.** Score distribution and reliability

	M	SD	Median	Range	% lowest score	% highest score	Skewness	$\alpha$
AAQ-ABI	11.18	8.40	8	0-31	2.7 %	0%	0.28	0.87
CFQ-7	22.73	12.24	24	7-45	13.7%	0%	0.18	0.97

AAQ-ABI, Acceptance and Action Questionnaire Acquired Brain Injury; CFQ-7, Cognitive Fusion Questionnaire

### Item-total correlations

All item-total correlations were above 0.3 for the AAQ-ABI ( $r = 0.40 - 0.78$ ) and CFQ-7 ( $r = 0.84 - 0.93$ ) as can be seen in Tables 3 and 4.



**Table 3.** The corrected item-total correlations of the Acceptance and Action Questionnaire Acquired Brain Injury

Item No.		Corrected Item-Total Correlation
1	I hate how my brain injury makes me feel about myself	0.69
2	I need to get rid of my anxiety about my brain injury	0.76
3	I stop doing things when I feel scared about my brain injury	0.64
4	My brain injury defines me as a person	0.54
5	I am moving forward with my life	0.44
6	I would give up important things in my life if I could make the brain injury go away	0.40
7	My worries and fears about my brain injury are true	0.78
8	Other people make it hard for me to accept myself	0.60
9	Most people are doing better than me	0.74

**Table 4.** The corrected item-total correlations of the Cognitive Fusion Questionnaire

Item No.		Corrected Item-Total Correlation
1	My thoughts cause me distress or emotional pain	0.91
2	I get so caught up in my thoughts that I am unable to do the things that I most want to do	0.84
3	I over-analyse situations to the point where it's unhelpful to me	0.88
4	I struggle with my thoughts	0.93
5	I get upset with myself for having certain thoughts	0.87
6	I tend to get very entangled in my thoughts	0.87
7	It's such a struggle to let go of upsetting thoughts even when I know that letting go would be helpful	0.90

### Convergent validity

Table 5 shows the correlations between the AAQ-ABI, CFQ-7 and the AAQ-II, HADS, DASS-21, SF-12, and VLQ. The AAQ-ABI and the CFQ-7 correlated strongly with each other and with the AAQ-II. Correlations between the AAQ-ABI and the HADS were moderate and between the AAQ-ABI and the DASS-21 strong, while the CFQ-7 correlated strongly with the HADS and moderately with the DASS-21. Both measures had weak correlations with the PCS and stronger correlations with the MCS. Lastly, the AAQ-ABI showed strong correlations with the VLQ and the CFQ-7 showed moderate correlations.

**Table 5.** Spearman's rank correlation matrix

	AAQ-ABI	CFQ-7	AAQ-II	HADS <sup>1</sup>	DASS-21 <sup>1</sup>	PCS <sup>1</sup>	MCS <sup>1</sup>	VLQ <sup>1</sup>
AAQ-ABI	-	0.72**	0.81**	0.47*	0.65**	-0.22	-0.57*	-0.70**
CFQ-7	0.72**	-	0.84**	0.65**	0.57**	-0.06	-0.67**	-0.50**

AAQ-ABI, Acceptance and Action Questionnaire Acquired Brain Injury; CFQ-7, Cognitive Fusion Questionnaire; AAQ-II, Acceptance and Action Questionnaire II; HADS, Hospital Anxiety and Depression Scale; DASS-21, Depression, anxiety and stress scale-21; PCS, Physical Component Summary; MCS, Mental Component Summary; and VLQ, Valued Living Questionnaire; \*  $p < .05$ ; \*\*  $p < 0.01$

<sup>1</sup> Based on a smaller sample (N=33)

## Discussion

The aims of this study were to perform a cross-cultural validation of the AAQ-ABI and to validate the CFQ-7 in a Dutch ABI population. The internal consistency of the AAQ-ABI was good (Cronbach's  $\alpha = 0.87$ ) and of the CFQ-7 excellent (Cronbach's  $\alpha = 0.97$ ). Neither of the questionnaires showed floor or ceiling effects and skewness levels were acceptable. The strong positive correlation between both the AAQ-ABI and the CFQ-7 and the AAQ-II indicated a good convergent validity. The AAQ-ABI showed a stronger correlation with the AAQ-II than with the CFQ-7. This was expected since the AAQ-II and AAQ-ABI both measure constructs related to psychological flexibility. Whiting et al. (19) found similar correlations between the English versions of the AAQ-II and the AAQ-ABI. However, in the current study, the AAQ-II correlated stronger with the CFQ-7 than with the AAQ-ABI, which was not expected. A possible explanation for this finding could be that the constructs measured by the AAQ-II and the CFQ-7 are closely related (20). Where the CFQ-7 measures psychological flexibility regarding cognition, the AAQ-II does this in a broader way regarding emotions and thoughts. Therefore, the AAQ-II contains items that may estimate levels of cognitive fusion (such as; I worry about not being able to control my worries and feelings). In addition, both questionnaires had positive correlations with measures of mood and negative correlations with measures of value-driven behavior, which was expected. Both questionnaires correlated significantly with quality of life, but only when related to mental health and less when related to physical health. The AAQ-ABI had a weak association with physical health-related quality of life. Lower associations between measures of psychological functioning and physical functioning are not uncommon (38). There was no association between the CFQ-7 and physical health-related quality of life. It could be that cognitive defusion is simply not as related to physical health-related quality of life as the other components of psychological flexibility or has a more indirect effect that the measures used did not capture. Finally, all separate items of the AAQ-ABI and CFQ-7 correlated adequately with the total score of the respective questionnaire, indicating that the items within each questionnaire measure the same construct.

The results suggest that the AAQ-ABI and the CFQ-7 measure psychological flexibility and cognitive defusion in patients with ABI. The questionnaires can therefore further help to improve the care for patients with ABI related anxiety and depressive complaints. Clinicians can use these scales to monitor their patients with ABI during an ACT intervention, to evaluate the treatment, and to give the patient insight into the treatment process. Furthermore, the questionnaires can be used in studies to further investigate the effectiveness of ACT for patients with ABI. This is important since psychological distress is common following ABI and more research into the effectiveness of different treatment options is needed (11, 39).

## Limitations and future research

The discriminant validity of the questionnaires was not investigated in this study, which should be further examined in future research, especially given the growing concern regarding the discriminant validity of the AAQ-II (40). Several studies have found that it measures psychological distress or neuroticism rather

than psychological flexibility (41, 42), which is a matter of concern and has to be taken into account when using the AAQ-II. The AAQ-ABI is based on the AAQ-II and therefore there might be doubts regarding the discriminant validity of the AAQ-ABI as well. Therefore, more research into the discriminant validity of the AAQ-ABI is needed.

Population-specific versions of the AAQ-II, such as the AAQ-ABI, are thought to be more treatment sensitive (17). However, their responsiveness to measuring change in treatment contexts has not well been examined yet. For these reasons, it is recommended to use an AAQ specific questionnaire in addition to the AAQ-II as the treatment sensitivity of the AAQ-II has been better studied (17, 43). Furthermore, this will aid the comparability between trials. Regarding the treatment sensitivity of the AAQ-ABI, the English version of the questionnaire was used in a pilot RCT investigating the effectiveness of ACT for people with severe traumatic brain injury (44). No significant change was measured on the AAQ-ABI, however, no significant difference was also found on the AAQ-II. This could be due to the small sample size of the study (N=19). More research is needed to investigate the treatment sensitivity of the AAQ-ABI.

The test-retest reliability of both scales was not examined in this study. However, the test-retest reliability of the English AAQ-ABI was good in an Australian ABI sample (19). Furthermore, the test-retest reliability of the CFQ-7 was good in student and community samples (20, 45). However, the test-retest reliability should still be examined in Dutch individuals with ABI.

The largest part of the data was collected online, which has several advantages. Patients are easy to reach and it takes them a minimal amount of time to participate in the study. However, the questionnaires are not filled in in a controlled environment. Furthermore, the sample may have limited representativeness since these are all participants who have access to and know how to use a computer.

## **Conclusion**

The current study shows that the Dutch AAQ-ABI and CFQ-7 have acceptable to good psychometric properties when measuring psychological flexibility and cognitive defusion in Dutch patients with ABI. The AAQ-ABI and CFQ-7 can help clinicians to monitor their patients with ABI during an ACT intervention and can help evaluate the treatment. Furthermore, the questionnaires can be used in studies further investigating the effectiveness of ACT for patients with ABI. When using the AAQ-ABI in intervention studies it is recommended to use it in combination with the AAQ-II, since the treatment sensitivity of the AAQ-II is better studied.

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## CHAPTER 4

Acceptance and Commitment Therapy for  
people with acquired brain injury: rationale  
and description of the BrainACT treatment

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## CHAPTER 5

Acceptance and Commitment Therapy for individuals with depressive and anxiety symptoms following acquired brain injury: a non-concurrent multiple baseline design across four cases

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## Abstract

*Background.* Patients with acquired brain injury (ABI; such as stroke or traumatic brain injury) often experience symptoms of anxiety and depression. Until now, evidence-based treatment is scarce. This study aimed to investigate the effectiveness of Acceptance and Commitment Therapy (ACT) for patients with ABI.

*Methods.* To evaluate the effect of ACT for people with ABI, a non-concurrent multiple baseline design across four cases was used. Participants were randomly assigned to a baseline period, followed by treatment and then follow-up phases. Anxiety and depressive symptoms were repeatedly measured. During six measurement moments over a year, participants filled in questionnaires measuring anxiety, depression, stress, participation, quality of life, and ACT-related processes. Randomization tests and NAP scores were used to calculate the level of changes across phases. Clinically significant change was defined with the Reliable Change Index.

*Results.* Three out of four participants showed medium to large decreases in anxiety and depressive symptoms (NAP=0.848 till 0.99). Furthermore, participants showed improvements regarding stress, cognitive fusion, and quality of life. There were no improvements regarding psychological flexibility, value-driven behaviour, or social participation.

*Conclusion.* This study shows that ACT is possibly an effective treatment option for people experiencing ABI related anxiety and depression symptoms. Replication with single case or large scale group studies is needed to confirm these findings.

## Introduction

Individuals suffering from acquired brain injury (ABI), such as a traumatic brain injury (TBI) or a stroke are at increased risk of developing anxiety or depressive symptoms (1, 2). These can have a significant impact on patients' quality of life. Post-ABI depressive and anxiety symptoms are related to higher re-hospitalization rates, less social participation (dependency in daily living and lower return to work rates), and more cognitive and physical impairments (3).

Studies investigating interventions for ABI related anxiety and depressive complaints are scarce (4, 5) and there are therefore limited evidence-based treatment options (6, 7). For instance, second wave behavioural therapies such as cognitive behavioural therapy (CBT) have shown to be effective in treating depression and anxiety, but seem less effective for patients with ABI compared to non-ABI samples (8). Second-wave therapies aim to influence how situations are experienced and dealt with by changing unhelpful or irrational thoughts and cognitive schemas (9). Third-wave therapies such as Acceptance and Commitment Therapy (ACT) utilize a different approach, thoughts and feelings are not changed, but the functions of and one's relationship to these psychological events are changed. This might be a fitting approach for people with ABI since they often have realistic thoughts which might be hard to challenge. The aim of ACT is to accept one's thoughts and feelings, without judgment, and to commit to pursuing value-driven behaviour, which is named psychological flexibility (10). ACT might help people to live in a meaningful way with the lasting and impairing consequences of an ABI (11, 12). Psychological flexibility is increased using the six core-components of ACT (acceptance, cognitive defusion, mindfulness, self-as-context, values, and committed action). For patients to become accustomed to these processes, behavioural change strategies, metaphors, and experiential exercises are used. Although the main treatment aim of ACT is not to reduce symptomatology, a reduction of anxiety and depressive complaints is often observed following ACT interventions (13). Furthermore, an increase in psychological flexibility is thought to be related to improved mental health (14).

There is some preliminary evidence that ACT is effective in treating psychological distress following TBI. Whiting et al. (15) found that patients with severe TBI experienced greater reductions in depression and stress following an ACT treatment (N=10) compared to a befriending treatment (N=9) in a pilot randomized controlled trial. However, these results were not maintained in the one-month follow-up. Sander et al. (16) compared ACT to devised usual care (which consisted of an intake and referral to a psychological service without a follow-up). The study concluded that patients receiving the ACT intervention showed greater improvements regarding psychological distress and psychological flexibility compared to the patients in the usual care group. Moreover, Majumdar and Morris (17) found that ACT reduced depression and increased self-rated health status and hopefulness in people with a stroke. These studies indicate that ACT can be a suitable treatment for patients with ABI related anxiety or depressive complaints, however more research is needed to confirm these findings. Moreover, the long-term effects of ACT in people with ABI remain unknown. Therefore, this study aimed to evaluate the BrainACT intervention, an ACT intervention specifically developed for people with ABI. This was done using single-case experimental design (SCED) methodology.

A non-concurrent multiple baseline design across four cases was performed with a follow-up period of one year. It was hypothesized that the BrainACT intervention would reduce anxiety and depressive symptoms. Since the trajectories of change during psychotherapy are diverse and vary per patient (18), both immediate and delayed effects of the interventions were tested. Furthermore, it was expected that the intervention would improve psychological flexibility, cognitive defusion, and value-driven behaviour. Lastly, the study investigated if these outcomes generalized to improvements in levels of stress, social participation, and quality of life.

## Methods

### Design

In the current study, a non-current multiple baseline design was used, meaning that the study contained four AB designs with a varying baseline length (19). Randomization was achieved by randomly assigning patients to a baseline (waiting) period. This was done separately for every patient as you would do in an AB design. The minimum baseline period was 20 days and the maximum baseline period was 42 days. The study was approved by the Ethical Review Committee of Psychology and Neuroscience of Maastricht University (reference number: ERCPN-192\_21\_04\_2018) and the medical ethics committee of Zuyderland Medical Centre (METCZ20180074). All participants gave informed consent.

### Participants

Patients were recruited at Zuyderland Medical Centre between August 2018 and January 2019. Patients with ACT treatment indicated as part of their regular care were screened for eligibility in the study. To participate in this study, participants had to meet all of the following criteria: having sustained any type of stroke or traumatic brain injury diagnosed by a neurologist; having a score of seven or higher on the anxiety and/or the depression subscale of the Hospital Anxiety and Depression Scale (HADS); being more than three months post-injury to prevent confounding by spontaneous recovery; being 18 years or older; when using psychopharmacological medication, the dose should be stable four weeks prior to the study and for the duration of the study; having access to the internet and a computer; mastering the Dutch language sufficiently to benefit from treatment; and giving informed consent. Exclusion criteria were: history of brain injury or disease (diagnosed by a neurologist and classified as moderate or severe) or a neurological disorder other than a stroke or traumatic brain injury; pre-morbid disability as assessed with the Barthel Index (score<19/20); severe co-morbidity that might affect outcome (e.g. cancer or major psychiatric illnesses) for which treatment is given at the moment of inclusion; ongoing mood and/or anxiety disorder based on the DSM 5 (20) for which pharmacological and/or psychological treatment was necessary at the onset of the brain injury; and ACT for comparable problems in the year preceding study entry.

## Measures

*Repeated measures.* During the baseline period, participants were asked daily to rate the following statements “I feel depressed” and “I feel anxious” on a 7-point Likert scale (with 1 being not depressed/anxious and 7 being very depressed/anxious). These questions were based on questions from a study using the experience sampling method, which have shown to be feasible for people with ABI (21). During the treatment and follow-up phase, patients answered these questions weekly. Participants received a link via email in the morning, which they had the whole day to complete. Since they always received the same link, they occasionally filled in questions more than once per day. If this happened, the first answer was chosen.

*Demographic information.* Participants completed a demographic questionnaire at the start of the study. Participants filled in information on gender, age, education, employment, and marital status. The patients’ medical files provided clinical information on injury-related factors; type of brain injury, time since brain injury, severity of injury, and lesion location.

### *Psychological distress*

*Hospital Anxiety and Depression Scale.* The anxiety and depression subscales of the HADS were used to measure anxiety and depressive symptoms (22). The scores range from 0 to 21 with higher scores indicating higher levels of depression or anxiety. The HADS was found to have good psychometric properties in a TBI sample (Cronbach’s  $\alpha$  depression scale = .88; anxiety scale = .92) (23). Furthermore, a good internal consistency for both subscales (Cronbach’s  $\alpha$  depression scale = .81; anxiety scale = .84) was found in a stroke population (24).

*Depression Anxiety Stress Scales-21.* The Depression Anxiety Stress Scales-21 (DASS-21) was used to measure the levels of anxiety, depression, and stress of the participants (25). It consists of 21 items which are rated on a 4-point Likert-scale. The scores range from 0 to 63 with higher scores indicating greater levels of depression, anxiety, or stress. The questionnaire has been validated in a TBI sample. The internal consistency was good for all three scales (Cronbach’s  $\alpha$  depression scale = .90; stress scale = .89; and anxiety scale = .82) (26). The DASS-21 was included next to the HADS because it includes a stress scale and includes items on devaluation of life, self-deprecation, and hopelessness which the HADS lacks (27).

### *Psychological flexibility*

*Acceptance and Action Questionnaire-Acquired Brain Injury.* The Acceptance and Action Questionnaire-Acquired Brain Injury (AAQ-ABI) was used to measure psychological flexibility about the thoughts, feelings, and behaviours that occur as a result of the brain injury (28). The AAQ-ABI is a nine-item self-report measure that is scored on a 5-point Likert scale from 0 (not at all true) to 4 (very true). The total scores range from 0 to 36, with a higher score indicating greater psychological inflexibility. This scale has a good internal consistency in a Dutch sample of patients with ABI (Cronbach’s  $\alpha$  = .87) (29) and in an Australian TBI population (Cronbach’s  $\alpha$  = .90) (28).

*Acceptance and Action Questionnaire II.* The Acceptance and Action Questionnaire II (AAQ-II) was administered to measure psychological inflexibility and experiential avoidance (30). The answers are scored on a seven-point Likert scale with a range of 0 to 49. Higher scores indicate less acceptance and psychological flexibility. Whiting et al. (28) validated the AAQ-II in a sample of patients with ABI (Cronbach's  $\alpha = .90$ ). The AAQ-II was included next to the AAQ-ABI for its added value as a measure with better studied treatment sensitivity (29, 31).

*Cognitive fusion.* The Cognitive Fusion Questionnaire (CFQ-7) measures cognitive fusion on a 7-point Likert scale (32). Scores range from 0 to 49. The higher the score, the more fused one is with one's thoughts. Gillanders et al. (32) showed that the CFQ has an excellent internal consistency (Cronbach's  $\alpha = .93$ ) in a sample of patients with multiple sclerosis. Furthermore, the CFQ-7 showed excellent internal consistency in a Dutch sample of people with ABI (Cronbach's  $\alpha = .97$ ) (29).

*Valued living.* The Valued Living Questionnaire (VLQ) is a two-part instrument that measures valued living (33). First, the participant rates the importance of ten value domains on a ten point Likert scale. Second, participants rate how consistently they have lived in accordance with their values within these domains. Scores from both parts are used to calculate a valued living component. The internal consistency of the valued living component has been demonstrated as adequate (Cronbach's  $\alpha = .74$ ) (33). The VLQ has been used in earlier research to measure valued living in patients with TBI (34).

*Quality of life.* Quality of life (QoL) was measured with the Short Form Survey (SF-12). The SF-12 was used to measure the health status of the participants, but it can also be described as a broad assessment of quality of life (35). The SF-12 has two subscales, the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The total score of both scales ranges from 0 to 100, with a higher score indicating a better health status. The SF-12 demonstrates good psychometric properties (Cronbach's  $\alpha$  PCS = .85 and MCS = .81) (36).

*Participation.* The Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P) was used to measure three aspects of participation: frequency of behaviours, participation restrictions experienced due to health condition, and satisfaction with participation (37). The frequency scale measures the objective level of participation, while the restrictions and satisfaction scales offer an insight into the subjective rating of participation. The questionnaire consists of 31 items. A score ranging from 0 to 100 is calculated for each scale. Higher scores indicate more participation, less restriction, and more satisfaction. It is a valid and reliable measure for patients with ABI with a good internal consistency (Cronbach's  $\alpha = .70-.91$ ) (37).

## **Blinding**

Blinding of the participants and therapists was not feasible, due to the nature of the intervention. However, research assistants who collected the data were blinded for the phase (baseline, intervention, or follow-up) the participant was in at the moment of assessment.

## Intervention

The BrainACT intervention is an ACT treatment adapted for the needs and possible cognitive deficits of people with ABI. The ACT intervention consisted of eight individual sessions of 90 minutes during a period of 3.5 months. The first four sessions were weekly, thereafter the sessions were biweekly, with a 3-week break between the seventh session and last session. Participants did homework exercises lasting approximately 30 minutes for 6 days per week. Homework consisted of reading or listening to summaries of the sessions, practising skills, and doing mindfulness exercises. At the start of the intervention, participants received a workbook with instructions to read at home after each session. We used an eight-session protocol (see Table 1) based on Jansen and Batink (38), Luoma et al. (39), and Whiting et al. (15) in which all six ACT core processes were addressed. The protocol was altered based on the recommendations by Kangas and McDonald (11) and Broomfield et al. (40). An expert group of six psychologists experienced in ACT and/or in working with people with ABI gave further advice on the alterations. Alterations consisted of adaptations taking into account the possible cognitive deficits of the participants, and brain-injury-related topics discussed during the treatment. The intervention was provided individually by three certified psychologists who completed an ACT training course of at least five days and are experienced in working with patients with ACT (from four to seven years of experience) and TBI (three to 20 years of experience). Furthermore, the therapists were trained by a researcher (JR) in delivering the protocol.

**Table 1.** Overview of the BrainACT intervention

Session number	Content	Experiential exercises and metaphors	Homework exercises
1	Value exploration and defining core values.	<ul style="list-style-type: none"> <li>- Bus of life metaphor</li> <li>- Values sorting exercise</li> <li>- Describing your gravestone or 80th birthday exercise</li> <li>- Writing down core values</li> </ul>	<ul style="list-style-type: none"> <li>- Reading or listening to the summary of this session</li> <li>- Explore which values deserve more or less attention</li> <li>- Making pictures of valuable moments</li> </ul>
2	Committed action on the long and short term in relation to values. Education about mindfulness and practising contact with the present moment.	<ul style="list-style-type: none"> <li>- What's the next stop of your bus of life? (defining short-term goals)</li> <li>- Keep driving (defining long-term goals)</li> <li>- Introduction mindfulness: raisin exercise</li> </ul>	<ul style="list-style-type: none"> <li>- Reading or listening to the summary of this session</li> <li>- Perform a daily activity with full attention</li> <li>- Valuable activity of the week: performing one concrete action that fits within one of the patient's values</li> <li>- Defining obstacles while making these homework exercises</li> </ul>
3	Creative hopelessness; the undeniability of human suffering and the consequences on the long term of trying to control it. Identifying strategies used to cope with negative thoughts and emotions.	<ul style="list-style-type: none"> <li>- Mindfulness exercise: mindful breathing</li> <li>- Identifying how the patient copes with unpleasant experiences.</li> <li>- Tug-of war with a monster or bouncing ball metaphor</li> <li>- Mindfulness exercise: body scan</li> </ul>	<ul style="list-style-type: none"> <li>- Reading or listening to the summary of this session</li> <li>- Keeping track of unpleasant thoughts or feelings and how the patient coped with them</li> <li>- Reread the metaphor of the monster or bouncing ball</li> <li>- Valuable activity of the week</li> </ul>



Session number	Content	Experiential exercises and metaphors	Homework exercises
4	Introducing acceptance as an alternative to control.	<ul style="list-style-type: none"> <li>- Tug-of war with a monster, unwanted guest in your bus of life, or the finger trap metaphor</li> <li>- Explanation of the difference between pain and suffering with the glass of water exercise</li> <li>- Mindfulness exercise: making space, and allowing what is there</li> </ul>	<ul style="list-style-type: none"> <li>- Reading or listening to the summary of this session</li> <li>- Willingness exercise</li> <li>- Valuable activity of the week</li> </ul>
5	Changing the relationship with thoughts, naming the mind.	<ul style="list-style-type: none"> <li>- Mindfulness exercise: attention for thoughts</li> <li>- The passengers in your bus of life (in combination with post-its)</li> <li>- Defusion exercise: naming the mind</li> <li>- Defusion exercise: singing difficult thoughts</li> <li>- Mindfulness exercise: floating leaves on a river</li> </ul>	<ul style="list-style-type: none"> <li>- Reading or listening to the summary of this session.</li> <li>- Watch the YouTube video of the bus of life</li> <li>- Practice defusion exercises</li> <li>- Valuable activity of the week</li> <li>- Observing the mind during valuable activity</li> </ul>
6	Changing the relationship with thoughts about oneself and introducing the constant self.	<ul style="list-style-type: none"> <li>- Metaphor: the sky and the weather</li> <li>- Exercise: lifeline</li> <li>- Metaphor: Suits (thoughts about oneself) that don't fit</li> <li>- Exercise: backpack</li> </ul>	<ul style="list-style-type: none"> <li>- Reading or listening to the summary of this session</li> <li>- Take off a suit that doesn't fit (anymore)</li> <li>- Practice a mindfulness exercise</li> <li>- Valuable activity of the week</li> </ul>
7	Repetition on defusion and mindfulness.	<ul style="list-style-type: none"> <li>- Mindfulness exercise: the body scan</li> <li>- Defusion exercises: physicalizing the thought</li> <li>- Mindfulness exercise: mindful breathing</li> </ul>	<ul style="list-style-type: none"> <li>- Reading or listening to the summary of this session</li> <li>- Practice a mindfulness exercise daily</li> <li>- Valuable activity of the week</li> </ul>
8	Review of the different core components, explanation on how these skills together lead to psychological flexibility, and preparation on relapse and setbacks.	<ul style="list-style-type: none"> <li>- Mindfulness exercise: attention for noise</li> <li>- Car metaphor</li> <li>- Bus of life metaphor and exercise</li> <li>- Strategies on how to keep using acquired ACT skills in daily life</li> </ul>	<ul style="list-style-type: none"> <li>- Reading or listening to the summary of this session</li> <li>- Try to keep practising with the different ACT skills</li> <li>- Start integrating ACT into your daily life</li> <li>- Live your life as is valuable to you! Stop fighting, start living!</li> </ul>

## Setting

The sessions were performed at Zuyderland Medical Centre, a general hospital in the Netherlands, at the rehabilitation and medical psychology department. The sessions took place in a therapy room where the psychologist and participant sat across from each other at a table.

## Treatment adherence

Treatment adherence was checked using a checklist which the therapists filled out following each session. In this checklist, they indicated which exercises and metaphors they had covered and which ones were skipped or altered. Based on this information, a percentage was calculated from the total number of exercises and metaphors (see table 1) in the protocol. Likewise, therapists indicated which homework assignments were

completed and a percentage was calculated. The treatment adherence rate was 60%, 80%, 82%, and 97% for participant one, two, three, and four respectively. Furthermore, participant one completed 83% of the homework exercises, participant two 86%, participant three 90%, and participant four 97%.

## Procedure

Participants with ABI for whom an ACT treatment was indicated were eligible for this study. Psychologists screened patients on the in- and exclusion criteria and when patients met the criteria they were informed about the study. After signing the informed consent, the pre-baseline measurements and baseline randomization took place. Participants were allocated to a baseline varying from 20 to 42 days, after which they started with the ACT intervention (treatment phase) and follow-up phase. During the baseline phase, repeated measures were filled in daily, and during the treatment and follow-up phase this was filled in weekly. There were five more measuring moments (pre-treatment, during treatment, post-treatment, and at seven and 12 months) during which participants filled in the questionnaires on paper. Research assistants performed these measurements after instructions of a researcher (JR) and following a protocol.

## Data analyses

For each participant, levels of anxiety and depressive symptoms were plotted graphically for visual analyses. Visual analyses were conducted following the recommendations of Ledford and Gast (41). Horizontal lines are depicted to observe changes in the average between phases. The trend was determined by the slope and direction of the best fitting straight line for each phase. This was done using the Split Middle Method as proposed by Ledford and Gast (41). Trend stability was defined by a stability window  $\pm 25\%$  of the trend line. Autocorrelation often occurs in SCED data and is associated with an increase in the occurrence of Type I or II errors (42) and therefore, it is important to assess and report it (43). Autocorrelation was calculated using the formula proposed by Box and Jenkins (44). A lag-1 autocorrelation coefficient of 0.5 or higher was considered high (45). Autocorrelation was not calculated for four phases (both treatment+follow-up phases of participant 1 and 4) because they were constant at floor level. Autocorrelation coefficients were higher than 0.5 for six phases (both baseline phases of participant 1, both treatment+follow-up phases of participant 2, and both baseline phases of participant 3).

Randomization tests were used to determine if the levels of anxiety and depression significantly differed between phases (baseline versus treatment+follow-up phase). This was done as described by Bulte and Onghena (46). These tests are permutation tests relying on random assignment (baseline length in our case) to test a null hypothesis (47, 48), the null hypothesis for the current study being no difference between phases (no treatment effect). In order to compare the phases, a t-statistic was calculated for each possible permutation. This t-statistic is the absolute difference between the mean of the baseline phase and the mean of the treatment+follow-up phase (mean of baseline phase - mean of treatment+follow-up phase). The t-statistic is calculated for every possible starting point of the intervention. The t-statistics that

are as large as or larger than the observed data point (starting point of treatment) are divided by the total number of possible permutations, which is the probability association (48). Therefore, there is a minimum number of possible starting points in order to obtain a p-value of  $<0.05$ . In the current study 23 possible randomization assignments permit a p-value of  $<0.05$  ( $1/23 = 0.043$ ). Since it was unclear beforehand when participants would start to respond to the intervention (i.e. decrease in anxiety or depressive symptoms), randomization tests were performed assuming a delayed effect. After the main randomization test, to test for immediate effect, the randomization tests were repeated until the smallest p-value was reached (49, 50). The smallest p-value is equivalent to the moment in which the difference between means (and thus the t-statistic) of both phases is the largest. We hypothesized that the delayed effect should take place during the first thirteen measurements of the treatment+follow-up phase since we did expect the effect to take place during the treatment. Additionally, the p-values of the immediate and delayed effects were combined following Edgington's (51) additive method. Randomization tests and combining of the p-values were performed using the SCDA plug-in package in R (52).

Non-overlap of all pairs (NAP) was used as a measure of effect (53). Since the participants were all more than three months post-ABI, we did not expect spontaneous improvements in the baseline phase. Therefore, NAP is a more appropriate measure than baseline corrected TAU (54). NAP is a non-overlap index that can be derived from Mann-Whitney U (55). NAP summarizes the data overlap between each baseline data point and each treatment+follow-up phase data point in turn. NAP is calculated by dividing the number of comparisons with no overlap by the total number of comparisons (53). Parker and Vannest (53) proposed the following ranges in order to interpret NAP; scores ranging from 0 to 0.65 are weak effects, from 0.66 to 0.92 are medium effects, and from 0.93 to 1.0 are large or strong effects. An online calculator was used to calculate NAP (56). High levels of autocorrelation can lead to overestimation of the effect measure and therefore NAP scores should be interpreted with some caution (57), however confidence intervals computed for NAP do assume independence, as I mentioned in the previous review.

In order to define clinical significant change, the Reliable Change Index (RCI) was calculated between the pre-treatment measurements and the other measurements. This was done using the formula of Jacobson and Truax (58). Since the outcomes are z-scores they are significant if  $z < -1.96$  or  $z > 1.96$ .

## Results

Four participants were included in the study. The demographic and injury-related characteristics can be found in table 2. There were some deviations from protocol. First, during the follow-up phase of participant 1, he did not want to continue to answer the weekly questions. He had been filling out the same answers for weeks and expected to continue to do so. It was therefore agreed that the researcher (JR) would fill in the answers for him and if the answer was different, he would let the researcher know. Participant 1 did fill in the questionnaires during the follow-up measurements, the scores of which corresponded with the answers that he had filled in. Second, participant 2 filled in 1 (the lowest score) for the anxiety score for the first 16 days. However, during the pre-treatment measuring moment, he explained that he misunderstood

the question and that the score should be higher in these first 16 days. It was agreed upon to impute these 16 days with the average score of the remaining 11 days (score of 3.18).

**Table 2.** Participant characteristics

Participant	1	2	3	4
<b>Sex</b>	Male	Male	Male	Female
<b>Age</b>	59	63	35	47
<b>Educational level</b>	Higher professional education	Secondary vocational education	Primary vocational education	Higher professional education
<b>Occupation</b>	Incapacitated	Employed	Incapacitated	Employed
<b>Marital status</b>	Married	Married	Married	Married
<b>Time since injury (months)</b>	22	64	10	36
<b>Type of injury</b>	Traumatic brain injury	Brainstem stroke	Traumatic brain injury	Right hemispheric stroke

## Case formulation

### *Participant 1*

Participant 1 is a 59-year old man, who sustained a TBI after falling down a set of stairs in 2016. After the accident he lost consciousness (unknown for how long) and experienced post-traumatic amnesia for one hour. He had no psychiatric history. After the accident, he completed an outpatient rehabilitation programme, during which he started an e-health module for panic disorder, which he did not finish. Several months after the rehabilitation programme he experienced a severe increase in fatigue, cognitive, and emotional complaints. His physiatrist (rehabilitation physician) then referred him to the department of medical psychology. He worried a lot about his future. He avoided busy or stressful situations. He for instance stopped seeing his friends from a cycling group. He did this to control his complaints, however, he felt frustrated that this did not reduce his complaints. The participant is married and has two adult children. He works in finance and was on sick leave.

During the intervention, he started to share his complaints and negative feelings with his wife and his friends. Instead of hiding his feelings, pretending he was okay, or avoiding others. This helped him to reconnect to others and to restart undertaking activities together. When introduced to the theme of fusion, he initially found it hard to recognize that this could apply to him. However, looking back at the intervention he felt that fusion, defusion, and self as context had been the most helpful and valuable parts of the intervention. Moreover, it is good to mention that during the treatment a financial dispute, which had caused a lot of stress, was resolved.

### *Participant 2*

Participant 2 is a 63-year-old man, who suffered from an ischemic brainstem stroke in 2013. He had no psychiatric history. He was referred by his general practitioner to the mental health care department because

of a depressive disorder based on the DSM criteria. He reported mood problems, excessive worrying, fatigue, and poor concentration. He was regarded as a very active and sporty man, who sets high standards for himself. In his free time, he was active as a swimming trainer, four evenings a week, for more than 30 years. In the year before the intervention, the emotional problems and fatigue slowly increased. He stopped running and slept a lot, also during the day. He was working as a lawyer, 32 hours a week. The patient is married and has two children and three grandchildren.

During the intervention, he decided to stop with his activities as a swimming coach, because he realized that this role cost him a lot of energy and was no longer satisfactory. He told the therapist: “my mind told me that I have to do this, but I realized that it was no longer satisfactory for me”. He also restarted running and going to the cinema with his wife. After the intervention, he needed less sleep during the day and the depressive disorder was in remission (based on the DSM criteria). His partner joined the treatment sessions and was actively involved in the homework assignments.

### *Participant 3*

Participant 3 is a 35-year-old man, who sustained a TBI after a bike accident in 2018. Symptoms he experienced following the accident were nausea, emesis, headache, tinnitus, and diplopia. He had no psychiatric history. He was referred by the neurologist to the mental health care department. He reported mood problems, including apathy, irritability, and restlessness. In addition, he suffered from fatigue, memory and attention problems, and tinnitus. Because of his symptoms, he often cancelled social appointments and was worrying about the future. He experienced pain in his shoulder for years. As a result of these, he could not carry out his work as a house painter and was receiving a disability payment. He could not carry out his work as a house painter because of severe shoulder dysfunction and was receiving a disability payment. The patient is married.

During the intervention, he discovered he did many activities because it was expected by others. He has become more assertive and makes more value-oriented choices regarding activities. After the intervention, he indicated that he mainly lived more in the here and now and he experienced fewer worries, also regarding his tinnitus. His wife was actively involved in the process at home, partly because of his severe dyslexia. The patient was satisfied with the treatment and experienced fewer emotional complaints.

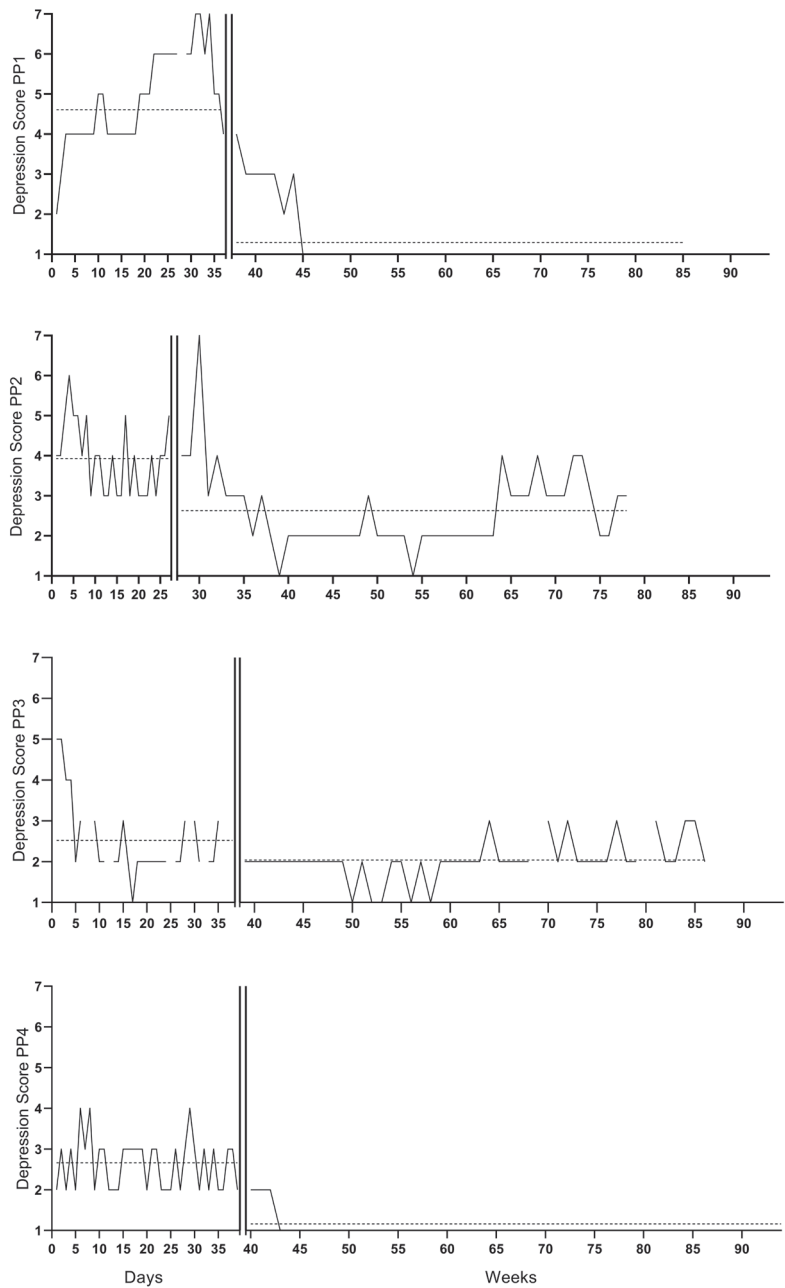
### *Participant 4*

Participant 4 is a 47-year old woman who had a lacunar stroke in 2016. She had no psychiatric history. Following the stroke, the patient followed a rehabilitation programme, which included psychological treatment consisting of 10 sessions CBT. After this first rehabilitation period, she had a 100% return to work. The patient tried to bring everything back to normal, leaving this difficult period in her life behind her and putting a lot of effort into her return to work. Soon, however, she noticed that things were everything but normal. She suffered from fatigue and could not return to her normal activities like leisure time with her

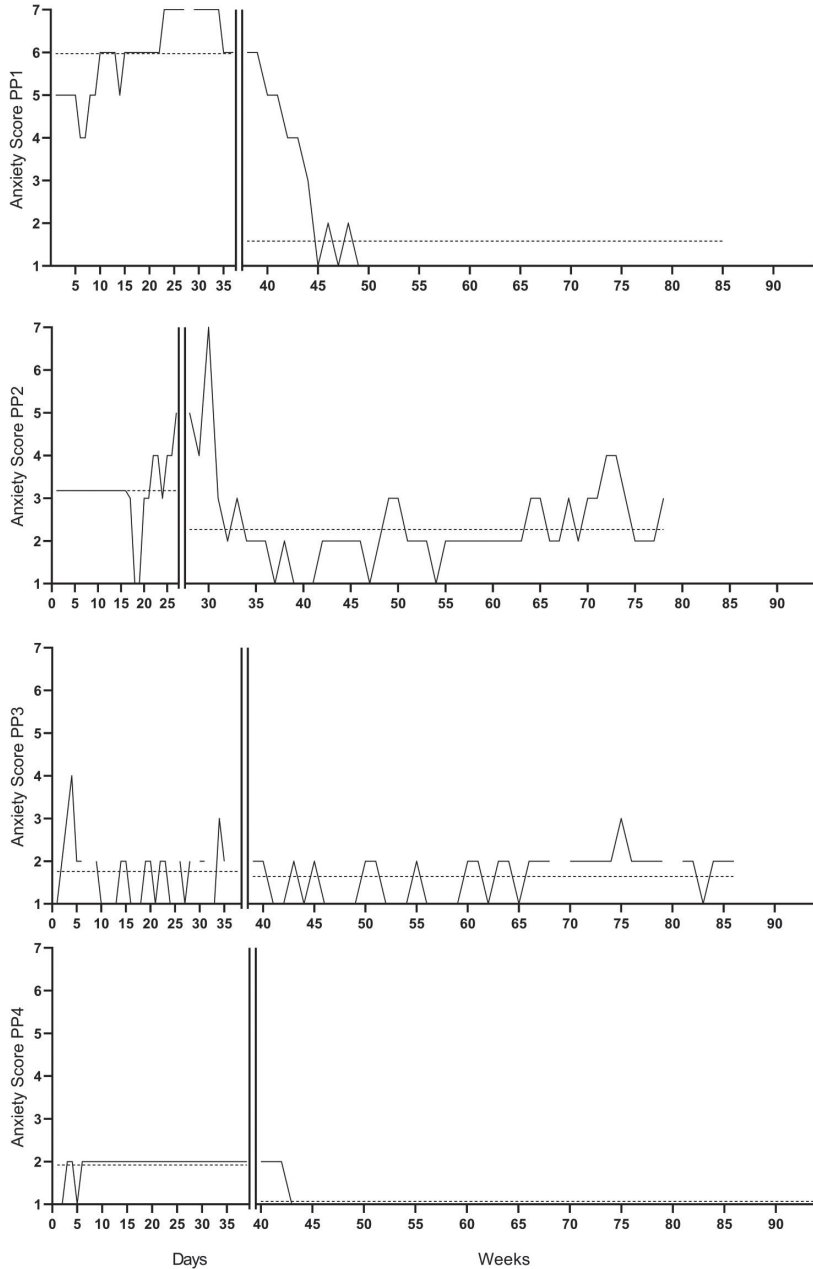
family and sports. The patient reported an agitated mood, fatigue, and a general loss of pleasure. Moreover, she reported feelings of guilt because of her lack of energy to spend time with her children. Next to that, she feared recurrence of a stroke when experiencing sudden dizziness or nausea. Finally, she experienced her relapse of these symptoms as a failure. She worked as a logistic manager in a peripheral hospital for 20 hours a week. She is married and has 2 children of which the eldest has an intellectual disability.

During the intervention, the patient was confronted with her experiential avoidance. Strategies she used to avoid difficult emotions were to endure in work and to trivialise or rationalize problems. Once confronted with her behaviour she started to open up, especially to her husband. Particularly, she discussed with him her negative feelings when her oldest child showed difficult behaviour. She learned to allow her negative feelings instead of suppressing them. The theme of cognitive defusion was difficult for her at first. In the end, however, it gave her new insights on how to accept her thoughts and feelings as they were. Additionally, she recognized her tendency to take control of everything herself. She began to share and delegate, both at home and at work. This resulted in more time to spend with her family. The patient reported feeling happier at the end of the intervention.

**Figure 1.** Repeated measures of depressive symptoms per participants 1, 2, 3, and 4 over time. The vertical lines are the start of the intervention. The horizontal line is the average score per phase. The participants started with the baseline phase at different dates (participant one started on 6-8-2018, participants two on 9-8-2018, participant 3 on 31-10-2018, and participant 4 on 22-1-2019).



**Figure 2.** Repeated measures of anxiety symptoms per participants 1, 2, 3, and 4 over time. The vertical line is the start of the intervention. The horizontal line is the average score per phase. The participants started with the baseline phase at different dates (participant one started on 6-8-2018, participants two on 9-8-2018, participant 3 on 31-10-2018, and participant 4 on 22-1-2019).





**Table 3.** Phase characteristics of the repeated depression scores

Participant	Number of measurements baseline phase	Baseline Mean (SD)	Number of measurements intervention + FU phase	Intervention + FU Mean (SD)
1	36	4.86 (1.17)	48	1.29 (0.74)
2	27	3.93 (0.87)	51	2.63 (1.00)
3	30	2.52 (0.95)	46	2.04 (0.51)
4	39	2.66 (0.63)	55	1.16 (0.46)

**Table 4.** Phase characteristics of the repeated anxiety scores

Participant	Number of measurements baseline phase	Baseline Mean (SD)	Number of measurements intervention + FU phase	Intervention + FU Mean (SD)
1	36	5.97 (0.88)	48	1.58 (1.38)
2	27	3.18 (2.37)	51	2.37 (1.06)
3	30	1.76 (0.74)	46	1.64 (0.53)
4	39	1.92 (0.27)	55	1.07 (0.26)

### Visual analyses, randomization tests, and NAP

The repeated anxiety and depression scores are represented visually in figure one and two. Characteristics of phase lengths and measurements are represented in table three and four.

#### *Participant 1*

Participant one was assigned to a baseline length of 37 days.

#### Depression scores

*Visual analyses.* There was a decrease in the average depression scores in the baseline compared to the treatment+follow-up phases. The trend in the baseline phase was accelerating, this levelled to zero-celerating in the treatment phase. Both phases had high trend stability, which was 88.89% for the baseline phase and 85.42% for the treatment+follow-up phase.

*Response to the intervention.* Randomization tests (Table 5) showed a statistically significant delayed effect ( $t = 3.63$ ,  $p = 0.043$ ), which reached significance after two weeks. Furthermore, there was a large difference between the baseline and treatment+follow-up phase ( $NAP = 0.99$ ,  $90\%CI = 0.95$  to  $1$ ).

#### Anxiety scores

*Visual analyses.* There was a decrease in the average anxiety scores in the baseline compared to the treatment+follow-up phases. The trend in the baseline phase was accelerating, this levelled to zero-celerating in the treatment+follow-up phase. Both phases had high trend stability, which was 100% for the baseline phase and 81.25% for the treatment+follow-up phase.

*Response to the intervention.* Randomization tests (Table 6) showed a statistically significant delayed effect ( $t = 4.72$ ,  $p = 0.043$ ), which reached significance after six weeks. Furthermore, there was a large difference between the baseline and treatment+follow-up phase ( $NAP = 0.97$ ,  $90\%CI = 0.92$  to  $0.99$ ).

### Participant 2

Participant two was assigned to a baseline length of 27 days.

#### Depression scores

*Visual analyses.* There was a decrease in the average depression scores in the baseline compared to treatment+follow-up phase. The trend in the baseline phase was decelerating and zero-celerating in the treatment+follow-up phase. Both phases had high trend stability, which was 96.3% for the baseline phase and 50.98% for the treatment phase.

*Response to the intervention.* Randomization tests showed a statistically significant delayed effect ( $t = 1.56$ ,  $p = 0.043$ ), which reached significance after six weeks. Furthermore, there was a medium difference between the baseline and treatment+follow-up phase ( $NAP = 0.85$ ,  $90\%CI = 0.75$  to  $0.91$ ).

#### Anxiety scores

*Visual analyses.* There was a decrease in the average anxiety scores in the baseline compared to treatment+follow-up phase. The trend in the baseline phase was zero-celerating, which stayed zero-celerating in the treatment+follow-up phase. Both phases had high trend stability, which was 85.19% for the baseline phase and 49.02% for the treatment phase.

*Response to the intervention.* Randomization tests showed a statistically significant delayed effect ( $t = 1.21$ ,  $p = 0.043$ ), which reached significance after five weeks. Furthermore, there was a medium difference between the baseline and treatment+follow-up phase ( $NAP = 0.85$ ,  $90\%CI = 0.77$  to  $0.91$ ).

### Participant 3

Participant three was assigned to a baseline length of 38 days.

#### Depression scores

*Visual analyses.* There was a decrease in the average depression scores in the baseline compared to treatment+follow-up phase. The trend in the baseline phase was decelerating and zero-celerating in the treatment+follow-up phase. Both phases had high trend stability, which was 62.07% for the baseline phase and 74.47% for the treatment+follow-up phase.

*Response to the intervention.* Randomization tests showed no statistically significant immediate or delayed effect ( $t = 3.63$ ,  $p = 0.27$ ). Furthermore, there was a weak difference between the baseline and treatment+follow-up phase ( $NAP = 0.63$ ,  $90\%CI = 0.52$  to  $0.73$ ).

#### Anxiety scores

*Visual analyses.* There was a small decrease in the average anxiety scores in the baseline compared to treatment+follow-up phase. The trend in the baseline phase was zero-celerating and accelerating in the treatment+follow-up phase. Both phases had high trend stability, which was 51.72% for the baseline phase and 74.47% for the treatment+follow-up phase.

*Response to the intervention.* Randomization tests showed a statistically significant immediate effect ( $t = 0.120$ ,  $p = 0.043$ ). However, there was a small difference between the baseline and treatment+follow-up phase (NAP = 0.53, 90%CI = 0.42 to 0.64).

#### *Participant 4*

Participant four was assigned to a baseline length of 39 days.

#### Depression scores

*Visual analyses.* There was a decrease in the average depression scores in the baseline compared to treatment+follow-up phase. The trend in the baseline phase was zero-celerating, which stayed zero-celerating in the treatment+follow-up phase. Both phases had high trend stability, which was 50% for the baseline phase and 87.27% for the treatment+follow-up phase.

*Response to the intervention.* Randomization tests showed a statistically significant delayed effect ( $t = 1.58$ ,  $p = 0.043$ ), which reached significance after five weeks. Furthermore, there was a large difference between the baseline and treatment+follow-up phase (NAP = 0.96, 90%CI = 0.90 to 0.98).

#### Anxiety scores

*Visual analyses.* There was a decrease in the average anxiety scores in the baseline compared to treatment+follow-up phase. The trend in the baseline phase was zero-celerating, which stayed zero-celerating in the treatment+follow-up phase. Both phases had high trend stability, which was 92.11% for the baseline phase and 92.73% for the treatment phase.

*Response to the intervention.* Randomization tests showed a statistically significant delayed effect ( $t = 0.91$ ,  $p = 0.043$ ), which reached significance after five weeks. Furthermore, there was a large difference between the baseline and treatment phase (NAP = 0.93, 90%CI = 0.86 to 0.96).

**Table 5.** Immediate and delayed randomization tests of the depression scores with combined p-values

Participant	Immediate effect p-values	Delayed effect after two week	Delayed effect after three weeks	Delayed effect after four weeks	Delayed effect after five weeks	Delayed effect after six weeks	Effect was significant at week
1	.261	.043*	.087	.174	.217	.130	2
2	.522	.478	.435	.087	.217	.043*	6
3	.217	.391	.478	.956	.607	.652	-
4	.217	.174	.130	.087	.043*	(not within randomization possibilities)	5
<b>Combined p-values</b>	.091	.058	.072	.119	.057	.935	

\*significant immediate or delayed effect

**Table 6.** Immediate and delayed randomization tests of the anxiety scores with combined p-values

Participant	Immediate effect p-values	Delayed effect after two week	Delayed effect after three weeks	Delayed effect after four weeks	Delayed effect after five weeks	Delayed effect after six weeks	Effect was significant at week
1	.261	.217	.174	.130	.087	.043*	6
2	.565	.478	.348	.087	.043*	.174	5
3	.043*	.217	.130	.083	.261	.565	1
4	.217	.174	.130	.087	.043	(not within randomization possibilities)	5
<b>Combined p-values</b>	.058	.058	.016*	.016*	<.01*	.079	

\*significant immediate or delayed effect

### Reliable Change Index

In table 7 the Reliable Change Index can be found between the different measurement moments of the HADS, DASS-21 stress scale, AAQ-II, AAQ-ABI, CFQ-7, and VLQ. The complete table including the DASS-21 anxiety and depression scale, Sf-12, and USER-P can be found in the supplemental materials.

**Table 7.** Reliable Change Index

	PP1	PP2	PP3	PP4
<b>HADS-D</b>				
Pre-baseline	7	9	9	5
Pre-treatment (RCI pre-baseline/pre-treatment)	6 (0.40)	11 (-0.80)	9 (0)	9 (-1.61)
During-treatment (RCI pre-treatment/During-treatment)	5 (0.40)	3 (3.21*)	8 (0.40)	6 (1.21)
Post-treatment (RCI pre-treatment/post-treatment)	2 (1.61)	7 (1.61)	5 (1.61)	3 (2.41*)
7 month FU (RCI pre-treatment/7FU)	1 (2.01*)	3 (3.22*)	11 (-0.80)	3 (2.41*)
12 months FU (RCI pre-treatment/12FU)	0 (2.41*)	3 (3.22*)	10 (-0.40)	0 (3.62*)
<b>HADS-A</b>				
Pre-baseline	10	3	6	7
Pre-treatment (RCI pre-baseline/pre-treatment)	10 (0)	16 (-5.66)	8 (-0.87)	8 (-0.43)
During-treatment (RCI pre-treatment/During-treatment)	10 (0)	6 (4.35*)	7 (0.44)	6 (0.87)
Post-treatment (RCI pre-treatment/post-treatment)	4 (2.61*)	8 (3.48*)	3 (2.17*)	5 (1.31)
7 month FU (RCI pre-treatment/7FU)	2 (3.48*)	4 (5.22*)	7 (0.43)	5 (1.31)
12 months FU (RCI pre-treatment/12FU)	0 (4.35*)	6 (4.35*)	10 (-0.87)	5 (1.31)
<b>DASS-21 stress</b>				
Pre-baseline	15	9	12	5
Pre-treatment (RCI pre-baseline/pre-treatment)	11 (1.65)	18 (-3.72)	11 (0.41)	6 (-0.41)
During-treatment (RCI pre-treatment/During-treatment)	12 (-0.41)	5 (5.37*)	9 (0.83)	6 (0)
Post-treatment (RCI pre-treatment/post-treatment)	5 (2.48*)	6 (4.96*)	6 (2.07*)	5 (0.41)
7 month FU (RCI pre-treatment/7FU)	3 (3.31*)	5 (5.37*)	8 (1.24)	4 (0.83)
12 months FU (RCI pre-treatment/12FU)	0 (4.54*)	4 (5.78*)	10 (0.41)	4 (0.83)
<b>AAQ-II</b>				
Pre-baseline	15	15	14	9
Pre-treatment (RCI pre-baseline/pre-treatment)	12 (0.66)	34 (-4.17)	11 (0.66)	11 (-0.44)
During-treatment (RCI pre-treatment/During-treatment)	15 (-0.66)	17 (3.73*)	12 (-0.22)	10 (0.22)
Post-treatment (RCI pre-treatment/post-treatment)	9 (0.66)	7 (5.93*)	9 (0.44)	9 (0.44)
7 month FU (RCI pre-treatment/7FU)	8 (0.88)	14 (4.39*)	16 (-1.09)	8 (0.66)
12 months FU (RCI pre-treatment/12FU)	8 (0.88)	11 (5.05*)	13 (-0.44)	7 (0.88)
<b>AAQ-ABI</b>				
Pre-baseline	12	7	8	9
Pre-treatment (RCI pre-baseline/pre-treatment)	7 (1.20)	27 (-4.80)	10 (-0.48)	9 (0)
During-treatment (RCI pre-treatment/During-treatment)	12 (-1.20)	10 (4.08*)	9 (0.24)	7 (0.48)
Post-treatment (RCI pre-treatment/post-treatment)	1 (1.44)	11 (3.84*)	7 (0.72)	5 (0.96)
7 month FU (RCI pre-treatment/7FU)	2 (1.20)	6 (5.04*)	-	3 (1.44)
12 months FU (RCI pre-treatment/12FU)	1 (1.44)	8 (4.56*)	12 (-0.48)	1 (1.92)
<b>CFQ-7</b>				
Pre-baseline	33	35	24	17
Pre-treatment (RCI pre-baseline/pre-treatment)	19 (3.61*)	44 (-2.32)	36 (-3.10)	12 (1.28)
During-treatment (RCI pre-treatment/During-treatment)	23 (-1.03)	32 (3.10*)	33 (0.77)	11 (0.26)
Post-treatment (RCI pre-treatment/post-treatment)	10 (2.32*)	17 (6.97*)	14 (5.68*)	12 (0)
7 month FU (RCI pre-treatment/7FU)	7 (3.10*)	11 (8.51*)	26 (2.58*)	10 (0.52)
12 months FU (RCI pre-treatment/12FU)	10 (2.32*)	20 (6.19*)	24 (3.10*)	9 (0.77)
<b>VLQ composite score</b>				
Pre-baseline	-	53.50	-	56.80
Pre-treatment (RCI pre-baseline/pre-treatment)	45.20	52.00 (0.14)	47.40	61.90 (-0.49)
During-treatment (RCI pre-treatment/During-treatment)	55.90 (-1.02)	48.20 (0.36)	33.90 (1.29)	53.20 (0.83)
Post-treatment (RCI pre-treatment/post-treatment)	-	57.60 (-0.54)	35.80 (1.11)	58.90 (0.29)
7 month FU (RCI pre-treatment/7FU)	53.60 (-0.80)	59.20 (-0.69)	34.40 (1.25)	66.70 (-0.46)
12 months FU (RCI pre-treatment/12FU)	-	48.40 (0.38)	49.30 (-0.20)	56.20 (0.60)

HADS, Hospital Anxiety and Depression Scale; DASS-21, Depression, Anxiety and Stress Scale-21; AAQ-II, Acceptance and Action Questionnaire II; AAQ-ABI, Acceptance and Action Questionnaire Acquired Brain Injury; VLQ, Valued Living Questionnaire; CFQ-7, Cognitive Fusion Questionnaire.

Table includes raw scores with the RCI, Reliable Change Index between brackets

\* clinical significant change

## Discussion

The main goal of this study was to examine the effectiveness of the BrainACT intervention for people experiencing ABI related anxiety and depressive symptoms. This was done using a non-concurrent multiple baseline design across four cases.

### Main outcome measures

Participants 1, 2, and 4 showed medium to large improvements in anxiety and depressive complaints. Furthermore, these three participants responded to the treatment within two to six weeks after starting the BrainACT intervention. The delayed effect of participant 1 reached significance after two weeks. A study by Keinonen et al. (59) found that 25% of patients can experience a sudden gain (an abrupt reduction in symptom severity after which they stabilize) after the first two sessions of an ACT intervention. It seems likely, also looking at his graph, that participant 1 experienced a sudden gain in depression scores after session two. Interestingly, all other delayed effects reached significance at week five or six. Furthermore, these three participants (except for the anxiety and stress symptoms of participant four, which however were low at the start of the intervention) showed clinically significant improvements in anxiety, depressive, and stress symptoms. These lasted up to a year after the start of the intervention. Based on these results it can be concluded that the BrainACT intervention was successful in decreasing anxiety and depressive complaints.

For participant 3 the results were less evident. NAP scores indicated that he experienced a weak decrease in depression and anxiety scores, while the randomization tests showed a significant immediate effect for anxiety and no significant effects for depression. There was a clinically significant change on the HADS-anxiety post-treatment of participant 3. However, this did not last and the HADS scores on the follow-up moments are even higher than before the treatment. The scores of the repeated measures on both graphs show a similar pattern. This could be an indication that the treatment was not long enough or that extra booster sessions after a few months would have been beneficial. While the patient did state that he was satisfied with the treatment and experienced fewer emotional complaints, these results do not indicate that the BrainACT intervention decreased his anxiety and depressive complaints.

For all four participants, the clinically significant changes in anxiety and depression are mostly seen on the subscales of the HADS and not on DASS-21. Although the DASS-21 was primarily included to measure stress and not anxiety or depression, it would have been more convincing if anxiety and depression had reached clinically significant change on the DASS-21 as well. Patients scored lower pre-treatment anxiety and depression scores on the DASS-21 compared to the HADS scores. As a result, there was less room for improvement on the DASS-21.

### ACT-process measures

Participants 1, 2, and 4 showed no clinically significant improvement regarding psychological flexibility, experiential avoidance, or psychological flexibility related to thoughts and feelings about ABI, although the scores did improve for these patients. Participant 3 did show clinically significant improvements in these

domains. However, this seems to be a result of a very high score for both measures on the pre-treatment measurement moment, making these results quite unreliable. The non-clinical significant improvement in psychological flexibility corresponds with the results of Whiting et al. (15), where an improvement in stress and depression was also found, but no improvement in psychological flexibility in severe TBI participants, who had received an ACT intervention. However, Sander et al. (16) did find a significant improvement regarding psychological flexibility in TBI participants who had received an ACT intervention. Clearly, more research is needed into the role of psychological flexibility during an ACT intervention for ABI related anxiety and depression symptoms. Although the psychometric properties of the AAQ-II and AAQ-ABI have been studied in patients with ABI (28, 29), there has been critique on the validity of the AAQ-II. Studies found that rather than measuring psychological flexibility it measures psychological distress or neuroticism (60, 61). This should be taken into account when using the AAQ-II. However, if the AAQ-II is a measure of psychological distress, one would expect greater reductions in scores, similar to the other measures of psychological distress in this study.

Furthermore, no improvements were found in value-driven behaviour for all four participants. This is somewhat surprising since the treatment protocol places a strong emphasis on the identification of values and afterwards, valued behaviours were followed up and encouraged each session (valuable activity of the week). Nonetheless, it might be possible that this was still not sufficient to elicit behavioural change, which has proven to be complex (62). Another explanation could be found in the instrument used for the measurement of valued behaviour, the VLQ. This questionnaire uses ten broad value domains, which leaves no room for personal values (that might have been targeted during treatment) outside these domains and the second part of the questionnaire is quite difficult to fill in. Moreover, changes in only one or two domains, may not be noticed in the total score of the VLQ. On the other hand, in other studies, the VLQ has shown improvements following ACT interventions (63). Currently, an adapted version for patients with ABI of the VLQ is being developed specifically to tackle these problems (64). It would be interesting to know if this adapted scale would be able to measure change regarding valued behaviour.

There was a reduction in cognitive fusion for all four participants, which was clinically significant for participants 1, 2, and 3. This could be the result of the emphasis placed on cognitive defusion in the treatment protocol. For instance, in session seven, information on cognitive defusion was rehearsed and practised to improve this skill. In other medical populations, cognitive fusion (and not illness-related symptoms) was related to levels of depression (65, 66). Furthermore, previous research has found that cognitive defusion significantly mediates changes in quality of life, behavioural avoidance, and depression in both ACT and CBT interventions (67, 68).

### **Secondary outcome measures**

There were no clear improvements in social participation or physical health-related quality of life. However, mental health-related quality of life did improve for all participants, which was a clinically significant improvement for two participants and very close to significance for the other two participants. These findings

are in line with results from previous studies which also found improvements in mental health-related quality of life but not in physical health-related quality of life following ACT interventions (69, 70). It can be concluded that all four participants, to some extent, benefited from the treatment regarding this outcome.

### Strengths and limitations

This study has several strengths. The follow-up time of a year is long compared to other single case studies. Therefore, there were a considerable number of data points in each phase (ranging from 27 to 54), especially considering the minimum of five data points per phase (71) and Michiels and Onghena (72) advise at least 30 measurements in total to achieve adequate power for randomization tests. Furthermore, the study succeeded in replicating the treatment effect in three different participants, thus strengthening the hypotheses that ACT is an effective treatment for psychological distress following ABI. Lastly, no adverse events occurred for any of the participants.

However, this study is not without its limitations. First, increased levels of autocorrelation were found for six phases. As mentioned earlier, NAP does not control for autocorrelation. High levels of autocorrelation can lead to overestimation of the effect measure and therefore NAP scores should be interpreted with some caution (57). This should be taken into account when the results in the phases with high autocorrelation. Second, the two participants with a stroke were relatively young and three participants had high education levels. As a result, these findings might not translate to older stroke patients or patients with a lower education level. Third, the treatment adherence rating was not done completely independently, which is recommended (71). Although the treatment adherence rate was calculated by the researcher, the checklists were filled in by the psychologists. Furthermore, the treatment adherence rate of the treatment delivered to participant 1, is quite low with 60%, while the minimum is an 80% compliance with the rating protocol (71). The patient experienced the treatment as cognitively challenging and in agreement with the researcher it was decided to decrease the number of exercises and metaphors discussed in the sessions. Fourth, from these results, no conclusions can be made as to whether ACT is more effective for patients with stroke or TBI, which was also not within the scope of this study. However, it seems that levels and aetiology of depression generally do not differ between stroke or TBI patients (73), nor does their coping style (74). Levels of anxiety can be higher for patients with a stroke, since they can experience fear of stroke recurrence (75, 76). Further research should focus on possible differences in the effectiveness of ACT for patients with different types of ABI.

### Conclusion

In conclusion, this study adds to the existing knowledge that ACT is likely helpful in treating psychological distress following ABI and that the BrainACT intervention can decrease anxiety and depressive complaints in individuals with ABI. Larger randomized controlled trials or replication with single case studies are needed to obtain additional evidence on the efficacy of ACT for individuals with ABI.



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## Supplementary material

**Table 1.** Reliable Change Index

	PP1	PP2	PP3	PP4
<b>HADS-D</b>				
Pre-baseline	7	9	9	5
Pre-treatment (RCI pre-baseline/pre-treatment)	6 (0.40)	11 (-0.80)	9 (0)	9 (-1.61)
During-treatment (RCI pre-treatment/During-treatment)	5 (0.40)	3 (3.21*)	8 (0.40)	6 (1.21)
Post-treatment (RCI pre-treatment/post-treatment)	2 (1.61)	7 (1.61)	5 (1.61)	3 (2.41*)
7 month FU (RCI pre-treatment/7FU)	1 (2.01*)	3 (3.22*)	11 (-0.80)	3 (2.41*)
12 months FU (RCI pre-treatment/12FU)	0 (2.41*)	3 (3.22*)	10 (-0.40)	0 (3.62*)
<b>HADS-A</b>				
Pre-baseline	10	3	6	7
Pre-treatment (RCI pre-baseline/pre-treatment)	10 (0)	16 (-5.66)	8 (-0.87)	8 (-0.43)
During-treatment (RCI pre-treatment/During-treatment)	10 (0)	6 (4.35*)	7 (0.44)	6 (0.87)
Post-treatment (RCI pre-treatment/post-treatment)	4 (2.61*)	8 (3.48*)	3 (2.17*)	5 (1.31)
7 month FU (RCI pre-treatment/7FU)	2 (3.48*)	4 (5.22*)	7 (0.43)	5 (1.31)
12 months FU (RCI pre-treatment/12FU)	0 (4.35*)	6 (4.35*)	10 (-0.87)	5 (1.31)
<b>DASS-21 depression</b>				
Pre-baseline	3	7	4	2
Pre-treatment (RCI pre-baseline/pre-treatment)	4 (-0.44)	7 (0)	7 (-1.33)	2 (0)
During-treatment (RCI pre-treatment/During-treatment)	1 (1.33)	7 (0)	3 (1.77)	2 (0)
Post-treatment (RCI pre-treatment/post-treatment)	1 (1.33)	3 (1.77)	0 (3.10*)	0 (0.89)
7 month FU (RCI pre-treatment/7FU)	1 (1.33)	2 (2.22*)	8 (-0.44)	1 (0.44)
12 months FU (RCI pre-treatment/12FU)	0 (1.77)	4 (1.33)	6 (0.44)	1 (0.44)
<b>DASS-21 anxiety</b>				
Pre-baseline	5	4	6	0
Pre-treatment (RCI pre-baseline/pre-treatment)	3 (0.83)	8 (-1.66)	6 (0)	0 (0)
During-treatment (RCI pre-treatment/During-treatment)	5 (-0.83)	1 (2.90*)	1 (2.07*)	1 (-0.41)
Post-treatment (RCI pre-treatment/post-treatment)	1 (0.83)	0 (3.32*)	3 (1.23)	0 (0)
7 month FU (RCI pre-treatment/7FU)	0 (1.24)	3 (2.07*)	4 (0.83)	1 (-0.41)
12 months FU (RCI pre-treatment/12FU)	0 (1.24)	6 (0.83)	4 (0.83)	0 (0)
<b>DASS-21 stress</b>				
Pre-baseline	15	9	12	5
Pre-treatment (RCI pre-baseline/pre-treatment)	11 (1.65)	18 (-3.72)	11 (0.41)	6 (-0.41)
During-treatment (RCI pre-treatment/During-treatment)	12 (-0.41)	5 (5.37*)	9 (0.83)	6 (0)
Post-treatment (RCI pre-treatment/post-treatment)	5 (2.48*)	6 (4.96*)	6 (2.07*)	5 (0.41)
7 month FU (RCI pre-treatment/7FU)	3 (3.31*)	5 (5.37*)	8 (1.24)	4 (0.83)
12 months FU (RCI pre-treatment/12FU)	0 (4.54*)	4 (5.78*)	10 (0.41)	4 (0.83)
<b>AAQ-II</b>				
Pre-baseline	15	15	14	9
Pre-treatment (RCI pre-baseline/pre-treatment)	12 (0.66)	34 (-4.17)	11 (0.66)	11 (-0.44)
During-treatment (RCI pre-treatment/During-treatment)	15 (-0.66)	17 (3.73*)	12 (-0.22)	10 (0.22)
Post-treatment (RCI pre-treatment/post-treatment)	9 (0.66)	7 (5.93*)	9 (0.44)	9 (0.44)
7 month FU (RCI pre-treatment/7FU)	8 (0.88)	14 (4.39*)	16 (-1.09)	8 (0.66)
12 months FU (RCI pre-treatment/12FU)	8 (0.88)	11 (5.05*)	13 (-0.44)	7 (0.88)
<b>AAQ-ABI</b>				
Pre-baseline	12	7	8	9
Pre-treatment (RCI pre-baseline/pre-treatment)	7 (1.20)	27 (-4.80)	10 (-0.48)	9 (0)
During-treatment (RCI pre-treatment/During-treatment)	12 (-1.20)	10 (4.08*)	9 (0.24)	7 (0.48)
Post-treatment (RCI pre-treatment/post-treatment)	1 (1.44)	11 (3.84*)	7 (0.72)	5 (0.96)
7 month FU (RCI pre-treatment/7FU)	2 (1.20)	6 (5.04*)	-	3 (1.44)
12 months FU (RCI pre-treatment/12FU)	1 (1.44)	8 (4.56*)	12 (-0.48)	1 (1.92)

	PP1	PP2	PP3	PP4
<b>CFQ-7</b>				
Pre-baseline	33	35	24	17
Pre-treatment (RCI pre-baseline/pre-treatment)	19 (3.61*)	44 (-2.32)	36 (-3.10)	12 (1.28)
During-treatment (RCI pre-treatment/During-treatment)	23 (-1.03)	32 (3.10*)	33 (0.77)	11 (0.26)
Post-treatment (RCI pre-treatment/post-treatment)	10 (2.32*)	17 (6.97*)	14 (5.68*)	12 (0)
7 month FU (RCI pre-treatment/7FU)	7 (3.10*)	11 (8.51*)	26 (2.58*)	10 (0.52)
12 months FU (RCI pre-treatment/12FU)	10 (2.32*)	20 (6.19*)	24 (3.10*)	9 (0.77)
<b>VLQ composite score</b>				
Pre-baseline	-	53.50	-	56.80
Pre-treatment (RCI pre-baseline/pre-treatment)	45.20	52.00 (0.14)	47.40	61.90 (-0.49)
During-treatment (RCI pre-treatment/During-treatment)	55.90 (-1.02)	48.20 (0.36)	33.90 (1.29)	53.20 (0.83)
Post-treatment (RCI pre-treatment/post-treatment)	-	57.60 (-0.54)	35.80 (1.11)	58.90 (0.29)
7 month FU (RCI pre-treatment/7FU)	53.60 (-0.80)	59.20 (-0.69)	34.40 (1.25)	66.70 (-0.46)
12 months FU (RCI pre-treatment/12FU)	-	48.40 (0.38)	49.30 (-0.20)	56.20 (0.60)
<b>SF-12 Physical health summary scale</b>				
Pre-baseline	31.60	40.22	28.00	44.02
Pre-treatment (RCI pre-baseline/pre-treatment)	34.51 (-0.49)	43.50 (-0.56)	28.65 (-0.11)	49.10 (-0.86)
Post-treatment (RCI pre-treatment/post-treatment)	34.62 (-0.02)	53.16 (-1.64)	29.71 (-0.18)	44.20 (0.83)
7 month FU (RCI pre-treatment/7FU)	37.71 (-0.54)	48.16 (-0.79)	28.30 (0.06)	45.08 (0.68)
12 months FU (RCI pre-treatment/12FU)	45.51 (-1.87)	44.32 (-0.14)	25.22 (0.58)	48.89 (0.04)
<b>SF-12 Mental health summary scale</b>				
Pre-baseline	36.40	40.80	40.35	41.03
Pre-treatment (RCI pre-baseline/pre-treatment)	36.30 (0.02)	31.73 (1.38)	37.83 (0.38)	45.16 (-0.63)
Post-treatment (RCI pre-treatment/post-treatment)	62.72 (-4.03*)	38.59 (-1.05)	47.84 (-1.53)	57.29 (-1.85)
7 month FU (RCI pre-treatment/7FU)	65.21 (-4.41*)	55.90 (-3.68*)	45.08 (-1.10)	57.54 (-1.89)
12 months FU (RCI pre-treatment/12FU)	62.03 (-3.92*)	44.76 (-1.99*)	50.27 (-1.90)	56.63 (-1.75)
<b>USER-P frequency</b>				
Pre-baseline	38.93	39.29	18.93	42.50
Pre-treatment (RCI pre-baseline/pre-treatment)	29.64 (1.07)	50.36 (-1.27)	27.14 (-0.95)	40.36 (0.25)
Post-treatment (RCI pre-treatment/post-treatment)	33.57 (-1.62)	35.36 (6.20)	27.50 (-0.15)	31.79 (3.54)
7 month FU (RCI pre-treatment/7FU)	37.86 (-3.40*)	29.29 (8.71)	16.43 (4.43)	41.43 (-0.44)
12 months FU (RCI pre-treatment/12FU)	36.43 (-2.81*)	39.29 (4.57)	24.64 (1.03)	40.71 (-0.14)
<b>USER-P restriction</b>				
Pre-baseline	63.64	90.00	73.33	90.91
Pre-treatment (RCI pre-baseline/pre-treatment)	63.64 (0)	90.91 (-0.11)	70.00 (0.38)	87.88 (0.35)
Post-treatment (RCI pre-treatment/post-treatment)	66.67 (-0.35)	84.85 (0.70)	70.00 (0)	84.85 (0.35)
7 month FU (RCI pre-treatment/7FU)	63.64 (0)	86.67 (0.49)	60.00 (1.15)	87.88 (0)
12 months FU (RCI pre-treatment/12FU)	84.85 (-2.45*)	72.73 (2.10)	66.67 (0.38)	100.00 (-1.40)
<b>USER-P satisfaction</b>				
Pre-baseline	65.00	97.50	72.22	67.50
Pre-treatment (RCI pre-baseline/pre-treatment)	69.44 (-0.48)	82.50 (1.64)	58.33 (1.51)	67.50 (0)
Post-treatment (RCI pre-treatment/post-treatment)	78.13 (-0.95)	77.50 (0.55)	72.22 (-1.52)	72.50 (-0.55)
7 month FU (RCI pre-treatment/7FU)	80.56 (-1.21)	75.00 (0.82)	50.00 (0.91)	85.00 (-1.91)
12 months FU (RCI pre-treatment/12FU)	86.11 (-1.82)	80.00 (0.27)	63.89 (-0.61)	92.50 (-2.73*)

HADS, Hospital Anxiety and Depression Scale; DASS-21, Depression, Anxiety and Stress Scale-21; AAQ-II, Acceptance and Action Questionnaire II; AAQ-ABI, Acceptance and Action Questionnaire Acquired Brain Injury; VLQ, Valued Living Questionnaire; CFQ-7, Cognitive Fusion Questionnaire; USER-P, Utrecht Scale for Evaluation of Rehabilitation-Participation; SF-12, Short Form Survey.

Table includes raw scores with the RCI, Reliable Change Index between brackets

\* clinical significant change





## CHAPTER 6

The BrainACT study: Acceptance and Commitment Therapy for depressive and anxiety symptoms following acquired brain injury: study protocol for a randomized controlled trial

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*Trials, 2019*



## Abstract

*Background.* Following an acquired brain injury, individuals frequently experience anxiety and/or depressive symptoms. However, current treatments for these symptoms are not very effective. A promising treatment is acceptance and commitment therapy (ACT), which is a third wave behavioural therapy. The primary goal of this therapy is not to reduce symptoms, but to improve psychological flexibility and general well-being which may be accompanied by a reduction of symptom severity. The aim of this study is to investigate the effectiveness of an adapted ACT intervention (BrainACT) for people with acquired brain injury who experience anxiety and/or depressive symptoms.

*Methods.* The study is a multicentre randomized controlled two-armed parallel trial. In total, 94 patients who survived a stroke or traumatic brain injury will be randomized into an ACT- or control (i.e. psycho-education and relaxation) intervention. The primary outcome measures are the Hospital Anxiety and Depression Scale and the Depression Anxiety Stress Scale. Outcomes will be assessed, by trained assessors blinded to treatment condition, pre-treatment, during treatment, post-treatment, and at seven and twelve months.

*Discussion.* This study will contribute to the existing knowledge on how to treat psychological distress following acquired brain injury. If effective, BrainACT could be implemented in clinical practice and potentially help a large number of patients with acquired brain injury.

*Trial registration.* The study is registered in the Dutch Trial Register (Trial NL691, NTR 7111) on 26-03-2018, <https://www.trialregister.nl/trial/6916>.

## Introduction

Patients with acquired brain injury (ABI) have an increased risk of developing emotional disturbances (1). After surviving a stroke, a quarter of the patients experience depressive symptoms at six months post-stroke (2); almost half of the patients who experienced a traumatic brain injury (TBI) suffer from a major depressive disorder and 38% suffer from anxiety symptoms (3). Depression has significant effects on the health of patients with ABI. It leads to more hospitalizations, less societal participation, reduces the return-to-work rates, places a greater burden on caregivers, affects social relationships, and has a vast impact on general quality of life (4). Moreover, anxiety and depressive symptoms have a negative influence on patient rehabilitation (5) and they increase the severity and number of reported health problems such as fatigue, memory, headaches, and concentration problems (6, 7).

Despite their high prevalence and negative consequences with a significant burden of disease, it is still not clear how to best treat post-ABI depressive and anxiety symptoms. Psychopharmacological interventions show mixed results when treating depression in stroke survivors. Additionally, stroke patients seem sensitive to the side effects of psychopharmacological medication (8). Furthermore, antidepressants have not shown to be more beneficial than placebo when treating depression following TBI (9). Cognitive behavioural therapy is widely used for treating depression and anxiety, but there is no strong evidence for its post-stroke effectiveness (10, 11), research into its effectiveness following TBI is inconclusive (12-15).

A recent therapy which has been proven to be effective over a wide range of clinical populations is Acceptance and Commitment Therapy (ACT) (16-19). ACT is a third wave cognitive behavioural therapy which uses commitment and behaviour change strategies to increase psychological flexibility (20). Psychological flexibility is described as “the ability to contact the present moment more fully as a conscious human being, and to change or persist in behaviour when doing so serves valued ends” (21, p. 7). This results from a combination of the six core processes of ACT: acceptance (accepting positive and negative thoughts to situations one cannot change), defusion (disentanglement of thoughts), sense of self (separating the self from the process of thinking), mindfulness (contact with the present moment), valued living (being aware of what really matters), and committed action (taking action guided by one’s values) (21). Although symptom reduction is not the primary treatment goal, an increase in psychological flexibility is often accompanied by a decrease in symptomatology (22, 23). ACT is an interesting approach for people with ABI who suffer from psychological distress (24). Instead of applying cognitive restructuring techniques as used in traditional cognitive therapy, ACT focusses on learning to accept both the negative and positive thoughts and feelings related to those circumstances which cannot be changed or controlled (25). It enables the individual to carry out value-based behaviour while feeling distressed (25). Higher levels of acceptance and valued living have been associated with better psychological outcomes in patients with ABI (26-28).

Currently, there is some evidence that people who developed depressive or anxiety symptoms after ABI can benefit from ACT. Majumdar and Morris (29) performed a RCT in which an ACT group-intervention of four weekly didactic PowerPoint sessions was compared to treatment as usual in stroke survivors. They found that people in the ACT intervention showed a significant reduction in depression and increased

hopefulness and self-rated health. However, no differences were found related to anxiety or quality of life. Graham et al. (30) described a case study in which a stroke patient no longer experienced chest pain, showed a decrease in anxiety and depressive symptoms, and improved illness perception and psychological flexibility following an ACT intervention. Whiting et al. (31) performed a pilot RCT comparing an ACT group intervention with befriending therapy in patients with severe TBI. Their results show that ACT decreased the levels of anxiety and depression significantly compared to the befriending treatment. However, it could not be confirmed that the mechanism through which this decrease was elicited was psychological flexibility (31). These findings should, however, be considered in light of the small sample size of the study and the restricted sample characteristics.

These studies provide preliminary support for the hypothesis that ACT can be effective in treating psychological distress following ABI. With the current BrainACT study, we aim to investigate whether an ACT intervention, adapted for the needs and possible cognitive deficits of people with ABI, results in decreased anxiety and depressive symptoms compared to a control intervention. Furthermore, we will examine ACT related processes, quality of life, social participation, and the cost-effectiveness of both interventions.

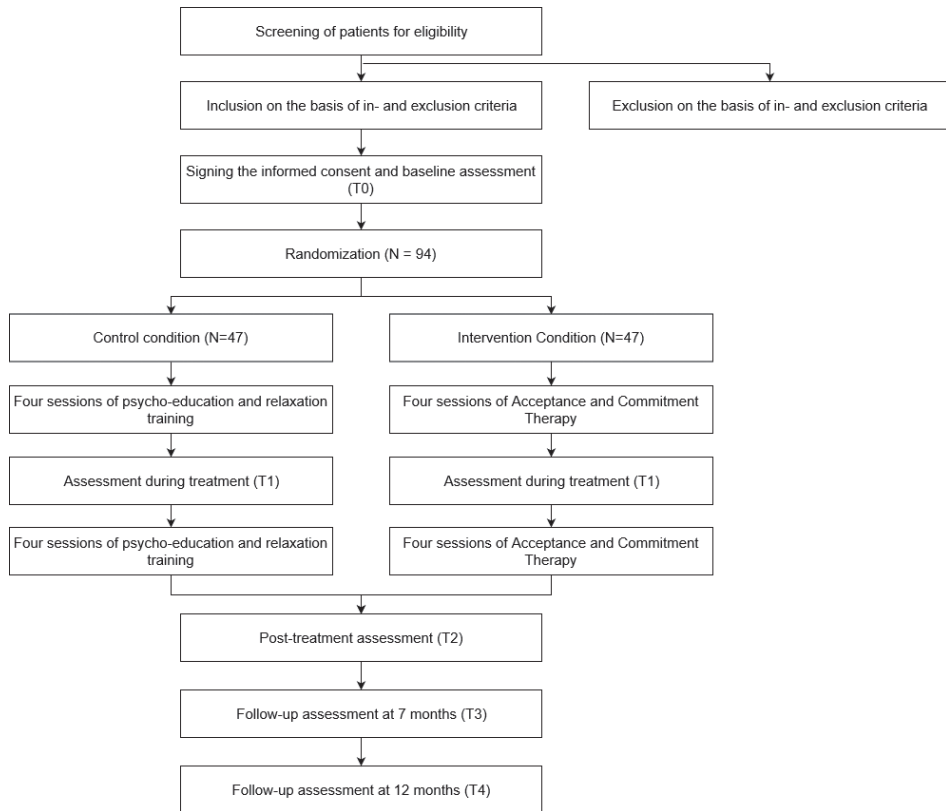
Research questions addressed in the study:

- 1) Does ACT lead to a greater reduction of depressive and anxiety symptoms in patients with ABI compared to an active control intervention (i.e. psycho-education and relaxation training)?
- 2) Is ACT more cost-effective in comparison to an active control intervention?
- 3) Is the (potential) reduction of anxiety and depressive symptoms mediated by an increase in psychological flexibility, acceptance, valued living, and/or cognitive defusion in the ACT group?
- 4) Does ACT lead to higher levels of participation and quality of life, compared to an active control condition?

## **Methods**

### **Study Design**

The design of the study is a multicentre randomized controlled two-armed parallel trial in which an 8-week ACT intervention will be compared to an active control intervention, namely psycho-education combined with relaxation training. Outcome measures will be collected at baseline (T0), after one month (T1; during treatment), and after three months (T2; post-treatment). At seven (T3) and twelve months (T4) there will be follow-up measurements. See figure 1 for the flow chart of the study. Ethics approval for the study has been given by the medical research ethics committee of Maastricht University Medical Centre and Maastricht University and the local committees of participating clinical centres. The study is registered in the Dutch Trial Register (TC: 7111).

**Figure 1.** Design of the study: multicentre randomized controlled two-armed parallel trial

## Participants

A total of 94 survivors of TBI or stroke will be recruited from rehabilitation or medical psychology departments at hospitals in the Netherlands. Patients who have been referred to a psychologist will be considered for participation. Possible participants will be screened and informed about the study by their psychologists for eligibility. Inclusion criteria are: (1) having sustained any type of stroke or TBI which is objectified by a neurologist; (2) scoring higher than seven on the depression and/or anxiety subscale of the Hospital Anxiety and Depression Scale (HADS); (3) being 18 years or older; (4) having a stable use of psychotropic medication (such as antidepressants) for the duration of the study and stable use of antidepressants during four weeks prior to the start of the study; (5) being able to access the internet and a computer because treatment materials such as patient videos are shown via the internet, (6) mastering the Dutch language sufficiently to benefit from treatment; and (7) giving informed consent. Exclusion criteria are: (1) history of brain injury or any neurological disorder other than a stroke and TBI; (2) pre-morbid disability as assessed with the Barthel Index (score < 19/20); (3) severe co-morbidity, for which treatment is given at the moment of inclusion, that might affect the outcome; (4) presence of a DSM 5-based mood and/or anxiety disorder for which pharmacological

and/or psychological treatment was necessary during the onset of the brain injury; and (5) attendance in a previous ACT intervention for comparable problems in the year proceeding entry to the current study.

### **Randomization and blinding**

Participants who are eligible and agree to participate in the study are randomly assigned to either the intervention group or the control group with an allocation ratio of 1:1. The randomization will be performed centrally by an independent third person using computerized block randomization. The block size is six and the randomization scheme includes pre-stratification on location (hospital) and type of brain injury (TBI versus stroke). The randomization scheme has been developed with the use of a random generator ([www.random.org](http://www.random.org)). After randomization, an opaque, sealed envelope will be prepared containing information about the group allocation of the participant by the independent third person. After the first measuring moment (T0) the researcher will open the sealed envelope and reveal treatment allocation to the patient and psychologist.

The trained research assistants that administer the questionnaires will be blinded to treatment allocation (i.e. intervention or control) and should never be unblinded. Participants will be asked not to tell research assistants about the treatment they received. In order to check the success of blinding, at T4 the research assistants will be asked to indicate group allocation for all participants who completed the trial. The research assistants will choose one of the following options: 'Intervention group', 'Control group', or 'I don't know'. Participants will not be blinded. Data analyses will be done by the principal investigator (JR) who will be blinded while performing the analyses.

### **Primary outcome measures**

*Psychological distress.* The subscales of the HADS will be used to measure anxiety and depressive symptoms over the past seven days. The scores for the scales, 7-items each, range from 0 to 21 with higher scores indicating higher levels of depression or anxiety. This questionnaire has been validated in a TBI sample (32). Furthermore, a good internal consistency for both subscales (Cronbach's  $\alpha$  depression scale: 0.81; anxiety scale: 0.84) was found in a stroke population (33). The Depression Anxiety Stress Scales-21 (DASS-21) will be used to measure the levels of anxiety, depression, and stress of the participants. It consists of 21 items which are rated on a 4-point Likert-scale. The score ranges from 0 to 63 with higher scores indicating greater levels of depression, anxiety, or stress. The questionnaire has been validated in a TBI sample. The internal consistency was good for the three scales (Cronbach's  $\alpha$  depression scale = 0.90; stress scale 0.89; and anxiety scale 0.82) (34). The primary outcome is the change in mood and anxiety symptoms between groups over all time points, as measured by the total scores of the respective subscales of the HADS and DASS-21.

*Cost-effectiveness.* Two questionnaires will be used to measure cost-effectiveness: the 5 level EQ-5D (EQ-5D-5L) and a 16-item cost-questionnaire. The EQ-5D-5L consists of five questions measuring health status. The dimensions covered are mobility, self-care, daily activities (such as work, housework, study, and leisure activities), pain or discomfort, and anxiety or depression. These domains are rated as 'no problem',

'slight problem', 'moderate problem', 'severe problem', or 'unable to do'. Consequently, the EQ-5D-5L can distinguish between different health states. For each of the different states a weight is contributed based on the valuation given by the general population (35). The healthcare costs of participants will be measured with a self-report cost-questionnaire which is constructed to collect cost data from a societal perspective, based on the steps described by Thorn et al. (36). The cost-questionnaire used in this study is based on a questionnaire used in the study of Kootker et al. (11). Several questions are altered based on response patterns and analyses in this prior study. The primary cost-effectiveness outcome is the change in the amount of care used between groups over all time points, as measured by the total scores of the cost-questionnaire and the EQ-5D-5L.

### Secondary outcome measures

*Participation.* The Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P) will be used to measure three aspects of participation: frequency of behaviours, experienced participation restrictions due to health condition, and satisfaction with participation. The frequency scale measures the objective level of participation, while the restrictions and satisfaction scales offer an insight into the subjective rating of participation. The questionnaire consists of 31 items. For each scale a score ranging from 0 till 100 is calculated. Higher scores indicate more participation, less restriction, and more satisfaction. It is a valid and reliable measure for patients with ABI; the internal consistency was good (Cronbach's  $\alpha = 0.70-0.91$ ) (37).

*Health status.* The Short Form Survey (SF-12) will be used to measure the health status of the participants. The total score ranges from 0 till 100 and a higher score indicates a better health status. The SF-12 has been validated for use in TBI research (38). Secondary outcome is the change in participation and health status between groups over all time point, as measured by the total scores of the respective subscales of the USER-P and SF-12.

### Secondary process measures

*Psychological flexibility.* The Acceptance and Action Questionnaire II (AAQ-II) is a seven-item questionnaire measuring psychological flexibility. The items are scored on a 7-point Likert scale and the total score ranges from 0 to 49 with a higher score indicating more psychological flexibility. The internal consistency of the AAQ-II is good (Cronbach's  $\alpha = 0.84$ ) (39). Furthermore, the questionnaire has been validated in an ABI sample (40). The Acceptance and Action Questionnaire Acquired Brain Injury (AAQ-ABI) measures psychological flexibility about the thoughts and feelings related to the brain injury, while the AAQ-II measures psychological flexibility around general psychological distress. The AAQ-ABI consists of seven items which are scored on a 5-point Likert scale. The score ranges from 0 to 36 with higher scores in indicating greater psychological flexibility. The questionnaire has a good internal consistency (Cronbach's  $\alpha = 0.89$ ) (40).

*Valued living.* The Valued Living Questionnaire (VLQ) is a two-part instrument which measures valued living. First, the participant rates the importance of ten value domains on a 10-point Likert scale. Second,

participants rate how consistently he or she has lived in accordance with their values within these domains. Scores from both parts are used to calculate a valued living component. The internal consistency of the valued living component was adequate (Cronbach's  $\alpha = 0.74$ ) (41). The VLQ has been used in earlier research to measure valued living in TBI patients (27).

*Cognitive fusion.* The Cognitive Fusion Questionnaire (CFQ-7) measures cognitive fusion on a 7-point Likert scale. Scores range from 0 to 49. The higher the score, the more fused one is with one's thoughts. Earlier research has shown that the CFQ has good factor structure, validity, reliability, and stability over time (42). The questionnaire has been validated in healthy and medical populations (42, 43). Secondary process outcome is the change in psychological flexibility, valued living, and cognitive fusion between groups over all time point, as measured by the total scores of the respective subscales of the AAQ-II, AAQ-ABI, VLQ, and CFQ-7.

### **Personal and brain-injury related characteristics and feasibility**



When the study commences participants will fill out a demographic questionnaire. This questionnaire will register age, gender, employment, and education. Injury related factors will be obtained from the medical files of the participants. These include type of brain injury, time since brain injury, severity of injury, and affected hemisphere. After ending the treatment, the participant's opinion and satisfaction on the ACT therapy (treatment feasibility) will be questioned by means of a short semi-structured interview.

### **Procedure**

Participants will be recruited at participating hospitals and rehabilitation centers in the Netherlands. To prevent unnecessary burden, the psychologists will check the in- and exclusion criteria. If the patient is willing to participate the investigator will meet (at the home of the patient, the hospital, or the university as is preferred by the patient) with the patient to discuss the participation in the study and answer questions. If all is clear the informed consent will be signed by the patient and the researcher (see additional file 2). Subsequently, the first measuring moment will take place (T0) and the participant will be randomly allocated to the experimental group receiving ACT or to the active control group receiving psycho-education. The therapy session will be scheduled with the psychologist or healthcare professional. One month after the start of the intervention both groups will fill in the questionnaires for T1 (see table 1). Questionnaires will be filled in on paper and measuring moment will be done by a research assistant blinded to allocation. After three, when the treatment program is completed, the participants will fill in the questionnaires for T2. At seven (T3) and twelve months (T4) there will be follow-up measurements. Again these measurements will be conducted by a research assistant blinded to allocation. Data entry will be done by research assistants and will be periodically checked during the monitoring visits. Follow-up appointments will be planned at the end of each visit. One week before the appointment the participant will be reminded of the appointment by the research assistant through telephone or e-mail. During the assessments, the researcher and research assistants will be alert for any adverse events such as suicidality. All adverse events related to mood

complaints reported spontaneously by the subject or observed will be systematically collected and reported to the medical research ethics committee. Based upon these events it can be decided to discontinue participation in the study. Furthermore, participants can leave the study without any consequences at any time for any reason if they wish to do so. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

**Table 1.** SPIRIT diagram

Time Point	Study Period					
	Enrolment	Assessments				
	-1 week	T0	T1	T2	T3	T4
<b>Enrolment</b>						
Eligibility screening	X					
Informed consent		X				
Allocation		X				
<b>Interventions</b>						
ACT intervention						
Control intervention						
<b>Assessments</b>						
Demographic and Injury characteristics		X				
Treatment feasibility*				X		
Primary Outcome measures HADS, DASS-21		X	X	X	X	X
Primary cost-effectiveness measures EQ-5D-5L, Cost-questionnaire		X		X	X	X
Secondary outcome measures USER-P, SF-12		X		X	X	X
Secondary process measures AAQ-II, AAQ-ABI, VLQ, CFQ-7		X	X	X	X	X

ACT, Acceptance and Commitment Therapy; HADS, Hospital Anxiety and Depression Scale; DASS-21, Depression, Anxiety and Stress Scale-21; EQ-5D-5L, 5 level EQ-5D; USER-P, Utrecht Scale for Evaluation of Rehabilitation-Participation; SF-12, Short Form Survey; AAQ-II, Acceptance and Action Questionnaire II; AAQ-ABI, Acceptance and Action Questionnaire Acquired Brain Injury; VLQ, Valued Living Questionnaire; CFQ-7, Cognitive Fusion Questionnaire.

\* Only administered in the ACT group

## Interventions

*The BrainACT intervention.* The ACT intervention involves eight weekly individual sessions of 60 minutes during a period of three and a half months. The first four sessions are weekly, thereafter the sessions will be biweekly, with a three-week break between the seventh session and last session. Participants will do homework exercises of around 30 minutes for six days a week. Homework consists of reading or listening to summaries of the sessions, practising skills, and doing mindfulness exercises. At the start of the intervention, participants will receive a workbook with instructions that they can read at home after each session. We use an eight-session protocol (see Table 2) based on Jansen and Batink (44), Luoma et al. (45), and Whiting et al. (31) in which all six ACT core processes are addressed. Psychologists are free to decide on the order of the sessions. We altered the treatment for people with ABI as suggested by Kangas and McDonald (24) and Broomfield et al. (46). An expert



group of psychologists experienced with ACT and/or in working with people with ABI gave further advice on the alterations. The possible cognitive deficits of the participants are taken into account and brain injury related topics are discussed during the treatment. A treatment protocol is specified to ensure comparability of the ACT intervention across settings. The intervention will be provided individually by certified psychologists who completed an ACT training course of at least five days and are experienced in working with patients with ABI. The therapy will take place at the outpatient facilities of hospitals.

**Table 2.** Overview of the BrainACT treatment program

Topic	Content
Values	Value exploration and difference between goals and actions.
Committed action and Mindfulness	Committed action on the long and short term in relation to values, education about mindfulness, and practising contact with the present moment.
Effect of control	Creative hopelessness; the undeniability of human suffering and the consequences on the long term of trying to control it.
Acceptance	Introducing acceptance as an alternative to control.
Defusion	Changing the relationship with thoughts, naming the mind.
Self-as-context	Changing the relationship with thoughts about oneself and introducing the constant self.
Defusion and Mindfulness	Review and exercises on defusion and mindfulness.
Psychological flexibility	Review of the different core components, explanation on how these skills together lead to psychological flexibility, and preparation on relapse and setbacks.

*Active control intervention.* The control condition (see Table 3 for an overview) consists of an eight-session psycho-education intervention combined with relaxation training with a duration of one hour. A Cochrane review concluded that active information provision is able to reduce depression and anxiety after brain injury (47). Furthermore, earlier research has shown that relaxation exercises reduce post-stroke anxiety (48). The psycho-education is based on the existing module ‘Niet rennen maar plannen’ (don’t run, plan) (49), which is a training and education program focusing on cognitive rehabilitation for patients with brain damage and mild cognitive problems. The intervention aims to offer information and education about brain injury and its consequences. Relaxation exercises consist of progressive muscle relaxation (50) and autogenic training (51). Participants will do homework exercises of around 30 minutes for six days a week. A treatment protocol is specified to ensure comparability of the education intervention across settings. This intervention will be provided individually by a health care professional with experience in working with brain injury patients (e.g. psychologist, social worker, occupational therapist, psychological assistant, but not the psychologist providing the ACT intervention) at outpatient facilities of hospitals.

**Table 3.** Overview of the psycho-education and relaxation treatment program

Session number	Content
1	Psycho-education on the basic functions of the brain and causes of brain injury.
2	Psycho-education on relaxation training and a progressive muscle relaxation exercise.
3	Psycho-education on the consequences of brain injury and a progressive muscle relaxation exercise.
4	Psycho-education on changes in behaviour and mood following brain injury and an autogenic training exercise.
5	Psycho-education on fatigue following brain injury and an autogenic training exercise.
6	Psycho-education on memory problems following brain injury. Participants can choose between autogenic training or a progressive muscle relaxation exercise. This technique will also be used in the following sessions.
7	Psycho-education on information processing and planning and an autogenic training exercise or a progressive muscle relaxation exercise.
8	Review of the different sessions, wrap up and an autogenic training exercise or a progressive muscle relaxation exercise.

**Adherence.** To ensure adherence to the intervention protocol, all therapists (of the intervention and control condition) will be trained by the principal investigator (JR). Furthermore, to examine the adherence during the different sessions, therapists have to fill in a checklist after every session. They tick off which exercises were done according to the treatment protocol and which exercises were added or left out.

### Sample size calculation

The sample size calculation was performed with G\*Power based on a repeated measures design. With a large effect size of 0.4, alpha value of 0.05, power value of 0.80, two groups (intervention and control), and five measurements, at least 80 participants are required. With an expected drop-out rate of 15%, 94 participants need to be recruited.

### Statistical analysis

The statistical analysis can be divided into four parts. First, the baseline characteristics will be described. Second, between-group differences at baseline will be analysed using chi-square tests and independent-sample t-tests to verify the success of randomization. Furthermore, groups will be compared on primary outcome measures at T2 using chi-square tests and independent-sample t-tests. Linear mixed models for repeated measures will be used to study the differences between groups with the primary and secondary outcome measures as dependent variables. Models will include main effects of the intervention (ACT or psycho-education) and time (T0, T1, T2, T3, and T4) as categorical variables and the interaction effect of intervention and time. Baseline-adjusted mean differences between groups at each time point with 95% confidence intervals will be presented. The effects of the intervention will be analysed according to the intention-to-treat principle. Alpha will be set at 0.05. All quantitative analyses will be conducted using SPSS software version 25 (52). Third, the clinically significant change will be determined on the primary outcome measures (53) to gain insight into a clinical improvement on an individual level. The first step is to identify

patients who 'recovered' by using the cut-off scores of the primary outcome measures (HADS and DASS-21). The second step is to calculate the Reliable Change Index which identifies the patients with a significant improvement. Patients who both recovered and showed a significant improvement will be considered clinically significantly improved. The amount of clinically significantly improved patients will be compared between interventions. Fourth, the trial-based economic evaluation will involve a combination of a cost-effectiveness analysis and a cost-utility analysis.

### **Ethical considerations and dissemination**

Data will be handled confidentially and reporting will be coded. Each participant is given a personal code which is only convertible to a person when the coding key is known. Collected data and personal information will be stored separately. The coded dataset will be available to the research team, health care inspectorate, study monitors, and members of the medical research ethics committee. The handling of personal data will comply with the General Data Protection Rule and the Research Data Management Code of Conduct of Maastricht University. Data will be used for future studies if the patient agreed upon this in the informed consent form. Data and material will be stored for 15 years on a repository of Maastricht University and can be made available to researchers upon request.

Participants will be compensated for any harm or injury due to participation in the study. The sponsor/investigator has a liability insurance which is in accordance with article 7 of the Medical Research Involving Human Subjects Act. All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. If further treatment for mood complaints is indicated after termination of the intervention this will be arranged within the healthcare system. Adverse events will not be reported in the publication unless an adverse event occurs often and will, therefore, lead to a bias.

Ethics approval for the study has been given by the medical research ethics committee of Maastricht University Medical Centre and Maastricht University (committee's reference number: NL65349.068.18). Any protocol modifications will be communicated to the ethics committee. The study will be monitored by the Clinical Trial Centre Maastricht. In every site, there will be a site initiation visit, two monitoring visits, and a close-out visit. The monitoring will be independently performed from investigators and the sponsor.

In accordance with the Central Committee on Research Involving Human Subjects statement on publication policy, the researchers aim to publish the results of the study (positive or negative) in international, peer-reviewed journals. Furthermore, results will be presented at professional conferences and provided to study participants upon request.

SPRIT checklist for this trial can be found here: <https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3952-9#Sec27>.

## Discussion

Currently, there are no evidence-based treatment options for people with ABI who experience psychological distress. To our knowledge, no large RCTs have been conducted investigating the effectiveness of ACT for anxiety and depressive symptoms following TBI or stroke. However, earlier studies have shown promising results (29-31). The aim of the proposed study is to investigate the clinical and cost-effectiveness of an upcoming cognitive-behavioural therapy, ACT, for anxiety and depressive symptoms following ABI.

We have taken into account recommendations made by Ost (18), to enhance the quality of studies in the field of ACT, such as having an active control intervention, timing of follow-up measurements, and choice of outcome measures. As described earlier, the aim of ACT is to change the functions and context of behaviour and thoughts; symptom reduction is not a treatment outcome (21). However, the primary outcome measures in this study are the HADS and DASS-21 (measures of anxiety and depression). We have chosen these outcome measures for several reasons. First, a reduction in symptomatology (such as a decrease in psychological distress) is still regarded as a beneficial treatment outcome in ACT next to an increase in psychological flexibility. Second, when psychological flexibility increases, a decrease is often observed in psychological distress (22, 23). We expect that a decrease in anxiety and depression is elicited through an increase in psychological flexibility. Psychological flexibility is measured with the secondary process outcomes. Lastly, choosing the HADS and DASS-21 as primary outcome measures will aid comparability with studies outside the field of ACT.

This study has several strengths. First, it has a relatively large sample size. Second, the study has a long follow-up period. Third, the ACT intervention will be compared to an active control intervention which was revealed to have positive effects on anxiety and depressive symptoms following brain injury. Fourth, the ACT treatment protocol was adapted to the needs and possible cognitive deficits of patients with brain injury. These adaptations were based on suggestions made in previous literature and knowledge gained in clinical practice. Fifth, the effectiveness of the ACT intervention will be investigated in a quantitative as well as qualitative manner.

This study also has certain limitations. First, its clinical nature prevents blinding of the participants and the therapists. However, the assessments will be performed by research assistants unaware of group allocation. Second, participant recruitment and loss to follow-up are known to be problematic in studies with patients with ABI. To aid study adherence research assistants will be trained and the outcome assessments will take place at the participants' home, the University, or the hospital, as preferred by the participant.

The results of this study, notwithstanding, should contribute to the limited knowledge on how to treat psychological distress following ABI. If effective, the BrainACT intervention can be implemented in clinical practice. Given the high prevalence of anxiety and depressive symptoms, it has the potential to help a large number of patients with ABI.

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## CHAPTER 7

Acceptance and Commitment Therapy is feasible for people with acquired brain injury: a process evaluation of the BrainACT treatment

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*Submitted*





# CHAPTER 8

General discussion

The prevalence of anxiety and depressive symptoms following acquired brain injury (ABI) is high. Previous research has concluded that there is a need to optimize treatment strategies for people experiencing these symptoms. The aim of this thesis was to improve the treatment for people with ABI-related anxiety and depressive symptoms. First, we developed a clinical prediction tool for people with post-stroke depressive symptoms. Additionally, we developed the BrainACT intervention; Acceptance and Commitment Therapy (ACT) adapted to the needs and possible cognitive deficits of people with ABI. Last, we investigated the feasibility and effectiveness of BrainACT for anxiety and depressive symptoms in people with ABI.

### **Main findings reported in this thesis**

**Chapter 2** describes the results of a study in which we developed a prognostic index for patients with post-stroke depressive symptoms. This was done for two outcome domains: post-stroke depressive symptoms and experienced restrictions regarding participation, using data from a randomized controlled trial (RCT) investigating cognitive behavioural therapy (CBT) and computerized cognitive training (CCT) for post-stroke depression. The results showed that many variables predict the outcome of post-stroke depressive symptoms, including characteristics of the stroke, the patients, and their spouses. Fewer variables predicted the outcome related to participation. The personalized predictions (prognostic index scores) of treatment outcome show promising results, which, after further replication and validation, could aid clinicians with treatment selection.

In order to validly measure the effect of ACT for people with ABI, **chapter 3** shows the results of a validation study investigating the psychometric properties of the Dutch versions of the Acceptance and Action Questionnaire for Acquired Brain Injury (AAQ-ABI; measuring psychological flexibility related to thoughts and feelings about ABI) and the Cognitive Fusion Questionnaire (CFQ-7; measuring cognitive defusion). It was concluded that these measures have acceptable to good psychometric properties when measuring psychological flexibility and cognitive defusion in Dutch individuals with ABI. In **chapter 4**, the rationale and description of the BrainACT treatment are presented. The BrainACT treatment is an ACT intervention adapted to the possible cognitive deficits and needs of people with ABI. General alterations are the use of visual materials, summaries, and repetition. ACT-specific adaptations include the Bus of Life metaphor as a recurrent exercise, shorter mindfulness exercises, a focus on experiential exercises, and the monitoring of committed actions. The intervention consists of eight one-hour face-to-face sessions. The order of the sessions, metaphors, and exercises can be tailored to the needs of the patients. In **chapter 5** the effectiveness of the BrainACT treatment was investigated in four people with ABI using a single case experimental design (SCED). Three out of four patients showed a significant decrease in anxiety and depressive symptoms. In addition, clinically significant improvements were observed regarding cognitive fusion, quality of life, and stress. No improvements were observed regarding psychological flexibility, value-driven behaviour, and social participation. In **chapter 6** the protocol of the BrainACT RCT is described. This study is a multicentre, randomized, controlled, two-arm parallel trial. People who survived a stroke or traumatic brain injury (TBI) are randomized into an ACT or control (i.e. psycho-education and relaxation)

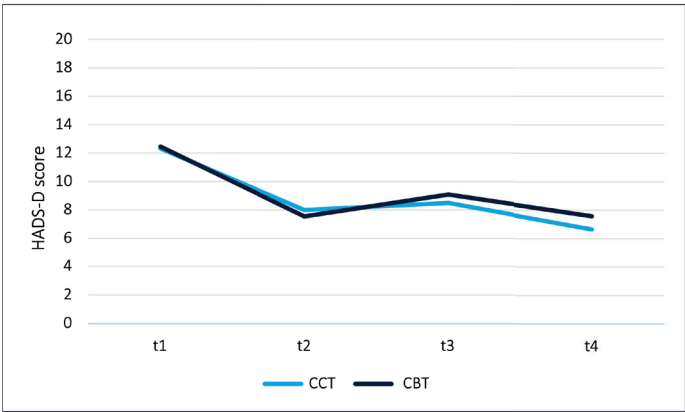
intervention. The primary outcome measures are the Hospital Anxiety and Depression Scale (HADS) and the Depression Anxiety Stress Scale (DASS-21). Secondary outcomes are psychological flexibility, valued living, cognitive defusion, social participation, and quality of life. Outcomes are assessed pre-treatment, during treatment, post-treatment, and at 7 and 12 months. In **chapter 7** the results of a process evaluation of the BrainACT treatment are presented. The BrainACT treatment was found to be feasible. The attendance rates were high and the compliance rate was relatively high. Participants and therapists rated the intervention positively, were satisfied, and identified several facilitators (such as the structured and experiential nature of the intervention). A clear barrier identified by the therapists was that the content of the sessions was too extensive. Adding two extra sessions was therefore recommended. The follow-up measurements of the BrainACT RCT are currently being conducted and will be finalized by the end of 2022. Results on the effectiveness of the BrainACT treatment as investigated by the BrainACT RCT are therefore not presented in this thesis.

## **Optimizing the treatment of depressive symptoms following acquired brain injury**

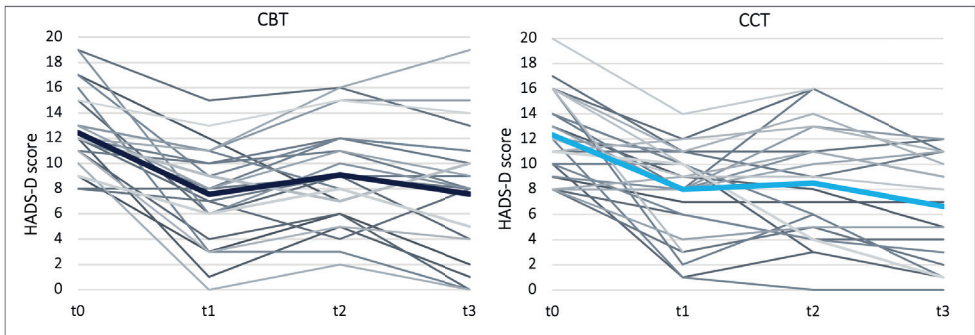
### *Predicting psychotherapy outcome*

Previous reviews have indicated that the effectiveness of psychotherapy for people experiencing depressive symptoms following an ABI is unclear (1, 2). Is it possible to gain additional insights from these trials that have already been conducted? In chapter 2 we re-analysed the data of a RCT comparing CCT with CBT in a group of patients with stroke and depressive symptoms (3). No significant group differences were found on the main outcome measure, the depression scale of the HADS, at any of the measurement moments. The average scores can be seen in figure 1. However, after adding the individual scores to the graph, as in figure 2, a different picture emerges. The variability between the participants becomes apparent. Some participants profited from the treatment, while others did not. A recent article by Kaiser et al. (4) found that there is indeed heterogeneity in the treatment response in people who receive psychotherapy. A group average does not tell clinicians what to do with the patient that sits in front of them, as the ‘average patient’ does not exist (5). Hence, the use of personalized treatment approaches might help to improve treatment response.

**Figure 1.** Results of the RCT investigating CBT for post-stroke depressive symptoms, adapted from Kootker et al. (3)



**Figure 2.** The individual scores in the CBT and CCT groups



For that reason, we developed a clinical prediction model for depressive symptoms and experienced restrictions regarding participation for people with post-stroke depression. The goal of personalized medicine and prediction models is to find the best fit between a patient and a certain treatment (6). Both the clinical prediction model for depression and the model for participation explained around 50% of the variance in the data. It raised the question which additional variables could influence the treatment outcome and therefore could be included in future studies as predictors. In people with depressive symptoms without ABI, no biomarkers have been found to be related to treatment response or dropout (7, 8). The predictive value of biomarkers in people with ABI might be higher. Biological mechanisms are likely to contribute to the development of depressive symptoms post-ABI. Previous studies identified biomarkers related to oxidative stress, lipids, and inflammation, which are predictive for the development of post-stroke depressive symptoms (9-11). Other variables which might influence the outcome of psychotherapy for people with ABI are deficits in self-awareness and cognitive functioning such as memory, attention, and executive difficulties. These factors are experienced as challenging by therapists when providing psychotherapy to people with ABI (12).

Moreover, next to predicting the treatment outcome related to depression and participation, future studies could consider additional outcomes as well. Even though a reduction in depressive symptoms can be an indication of a successful treatment, it is not the whole picture (13). Not all patients who improved according to a self-report depression questionnaire also experience this improvement following psychotherapy (13, 14). For instance, patients describe a ‘good outcome’ as feeling empowered and finding balance when experiencing personal struggles (13). Solely focussing on remission based on depressive symptoms does not reflect the multidimensional nature of depression and the experience of patients receiving psychotherapy. Hence, clinical prediction models should be developed related to other outcomes as well. These could include quality of life or the feeling of purpose and empowerment, which would align with the idea of positive health (15). Taking the personalized medicine approach even a step further, the meaning of a successful outcome differs between patients (13). For some, it would mean a reduction in complaints while for others it would mean an increase in valued activities. It would be interesting to investigate if it is possible to match different primary outcomes to different patients. Moreover, when providing third-wave behavioural therapy such as ACT, outcomes such as mindfulness, psychological flexibility, and value-driven behaviour could be considered. These measures, however, also have some disadvantages as will be discussed later.

In people with depression but without ABI, clinical prediction models are in a further developmental phase as more studies have been performed (16). Nonetheless, they have not reached a stage in which they can be implemented in clinical practice yet, since these models need further validation. The use of prediction models for people with ABI is even further away. As we found that ABI-related variables, such as lesion location, have a predictive value, models developed with data from people without ABI will likely not be readily applicable for people with ABI. Therefore, it is important to further develop and validate these models specifically for people with ABI.

### *Randomized controlled trials in psychotherapy research*

RCTs are often considered the gold standard in investigating the effectiveness of psychotherapies or any other intervention (17). They are used to study the cause-effect relationship between a treatment and outcome (18). Next to comparing the average effects of different treatment outcomes, process measures can be used to study the mechanisms by which the outcome is reached (i.e. moderating and mediating effects). For instance, by including process measures in the BrainACT RCT, namely cognitive defusion, value-based behaviour, and psychological flexibility, it can be investigated if these changed as hypothesized.

Nevertheless, RCTs also have some disadvantages. They are costly and time-consuming (19). Furthermore, the recruitment of people with ABI is challenging and many RCTs in the field have small sample sizes (20-22). Consequently, it is interesting to explore additional study designs as they have some substantive advantages. SCED designs can form a viable alternative or addition to psychotherapy research. Single case research is increasingly included in evidence standards by, for instance, the American Psychological Association (23, 24). An obvious advantage of SCED studies is that no large sample sizes are needed. Hence, they are less time-consuming and easier to implement in clinical practice. SCEDs can



bridge the gap between research and everyday clinical practice and fit with the idea of evidence-based clinical-practice (25). In addition, insights into how and why individuals change during the treatment can be evaluated in a more detailed manner. A result of repeated assessing outcomes over multiple experimental phases is that individual change patterns in the data can be investigated as well as the temporal relation with mediators (26, 27). Lastly, due to the rapidly developing statistical techniques, such as meta-analytic procedures, results can be generalized to specific populations (28).

As RCTs and SCED studies have different properties and strengths they can complement each other. This is demonstrated in the BrainACT studies in this thesis. The SCED study in chapter 5 was used as an initial exploration on the effectiveness and feasibility of the BrainACT treatment, before testing it in a larger sample. Next to a SCED design, qualitative studies can provide valuable insights into psychological mechanisms related to the effect of psychotherapy, which cannot be fully captured in questionnaires. In addition, qualitative studies can help to unravel how psychotherapies aid people in the adaptation process following ABI. Next to studying effectiveness, it is important to also study the feasibility, implementation, and delivery of the intervention by means of a process evaluation as this will help to interpret the results on effectiveness (29). Utilizing different types of research designs can complement each other in order to better understand how and why people with ABI benefit from psychotherapy (17).

### **Acceptance and Commitment Therapy for people with acquired brain injury**

In the studies in chapters 3 to 7, the effect of ACT in people with ABI was investigated, adaptations of ACT for cognitive impairments were investigated, and the effectiveness and feasibility of ACT for people with ABI were assessed. Both anxiety and depressive symptoms were considered since these often co-occur in people with ABI (30) and because ACT is a transdiagnostic treatment (31).

#### *Measuring the outcome of ACT*

In the BrainACT RCT the primary outcome measures are anxiety and depressive symptoms. When looking at the psychological flexibility model, a decrease in mood symptoms is expected despite it not being the main treatment aim (it is however viewed as a beneficial treatment outcome) (32). The control strategies people use to decrease thoughts, feelings, and sensations, such as avoidance or numbing, often cause suffering. If people accept their thoughts, feelings, and sensations instead of trying to control them, one would expect that suffering would become less and that mood symptoms would decrease as a result. Also, an increase in psychological flexibility is often related to a decrease in mood symptoms (33, 34). This corresponds with the results of chapter 5, where (clinically) significant improvements were found on repeated measures of anxiety and depression, the HADS (35), and DASS-21 (36) following the BrainACT intervention. Furthermore, Whiting et al. (37), Sander et al. (38), and Majumdar and Morris (39) found significant improvements in mood symptoms in people with ABI in the ACT condition compared to the control condition. Using the HADS and DASS-21 as primary outcome measures aids comparability with other studies investigating interventions for anxiety and depressive complaints following ABI.

Next to measuring outcomes related to symptom reduction, it is important to measure outcomes related to the theoretical mechanisms of change. Consequently, in the BrainACT studies, several ACT process measures are included, namely cognitive defusion, valued living, and psychological flexibility. In chapter 5 participants experienced a clinically significant increase in cognitive defusion. However, not all process outcomes measured change.

*Valued living.* Surprisingly, we found no clinically significant changes regarding valued living (chapter 5), while the BrainACT treatment places extra emphasis on values and committed actions (chapter 3). Whiting et al. (37) also found no significant differences regarding value-directed behaviour in the ACT intervention compared to the control intervention. Additionally, a study researching an intervention developed to increase valued living following ABI, found no improvements regarding value-driven behaviour (40). The measure that was used in chapter 5 to measure value-driven behaviour is the Valued Living Questionnaire (VLQ). The VLQ consists of ten broad value domains which are not exhaustive and people might show more value-consistent behaviour related to different values which is then not reflected in the score on the questionnaire (41). Additionally, a recent study found that the VLQ is not suitable for people with ABI (42). People with ABI experienced confusion due to the phrasing and structure of the questions and made errors while rating the value-consistency of actions in the last week. This measure was also used in the study by Sathananthan et al. (40) and the authors reasoned that it likely explained the lack of improvement in valued living following their intervention targeting valued living. After the commencement of our RCT, a version of the VLQ adapted for people with cognitive deficits was developed and the use of this measure is recommended in future studies researching ACT for people with ABI (43). Furthermore, processes related to psychological flexibility will often be novel for people. For instance, people might believe they are living consistently with what is important to them prior to the start of an ACT intervention. However, during the value exploration, they might realize they have different values which are being neglected. Wilson et al. (41) suggested this might even lead to a decrease in scores on a value questionnaire without behaviour being altered. A decrease in scores on the VLQ was observed for three out of the four participants on the post-treatment measurement in chapter 5, albeit not clinically significant. At the follow-up measures, the scores did increase somewhat again, but only slightly. Moreover, measuring ACT processes can be an intervention in and of itself. One of the participants mentioned that the measuring moments of the RCT gave her increased insights (chapter 7):

“This also came back with the measuring moments; how have you acted on your values lately? That did make me aware again that I had to pay more attention to my husband, for example. That insight helped.”

As people in the control condition also complete ACT questionnaires this might reduce the effects in the RCT, but does not explain the lack of effects in the SCED study.

*Psychological flexibility.* The AAQ-ABI was included in the studies in this thesis as a measure of psychological inflexibility related to thoughts and feelings about ABI (44, 45). Population-specific outcomes can measure the change in how flexible patients can cope with the symptoms or complaints for which

they sought help. They, therefore, might outperform more generic measures of psychological flexibility regarding treatment sensitivity and incremental validity (46). In chapter 3 the psychometric properties of the AAQ-ABI and the CFQ-7, measuring cognitive defusion were investigated in Dutch individuals with ABI. For both measures, good psychometric properties were found. However, in chapter 5 no clinically significant differences were found on the AAQ-ABI or the original questionnaire, the AAQ-II. Likewise, Whiting et al. (37) found no significant improvements in the psychological flexibility on both the AAQ-II and the AAQ-ABI compared to the control intervention. This could be attributed to the small sample size in the study of people with severe TBI. A study with a larger sample size by Sander et al. (38) did find significant improvements on the AAQ-II compared to the control condition in people with TBI. Another possible explanation for these mixed findings might be found in the outcomes used to measure psychological flexibility processes. As discussed earlier in this thesis, the AAQ-II, the most used measure of psychological inflexibility, has been criticized for its validity, specifically the discriminant validity (33, 47). Given the concerns regarding the discriminant validity of the AAQ-II, the discriminant validity of the AAQ-ABI should be further investigated. This should be kept in mind when using the AAQ-ABI and the AAQ-II. The AAQ-ABI is currently the only available measure for psychological flexibility related to thoughts and feelings about ABI and can thus be considered the best option, although its limitations should be kept in mind.

### *Flexibility processes*

As ACT does improve psychological flexibility and valued living, as measured by the AAQ-II and VLQ in other populations, there could be additional explanations for the lack of effects in our and other studies regarding these processes. Perhaps, the possible cognitive deficits experienced by people with ABI play a role, such as deficits in cognitive flexibility (34, 48). Cognitive flexibility is a subcomponent of executive functioning and is defined as the ability to change behaviour in accordance with environmental change (49). This concept likely partly overlaps with psychological flexibility. Both are dynamic, related to behavioural change processes, and describe the interplay between behaviour (thoughts and actions) and the environmental context. However, the conceptualization of psychological flexibility is more comprehensive and includes the psychological processes of acceptance and self-as-context which cognitive flexibility does not (48). Cognitive and psychological flexibility stem from different conceptual backgrounds; cognitive flexibility originates from neuropsychology and psychological flexibility is most often studied in relation to ACT. Tyrberg et al. (50) performed a study on the intersection of these two fields. The authors studied the Wisconsin Card Sorting Test (a commonly used task of cognitive flexibility) using a behavioural analytic approach. During the task when cognitive flexibility was most needed (switches) the behaviour of participants was based on temporal and deictic framing, while this was less for coordination and spatial framing. It would be interesting to know whether the relational frames that are dominant in the behaviour of people with deficits in cognitive flexibility would differ. There is some evidence that cognitive and psychological flexibility are related. The study of Grant and Cassidy (51) found that self-report cognitive flexibility is related to psychological flexibility, but task-based cognitive flexibility is not. Following an ABI people often experience deficits in executive

functioning and cognitive flexibility (52). What this implies for improving psychological flexibility in people with impaired cognitive flexibility is unclear. People with deficits in cognitive flexibility might have difficulties adapting their behaviour based on contextual changes and their values, which therefore might explain the lack of improvements in psychological flexibility and value-driven behaviour. Given the impairments in cognitive flexibility in people with ABI, it is likely beneficial to pay increased attention to behavioural change strategies when providing ACT to this patient population. Moreover, while values and committed actions are introduced early on in the BrainACT treatment and receive attention in the following sessions, this might not be sufficient for everyone to elicit behavioural change.

### *Adapting ACT for people with ABI*

As is shown in the previous paragraph, the treatment of anxiety and depressive complaints following ABI is still complex. Many factors influence treatment response (chapter 2) and standard psychological interventions are not suitable for people with ABI. Psychotherapy needs alteration for possible cognitive deficits when provided to people with ABI. When adapting psychotherapeutic interventions several recourses can be consulted such as recommendations from the literature, clinical experience of therapists working with this population, and the patients themselves. Furthermore, it seems important to pilot the adapted psychotherapy and further adjust it based on feedback from patients and therapists. Some major changes were made to the BrainACT treatment based on the results of the pilot study (chapter 5), such as decreasing the amount of content and length of the sessions and offering the possibility to change the order of the sessions to the patients' needs (as described in chapter 4). The studies in this thesis illustrate that it is possible to adapt ACT for people with ABI. When providing ACT to this patient population, it seems essential to integrate concepts from contextual behavioural science and clinical neuropsychology. Therapists should therefore be knowledgeable on both the psychotherapeutic processes they are providing as well as the possible consequences of an ABI.

Moreover, the results in chapter 7 demonstrate that the BrainACT treatment was found feasible for people with ABI. Participants implemented the different ACT processes, with acceptance being an important outcome mentioned by participants, indicating that people with ABI were able to comprehend and utilize ACT skills. Key strengths of the BrainACT intervention are the experiential nature of the intervention, the simplified materials in the workbook and homework, and the structured nature of the protocol by means of the bus of life metaphor. It emphasizes the importance of repetition, structure, and a focus on behavioural activation strategies which confirms the recommendations made by previous articles (48, 53, 54). These recommendations could be considered when adapting interventions for people with ABI.

### *Psychological flexibility in rehabilitation*

Several reviews have pointed out that psychological flexibility has likely been studied before but under different names, such as ego resilience, executive control, response modulation, or self-regulation (33, 34).

Over the past years, rehabilitation programmes for people with ABI have increasingly been aimed at improving these concepts, which might be an explanation for the popularity of ACT for people with ABI. An example of a potential overlap between underlying concepts can be taken from the literature on post-traumatic growth, which describes that following a traumatic event, people can experience positive psychological growth (55). It is a concept that has been studied intensively in relation to ABI (56). Lyon et al. (57) found that following ABI people can experience positive changes related to acceptance, strengthened relations with others, and discovering a new meaning and perspective on life. These themes seem to overlap with several core components of the psychological flexibility model. Post-traumatic growth is related to value-directed living (58), which might indicate that when people experience post-traumatic growth, they have identified new values and live more in alignment with these values. Moreover, acceptance and resilience (a concept closely related to psychological flexibility) have been studied in people with ABI and are seen as important outcomes related to rehabilitation (59, 60). It seems that components of the psychological flexibility model have been part of rehabilitation following ABI for a longer period of time. The studies in this thesis stress that interventions targeting these processes can be beneficial to recovery after ABI.

### *Clinical recommendations*

Before implementing the BrainACT treatment in the clinic, the effectiveness should be confirmed by means of the BrainACT RCT. However, clinicians can use the BrainACT treatment protocol as described in chapter 4 to provide the treatment to patients with similar patient profiles as the three participants for whom the BrainACT treatment was found effective in chapter 5. The BrainACT treatment can then be adapted according to the recommendations in chapter 7. When the content of the sessions is too much for a patient, the BrainACT treatment can be provided in ten sessions instead of eight. Moreover, when face-to-face sessions are not possible, the BrainACT treatment can be provided through video-conferencing as this was found feasible in chapter 7. However, face-to-face is the preferred treatment format.

No clear clinical recommendations can yet be made on what the best timing of the BrainACT treatment following an ABI would be. During the span of our research, many clinicians have mentioned that ACT seems most appropriate for people in the more chronic phase following ABI when they might be struggling with acceptance. However, others have discussed to provide ACT as early as possible (as a preventative intervention) and that it is never too late to provide ACT (61). In chapter 2 we found that time since injury influenced the outcome of depressive symptoms following CBT or CCT. There was a greater reduction in depressive symptoms after the treatment if time since injury was longer. This effect was, however, very small.

## **Strengths and methodological considerations**

The studies in this thesis utilized a wide variety of designs, measurement techniques, and novel analysis techniques. A questionnaire measuring ACT processes was developed specifically for people with ABI and an ACT intervention was specifically developed for this patient population. Chapter 5 was the first study

utilizing a SCED design to investigate ACT (or psychotherapy) for people with ABI. The process evaluation in chapter 7 reveals a more qualitative perspective on the experience of the therapists and participants who, respectively, provided and received the BrainACT intervention. Finally, the results of the BrainACT RCT will provide information on the effectiveness on a group level, although the data will also be analysed from an individual perspective by calculating if participants surpassed the threshold of minimally important, reliable, or clinically significant change. Finally, a novel variable selection approach (i.e. elastic net regression) was used to develop a clinical prediction model.

Several methodological considerations have already been discussed above, such as the strengths and limitations of a RCT and the measurement of ACT processes. Furthermore, as can be seen in the patient characteristics of the sample included in the study in chapter 7, most participants acquired a stroke. Therefore the results of the feasibility study and the RCT might not be as generalizable for people with TBI as for people with a stroke. Nevertheless, it seems that levels and aetiology of depressive symptoms do not greatly vary between people with stroke or TBI (62), nor does their coping style (63). Levels of anxiety might be higher for patients with a stroke since they can experience fear of stroke recurrence (64, 65). Moreover, the participants included in the SCED study in chapter 5 were relatively young and three had a high education level. Looking at their case descriptions, the experienced consequences following ABI were not very severe. The results might therefore not generalize to older people with a lower education level and with more severe (cognitive) deficits. Additionally, previous studies have shown that psychotherapies can also elicit negative effects such as worsening of symptoms or the emergence of new symptoms (66) which often receive little attention in clinical trials. This also holds for the BrainACT RCT. While adverse events are registered, negative therapeutic effects are not. In the SCED study, these negative effects would have been noticed since the participants were closely monitored. To our knowledge, no studies have been performed on the negative side effects of ACT. Future studies should be attentive and register these effects.

## Future directions

The studies in this thesis give rise to several recommendations and leads for future studies.

### *Developing and validating clinical prediction models*

The first step towards a more personalized approach to the treatment of anxiety and depressive symptoms was made in chapter 2. Our developed prediction model could be replicated and externally validated. Most likely the BrainACT treatment will not be effective for all participants included in the BrainACT RCT. It would therefore be interesting to identify which patients benefited from the BrainACT and psycho-education and relaxation intervention by developing a clinical prediction model for both treatments and investigating which characteristics are related to these beneficial effects.

### *BrainACT for people with ABI, other populations, and in different formats*

The results in chapters 5 and 7 are promising and together with the existing data permit further investigation into the effectiveness of ACT for people with ABI. Future studies could investigate the effect of ACT from a qualitative perspective building upon the work of Large et al. (67), who examined the experiences of people with stroke following a group ACT intervention. Furthermore, theoretical and clinical processes underlying treatment effects should be investigated, utilizing moderation and mediation analyses. This could lead the way towards process-based therapy targeting these mediators and moderators (68).

After evaluation of the long-term effect of ACT for people with ABI, future studies could investigate the added effect of booster sessions and their usefulness for implementing ACT skills in daily life in the long term. Moreover, while the BrainACT treatment is specifically developed for people with ABI, it might also be of use for other populations with cognitive deficits, such as people with multiple sclerosis, mild cognitive impairment, or Parkinson's disease. The references to brain injury would have to be altered, but no major changes to the protocol would be necessary. Additionally, the studies in this thesis focus on people with an objectified ABI. However, clinicians from participating centres indicated that they often see patients with ABI which is not objectified, such as a mild TBI or concussion. Patients with mild TBI were excluded from participation in the BrainACT studies but there are indications that psychological flexibility plays a role in persistent post-concussion symptoms (69). Therefore, the potential of ACT for people with persistent post-concussion symptoms following mild TBI or a transient ischemic attack should be further investigated.

One of the outcomes of the process evaluation in chapter 7 was that the BrainACT treatment could be investigated for its effectiveness and feasibility as a group intervention. At Maastricht University Medical Centre, the first ACT group based on the BrainACT treatment was provided to people with ABI as a pilot. While not empirically investigated, the BrainACT treatment seemed appropriate to be provided in a group format and patients were satisfied with the intervention. Another format which could be considered is to provide the BrainACT treatment in a dyadic format. A study by Kraus et al. (70) found it beneficial when people with dementia followed a CBT intervention together with a caregiver. The caregivers could help patients learn and practice skills between sessions. This could be an interesting option for people with ABI and more severe cognitive deficits or for instance aphasia. Future research could investigate BrainACT in a dyadic format, especially since ACT seems to be helpful for caregivers of people with ABI as well (71).

### *Conceptualizing and measuring psychological flexibility*

The concept of psychological flexibility seems a vital process in relation to mental health and has a clear clinical implications (34). However, more research is needed on its conceptualization and assessment. Approaches and perspectives from neuropsychology could help in this regard. The association between cognitive and psychological flexibility could, for instance, be further investigated. Moreover, alternative manners of measuring psychological flexibility could be explored. Wolgast (47) mentioned that because psychological flexibility is a dynamic, context-dependent, and shifting psychological process, it might be

difficult to fully capture it in a static and global self-report measure. Therefore, measuring psychological flexibility through different outcome modalities, next to self-report measures, might increase our understanding of the construct. Malo et al. (72) propose to do this from a transdiagnostic perspective utilizing virtual reality and qualitative techniques. It would be interesting to investigate if it is possible to develop a behavioural measure of psychological flexibility. Additionally, the experience sampling method could be an interesting approach to studying psychological flexibility and related ACT processes in a real-world context, by investigating how these concepts are related to different contexts and mood states. Furthermore, in the SCED study in chapter 5, we measured anxiety and depressive symptoms repeatedly over time. It would be interesting to use a SCED design to investigate how ACT processes evolve and change during the BrainACT intervention. The temporal relation between mood and process measures could be studied, for instance, a decrease in experiential avoidance would be expected before a decrease in mood symptoms. The Brief Acceptance Measure, as used by Hulbert-Williams et al. (73), seems appropriate to assess the ACT processes repeatedly over time. This is a three-item measure of psychological flexibility related to the three pillars of ACT openness, awareness, and engagement. However, the psychometric properties of this measure should be further investigated.

### Concluding remarks

The puzzle of helping people with anxiety and depressive symptoms following ABI is far from solved. With this thesis, we hope to have added some pieces to the puzzle. By successfully developing a clinical prediction model, the first step towards a more personalized treatment approach for post-stroke depressive symptoms was made. Moreover, the studies in this thesis add to the existing knowledge that people with ABI can benefit from ACT. The BrainACT treatment is feasible for people with ABI and can improve anxiety and depressive complaints. These findings will be strengthened if the BrainACT treatment is found to be effective in the BrainACT RCT. The outcomes of this thesis are promising and we hope our studies will contribute to a further advancement in the treatment of anxiety and depressive symptoms in people with ABI.



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# ADDENDUM

## Summary

People with acquired brain injury (ABI) often experience anxiety and depressive symptoms. Previous studies have concluded that there is a need to optimize treatment strategies for people with ABI-related anxiety and depressive symptoms. The aim of this thesis therefore was to improve treatment for people experiencing anxiety and depressive symptoms following ABI. We first developed a clinical prediction tool for people with post-stroke depressive symptoms (i.e. whom to treat). Furthermore, the BrainACT intervention was developed; Acceptance and Commitment Therapy (ACT) adapted for the needs and possible cognitive deficits of people with ABI. We investigated the feasibility and effectiveness of BrainACT for anxiety and depressive symptoms post-ABI.

**Chapter 2** describes the results of the study in which we developed a prognostic index for patients with post-stroke depressive symptoms. This was done for two outcome domains: post-stroke depressive symptoms and experienced restrictions regarding participation, using the data of a randomized controlled trial (RCT) investigating cognitive behavioural therapy and computerized cognitive training for post-stroke depression. From 18 pre-treatment variables of patients and caregivers, predictors were selected using elastic net regression analyses. Based on this selection, prognostic index scores (i.e. predictions) for both outcome domains were computed for each individual patient. The depression model included all pre-treatment variables, explaining 44% of the variance. The strongest predictors were lesion location, employment status, participation, comorbidities, mobility, sex, and presence of pre-treatment depression. Six predictors of post-treatment participation were identified, explaining 51% of the variance: mobility, pre-treatment level of participation, age, satisfaction with participation, caregiver strain, and psychological distress of the spouse. The cross-validated prognostic index scores correlated highly with the actual outcome scores. From this study, it can be concluded that post-stroke depressive symptoms form a complex and multifactorial problem. Treatment outcome is influenced by the characteristics of the stroke, the patients, and their spouses. The results show that psychological distress is probably no obstacle when attempting to improve participation. The personalized predictions (prognostic index scores) of treatment outcome show promising results, which, after further replication and validation, could aid clinicians and patients with treatment selection.

Furthermore, in order to measure psychological flexibility related to thoughts and feelings about ABI, the Acceptance and Action Questionnaire for Acquired Brain Injury (AAQ-ABI) was developed. Population-specific outcomes can measure the change in how flexible patients can deal with the symptoms or complaints for which they sought help. They, therefore, might outperform more generic measures of psychological flexibility regarding treatment sensitivity and incremental validity. In **chapter 3** the results of a validation study investigating the psychometric properties of the Dutch versions of the AAQ-ABI (measuring psychological flexibility related to thoughts and feelings about ABI) and the Cognitive Fusion Questionnaire (CFQ-7; measuring cognitive defusion) are presented. Score distribution, reliability, and convergent validity of the AAQ-ABI and the CFQ-7 were examined in Dutch individuals with ABI. In total 73 patients with ABI were included. The AAQ-ABI showed good reliability and the CFQ-7 excellent reliability. Both did not show a floor or ceiling effect, nor a skewed distribution. There were strong to moderate correlations between the

questionnaires and measures of psychological flexibility, mood, quality of life, and value-driven behaviour. Inter-item total correlations indicate that the questions within each questionnaire measure the same construct. This study shows that the Dutch AAQ-ABI and CFQ-7 have acceptable to good psychometric properties when measuring psychological flexibility and cognitive defusion in patients with ABI.

**Chapter 4** describes the theoretical underpinning, development, and content of the BrainACT intervention. Existing ACT protocols were adapted for the needs and potential cognitive deficits of people with ABI. General alterations are the use of visual materials, summaries, and repetition. ACT-specific adaptations include the Bus of Life metaphor as a recurrent exercise, shorter mindfulness exercises, simplified explanations, a focus on experiential exercises, and the monitoring of committed actions. The intervention consists of eight one-hour face-to-face sessions provided by a psychologist who has experience with ACT and in working with people with ABI. The order of the sessions, metaphors, and exercises can be tailored to the needs of the patients. The BrainACT intervention is expected to be a feasible and effective intervention for people with anxiety or depressive symptoms following ABI.

To evaluate the effect of ACT for people with ABI, in **chapter 5** a non-concurrent multiple baseline design study across four cases is described. Participants were randomly assigned to a baseline period, followed by a treatment phase using the BrainACT protocol, and a follow-up phase. Anxiety and depressive symptoms were repeatedly measured. During six measurement moments over a year, participants filled in questionnaires measuring anxiety, depression, stress, participation, quality of life, and ACT-related processes. Randomization tests and NAP (non-overlap of all pairs) scores were used to calculate the level of change across phases. The clinically significant change as measured by the questionnaires was defined with the Reliable Change Index. Three out of four participants showed medium to large decreases in anxiety and depressive symptoms. Furthermore, participants showed improvements regarding stress, cognitive fusion, and quality of life. There were no improvements regarding psychological flexibility, value-driven behaviour, or social participation. It can be concluded that ACT is possibly an effective treatment option for people experiencing ABI-related anxiety and depression symptoms.

In **chapter 6** the protocol of the BrainACT RCT is described. The study is a multicentre, randomized, controlled, two-arm parallel trial. In total, 80 patients who survived an ABI will be randomized into the BrainACT or control (i.e. psycho-education and relaxation) intervention. BrainACT and the control intervention are offered by psychologists in Dutch hospitals and rehabilitation centres during regular care. Measurements are conducted by the researchers. The primary outcome measures are the Hospital Anxiety and Depression Scale and the Depression Anxiety Stress Scale. Secondary outcomes are psychological flexibility, valued living, cognitive defusion, social participation, and quality of life. Outcomes will be assessed by trained assessors, blinded to treatment condition, pre-treatment, during treatment, post-treatment, and at 7 and 12 months. At the moment (July 2022) the follow-up measurements of the RCT are being conducted. Data on the effectiveness of BrainACT are therefore not presented in this thesis.

The study described in **chapter 7** aimed to evaluate the feasibility of BrainACT for people with ABI. In addition, the feasibility of providing the BrainACT treatment through videoconferencing during COVID-19



lockdowns was investigated. Therefore, a process evaluation of the BrainACT treatment was conducted. The attendance and compliance rates, engagement with the protocol, satisfaction of participants and therapists, and perceived barriers and facilitators for delivery in clinical practice were investigated using therapy logs and semi-structured interviews with participants and therapists. Qualitative data were categorized based on content. Quantitative data were reported using descriptive statistics. Twenty-seven participants and 11 therapists participated in the study. We found high attendance rates and both participants and therapists were satisfied with the intervention. Moreover, participants were motivated and engaged in homework exercises. The compliance rate, however, was relatively low. After finishing the treatment, patients reported to still apply the ACT skills obtained during the BrainACT intervention. Key strengths are the structure provided with the Bus of Life metaphor, the experiential nature of the intervention, and the materials and homework exercises. Although participants and therapists often preferred face-to-face sessions, it is feasible to deliver ACT through video conferencing for people with ABI. In conclusion, the BrainACT treatment is a feasible intervention for people with anxiety and depressive symptoms following ABI. However, for patients for whom the content of the sessions is too extensive, it is recommended to add two extra sessions. In case the BrainACT treatment appears to be effective in the accompanying RCT, we recommend implementation in clinical practice.

**Chapter 8** describes the main findings of this thesis and provides a general discussion, including methodological considerations as well as implications for future research. The studies in this thesis demonstrated that ACT can be a suitable treatment option for people with ABI-related anxiety and depressive symptoms. These findings will be strengthened if the BrainACT treatment is found to be effective in the BrainACT RCT. By successfully developing a clinical prediction model, the first step towards a more personalized treatment approach for post-stroke depressive symptoms was taken. This can be further explored in future studies. The outcomes of this thesis are promising and we hope they will contribute to a further advancement in the treatment of anxiety and depressive symptoms in people with ABI.



## Nederlandse samenvatting (dutch summary)

Mensen met niet-aangeboren hersenletsel ervaren vaak stemmingsklachten, zoals angst- of depressieve gevoelens. We weten uit eerder onderzoek dat er behoefte is aan het verbeteren van de behandeling voor mensen met hersenletselgerelateerde angst- en depressieve symptomen. Het doel van het onderzoek in dit proefschrift was daarom het verbeteren van de behandeling voor mensen die angst- en depressieve symptomen ervaren na een hersenletsel. Op basis van een eerder uitgevoerde studie, ontwikkelden we een klinisch voorspellingsmodel voor mensen met depressieve symptomen na een beroerte. Dit zou kunnen helpen bij het koppelen van de juiste behandeling aan de juiste persoon. Vervolgens ontwikkelden we de BreinACT-behandeling op basis van *Acceptance and Commitment Therapy* (ACT). ACT is een psychologische behandeling met als belangrijkste behandeldoel het verhogen van psychologische flexibiliteit. Psychologische flexibiliteit, oftewel veerkracht, betekent dat je flexibel om kunt gaan met gedachten, gevoelens of lichamelijke gewaarwordingen, ook als ze moeilijk of pijnlijk zijn - en dat je tegelijkertijd keuzes kunt maken op basis van wat echt belangrijk voor je is (je waarden). We pasten de BreinACT-behandeling op zo'n manier aan dat het beter past bij de behoeften en veelvoorkomende problemen van mensen met een hersenletsel, zoals cognitieve klachten. We onderzochten of de BreinACT-behandeling een haalbare interventie is en of het angst- en depressieve symptomen na hersenletsel vermindert.

**Hoofdstuk 2** beschrijft de resultaten van een studie waarin we een prognostische index (klinisch voorspellingsinstrument) ontwikkelden voor patiënten met depressieve symptomen na een beroerte. Dit deden we voor twee uitkomst domeinen: depressieve symptomen na een beroerte en ervaren beperkingen met betrekking tot sociale participatie. We maakten gebruik van de gegevens van een gerandomiseerde gecontroleerde studie waarin cognitieve gedragstherapie en cognitieve training op de computer werden onderzocht als behandeling voor depressie na een beroerte. Uit 18 pre-behandelingsvariabelen van patiënten en partners werden voorspellers geselecteerd met behulp van een *elastic net regressie-analyse*. Op basis van deze selectie werden prognostische indexscores (voorspellingen) voor beide uitkomst domeinen berekend voor elke individuele patiënt. In het depressiemodel werden alle pre-behandelingsvariabelen geselecteerd en het model verklaarde 44% van de variantie. De sterkste voorspellers waren: locatie van de laesie, werkstatus, participatie, comorbiditeiten, mobiliteit, geslacht en het niveau van depressie voor de behandeling. Er werden zes voorspellers van participatie na de behandeling vastgesteld, die 51% van de variantie verklaarden: mobiliteit, niveau van participatie vóór de behandeling, leeftijd, tevredenheid met participatie, belasting en stemmingsklachten van de partner. De kruis-gevalideerde prognostische indexscores correleerden sterk met de werkelijke uitkomst scores. Uit deze studie kan worden geconcludeerd dat depressieve symptomen na een beroerte een complex en multifactorieel probleem vormen. Het resultaat van de behandeling wordt beïnvloed door de kenmerken van de beroerte, de patiënten en hun partners. De resultaten laten zien dat stemmingsklachten waarschijnlijk geen belemmering vormen bij pogingen om de participatie te verbeteren. De gepersonaliseerde voorspellingen (prognostische indexscores) van het behandelresultaat zijn veelbelovend en kunnen na verdere replicatie en validatie zowel clinicus als patiënten helpen bij de keuze voor de meest geschikte behandeling.

In **hoofdstuk 3** worden de resultaten gepresenteerd van een validatieonderzoek naar de psychometrische eigenschappen van twee Nederlandse vragenlijsten namelijk; de Acceptance and Action Questionnaire voor Niet-Aangeboren Hersenletsel (AAQ-NAH; deze meet psychologische flexibiliteit met betrekking tot gedachten en gevoelens over hersenletsel) en de Cognitive Fusion Questionnaire (CFQ-7; deze meet cognitieve defusie). Scoreverdeling, betrouwbaarheid en convergente validiteit van de AAQ-NAH en de CFQ-7 werden onderzocht bij Nederlandse personen met hersenletsel. In totaal werden 73 patiënten met hersenletsel geïnccludeerd. De AAQ-NAH toonde een goede betrouwbaarheid en de CFQ-7 een uitstekende betrouwbaarheid. Beide vertoonden geen bodem- of plafondeffect, noch een scheve verdeling. Er werden sterke tot matige correlaties tussen de vragenlijsten en maten van psychologische flexibiliteit, stemming, kwaliteit van leven en waardegericht gedrag gevonden. Inter-item totaalcorrelaties lieten zien dat de vragen binnen elke vragenlijst hetzelfde construct meten. Dit onderzoek laat zien dat de Nederlandse AAQ-NAH en CFQ-7 acceptabele tot goede psychometrische eigenschappen hebben bij het meten van psychologische flexibiliteit en cognitieve defusie bij patiënten met hersenletsel.

**Hoofdstuk 4** beschrijft de theoretische onderbouwing, de ontwikkeling en de inhoud van de BreinACT-interventie. Bestaande ACT-protocollen werden aangepast aan de behoeften en potentiële cognitieve problemen van mensen met een hersenletsel. Algemene aanpassingen zijn het gebruik van visuele materialen, samenvattingen en herhaling. ACT-specifieke aanpassingen omvatten de levensbusmetafoor als rode draad in de behandeling, kortere mindfulnessoefeningen, vereenvoudigde uitleg, een focus op ervaringsgerichte oefeningen en het monitoren van waardengerichte acties. De interventie bestaat uit acht face-to-face sessies van een uur met een psycholoog, ervaren in ACT en in het werken met mensen met een hersenletsel. De volgorde van de sessies, de metaforen en de oefeningen kunnen worden aangepast aan de behoeften van de patiënten. Verwacht wordt dat de BreinACT-interventie een haalbare en effectieve interventie is voor mensen met angst- en/of depressieve symptomen na een hersenletsel.

Om het effect van de BreinACT-interventie voor mensen met een hersenletsel te evalueren, wordt in **hoofdstuk 5** een studie beschreven met een non-concurrent multiple baseline design waar vier mensen met hersenletsel aan hebben deelgenomen. Participanten startten met een gerandomiseerde baselineperiode, die werd gevolgd door de BreinACT-behandeling en vervolgens een follow-upfase. Angst- en depressieve symptomen werden herhaaldelijk gemeten. Tijdens zes meetmomenten, gedurende het jaar dat de participanten deelnamen aan de studie, vulden ze vragenlijsten in die angst, depressie, stress, participatie, kwaliteit van leven en ACT-gerelateerde processen maten. Randomisatietests en NAP-scores (non-overlap of all pairs) werden gebruikt om het niveau van veranderingen over de fases heen te berekenen. Klinisch significante veranderingen werden berekend met de Reliable Change Index. Drie van de vier deelnemers vertoonden een gemiddelde tot grote afname van angst- en depressieve symptomen. Verder vertoonden de deelnemers verbeteringen met betrekking tot stress, cognitieve fusie en kwaliteit van leven. Er waren geen verbeteringen met betrekking tot psychologische flexibiliteit, waardengericht gedrag of sociale participatie. Geconcludeerd kan worden dat ACT mogelijk een effectieve behandeloptie is voor mensen met hersenletselgerelateerde angst- en depressiesymptomen.

In **hoofdstuk 6** wordt het protocol van de gerandomiseerde gecontroleerde studie naar de haalbaarheid en effectiviteit van BreinACT beschreven. De studie is een multicenter parallelle studie met twee groepen. In totaal worden 80 patiënten met hersenletsel gerandomiseerd in de BreinACT-behandeling of de controlebehandeling (een behandeling die bestaat uit psycho-educatie en relaxatietraining). De BreinACT- en controlebehandeling worden aangeboden door psychologen in Nederlandse ziekenhuizen en revalidatiecentra tijdens de reguliere zorg. Uitkomstmetingen worden uitgevoerd door de onderzoekers. De primaire uitkomstmaten zijn de *Hospital Anxiety and Depression Scale* en de *Depression Anxiety Stress Scale*. Secundaire uitkomsten zijn psychologische flexibiliteit, waardengericht leven, cognitieve defusie, sociale participatie en kwaliteit van leven. Uitkomsten zullen worden beoordeeld door getrainde beoordelaars die blind zijn voor de behandelconditie. Zij meten voor de behandeling, tijdens de behandeling, direct na de behandeling en 7 en 12 maanden na start van de studie. Op dit moment (juli 2022) worden de follow-up metingen van de RCT uitgevoerd. Gegevens over de effectiviteit van de BreinACT-behandeling worden daarom in dit proefschrift niet gepresenteerd.

Het doel van de in **hoofdstuk 7** beschreven studie was om de haalbaarheid van de BreinACT-behandeling voor mensen met hersenletsel te evalueren. Daarnaast werd de haalbaarheid onderzocht van het aanbieden van de BreinACT-behandeling via beeldbellen tijdens de COVID-19-lockdowns. Daarom werd er een procesevaluatie van de BreinACT-behandeling uitgevoerd. Aanwezigheid, therapietrouw, betrokkenheid bij het protocol, tevredenheid van deelnemers en therapeuten, en barrières en faciliterende factoren bij het implementeren van de behandeling in de klinische praktijk werden onderzocht met behulp van therapielogboeken en semigestructureerde interviews met deelnemers en therapeuten. Kwalitatieve gegevens werden gecategoriseerd op basis van inhoud. Kwantitatieve gegevens werden gerapporteerd met behulp van beschrijvende statistieken. Zevenentwintig deelnemers en 11 therapeuten namen deel aan het onderzoek. We vonden een hoge opkomst en zowel deelnemers als therapeuten waren tevreden over de interventie. Bovendien waren de deelnemers gemotiveerd en betrokken bij de huiswerkoefeningen. De therapietrouw was echter relatief laag. Na afloop van de behandeling gaven patiënten aan dat ze de ACT-vaardigheden die ze tijdens de interventie leerden nog steeds toepassen. Belangrijke sterke punten zijn de geboden structuur met de levensbusmetafoor, de ervaringsgerichte aard van de interventie en de materialen en huiswerkoefeningen. Hoewel deelnemers en therapeuten vaak de voorkeur gaven aan face-to-face sessies, is het voor mensen met hersenletsel haalbaar om ACT via beeldbellen aan te bieden. Concluderend is de BreinACT-behandeling een haalbare interventie voor mensen met angst- en depressieve symptomen na hersenletsel. Echter, voor patiënten voor wie de inhoud van de sessies te uitgebreid is, kunnen twee extra sessies worden toegevoegd. Indien de BreinACT-behandeling effectief blijkt te zijn in de BreinACT-RCT, bevelen wij implementatie in de klinische praktijk aan.

**Hoofdstuk 8** beschrijft de belangrijkste bevindingen van dit proefschrift en geeft een algemene discussie, inclusief methodologische overwegingen en implicaties voor toekomstig onderzoek. De studies in dit proefschrift toonden aan dat ACT een geschikte behandeloptie kan zijn voor mensen met hersenletselgerelateerde angst- en depressieve symptomen. Deze bevindingen zullen worden versterkt

als de BreinACT-behandeling effectief blijkt te zijn in de BreinACT-RCT. Door met succes een klinisch voorspellingsmodel te ontwikkelen is de eerste stap gezet naar een meer gepersonaliseerde behandelaanpak voor depressieve symptomen na een beroerte. Dit kan in toekomstige studies verder worden onderzocht. De resultaten van dit proefschrift zijn veelbelovend. We hopen dan ook dat ze zullen bijdragen aan een verdere vooruitgang in de behandeling van angst- en depressieve symptomen bij mensen met een hersenletsel.

## Impact paragraph

Acquired brain injury (ABI), such as stroke or traumatic brain injury due to a fall or accident, can lead to physical disabilities (e.g. problems with walking), persistent cognitive deficits (e.g. forgetfulness), behavioural dysregulations (e.g. impulsivity), and emotional consequences (e.g. depression and anxiety). People with ABI are at an increased risk of developing symptoms of depression and anxiety. These symptoms are related to decreased participation in society (dependency in daily life and lower return-to-work rates), higher re-hospitalization rates, and increased cognitive and physical impairments. Furthermore, anxiety and depressive symptoms following ABI are determined by many different factors related to the injury to the brain, but also to personal factors such as coping style and environmental factors such as social support. Therefore, the treatment of ABI-related anxiety and depressive symptoms is challenging. The effectiveness of psychological treatments for depression is less robust for patients with ABI than for patients with depression but without an ABI. For that reason, the studies in this thesis aimed to improve the treatment for people experiencing anxiety and depressive symptoms following ABI.

### *Main findings*

First, it was examined whether it was possible to predict the treatment outcome for individuals who survived a stroke and have received psychological treatment for depressive symptoms. A statistical model (clinical prediction model) was developed to predict the level of depressive symptoms and social participation for individual patients following the treatment. We found that characteristics of the stroke (e.g. location of the stroke in the brain), patients themselves (e.g. presence of depression before the stroke), and their caregivers (e.g. level of burden) were predictive of treatment outcome. Second, we investigated Acceptance and Commitment Therapy (ACT) as a possible treatment option for people with ABI-related anxiety and depressive symptoms. ACT is a psychological treatment which focuses on the acceptance of thoughts and feelings and on living according to your values. Such a treatment should lead to an increase in psychological flexibility, which is the main treatment goal of ACT and is described as “the ability to contact the present moment more fully as a conscious human being and to change, or persist in, behaviour when doing so serves valued ends”. In order to measure the effectiveness of ACT for people with ABI, we translated two questionnaires measuring ACT processes into Dutch. The questionnaires measure cognitive defusion (creating a distance from thoughts) and psychological flexibility related to thoughts and feelings about ABI. Subsequently, their performance was investigated which was found to be good. Furthermore, we developed an ACT intervention adapted for the needs and possible cognitive deficits (e.g. memory problems) of people with ABI: the BrainACT treatment. Existing ACT treatments were adapted based on suggestions made in previous studies, recommendations by clinicians, and feedback from patients and therapists who, respectively, received and provided the treatment during a pilot study. The BrainACT treatment is simple, structured, and includes many behavioural and experiential exercises. We found that the BrainACT treatment is feasible for people with ABI. Both participants and therapists were satisfied with the treatment.

Patients engaged with the protocol and even after the intervention patients reported to still apply the ACT skills obtained during therapy. Furthermore, we studied the effectiveness of the new BrainACT treatment in four individuals with brain injury and we found that the BrainACT treatment can reduce stress, anxiety and depressive symptoms and improve cognitive fusion and quality of life. No improvements were observed regarding psychological flexibility, value-driven behaviour, and social participation. We are performing a large-scale experiment in which we compare BrainACT to an education and relaxation treatment to further evaluate the effectiveness of ACT for people with ABI. The follow-up measurements are currently (July 2022) being conducted and will be finalized by the end of 2022. The results of the large-scale experiment are therefore not presented in this thesis.

### *Scientific and societal impact*

The studies described in this thesis have been published or submitted to international peer-reviewed scientific journals. Chapters 2, 3, 5, and 6 have been published open access which makes them freely available to researchers across the world. Chapters 4 and 7 will be made freely available once accepted for publication.

The statistical model to predict the level of depressive symptoms and social participation for individual patients could be further explored by **researchers** and the developed model could be validated using different data. When these clinical prediction models are ready for use in clinical practice, they can optimize the care for people with ABI-related anxiety and depressive complaints. The models can help **psychologists** decide which psychological treatment would be the best option for a particular patient. In current practice, the decision which treatment a patient will receive is mostly based on therapist and patient preferences. Consequently, patients may receive different treatments before the intended outcome is reached. The clinical prediction models might enable more patients to be provided with personalized treatment that could alleviate their depressive symptoms. As a result, treatment trajectories will become shorter, mental health care will become more efficient and cost-effective, and most importantly, it would improve the quality of life of **people with ABI** and ABI-related anxiety and depressive symptoms.

Additionally, the results of this study permit further investigation into the effectiveness of ACT for people with ABI. The detailed description of the BrainACT treatment described in chapter 4, can be used by other **researchers** to replicate and build upon the studies in this thesis. Moreover, a collaboration between the BrainACT Team and MindLink Psychology in Perth, Australia was started to evaluate the feasibility and effectiveness of the BrainACT treatment in a Western Australian context. Therefore, the BrainACT protocol will also become available in English for **researchers and clinicians**. Furthermore, researchers could use the BrainACT treatment protocol to investigate the effectiveness of ACT for **other patients** who might experience cognitive complaints, such as people with multiple sclerosis, Parkinson's disease, and mild cognitive impairment. Moreover, the adaptations that were made to adjust ACT for people with ABI could be used for further research to adjust other psychological interventions for this patient population as well.

During the span of our research, **clinicians** have repeatedly inquired about the availability of the BrainACT treatment. It shows the need for evidence-based psychological treatments adapted for people



with ABI. When the BrainACT treatment is found to be effective in the large-scale BrainACT study, it can be implemented in the clinical practice. The BrainACT treatment protocol will become freely available. At the moment clinicians can use the BrainACT treatment protocol as described in chapter 4 to provide the treatment to patients with the same patient profile as one of the three participants for which the BrainACT treatment was found effective in chapter 5. The BrainACT treatment can then be adapted according to the recommendations in chapter 7 and based on the severity of cognitive deficits of patients, as for instance objectified by a neuropsychological assessment. Furthermore, since the BrainACT treatment was found feasible to be delivered through a video-conferencing format, it can be provided to patients during a lockdown or when patients are not able to come to the hospital, rehabilitation, or mental health care facility.

Anxiety and depressive complaints are common in people with ABI; around 1 out of 3 people will experience them. The BrainACT treatment, therefore, has the potential to help a large number of **patients with ABI**.

Moreover, the Dutch questionnaires measuring cognitive defusion and psychological flexibility related to thoughts and feelings are made available and can already be used in future studies and clinical practice. These questionnaires can help **clinicians** to monitor patients with ABI during an ACT intervention and can help evaluate the treatment. Furthermore, they can give **patients** insight into their treatment process. Both questionnaires are available at [www.hersenletsellimburg.nl](http://www.hersenletsellimburg.nl).

As a result, the studies in this thesis provide **clinicians** with many materials ready to use in the clinical practise. This includes the BrainACT treatment protocol with the content of the sessions, homework and mindfulness exercises specially designed for patients with ABI. In addition, two Dutch questionnaires are available to be used in clinical and research settings. These products will hopefully be integrated into care for people with ABI and therefore will help people in the adaptation process following ABI.

### *Dissemination activities*

The results from the studies in this thesis have been and will be communicated in several ways. The results have been presented at national and international conferences, such as the Association for Contextual Behavioral Science (ACBS) Conference, the 6th Pacific Rim Conference, the ACT in Actie conference, the Conference in Neuropsychological Rehabilitation of the Special Interest Group of the WFNR, and at webinars of the Limburg Brain Injury Centre. Besides, we provided training for therapists who participate in the BrainACT study to familiarize them with the BrainACT treatment protocol. Participating sites and other people who have shown their interest in the BrainACT treatment were (and still are) kept informed on the development and results of the BrainACT studies through the BrainACT newsletters. The mailing list now includes 125 clinicians, researchers, and lay experts. Furthermore, webinars and masterclasses were organized for members of the Dutch ACBS chapter, the association for cognitive therapists, and participants of the ACT in Actie training. Moreover, findings were shared via online platforms such as LinkedIn, Twitter, and Facebook. Besides, results were shared and discussed with colleagues via research days and informal interactions. The results were shared with people with ABI and their partners, caregivers, and relatives at Brain cafes in Kerkrade and Sittard. Finally, a blog post on the meaning of health was written and shared on the

website of the Limburg Brain Injury Centre (<https://www.hersenletsellimburg.nl/ehl-blog-hersenkronkels/wanneer-ben-je-gezond>).

The results of the large-scale BrainACT study that we are currently conducting will be communicated via the same organizations and (social) media. The BrainACT treatment protocol will be made available for psychologists experienced in ACT and in working with people with ABI if the new treatment is found to be effective.

## Curriculum vitae

Johanne Rauwenhoff werd geboren op 28 november 1993 te Leicester, Groot-Brittannië. In 2011, behaalde ze haar diploma Algemeen Secundair Onderwijs binnen de studierichting Humane Wetenschappen aan het Heilig Graf College in Turnhout, België. Hierna ging zij een jaar studeren aan Elizabethtown College in de Verenigde Staten. In 2012 begon zij aan de studie Psychologie aan de Universiteit Leiden. Tijdens haar bachelor werd zij geselecteerd om deel te nemen aan het Honours Research Bachelor Project. Deze ervaring wakkerde haar interesse in het onderzoek aan. In 2015 verhuisde Johanne naar Maastricht voor de Research Master in Cognitive and Clinical Neuroscience. Naast het cursorisch onderwijs koos zij voor een combistage. Deze bestond uit een klinische stage bij de afdeling Medische Psychologie van het Zuyderland Medisch Centrum te Sittard/Geleen en een onderzoeksstage bij de Universiteit Maastricht. Johanne schreef haar master thesis over hoe angst en catastroferen over mentale activiteiten gerelateerd is aan vreesvermijdendgedrag. In 2017 studeerde Johanne af en begon aan haar promotietraject. Zij werd onderdeel van het Expertisecentrum Hersenletsel Limburg (EHL), waar zij onderzoek deed naar het behandelen van stemmingsklachten bij mensen met hersenletsel. Dit deed zij onder supervisie van haar promotieteam bestaande uit Prof. Dr. Caroline van Heugten, Prof. Dr. Frenk Peeters en Dr. Yvonne Bol. Johanne ontving de Van der Gaagbeurs van de Koninklijke Nederlandse Academie van Wetenschappen (KNAW) om onderzoek te doen bij het Ingham Institute for Applied Medical Research en MindLink Psychology in Australië. Dit werkbezoek ging helaas niet door vanwege de Covid-19 pandemie. In het laatste jaar van haar promotietraject werkte Johanne twee dagen in de week als basispsycholoog bij de Geestelijke Gezondheidszorg Eindhoven in de Kliniek Neuropsychiatrie. Momenteel werkt zij als postdoctoraal onderzoeker bij de afdeling Psychiatrie en Neuropsychologie aan de Universiteit Maastricht en bij het EHL.

## List of publications

Rauwenhoff J., Peeters F., Bol Y. & Van Heugten C. (2019). The BrainACT study: Acceptance and Commitment Therapy for depressive and anxiety symptoms following acquired brain injury: study protocol for a randomized controlled trial. *Trials*.

Rauwenhoff J., Bronswijk S., Peeters F., Bol Y., Geurts A. C. & Van Heugten C. (2020). Personalized predictions of treatment outcome in patients with post-stroke depressive symptoms. *Journal of Rehabilitation Medicine*.

Wijenberg M. \*, Rauwenhoff J. \*, Stapert S., Verbunt J. & Van Heugten C. (2021). Do fear and catastrophizing about mental activities relate to fear-avoidance behavior in a community sample? An experimental study. *Journal of Clinical Experimental Neuropsychology*.

\*Co-first authorship

Rauwenhoff J., Peeters F., Bol Y. & Van Heugten C. (2021). Measuring psychological flexibility and cognitive defusion in individuals with acquired brain injury. *Brain Injury*.

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Rauwenhoff J. \*, Bol Y. \*, Van Heugten C., Batink T., Geusgens C., Van den Hout A., Smits P., Verwegen C., Visser A. & Peeters F. (2022). Acceptance and Commitment Therapy for people with acquired brain injury: rationale and description of the BrainACT treatment. Under revision.

\*Co-first authorship

Rauwenhoff J., Peeters F., Bol Y. & Van Heugten C. (2022). Acceptance and Commitment Therapy is feasible for people with acquired brain injury: a process evaluation of the BrainACT treatment. Submitted for publication.

### **PhD defences at the school for mental health and neuroscience (MHeNs)**

Previous and upcoming PhD defences can be found at the website of MHeNs which can be reached through the following QR-code.



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