Timing of Aphasia Treatment in Stroke Patients

Early Interventions and Outcome

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Timing of Aphasia Treatment in Stroke Patients

Early Interventions and Outcome

Timing van taaltherapie voor afasie ten gevolge van een beroerte

Vroege interventies en uitkomsten

Proefschrift

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The time is now

You're my last breath,
you're a breath of fresh air to me
I am empty
So tell me you care for me

You're the first thing
And the last thing on my mind
In your arms I feel
Sunshine

Give up yourself unto the moment
The time is now
Give up yourself unto the moment
Let's make this moment last

(Moloko, 2000)

Voor jou, kleintje♥
Alles kan

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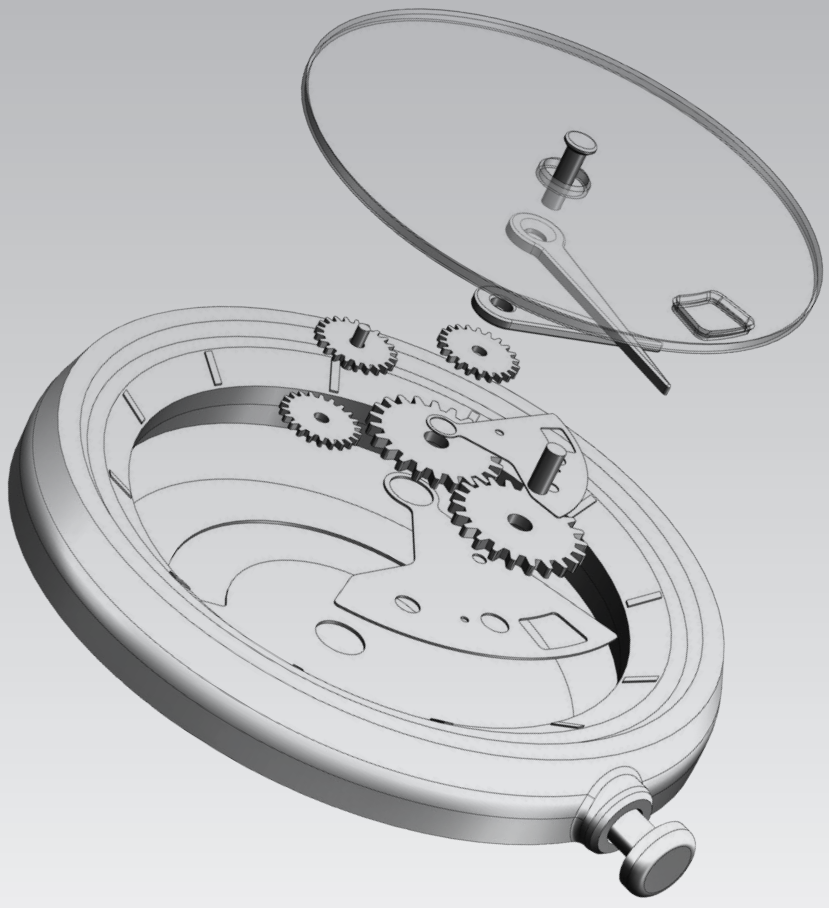

Chapter 1

General introduction

APHASIA

According to the World Heart Federation each year 15 million people suffer from a stroke.[1] One possible consequence of stroke is the acquired language deficit aphasia. Aphasia occurs in approximately 30% of stroke patients.[2] This amounts to 4.5 million new stroke patients with aphasia each year across the world.

The language system is predominantly located in the left hemisphere. Thus, aphasia is usually caused by a left hemisphere stroke, either hemorrhagic or ischaemic.[3] Aphasia may affect all language modalities, i.e. auditory comprehension, speaking, reading and writing.[4] Also, one or more linguistic components such as semantics (meaning), phonology (sound), syntax (grammar) and morphology (form) can be affected. All of these deficits influence language processing differently; hence aphasia can manifest itself in numerous different ways.

As aphasia affects language processing, it affects verbal communication. People with aphasia may find themselves not being able to participate adequately in conversations, and often they are incapable of understanding route directions, or unable to read a book. Aphasia has a large impact on daily life. Therefore, early recognition and diagnosis of aphasia in stroke patients is of importance both for prognostication and providing adequate treatment, aimed at improving patients' wellbeing and quality of life.

DIAGNOSIS OF APHASIA

Usually, in the acute stage after stroke patients are assessed by a neurologist or stroke physician for focal neurological deficits, including aphasia.[5, 6] Early after stroke it is often not feasible to diagnose individual aphasia characteristics in detail, as extensive examinations may be too burdensome for the often seriously ill patients. Furthermore, speech and language therapists (SL-therapists) are not always available for performing specific linguistic testing in this phase. Yet, timely evaluation of presence and severity of aphasia is crucial for adequate treatment, and by rapid recognition of language deficits medical staff is able to promptly adapt to the communication problems.[7] It has been shown that when adequate communication strategies are applied by medical staff, this may prevent patients from developing maladaptive strategies occurring in response to the language deficits.[8, 9] Early recognition of problems with language processing is also of importance to educate the social environment of the patient to avert communication distress.

Hence, it is crucial to have a brief and easy screening test for aphasia that may be administered by SL-therapists as well as other health professionals shortly after aphasia onset and is also appropriate for vulnerable stroke patients.[5, 6]

PROGNOSIS OF APHASIA

After a stroke, patients and their relatives are faced with uncertainties and patients may ask themselves whether they will be able to fulfil their professional and household tasks and social activities again. Consequently, providing patients with aphasia due to stroke and their proxies with a well-defined prognosis is of great importance.

However, prediction of functional outcome in patients with aphasia is complicated. Rehabilitation physicians and neurologists often use prognostic models, derived from data collected in large groups of patients to distinguish relevant factors in predicting recovery.[10, 11] To date, not all factors influencing recovery following a stroke are identified and new models are being composed. It is important that these models are adequate and valid, and generalize well to the patients with aphasia in order to optimize individual care.[12]

RECOVERY OF LANGUAGE

Spontaneous recovery

In the first period after stroke, aphasia is often fairly severe, due to direct damage to the neural networks dedicated to language, but also because of diaschisis; a state of global functional breakdown of widespread cortical networks involved in language processing, which are not directly damaged by the stroke.[13] Diaschisis can resolve relatively quickly, when perfusion is restored and edema is reduced. As a consequence, in the hours to days after stroke language recovery is capricious, and language function can be instable and change rapidly. A patient, who is unable to verbally communicate hours after stroke, may be talking fluently the next day.

After the acute stage, during which spontaneous recovery is mostly attributed to saving the perilesional region and resolution of diaschisis, spontaneous language recovery is still ongoing.[13, 14] It is unclear which exact mechanisms are at play during this stage of recovery, but at least it involves widespread neural networks.[13, 15] It has been speculated that speech and language therapy (SLT) may interfere with these processes.[13, 16-19] Hence, we need to understand the recovery mechanisms and the effect of SLT on these processes better, in order to generate maximal gains from SLT.

Treatment induced recovery

Most stroke patients with aphasia receive SLT. SLT is a diverse intervention, and comprises many components, e.g. type of treatment, treatment intensity, timing and duration of treatment.[4] Furthermore, specific therapeutic principles may be implemented, such as massed practice, a highly intensive and repetitive treatment regimen or errorless learning, by which only correct responses are enforced in order to reduce errors.[19]

SLT can be roughly divided into impairment-based treatment and communicative treatment. The first is focused on repairing language deficits, thus aimed at restoration of language function, while the latter focuses on regaining the capability to communicate in whatever way possible.[18, 20]

Impairment-based SLT is based on language processing models and may include specific exercises for the different language modalities; auditory or visual comprehension and oral or written production. Treatment may also target linguistic components, such as semantics, phonology or syntax; i.e. cognitive-linguistic treatment (CLT).[21, 22] In the Netherlands, two CLT therapy programs, BOX and FIKS, are applied frequently. Both programs aim to improve word finding deficits, a common problem in aphasia; BOX through semantic exercises and FIKS through phonological exercises.[23-25]

Communicative treatment is not based on language processing models or linguistic models, but on communication in its broadest form. The goal is to improve everyday communication by using residual verbal capacities and alternative ways of communication,

e.g. a communication aid or gestures. Consequently, this treatment approach is more directed at compensation, rather than restoration of premorbid language function. Well-known communicative treatment approaches are the Conversational Coaching[26] and the Promoting Aphasics' Communication Effectiveness (PACE)[27] method.

Hypotheses on the underlying processes explaining the effectiveness of these different treatment approaches are manifold. Some have argued that impairment-based treatment, including CLT, is to be preferred in the acute and post-acute stage, because the greatest benefits are achieved when recovery of language function occurs, due to plasticity of the brain.[18, 19, 28] Furthermore, it has been argued that this cognitive-linguistic approach alters neural processing, thus inducing permanent improvement.[29] Others claim that the focus of SLT should be on regaining the ability to communicate by stimulating communication in its broadest sense, because that is the main goal of language processing and prevents social isolation.[30] Hereby, new neural pathways may be created, dedicated to the new way of communicating.

EFFICACY OF SPEECH AND LANGUAGE THERAPY

Determining the efficacy of language treatment in aphasia due to stroke is substantial, as ineffective treatment programs or ineffective modes of delivery are a waste of time, patients' precious energy and costly resources. Obviously, when treatments have been proven efficacious, effectiveness research may be carried a step forward and results can be implemented, which may benefit many of the 4.5 million new stroke patients with aphasia each year worldwide.

The authors of the latest update of the Cochrane review on the efficacy of SLT for aphasia due to stroke conclude that SLT is more effective than no intervention, and that there are potential benefits of intensive treatment over regular therapy.[4] However, there were more dropouts, either from intervention or follow-up, in studies with high-intensity treatment, indicating that not all stroke patients with aphasia tolerate frequent treatment. Insufficient evidence was found to prefer one type of treatment over another or to recommend an optimal treatment regimen. Despite the authors acknowledging that aphasia research has improved since the first Cochrane review dated 1999 and that the evidence base for SLT is getting more solid, the optimal i.e. proven effective treatment approach is still not established.

Nowadays imaging techniques are used more and more to study whether specific types of treatment have an impact on neural processes, but results have been inconclusive.[29, 31]

Timing of treatment

An important, yet unanswered clinical question is whether there is an optimal time window after stroke in which treatment should be initiated.[32] In rehabilitation medicine early intensive treatment for motor deficits is often promoted with statements such as "Use it or lose it" and "The sooner, the better".[33] Some researchers and clinicians advocate starting impairment-based SLT for aphasia as soon as possible after stroke, to make use of the supposed hyperexcitable brain as a result of increased brain plasticity, while it may be better to wait until the brain has stabilized.[15, 19] Most clinicians agree that guidance and counseling by an SL-therapist aimed at prevention of communication distress are essential early after stroke, but they are also faced with very tired and ill patients who do not tolerate intensive

rehabilitation therapies.[34] As yet, there is little evidence supporting a relationship between timing of treatment and its efficacy.[35]

The Rotterdam Aphasia Therapy Studies (RATS)

Studying the efficacy of CLT has been the aim of the prior two Rotterdam Aphasia Therapy Studies.[20, 36] In RATS-1 the hypothesis was tested that semantic treatment is more effective for recovery of aphasia than phonological treatment, as it has long been assumed that semantic treatment is more effective than phonological treatment for restoring word finding, the most frequently occurring deficit in aphasia.[36] In RATS-1 we studied whether lexical semantic treatment with the Dutch treatment program BOX was more effective for recovery of aphasia than phonological treatment with the program FIKS, when initiated more than three months after stroke.[36] We found no difference in treatment effect on everyday verbal communication, measured with the Amsterdam-Nijmegen Everyday Language Test (ANELT)[37]. However, findings suggested a therapy specific treatment effect, as patients that were treated with semantic therapy improved more on semantic tests than the group that received phonological treatment, and patients receiving phonological treatment improved more on phonological tests than those in the semantic treatment group. This therapy specific treatment effect in both groups was correlated with improvement on the ANELT, ruling out the effect of spontaneous recovery.

Since most patients with aphasia have both a semantic and phonological deficit, we subsequently hypothesized that combining impairment-based lexical semantic and phonological treatment, i.e. CLT, would be profoundly effective in the sub-acute phase compared to other treatment approaches, also because of the supposed interaction of CLT with spontaneous neural recovery.[18]

These hypotheses were tested in RATS-2.[20] In this multicenter randomized controlled trial (RCT), patients received six months of either CLT or communicative treatment starting within three weeks of stroke onset. Communicative treatment was chosen as control condition, as this non-linguistically based method contrasts maximally with CLT. After six months there were no differences between groups with regard to everyday verbal communication as measured with the ANELT, refuting that CLT in the sub-acute phase would have a greater impact on aphasia recovery than communicative treatment. Yet, we did find differences in favor of CLT on linguistic tests, still suggesting that CLT may positively affect language recovery.

OUTLINE OF THIS THESIS

The aim of this thesis is to study various aspects of language rehabilitation in stroke patients with aphasia, with a major focus on the relationship between the timing of CLT and its efficacy. In this thesis three questions are addressed:

How accurately can we diagnose the presence of aphasia in the early stage after stroke onset?

In *Chapter 2*, a systematic review is presented aimed at identifying linguistic screening tools to detect aphasia early after admittance to hospital. Vital elements of adequate language screening tests are sensitivity, i.e. the ability to pick up language deficits; and specificity, i.e. the ability to distinguish language deficits from other deficits.[38] Several aspects of the

selected screening tools are addressed, together with a detailed appraisal of the tests, taking into account these vital elements.

Which factors are of importance for an accurate prediction of aphasia outcome in stroke?

The most common cause of aphasia is cerebral infarction, which may be treated with a form of endovascular intervention to improve perfusion to the affected brain area. This treatment affects the prognosis of recovery, because it is aimed at saving as much brain tissue as possible. In *Chapter 3.1*, we present the results from a post-hoc analysis of the MR CLEAN trial, a large phase III RCT evaluating the effectiveness of intra-arterial treatment with retrievable stents in ischemic stroke.[39] We selected all patients with aphasia from this trial and evaluated whether usual care plus endovascular treatment was more effective than usual care alone for the early recovery from aphasia in acute ischemic stroke. Furthermore, we evaluated whether the effect of endovascular treatment on early aphasia recovery differed from the effect on early recovery of motor function. In *Chapter 3.2* the external validity of a prognostic model for the outcome of aphasia, derived from an observational prospective study, is determined using data from another RCT: RATS-3. The original model consisted of a number of factors that can easily be recorded from newly admitted patients to the stroke ward. The discriminative power and calibration properties of the model are assessed to verify the validity of the model.

Is there a relationship between the timing of aphasia treatment and its efficacy?

In the narrative review in *Chapter 4.1* we discuss that there is little evidence for a relationship between the timing of SLT and its efficacy, as there are no RCT's directly comparing early initiated treatment to deferred treatment. Evidence from the field of animal studies and motor rehabilitation is explored to provide insights into a possible relationship between timing of treatment and its efficacy.

The design and methods of the third Rotterdam Aphasia Therapy Study, RATS-3, are introduced in *Chapter 4.2*. The results of this randomized controlled trial on the efficacy of early initiated CLT are presented and discussed in *Chapter 4.3*.

As initial aphasia severity is thought to be related to recovery potential, we compare recovery profiles according to three levels of baseline aphasia severity in *Chapter 4.4*. The impact of CLT and communicative treatment on the recovery of aphasia in these three severity groups are compared also.

The principal findings of the studies discussed in the chapters of this thesis, and their clinical implications, as well as directions for future research are discussed in *Chapter 5*. A summary of the main findings is provided in *Chapter 6*.

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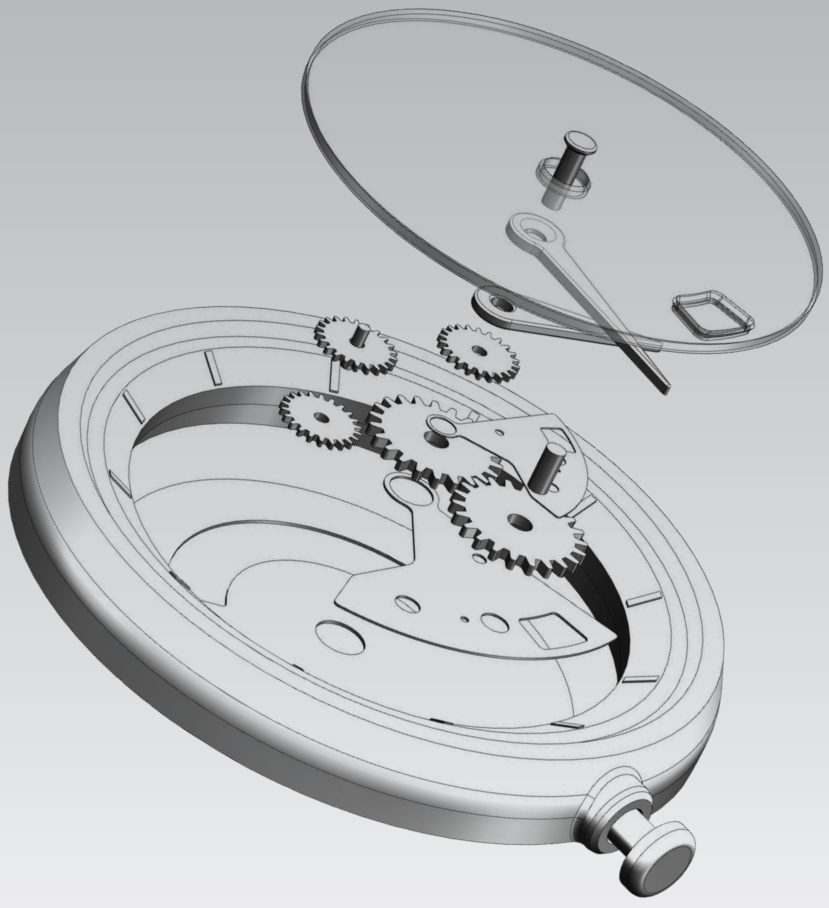
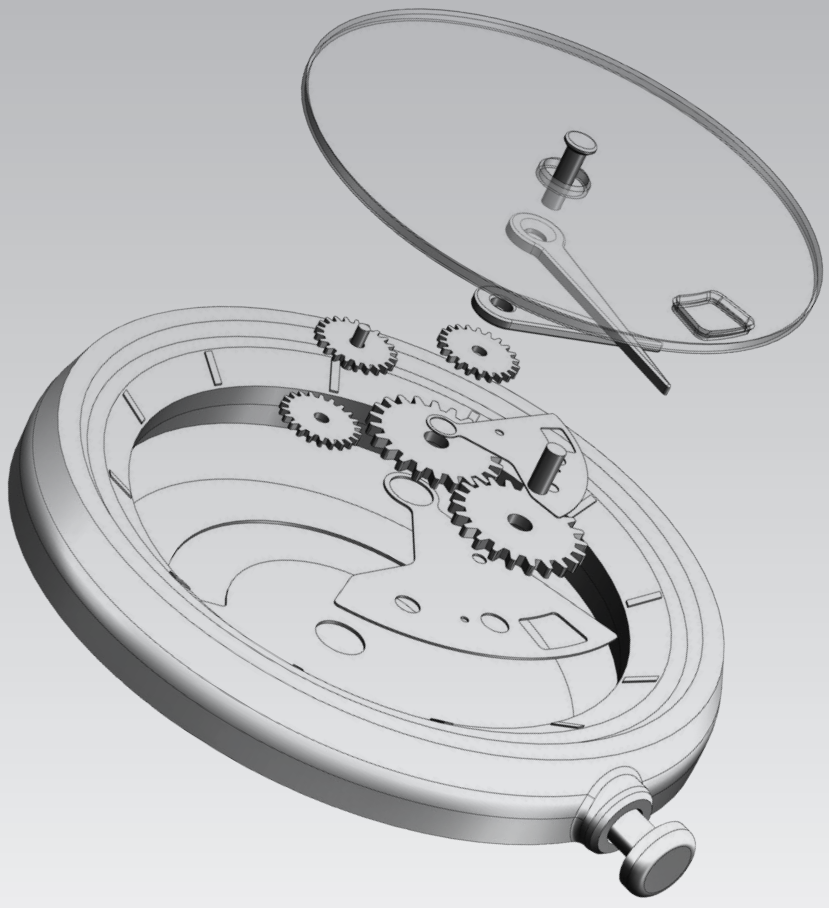


Chapter 2

Diagnosis of aphasia



Chapter 2.1

Screening tests for aphasia in patients with stroke: a systematic review

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ABSTRACT

Background

Aphasia has a large impact on quality of life and adds significantly to the costs of stroke care. Early recognition of aphasia in stroke patients is important for prognostication and well-timed treatment planning.

Objective

We aimed to identify available screening tests for differentiating between aphasic and non-aphasic stroke patients, and to evaluate test accuracy, reliability, and feasibility.

Methods

We searched PubMed, EMbase, Web of Science, and PsycINFO for published studies on screening tests aimed at assessing aphasia in stroke patients. The reference lists of the selected articles were scanned and several experts were contacted to detect additional references. Of each screening test, we estimated the sensitivity, specificity, likelihood ratio of a positive test, likelihood ratio of a negative test, and diagnostic odds ratio (DOR), and rated the degree of bias of the validation method.

Results

We included ten studies evaluating eight screening tests. There was a large variation across studies regarding sample size, patient characteristics, and reference tests used for validation. Many papers failed to report on consecutiveness of patient inclusion, time between aphasia onset and administration of the screening test, and blinding. Of the three studies that were rated as having an intermediate or low risk of bias, the DOR was highest for the Language Screening Test and ScreeLing.

Conclusion

Several screening tools for aphasia in stroke are available, but many tests have not been verified properly. Methodologically sound validation studies of aphasia screening tests are needed in order to determine their usefulness in clinical practice.

INTRODUCTION

For people aged 65 years or more, the worldwide prevalence of stroke ranges from 46 to 73 per 1000 people.[1] This number is likely to increase in the coming years due to aging of the population. Approximately 30% of stroke survivors have aphasia in the acute phase of stroke, a condition affecting daily communication and thus quality of life.[2] Aphasia adds significantly to the costs of patient care after stroke due to a longer hospital stay, and patients with aphasia are more frequently discharged to a rehabilitation center than those without.[3, 4] Initial severity of aphasia is an important factor determining the prognosis of patients with aphasia due to stroke.[5, 6] It has repeatedly been suggested that treatment of aphasia should be initiated as soon as possible after stroke, although consistent evidence for a beneficial effect of early language therapy has not been published yet.[7]

Altogether, it is pivotal that presence and severity of aphasia are adequately evaluated in patients who suffered a stroke. A large number of diagnostic instruments is available to examine the type and degree of aphasia. As many of these diagnostic test batteries are fairly demanding and time-consuming, they may be too cumbersome for stroke patients in the acute phase. Given that aphasia characteristics are generally instable shortly after stroke and can change rapidly, extensive testing may be a waste of time and resources. Also, a speech and language therapist (SL-therapist) is not always sufficiently available in the first days after stroke to obtain a detailed linguistic profile. Hence, a short and simple screening test, easy to administer by various disciplines, is essential for referring patients for additional assessment and adequate language therapy. Furthermore, advice regarding communication may be better personalized using results from screening tests.

The aim of this review was to identify available screening tests for differentiating between aphasic and non-aphasic patients after stroke, and to evaluate the accuracy, reliability, and feasibility of those tests.

METHODS

Search strategy

We searched PubMed, EMbase, Web of Science, and PsycINFO for published studies on screening tests aimed at assessing presence and/or severity of aphasia in patients who suffered an ischemic or hemorrhagic stroke. The following search string was used for NLM PubMed-Medline and was adapted for the other databases:

(cerebrovascular disorders[mesh:noexp] OR brain ischemia[mesh] OR intracranial embolism and thrombosis[mesh] OR intracranial hemorrhages[mesh] OR stroke[mesh:noexp] OR vertebral artery dissection[mesh:noexp] OR stroke*[tw] OR poststroke*[tw] OR cva[tw] OR cvas[tw] OR cerebrovasc*[tw] OR cerebral vasc*[tw] OR ((cerebr*[tw] OR intracerebr*[tw] OR cerebell*[tw] OR brain*[tw] OR vertebrobasilar*[tw] OR intracran*[tw]) AND (infarct*[tw] OR ischem*[tw] OR ischaem*[tw] OR hemorrh*[tw] OR haemorrh*[tw] OR hematom*[tw] OR haematom*[tw] OR thrombos*[tw] OR thrombot*[tw] OR thromboembol*[tw] OR thrombol*[tw] OR apoplex*[tw] OR emboli*[tw] OR bleed*[tw]))) AND (aphas*[tw] OR logastheni*[tw] OR logagnos*[tw] OR logamnes*[tw] OR alogi*[tw] OR anepia*[tw] OR dysphasi*[tw] OR lichtheim*[tw]) AND (test[tw] OR tests[tw] OR testing*[tw] OR screen*[tw] OR tool*[tw] OR instrument*[tw] OR assessment*[tw]) AND (accura*[tw] OR sensitiv*[tw] OR specificit*[tw] OR psychometr*[tw] OR psycho-metr*[tw]

OR predictive value*[tw]). We applied no search limits. The reference lists of the selected articles were checked and experts in the field of aphasia research were contacted to detect additional published studies. The initial search was carried out in March 2012 and updated in May 2015 with a search in PubMed.

Selection of studies

Eligible for inclusion were full-text articles, written in Dutch, English, French, German or Spanish, on cohort or cross-sectional studies of stroke patients who underwent a screening test to detect aphasia. A screening test was defined as a diagnostic test designed to assess presence and/or severity of aphasia, requiring a short turnaround time that is at most 15 minutes. Studies evaluating patients with aphasia due to other causes than stroke or with an unspecified etiology were not included. We also excluded studies in which test scores of aphasic stroke patients were compared with those from healthy controls instead of stroke patients without aphasia, as we specifically aimed to evaluate screening tests suitable for use in clinical practice.

Articles had to report the results of the screening test for aphasia as well as those from a reference test or gold standard. Data should be described in such a way that sensitivity and specificity of the screening test could be calculated. If sensitivity and specificity were given without reporting the original data the authors of the paper were contacted. In case authors were not able to provide the requested data the study was excluded from this review.

First, titles and abstracts of the retrieved studies were checked and obviously irrelevant articles were excluded. If a decision could not be made based on the information in the title and abstract, then the full-text article was checked for the above mentioned in- and exclusion criteria.

Data extraction

From the selected studies we recorded clinical characteristics of the patient sample (age, sex, stroke type, number of patients with and without aphasia). The following features of the validation method were collected: consecutiveness of patient inclusion, the type of reference test that was used, and blinding of the test assessors. All estimates of test accuracy reported in the studies had to be based on exact numbers of patients and were recalculated in order to check for errors and non-verification (that is whether only patients who could be assessed with the reference as well as with the screening test were included and reported which indicates selection bias). We collected the following data on the screening tests: the language in which the validation study was conducted, subtests, score range, time needed for administration, type of patients for which the test was initially developed, and reported suitability for bedside use.

Data analysis

We expressed the results of the validation studies of each screening test in 2x2 tables and estimated the sensitivity, specificity, likelihood ratio of a positive test (LR+), and the likelihood ratio of a negative test (LR-). Sensitivity was estimated by the number of aphasic patients who were correctly classified with the screening test divided by the total number of patients with aphasia. Specificity was estimated by the number of patients without aphasia who were correctly classified divided by the total number of patients without aphasia. LR+ was estimated by the sensitivity divided by 1-specificity. LR- was estimated by dividing 1-

sensitivity by the specificity.[8] The diagnostic odds ratio (DOR) was used as a single measure of test accuracy and was calculated by dividing the LR+ by the LR-.[9]

We evaluated the methodological quality of the selected studies by scoring three items: consecutiveness of patient inclusion, representativeness of the patient sample, and blinding. Consecutive patient inclusion is essential to eliminate selection bias and to ensure that the full range of aphasia types and severities is represented in the patient sample. Furthermore, the patient sample should be representative for the general stroke population, since this is the population in which the screening test will be used. Blinding is of importance to minimize expectation bias. The assessor of the screening test should not be aware of the results of the reference test, and vice versa.[8]

The score assigned for the representativeness of the patient sample in the validation study was 0 = not representative or not reported, 1 = fairly representative or partially not reported, or 2 = very representative. This was based on the size of the cohort, available data on stroke type, and mean age and sex of the patient sample. Consecutiveness was scored as either 0 = no consecutive inclusion or consecutiveness not reported or 2 = consecutive inclusion of patients. The degree of blinding was rated as 0 = when assessment was not blinded or blinding was not reported on; 1 = in case of blinding for the screening test only, or blinding without further specification; or 2 = in case of blinding for both the reference and the screening test.

Finally, we assigned a score for the risk of bias based on the three above mentioned items. A total score of ≤2 was classified as high risk of bias, a total score of 3 or 4 as intermediate risk of bias, and a total score of ≥5 as low risk of bias.

RESULTS

The electronic search resulted in 1004 records. We identified 13 additional articles after hand-searching the reference lists and another four by asking experts in the field. After screening all titles and abstracts, 956 records were excluded (Figure 1). Sixty-five full-text articles were assessed for eligibility, of which 14 were selected. There were no articles excluded because of the administration time of the test. In three articles the sensitivity and specificity were reported, but the exact numbers of evaluated patients were lacking. After contacting the publication authors we retrieved the data for one of these papers. The other two studies were excluded as the requested data were not available.[10, 11] One article reported on the aphasia item of the Scandinavian Stroke Scale (SSS). This study did not meet the inclusion criteria, since the SSS is a post-hoc scoring system and not a screening test. Eventually we included 11 articles, including one review.[12] In total, eight screening tests for aphasia were evaluated.

Included studies

Table 1 shows the characteristics of the patient samples of the ten included validation studies (the table does not contain the review article[12]) ordered alphabetically by screening test. One paper reported on the validation of two screening tests[13], a full version and a short version of the same test, and two tests were evaluated in more than one study.[13-18] Sample sizes ranged from 37[19] to 194[16] patients. Only two studies provided details concerning the type of stroke (i.e. ischemic versus hemorrhagic).[18, 20] In two papers information on age and sex of the patient sample was lacking,[14, 15] and another three evaluated a rather young

cohort (i.e. mean age of 54[13, 18] and 55[17] years). In one study, the screening test was validated in the chronic stage,[17] and in three studies the time since stroke onset was not reported.[13, 21, 22]

Table 1. Characteristics of the study cohorts of the validation studies

Study	Screening test	n	Stroke type◊ (n/n)	Mean age (years)	Male sex n (%)	Time since onset (days)
Al-Khawaja, 1996[13]	FAST	50	n.r.△	54	32 (64%)	n.r.
Enderby, 1987[14]	FAST	50	n.r.	n.r.	n.r.	1-36
O'Neill, 1990[15]	FAST	54	n.r.	n.r.	n.r.	1
Flamand-Roze, 2011[21]	LAST	102	n.r.	62	52 (51%)	n.r.
Choi, 2015[18]	MAST*	60	41/19	54	47(78%)	2-8
Kostalova, 2008[16]	MAST	194	n.r.	68/71○	97 (50%)	1-46
Romero, 2011[17]	MAST	58	10/19	55	32 (55%)	277□
Doesborgh, 2003[20]	ScreeLing	63	54/9	62	43 (68%)	2-11
Al-Khawaja, 1996[13]	SST	50	n.r.△	54	32 (64%)	n.r.
Kim, 2011[22]	SVF	53	27/n.r.	66	36 (68%)	n.r.
Thommessen, 1999[19]	UAS	37	n.r.	76	15 (41%)	3-8

Abbreviations: n = number; FAST = Frenchay Aphasia Screening Test; LAST = Language Screening Test; MAST*= Mobile Aphasia Screening Test; MAST = Mississippi Aphasia Screening Test; SST = Sheffield Screening Test for Acquired Language Disorders; SVF = Semantic Verbal Fluency; UAS = Ullevaal Aphasia Screening Test; n.r. = not reported.

◊ n (ischemic stroke) / n (hemorrhagic stroke); △ 8 patients with traumatic brain injury were included in the study; ○ median, subjects with aphasia/controls with right hemisphere stroke; □ mean.

Screening tests included in the review

We included validation studies for nine screening tools: the full and the short version of the Frenchay Aphasia Screening Test (FAST),[13-15] Language Screening Test (LAST),[21] Mississippi Aphasia Screening Test (MAST),[16, 17, 23] the mobile aphasia screening test (also abbreviated as MAST),[18] ScreeLing,[20] Sheffield Screening Test for Acquired Language Disorders (SST),[13] Semantic Verbal Fluency (SVF),[22] and Ullevaal Aphasia Screening test (UAS).[19] Characteristics of the screening tests, including language, subtests, score range, administration time, type of patients the test was originally designed for, and applicability as a bedside screening tool are given in Table 2. Two of the validation studies were conducted in English, two were conducted in Korean, one in Norwegian, one in French, one in Czech, one in Spanish and one in Dutch.[13-15, 23, 24] All tests can be administered within 15 minutes and most of them are judged to be suitable for bedside use. The SVF was originally designed for patients with dementia.[22, 24] The SST and the MAST were not developed specifically for stroke patients, but to assess language deficits in general.[13, 23] The mobile aphasia screening test is a tablet application based on the Korean version of the FAST and explicitly designed with no tool requirements so to be used for patients in remote locations easily.[18]

Figure 1. Flowchart of the search results

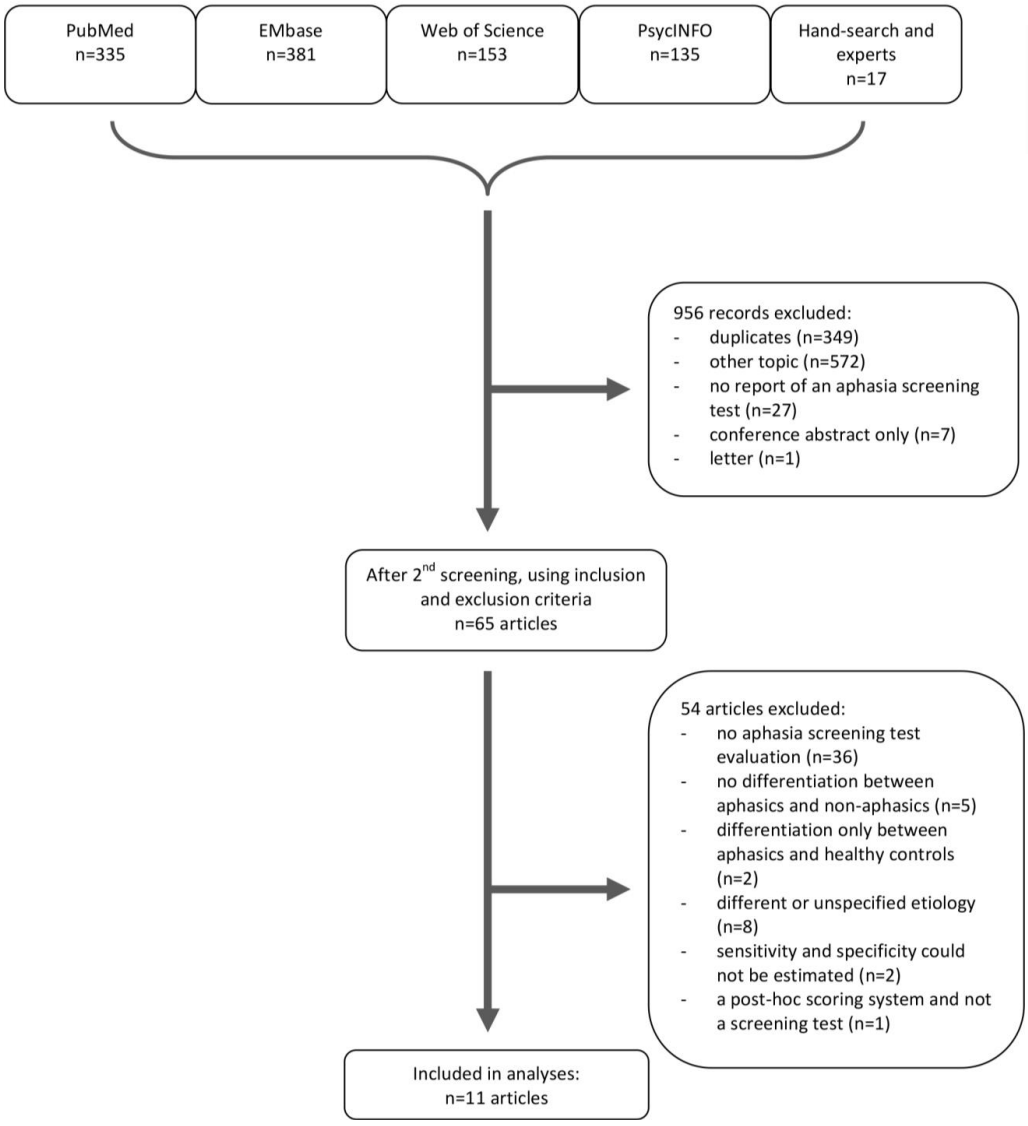

Table 2. Characteristics of the screening tests

Screening test	Language in which the study was conducted	Subtests	Score range	Administration time	Designed for	Bedside
FAST	English	full form: comprehension; expression; reading; writing short form: comprehension; expression	0-30 (full)	10 min	Stroke	Yes
LAST	French	naming; repetition; automatic speech; picture recognition; executing verbal orders	0-15	2 min	Stroke	Yes
MAST*	Korean	expression; comprehension	0-20	3 min	Stroke	n.r.
MAST	Czech and Spanish	naming; automatic speech; repetition; following instructions; yes/no responses; writing/spelling; object recognition; reading and executing instructions; verbal fluency	0-100	5-10 min	Severely impaired language /communication	Yes
ScreeLing	Dutch	semantics; phonology; syntax	0-72	15 min	Stroke	Yes
SST	English	receptive skills; expressive skills	0-20	3-5 min	Suspected language disorders	Yes
SVF	Korean	semantic fluency: animals	n.a.	i. 60 sec ii. 30 sec	Dementia	n.r.
UAS	Norwegian	expression; comprehension; repetition; reading; word strings; writing; free communication	n.r.	5-15 min	Stroke	n.r.

Abbreviations: n.a. = not applicable; n.r. = not reported.

Methodological quality of the validation studies

Table 3 provides information on methodological features for each validation study, including reference test used, test assessors and blinding of test assessors, and consecutiveness of patient inclusion. In more than half of the studies, patients were not included consecutively;[13, 16-18, 21, 22] and for one study this information was missing.[14] The diagnostic test that was applied as the gold standard varied from an informal evaluation by an SL-therapist to extensive aphasia test batteries. In most studies, the reference diagnosis was made by an SL-therapist,[13-16, 19] in two studies this information was not reported,[21, 22] or not exactly specified.[17] The screening tests were carried out by various disciplines. Most studies did not provide information on the time interval between the assessment of the reference test and the screening test,[13-15, 20-22] as was the case with respect to the order in which the assessments were conducted.[13, 14, 16, 17, 22]

One study lacked blinding,[17] in one study blinding was reported to be secured, but it was not specified how,[21] and seven studies did not describe whether or not test assessors were blinded.[13-16, 18, 22] Three studies reported on cut-off scores for the screening test indicating presence or absence of aphasia that were stratified for age,[13, 16, 18] and in one study no cut-off score was reported.[19] In three studies the cut-off value for the screening test was based on previous studies comparing subjects with aphasia and healthy controls.[13, 15, 16]

Table 4 shows the diagnostic properties of the identified aphasia screening tests (sensitivity, specificity, LR+, LR-, and DOR). In all studies, each patient was reported to be assessed with the reference test as well as with the screening test. Four studies included a larger group of patients with aphasia than without aphasia,[13, 16, 21, 22] and two included groups of equal sample size.[17, 18] In five studies the DOR was infinite, because either LR- was nil or LR+ was infinite.[13, 14, 17, 21]

In Table 5 the estimated degree of bias is given based on scores for blinding of test assessors, consecutiveness of inclusion, and representativeness of the patient sample. Seven studies were judged as having a high risk of bias, two as having an intermediate risk of bias, and in one study the risk of bias was judged low. Four screening tools seemed to perform very good (Table 4), with sensitivity and specificity of 100% and 90% respectively (short version of FAST[14]), 98% and 100% (LAST[21]), 86% and 96% (ScreeLing[20]), and 90% and 100% in one (MAST[17]) and 96% and 89% in another study (MAST[16]). However, the validation studies for the FAST short version and both validation studies for the MAST were considered as having a high risk of bias. Of the three studies with an intermediate or low risk of bias, the calculated DOR was highest for the LAST[21] and Screeling[20].

Table 3. Methodological features of the validation studies

Study	Screening test	Reference	Assessor of reference test	Assessor of screening test	Cut-off for screening test◊	Blinding△	Consecutive inclusion
Al-Khawaja, 1996[13]	FAST	SLT	SLT	Non-specialist, n.f.s.	17[a]; 16[b]; 15[c] (short)	n.r.	No
Enderby, 1987[14]	FAST	SLT, FCP, sS	SLT	n.r.	23 (full); 14 (short)	n.r.	n.r.
O'Neill, 1990[15]	FAST	sS, BDAE	SLT	Physician	25	n.r.	Yes
Flamand-Roze, 2011[21]	LAST	BDAE	n.r	SLT, nurse, neurologist, or student	15	Yes, n.f.s.	No
Choi, 2015[18]	MAST*	Physiatrist	Physiatrist	Research assistant, test scored by SLT	16[i]; 14[j]	n.r.	No
Kostalova, 2008[16]	MAST	SLT	SLT	Neurology resident and student	93[d]; 96[e]; 98[f]	n.r.	No
Romero, 2011[17]	MAST	BDAE, TT	Clinical expert, n.f.s.	Clinical expert, SLT, neurologist	90	No	No
Doesborgh, 2003[20]	ScreeLing	TT, exp.	Neurologist, linguist	n.r.	66	Yes, 3	Yes
Al-Khawaja, 1996[13]	SST	SLT	SLT	Non-specialist, n.f.s.	17[g]; 16[h]; 15[c]	n.r.	No
Kim, 2011[22]	SVF	STAND	n.r.	n.r.	60 sec; 7 / 30 sec; 6	n.r.	No
Thommessen, 1999[19]	UAS	SLT, parts of NGA	SLT	Nurse	n.r.	Yes, 2	Yes

Abbreviations: SLT = speech and language therapist; FCP = Functional Communication Profile; sS = short Schuell; BDAE = Boston Diagnostic Aphasia Examination; TT = Token Test; exp. = expert assessment; NGA = Norsk Grunntest for Afasi (Norwegian Basic Aphasia Assessment); STAND = Screening Test for Aphasia and Neurologic-Communication Disorders; n.f.s. = not further specified; n.r. = not reported.

◊ Cut-off for: [a] age ≤59 years; [b] age 60-70 years; [c] age ≥71 years; [d] age ≤60 years; [e] age 61-70 years; [f] basic and secondary education; [g] academic education and age ≥ 60 years; [h] academic education and age <60 years; [i] age ≤ 64 years; [j] age> 64 years.

△ Blinding: 1 for reference test only, 2 for screening test only, 3 for reference and screening test.

Table 4. Diagnostic properties of the validation studies

Study	Screening test	Aphasia (n)	No aphasia (n)	Aphasia correctly classified (n)	No aphasia correctly classified (n)	Sensitivity	Specificity	Non-verified (n)	LR+	LR-	DOR [95% CI]
Al-Khawaja, 1996[13◊]	FAST	45	5	39	4	87%	80%	0	4.4	0.2	27.5 [2.6 – 289.5]
Enderby, 1987[14]	FAST, full	20	30	20	23	100%	77%	0	4.4	0.0	∞
Enderby, 1987[14]	FAST, short	20	30	20	27	100%	90%	0	10	0.0	∞
O'Neill, 1990[15]	FAST	23	31	22	19	96%	61%	0	2.5	0.1	35.7 [4.2 – 300.5]
Flamand-Roze, 2011[21]	LAST	52	50	51	50	98%	100%	0	∞	0.0	∞
Choi, 2015[18]	MAST*	30	30	27	22	90%	73%	0	3.4	0.1	24.7 [5.9 – 104]
Kostalova, 2008[16]	MAST	149	45	143	40	96%	89%	0	8.7	0.0	217.5 [63.1 – 749.7]
Romero, 2011[17]	MAST	29	29	26	29	90%	100%	0	∞	0.1	∞
Doesborgh, 2003[20]	ScreeLing	14	49	12	47	86%	96%	0	21.5	0.2	143.3 [18.3 – 1124.3]
Al-Khawaja, 1996[13◊]	SST	38	4	35	4	92%	80%	0	∞	0.1	∞
Kim, 2011[22]	SVF, 60 sec	27	26	23	22	85%	85%	0	5.7	0.2	31.7 [7.0 – 142.5]
Kim, 2011[22]	SVF, 30 sec	27	26	23	23	85%	88%	0	7.1	0.2	41.8 [8.4 – 208.0]
Thommessen, 1999[19]	UAS	8	29	6	26	75%	90%	0	7.5	0.3	26.8 [3.6 – 197.5]

Abbreviations: n = number; LR+ = Likelihood Ratio of a Positive Test; LR- = Likelihood Ratio of a Negative Test; DOR = diagnostic odds ratio.
◊ Eight patients have traumatic brain injury.

Table 5. Risk of bias in evaluated validation studies

Study	Screening test	Score for blinding◊	Score for consec.△	Score for repres.○	Risk of bias□
Al-Khawaja, 1996[13]	FAST	0	0	1	high
Enderby, 1987[14]	FAST	0	0	0	high
O'Neill, 1990[15]	FAST	0	2	0	high
Flamand-Roze, 2011[21]	LAST	1	0	2	intermediate
Choi, 2015[18]	MAST*	0	0	2	high
Kostalova, 2008[16]	MAST	0	0	2	high
Romero, 2011[17]	MAST	0	0	1	high
Doesborgh, 2003[20]	ScreeLing	2	2	2	low
Al-Khawaja, 1996[13]	SST	0	0	1	high
Kim, 2011[22]	SVF	0	0	2	high
Thommessen, 1999[19]	UAS	1	2	1	intermediate

Abbreviations: consec. = consecutiveness; repres. = representativeness.
◊ 0 = assessment was not blinded or blinding was not reported on; 1 = blinding for the screening test only, or blinding without further specification; 2; blinding for both the reference and the screening test.
△ 0 = no consecutive inclusion or consecutiveness not reported; 2 = consecutive inclusion of patients.
○ Based on the size of the cohort, available data on stroke type, and mean age and sex of the study population, 0 = not representative or not reported; 1 = fairly representative or partially not reported; 2 = very representative.
□ Total score ≤2 = high, total score ≥3 and ≤4 = intermediate, total score ≥5 = low.

DISCUSSION

Given the impact of aphasia on quality of life, rehabilitation after stroke and the costs of stroke care, it is of great importance that aphasia in stroke patients is immediately recognized, allowing for adequate referral and treatment as soon as possible.[25] Hence, it is crucial to have a brief and easy screening test for aphasia that may be administered by SL-therapists as well as other health professionals shortly after aphasia onset and is also suited for ill stroke patients for whom an extensive test battery is too demanding. A simple screening tool for aphasia may also be of use for research purposes, in order to identify patients with aphasia in stroke trials.

In this systematic review, we evaluated ten studies reporting on the validation of eight screening tests for aphasia after stroke, with emphasis on methodological quality of the validation study. Nearly all included screening tools usually reflect the approach taken in traditional aphasia test batteries that assess language modalities such as spontaneous speech, auditory and written comprehension, reading and writing in addition to naming and repetition, except the ScreeLing and the SVF. The ScreeLing comprises tasks directly aimed at the basic linguistic components (semantics, phonology and syntax). The SVF addresses semantic verbal fluency only. Although it is not always explicitly mentioned in the test descriptions, all tests are suitable to be administered at bedside, a requirement for the use in the acute stage.

Several issues have to be taken into account when appraising studies that claim to validate a screening test against a reference test.[8] Clearly, the patient sample of the

validation study should be representative for the population in which the screening test will be applied. This means that a screening tool for aphasia due to stroke should be verified in a cohort representative for the general stroke population. For this reason we only included validation studies performed on stroke patients with and without aphasia, and excluded studies investigating test performance by examining aphasic stroke patients and healthy controls. We attempted to assign a score for representativeness to each included study based on the available information on patient characteristics. Unfortunately, data on age and sex of the patient sample were not reported for all studies. Furthermore, in more than half of the validation studies patients were not included consecutively, or this information was missing. Consecutive inclusion increases the likelihood that the full spectrum of aphasia severity is represented in the study cohort and minimizes the risk of selection bias. The 1:1 ratio of patients with and without aphasia in some of the validation studies however suggests that patients were not recruited consecutively but rather selected.[17, 18, 22] One study that reported consecutive inclusion only enrolled patients already suspected to have aphasia, resulting in a study cohort containing a majority (i.e. 90%) of stroke patients with aphasia.[13] In all studies the number of non-verified patients was nil, which indicates that selection bias may have been present to some extent. It is possible that only patients who were able to undergo the screening test as well as the reference test were enrolled, while patients for whom the burden of the reference test (which is likely to be more time-consuming and more difficult) was too high were not included. In addition, administration of the reference test should not be restricted to patients in whom the screening test was positive, in order to avoid workup bias. In each study included in this review, all patients were reported to be assessed both with the screening test and the test used as the gold standard.

For many of the screening tools the cut-off value below or above which the test result is considered abnormal (i.e. the patient is diagnosed as having aphasia) was derived from studies performed in stroke patients with aphasia and healthy control subjects, while cut-off values based on a general stroke population are preferred. Finally, the assessor of the screening test should be blind for the result of the reference test and the other way around. Many of the evaluated studies did not report whether or not blinding was secured, making it difficult to estimate the risk of expectation bias. Altogether, most of the validation studies had serious methodological limitations, thus hampering firm conclusions about utility of the aphasia screening tools for clinical practice.

Of the four studies with an intermediate or low risk of bias, the LAST[21] and ScreeLing[20] seem to have the best diagnostic properties. An advantage of the LAST is the short administration time. The ScreeLing, a measure for the patients' functioning in the main linguistic levels semantics, phonology and syntax, gives more detailed information for language treatment. It is notable that the SVF, a very short screening test that was initially developed for use in patients with dementia, also performs quite reasonably as a screening test for aphasia in stroke patients.[22]

Besides the screening tools evaluated in this review, there are several well-known screening tests for aphasia that are widely used in clinical practice. For the Acute Aphasia Screening Protocol,[26] the Aachen Aphasia Bedside Test,[27] and the Bedside Western Aphasia Battery,[28] strikingly we were unable to find any peer-reviewed articles in which these tests were validated in stroke patients with and without aphasia. The Token Test[29] is one of the first recommended screening tests for the detection of aphasia in patients with neurological

damage and therefore exists in a lot of variations.[30-32] However, although this test is generally considered very useful in clinical practice it could not be included because etiology of aphasia was too diverse or unspecified in the validation studies for this test. Finally, general stroke scales quantifying stroke severity in the acute stage contain specific subparts for speech and language, such as the NIH Stroke Scale (NIHSS),[33] the Canadian Neurological Scale (CNS)[34] and the European Stroke Scale (ESS)[35]. These standardized scales are often used in clinical practice to identify stroke patients with aphasia, but have not been systematically validated as such.

CONCLUSION

In conclusion, several screening tools for aphasia in stroke are available, but many tests have not been verified in a proper way. Future studies should focus on a better validation of the available aphasia screening tests in large stroke populations. The design should include a reliable reference diagnosis, a consecutive inclusion of stroke patients to make them representative of a general stroke population, a secured blinding of the assessments, details on the numbers of patients with and without aphasia correctly classified, and a good description of the subtests of the screening test, in order to eliminate the risk of bias as much as possible.

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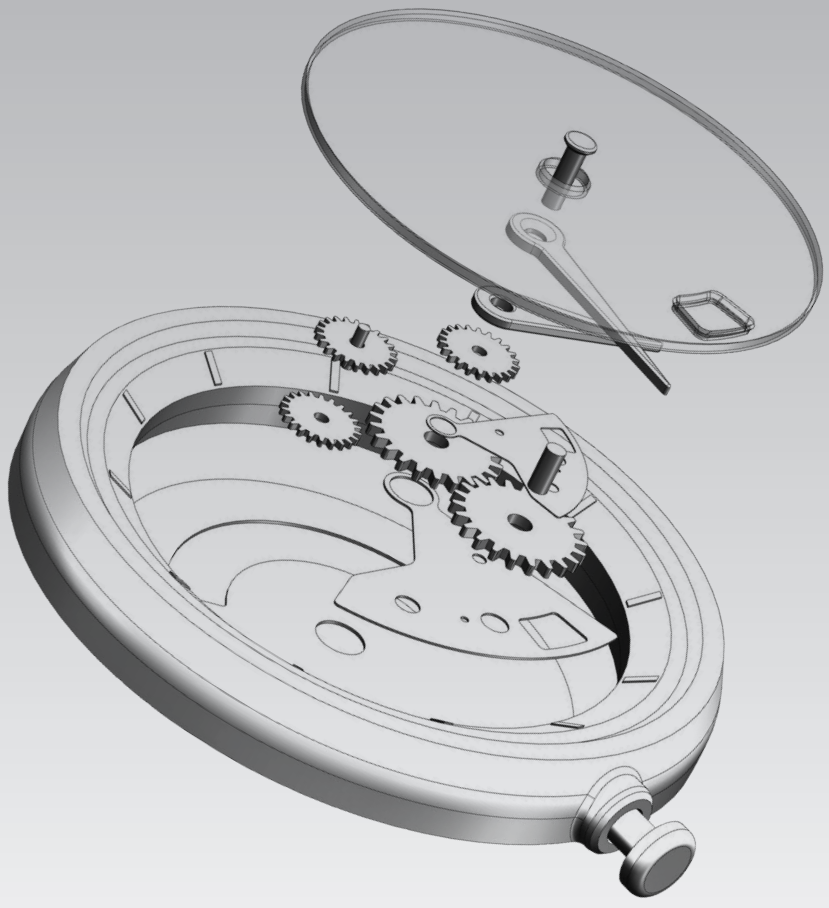
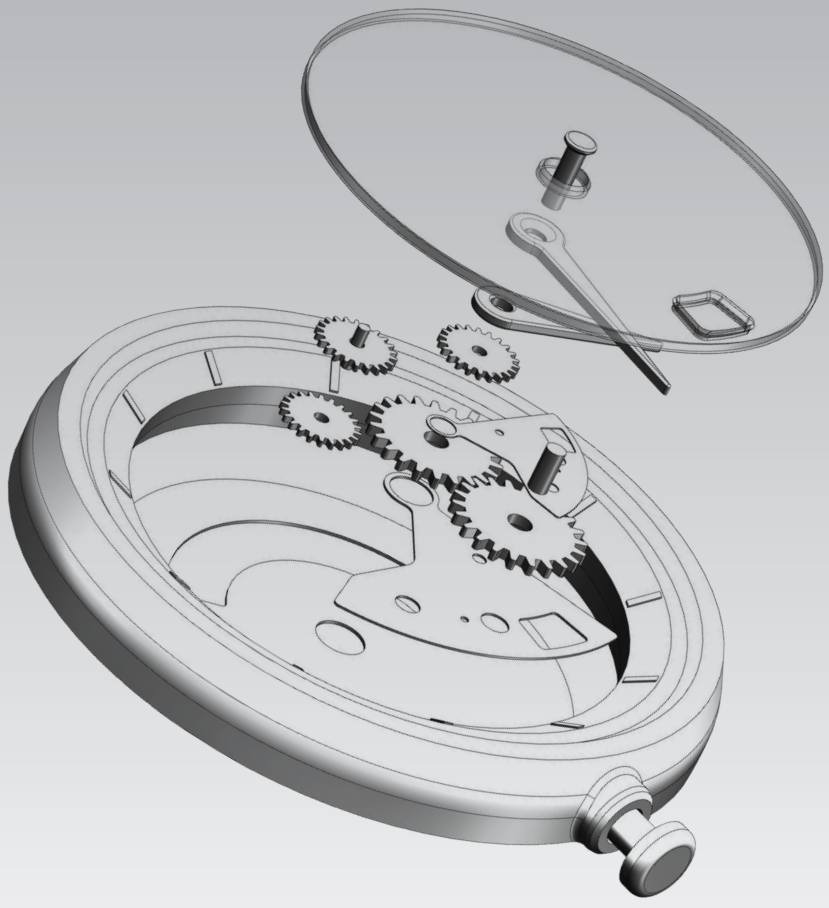


Chapter 3

Prognosis of aphasia



Chapter 3.1

Early effect of intra-arterial treatment in ischemic stroke on aphasia recovery in MR CLEAN

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ABSTRACT

Objective

To investigate the effect of intra-arterial treatment (IAT) on early recovery from aphasia in acute ischemic stroke. We hypothesized that the early effect of IAT on aphasia is smaller than the effect on motor deficits.

Methods

We included patients with aphasia from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), in which 500 patients with a proximal anterior circulation stroke were randomized to usual care plus IAT (<6 hours after stroke, mainly stent retrievers) or usual care alone. We estimated the effect of IAT on the shift on the NIH Stroke Scale (NIHSS) item language and the NIHSS item motor arm at 24 hours and one week after stroke with multivariable ordinal logistic regression as a common odds ratio, adjusted for prognostic variables (acOR). Differences between the effect of IAT on aphasia and on motor deficits were tested in a multilevel model with a multiplicative interaction term.

Results

Of the 288 patients with aphasia, 126 were assigned to IAT and 162 to usual care alone. The acOR for improvement of language score at 24 hours was 1.65 (95% confidence interval, CI: 1.05 to 2.60), and at one week 1.86 (95% CI: 1.18 to 2.94). The acOR for improvement of motor deficit at 24 hours was 2.44 (95% CI: 1.54 to 3.88), and at one week 2.32 (95% CI: 1.43 to 3.77). The effect of IAT on language deficits was significantly different from the effect on motor deficits at 24 hours and one week ($p = 0.01$ and $p = 0.01$).

Conclusion

IAT results in better early recovery from aphasia than usual care alone. The early effect of IAT on aphasia is smaller than the effect on motor deficits. This study provides Class II evidence that for patients with acute ischemic stroke IAT increases early recovery from aphasia and that the early effect on aphasia, as measured by the NIHSS, is smaller than the effect on motor deficits.

INTRODUCTION

Recently, several randomized clinical trials showed that intra-arterial treatment (IAT) with retrievable stents for patients with acute ischemic stroke (AIS) caused by a proximal intracranial occlusion in the anterior circulation is safe and improves functional outcome at 90 days.[1-5]

Aphasia is diagnosed in 15% to 40% of patients at ischemic stroke onset.[6-11] Stroke patients with aphasia have increased mortality,[7] decreased functional recovery,[12] and reduced probability to return to work,[13] and they have a higher risk of depression,[8] compared to those without aphasia.[9] Clinical observations and previous studies suggest that language deficits in AIS do not respond as rapidly to reperfusion therapy as other neurologic deficits, especially upper limb paresis.[14-16] To our knowledge, no study thus far has assessed the effect of IAT on aphasia.

Our first aim was to determine whether usual care plus IAT would be more effective than usual care alone for the early recovery from aphasia in patients with AIS. The second aim was to evaluate whether the effect of IAT on early aphasia recovery differed from the effect on early motor deficit recovery.

METHODS

Study design

For this study, we used data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN),[1] a randomized, pragmatic phase III, multicenter clinical trial with a Prospective Randomized Open Blinded Endpoint (PROBE) design,[17] among 500 AIS patients with a proximal intracranial arterial occlusion of the anterior circulation. In this trial, usual care plus IAT (mainly with retrievable stents) was compared with usual care alone. Usual care in MR CLEAN could include intravenous administration of alteplase. The MR CLEAN study design has been described in detail elsewhere.[18]

Participants

Patient characteristics and intervention details for MR CLEAN have been extensively described previously.[1] For this study, we selected all patients with aphasia at baseline, affirmed with a deficit on the item language (item 9) of the NIH Stroke Scale (NIHSS). Patients who were comatose at baseline (defined as a score of 3 on the item orientation, item 1A of the NIHSS) were excluded.

Clinical and radiologic assessment

All patients underwent clinical assessment at baseline, which included demographics, risk factors, medical history, pre-stroke modified Rankin Scale score (mRS), and NIHSS score. Assessment of the NIHSS score was repeated after 24 hours and at one week (range 5 to 7 days) or discharge. Investigators were trained to conduct the NIHSS. The NIHSS consists of standardized items, with good interrater reliability.[19, 20] The imaging committee evaluated the baseline vessel images (CT angiography, magnetic resonance angiography, or digital subtraction angiography) to ascertain the location of the occlusion.

Outcomes

The first outcome was the score on the item language of the NIHSS at 24 hours and at one week. This item was scored by asking the patient to name items, perform a complex picture description task (cookie theft), and perform a repetition task, according to the NIHSS manual.[21] Scores on the language item range from 0 to 3, with a score of 0 indicating no aphasia; 1 = mild to moderate aphasia; 2 = severe aphasia; and 3 = mute or global aphasia.

To evaluate the difference with the effect of IAT on motor arm deficits, we used the NIHSS item motor arm at 24 hours and at one week. The item motor arm (item 5) was measured by determining motor arm strength contralateral to the affected hemisphere. The patient was asked to extend the arms 90° and hold this for ten seconds. Scores on this item range from 0 to 4, with a score of 0 indicating no drift; 1 = drift; 2 = some effort against gravity; 3 = no effort against gravity; and 4 = no movement.

Statistical analyses

Missing values for baseline variables that were used to adjust the regression models were imputed with mean or mode, as applicable. Single missing values of items on the NIHSS at 24 hours and at one week were imputed by mode. The percentage of single imputed data was 0.28%. There were no single missing values on the items language and motor arm at 24 hours and at one week. Patients who died within seven days after stroke onset were given the worse score for missing values on the items language (score 3) and motor arm (score 4). Patients who were lost to follow-up because of early discharge and did not die within seven days after stroke onset were not included in the analyses.

All analyses were based on the intention-to-treat principle. The primary effect estimate was the adjusted common odds ratio (acOR) for a shift in the direction of a better outcome on the item language. The acOR estimates the likelihood that IAT would lead to lower NIHSS scores, as compared with usual care alone (shift analysis).[22] This ratio was estimated with multivariable ordinal logistic regression. Estimates were adjusted for age, stroke severity (total NIHSS score) at baseline, history of ischemic stroke, atrial fibrillation, diabetes mellitus, carotid top occlusion, and time from stroke onset to randomization. The acOR for the effect of IAT on the item motor arm was estimated similarly.

In order to summarize the data, we plotted proportions of patients with good outcome at 24 hours and one week. Good outcome was defined, both for aphasia and for motor arm deficit, as a score of 0 or 1 on the NIHSS item. For further analyses, the total distribution of scores was used.

To evaluate whether there is a differential effect of IAT on language versus motor arm recovery, two records per patient were created in the database, one with the language outcome and one with the motor arm outcome. We then fitted a multilevel model with a random intercept for patient, to account for the correlation within patients, and a multiplicative interaction between outcome type and treatment. Since common odds ratios were used, the scales with different ranges could be accurately compared, because they represent weighted averages of odds ratios for each possible dichotomization of the ordinal scale. This analysis was conducted with and without imputed data.

The adjusted and unadjusted odds ratios are reported with 95% confidence intervals (95% CI) to indicate statistical precision. All analyses were performed using Stata/SE statistical package, version 13.1 (StataCorp, College Station, TX).

Standard protocol approvals, registrations, and patient consents

This study is a post-hoc study of MR CLEAN. The trial protocol has been approved by a central medical ethics committee and the research board of each participating center.[18] MR CLEAN is registered in the Dutch trial register (NTR1804) and in the ISRCTN register (ISRCTN10888758). Written informed consent was obtained from all participants or their legal representatives before randomization.

RESULTS

Study population

We identified 289 patients with a language score of >0 at baseline. One comatose patient was excluded. In total, 288 patients were selected for analyses, of whom 126 (44%) had been assigned to the intervention group and 162 (56%) to the control group. One patient received IAT after being assigned to the control group. IAT was never initiated in 12 patients (9.5%) assigned to the intervention group. Baseline characteristics were similar in the two treatment groups (Table 1).

Imputation

After 24 hours and one week, respectively, nine and 37 patients had died and were imputed with a maximum score of 3 on the item language and 4 on the item motor arm. Seven patients at 24 hours and 16 patients at one week were lost to follow-up and were not included in the analyses.

Effect of IAT on language function

There was a shift in the distribution of language scores in favor of IAT at both 24 hours and one week. The acORs for improvement were 1.65 at 24 hours (95% CI: 1.05 to 2.60) and 1.86 at one week (95% CI: 1.18 to 2.94) (Table 2). The shift towards better outcomes in favor of the intervention was consistent for all categories of the item language (Figure 1). At 24 hours, 13% of the patients in the intervention group had no aphasia versus 4% in the control group (acOR: 3.51, 95% CI: 1.28 to 9.67) and at one week these percentages were 21% versus 10% (acOR: 2.45, 95% CI: 1.17 to 5.10) (Table 2).

Table 1. Baseline characteristics of the study population

Characteristics	Intervention (n = 126)	Control (n = 162)
Age in years, median (IQR)	65 (56-76)	66 (58-76)
Male sex, n (%)	75 (60%)	105 (65%)
Total NIHSS score◊, median (IQR)	20 (16-23)	21 (16-23)
NIHSS score item language, n (%)		
1	15 (12%)	13 (8%)
2	41 (33%)	54 (33%)
3	70 (56%)	95 (59%)
NIHSS score item motor arm△, n (%)		
0	3 (2%)	4 (3%)
1	10 (8%)	14 (9%)
2	19 (15%)	14 (9%)
3	14 (11%)	24 (15%)
4	80 (64%)	106 (65%)
Pre-stroke modified Rankin score○, n (%)		
0	104 (83%)	128 (79%)
1	10 (8%)	18 (11%)
2	8 (6%)	9 (6%)
>2	4 (3%)	7 (4%)
History of ischemic stroke, n (%)	13 (10%)	17 (11%)
Atrial fibrillation, n (%)	34 (27%)	51 (25%)
Diabetes mellitus, n (%)	24 (19%)	20 (12%)
Systolic blood pressure, mm Hg, mean (SD)	147 (28)	145 (23)
Location of stroke in left hemisphere, n (%)	114 (91%)	148 (91%)
Carotid top occlusion, n (%)	34 (27%)	43 (27%)
Treatment with IV alteplase, n (%)	112 (89%)	142 (88%)
Time from stroke onset to start of IV alteplase, min		
Median (IQR)	94 (70-108)	100 (65-116)
Time from stroke onset to randomization, min		
Median (IQR)	208 (158-249)	212 (159-264)
Time from stroke onset to IAT, min		
Median (IQR)	266 (215-315)	n.a.

Abbreviations: n = number; IQR = interquartile range; n.a. = not applicable; NIHSS = NIH Stroke Scale; SD = standard deviation; IV = intravenous.

◊ Scores on the NIHSS (a 15-item scale) range from 0 to 42, with higher scores indicating more severe neurologic deficits.

△ NIHSS score on the item motor arm was measured on the arm contralateral to the affected hemisphere.

○ Scores on the modified Rankin scale of functional disability range from 0: no symptoms to 6: death. A score of 2 or less indicates functional independence.

Table 2. Effect of IAT on language function

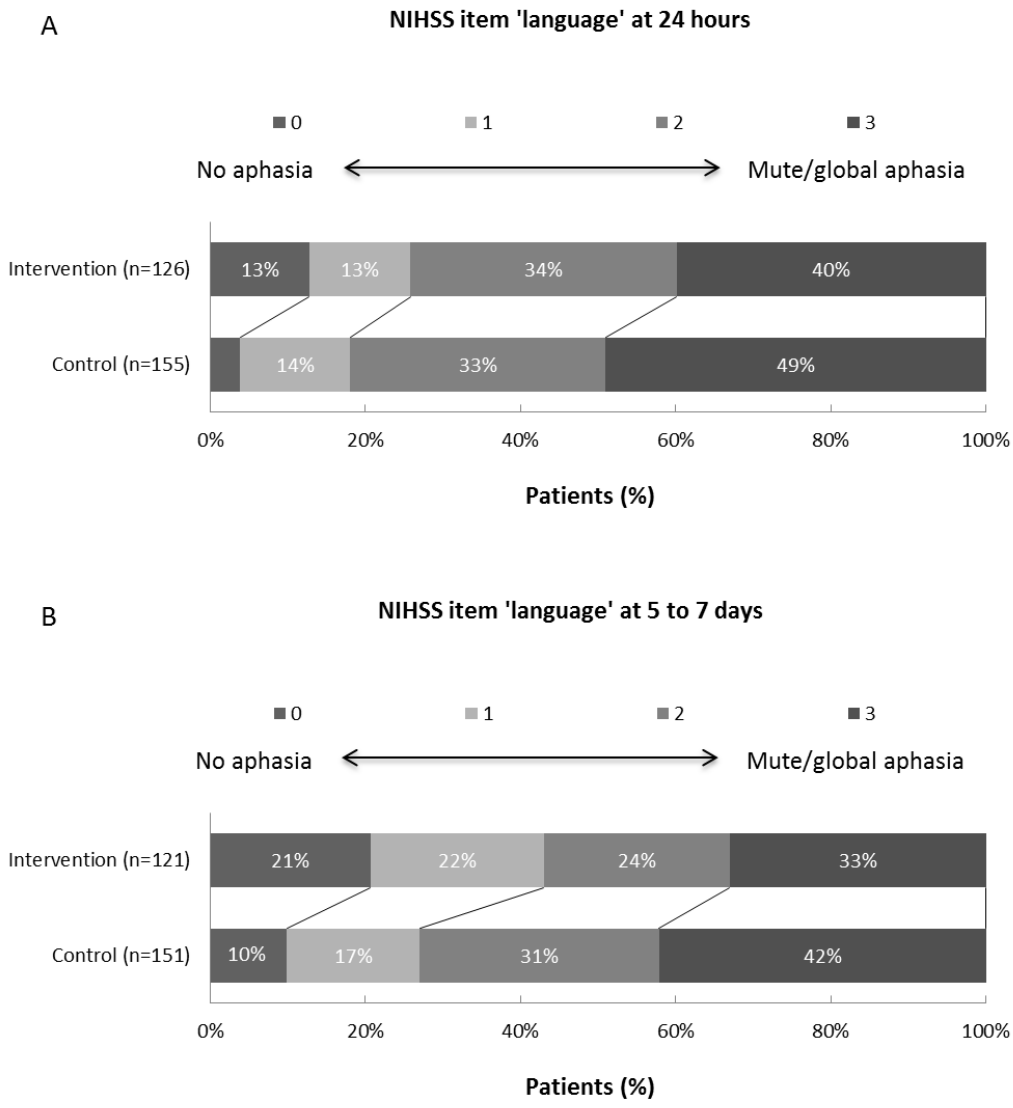
Outcome	Intervention	Control	Effect variable	Unadjusted value [95% CI]	Adjusted value [95% CI]
NIHSS item language at 24 h[◊]	n = 126	n = 155	Common odds ratio	1.58 [1.02 – 2.44]	1.65 [1.05 – 2.60]
Score of 0, n (%)	16 (13%)	6 (4%)	Odds ratio	3.61 [1.37 – 9.53]	3.51 [1.28 – 9.67]
Score of 0 to 1, n (%)	33 (26%)	28 (18%)	Odds ratio	1.61 [0.91 – 2.85]	1.59 [0.85 – 2.98]
Scores of 0 to 2, n (%)	76 (60%)	79 (51%)	Odds ratio	1.46 [0.91 – 2.35]	1.54 [0.92 – 2.59]
NIHSS item language at 1 week[△]	n = 121	n = 151	Common odds ratio	1.78 [1.15 – 2.76]	1.86 [1.18 – 2.94]
Score of 0, n (%)	25 (21%)	15 (10%)	Odds ratio	2.36 [1.18 – 4.71]	2.45 [1.17 – 5.10]
Score of 0 to 1, n (%)	52 (43%)	41 (27%)	Odds ratio	2.02 [1.22 – 3.36]	2.21 [1.25 – 3.94]
Scores of 0 to 2, n (%)	81 (67%)	87 (58%)	Odds ratio	1.49 [0.91 – 2.45]	1.55 [0.89 – 2.70]

Abbreviations: IAT = intra-arterial treatment; 95% CI = 95% confidence interval; n = number; NIHSS = NIH Stroke Scale.

[◊] The NIHSS score was not available for seven patients who were lost to follow-up at 24 hours and did not die within seven days after stroke.

[△] The NIHSS score was not available for 16 patients who were lost to follow-up at one week and did not die within seven days after stroke.

Figure 1. Distribution of scores on the item language of the NIH Stroke Scale (NIHSS) in the intention-to-treat population

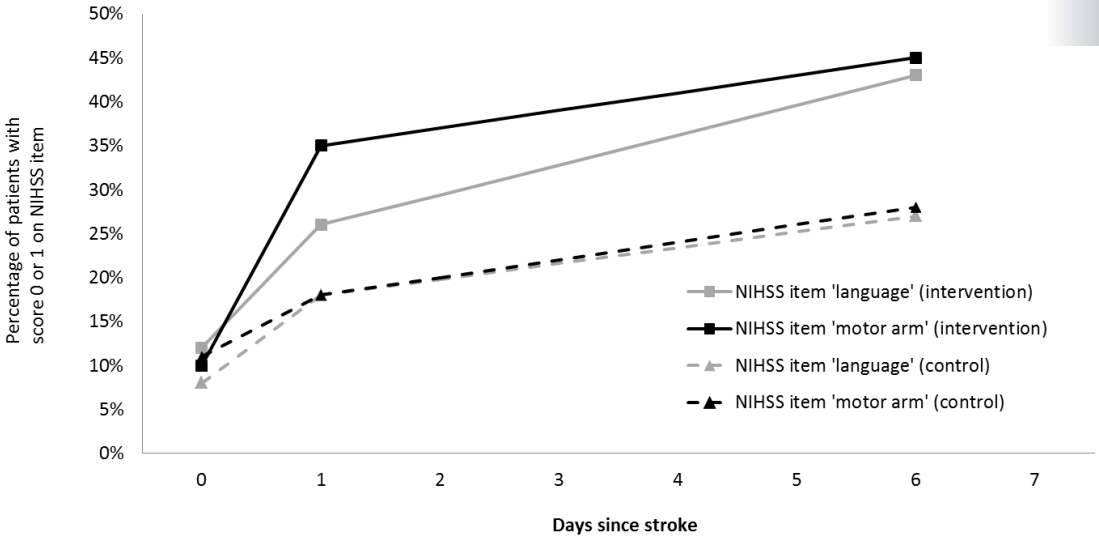


Distribution of scores on the item language of the NIHSS at 24 hours (A) and one week (B) after stroke. Scores range from 0 to 3. At 24 hours, 4% of the patients in the control group had a score of 0.

Effect of IAT on aphasia versus motor arm deficits

We visualized the effects of treatment by plotting proportions of patients with good outcome (score 0 or 1 on the items motor arm and language) at 24 hours and one week. At baseline, the proportions of patients with little or no language or motor deficits in the intervention group were similar. At 24 hours, more patients had a good outcome on the item motor arm than on the item language, but at one week these proportions were again equal (Figure 2).

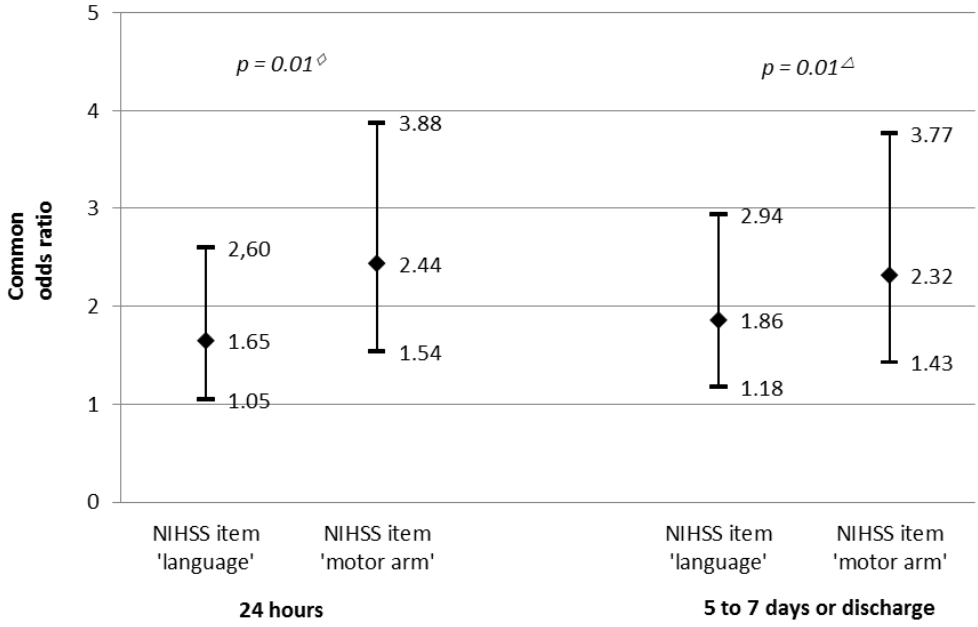
Figure 2. Good outcome scores of language and motor arm



Proportions of patients with good outcome (score 0 or 1) on the item language and on the item motor arm at 24 hours and at one week.
Proportions displayed at day six are based on the NIH Stroke Scale (NIHSS) scores measured at five to seven days or discharge if earlier.

We observed a shift in the distribution of all scores for the NIHSS item motor arm in favor of IAT. Figure 3 shows acORs for the language item and the motor arm item. At 24 hours, the acOR was 1.65 (95% CI: 1.05 to 2.60) for the item language and 2.44 (95% CI: 1.54 to 3.88) for the item motor arm, in favor of the intervention, meaning that chances of improvement of one or more points on the NIHSS are larger for motor function than for aphasia. The difference between these two ratios was statistically significant (p = 0.01). At one week after stroke, the acOR was 1.86 (95% CI: 1.18 to 2.94) for the item language and 2.32 (95% CI: 1.43 to 3.77) for the item motor arm. This difference was also significant (p = 0.01). Treatment effects on the NIHSS item motor leg were similar (data not shown).

Figure 3. Effect of IAT on aphasia versus motor arm deficits



Adjusted common odds ratios for improvement, expressed by a shift on the overall categories of the items language and motor arm at 24 hours and at one week, between intervention and control group.
Abbreviations: NIHSS = NIH Stroke Scale.
◊ *p*-value for interaction between treatment and outcome (language or motor arm) at 24 hours.
△ *p*-value for interaction between treatment and outcome (language or motor arm) at one week.

Repeated analyses without imputed data yielded slightly more significant differential effects (differential effect between scores on items language and motor arm at 24 hours: p = 0.00, and at one week: p = 0.01).

DISCUSSION

This study shows that in patients with AIS caused by a proximal intracranial arterial occlusion of the anterior circulation, greater improvement of aphasia in the first week can be accomplished when IAT is added to usual care within six hours after stroke onset. Second, we showed that early recovery of aphasia was less than the early recovery of motor function.

In the acute phase, rapid recovery can be attained within hours to days by rapid reperfusion of brain tissue.[23] Subacute recovery follows and is thought to be primarily due to neural reorganization, which is complex and can take several weeks to months.[23]

With the addition of IAT to usual care, recovery of aphasia is accelerated. This is important because aphasia can be severely socially disabling and can affect daily life

tremendously.[7-9, 12, 13] Faster recovery will also reduce the substantial costs associated with post-stroke care and communication rehabilitation. The 1-year cost of caring for stroke patients with aphasia was on average $1,700 more than the cost of caring for stroke patients without aphasia.[24]

Visualizing proportions of patients with good outcome on language and motor items after IAT shows that the proportions with good outcome are divergent at 24 hours, but at one week these proportions are similar. However, analyzing the results by ordinal logistic regression, we found that the early effect of IAT on aphasia remains smaller than the effect on motor arm deficit both at 24 hours and at one week, taking into consideration all categories of deficit. Hence, although the outcome at one week is similar for language and motor functioning, the trajectory of recovery differs after IAT from usual care, which is most likely an effect of IAT.

The effect of treatment with intravenous alteplase on early recovery from aphasia compared to other neurologic deficits has been examined previously, but treatment effects are difficult to compare as these studies present results from different time points and had no control group. In a study among 53 patients with an acute middle cerebral artery (MCA) stroke syndrome, aphasia recovered more slowly than limb motor deficit during treatment with tissue plasminogen activator (tPA).[14] In another study in which NIHSS scores were measured 120 minutes after intravenous tPA treatment in 113 patients with MCA occlusion it was found that aphasia responded less than the other impairments.[15] A retrospective cohort study among 243 patients showed a better recovery from other neurologic deficits than aphasia at 24 hours in patients with severe strokes.[16] On the other hand, in another study, similar improvement of aphasia and limb motor deficit was found at 24 hours and one week after stroke in 109 patients who were mainly treated with intravenous thrombolysis.[10] This last study is difficult to compare with the other studies because of the use of composite NIHSS scores by combining the language item with items for cognitive functioning, which were not specifically designed to test language.

There is a tight link between language and motor systems.[25-27] The recovery of these two systems operates on similar principles,[28] so theoretically, aphasia and motor arm deficit contralateral to the affected hemisphere would be expected to show the same recovery pattern. Clinical observations, however, suggest that language deficits in AIS do not respond as rapidly to IAT as motor deficits, which was confirmed by our findings. The most plausible explanation is that the recovery of language processing is more complex than the recovery of the measured motor functions.[23] There is increasing evidence for a neural multifunctionality in the recovery from aphasia, i.e. an interaction between the neural networks engaged in linguistic and nonlinguistic cognitive and emotional functions.[29] Further improvement of language deficits may require time and language therapy. It is reassuring, however, that the proportions of patients with good outcome are similar for motor and language deficits at one week after stroke.

It is remarkable that 58% of the AIS patients in MR CLEAN (288 of 500) had aphasia, compared to 15% to 40% in earlier studies.[6-11] A probable explanation is that only patients with a proven proximal occlusion were included in the present study, while in other studies imaging of intracranial vessels was not routinely performed, resulting in inclusion of patients with more distal occlusions. It is known that the more proximal the occlusion, the higher the risk of aphasia, especially in case of an occlusion of the MCA.[10]

While other studies have reported left lateralized language functioning in at least 96% of the individuals, in the present study only 91% of the aphasic patients had a stroke in the left hemisphere.[23, 30] This implies an uncommonly high proportion of patients with crossed aphasia in our study. However, in the previously cited study among 109 aphasia patients, a similar percentage of patients with aphasia due to left hemisphere stroke of 94% was found.[10] The authors ascribe this to the very early evaluation of their study, as crossed aphasia tends to recover more rapidly.[31-35] In the current study, language deficits were also evaluated in an early stage.

This study has several methodologic limitations. At first, randomization was slightly unbalanced for this post-hoc analysis, because of block size and multiple stratifications in MR CLEAN. This resulted in more patients in the control group than in the intervention group.

Second, in our study the presence of pre-stroke aphasia and pre-stroke motor deficits were not documented. Although we could not rule out preexisting aphasia and motor deficits, the pre-stroke mRS score of 0 in 80% of the patients and the rate of 90% without previous stroke suggests that pre-stroke aphasia and pre-stroke motor deficits were not likely. Higher pre-stroke mRS scores were evenly distributed between the intervention and control group.

Third, the follow-up time of at most seven days after stroke is relatively short to study recovery of neurologic deficits. However, in this first week great improvement of aphasia was observed, especially in patients who were treated with IAT. This therapy induces early reperfusion, occurring within the first hours after stroke. The first week after stroke already gives a good impression of the effect of IAT on the recovery from aphasia. Differences in functioning after this period can be also attributed to adaptation, learning, or rehabilitation, which obscures the effect of IAT on these changes. However, as the recovery from language deficits can be observed up to several weeks after stroke onset, it would have been worthwhile to extend the follow-up period in subsequent studies.[36]

Finally, this study was not specifically designed to investigate and compare language and motor deficits as it is a post-hoc analysis of a randomized trial. The NIHSS provides a coarse categorization for aphasia severity with only four categories, designed to merely detect aphasia and roughly assess the severity. Nevertheless, NIHSS examination is proven to be reliable in the setting of acute stroke evaluation.[19] The assessment of language and motor function is among the most reliable test items.[20] In addition, more advanced tests are difficult to apply in the acute phase after stroke, because these tests are more time-consuming. However, more specific research of treatment effect on different language modalities is needed. A well-known and validated screening tool that can be administered without special training is the Frenchay Aphasia Screening Test, measuring comprehension, expression, reading, and writing in only ten minutes.[37]

Methodologic strengths of this study are the multicenter character, randomized treatment group assignments, and open-label treatment. The broad inclusion criteria led to a wide generalizability of our results. Research on the implementation of IAT is ongoing. Although the positive effect of IAT on functional outcome has been shown, the effects on specific domains are unknown. As yet, studies on aphasia recovery are scarce, so these results are fairly unique.

CONCLUSION

We found that IAT within six hours after stroke onset results in better early recovery from aphasia than usual care alone in patients with a proximal intracranial arterial occlusion of the anterior circulation. Our hypothesis that the very early effect of IAT on aphasia would be smaller than the effect on motor deficit was confirmed, supporting the notion that language, as a more complex function, recovers more slowly than motor function.

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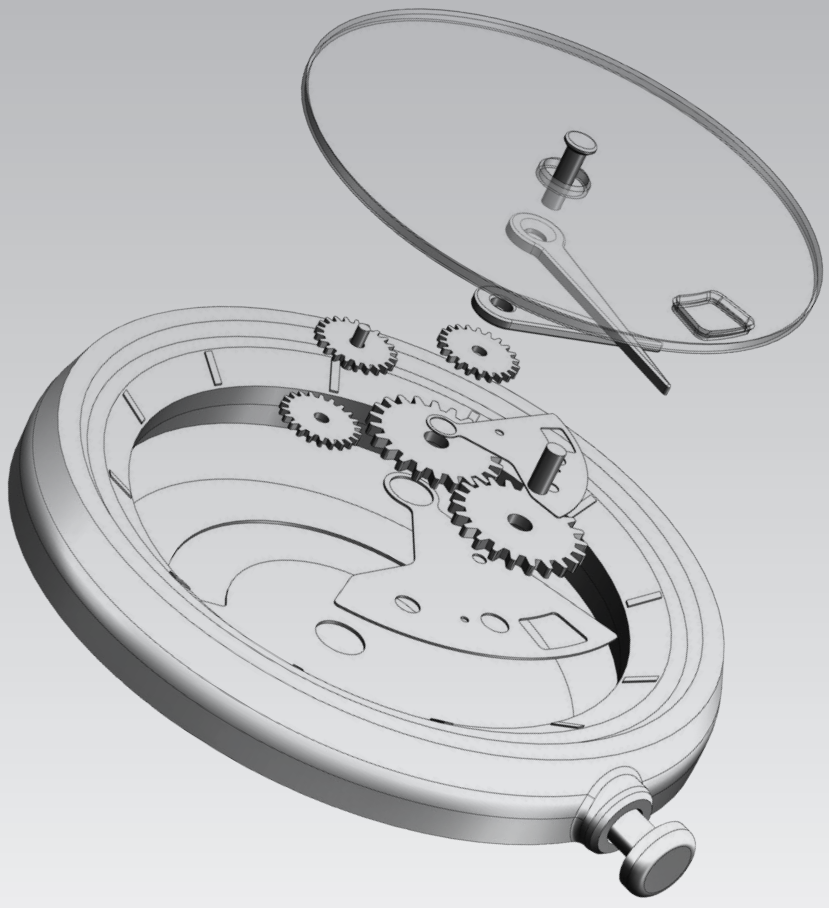

Chapter 3.2

Validation of a prediction model for long-term prognosis of aphasia recovery after stroke

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ABSTRACT

Objective

To externally validate the SPEAK model for the prediction of long-term outcome of aphasia caused by stroke.

Methods

We used data from RATS-3, a multicenter RCT with inclusion criteria similar to SPEAK, an observational prospective study. Baseline assessment in SPEAK was four days after stroke and in RATS-3 eight days. Outcome of the SPEAK model was the Aphasia Severity Rating Scale (ASRS) at 1 year, dichotomized into good (score of 4 or 5) and poor outcome (score <4). In RATS-3 ASRS scores at one year were not available, but we could use six month ASRS scores as outcome. Model performance was assessed with calibration and discrimination.

Results

We included 131 stroke patients with first-ever aphasia. At six months, 86 of 124 patients (68%) had a good outcome, whereas the model predicted 88%. Discrimination of the model was good with an AUC of 0.87 (95% CI: 0.81 to 0.94), but calibration was unsatisfactory. The model overestimated the probability of good outcome (calibration-in-the-large α = -1.98) and the effect of the predictors was weaker in the validation data than in the derivation data (calibration slope β = 0.88). We therefore recalibrated the model to correctly predict good outcome at six months.

Conclusion

After further external validation, the updated SPEAK model, SPEAK-6, may be used in daily practice to discriminate between stroke patients with good and patients with poor outcome of aphasia at six months after stroke. The original model, renamed SPEAK-12, needs further external validation. This study provides Class II evidence that the SPEAK model has good discriminative properties.

INTRODUCTION

Aphasia occurs in approximately 30% of stroke patients and has a strong impact on everyday communication and daily functioning.[1, 2] Shortly after stroke, patients and their family are faced with major uncertainties regarding recovery of communication. Consequently, there is a need for individual estimation of the expected recovery. Adequate personal prognosis may also contribute to optimizing individual care, which is important as medical and paramedical care becomes increasingly personalized.[3] Prediction of aphasia outcome in aphasia due to stroke is often based on models that consist of determinants identified in a single dataset, e.g. age, sex, aphasia severity and subtype; site, size and type of the lesion; vascular risk factors and stroke severity.[4-11] Before a model can be used in daily practice, it should be externally validated.[3, 12] This means that the generalizability of a model is assessed in different cohorts with more recent recruitment (temporal validation), from other institutions (geographical validation), and by different researchers.[3] To our knowledge, none of the few available prognostic models predicting aphasia recovery has been externally validated.[13-16]

Previously, our group has constructed a prognostic model for the outcome of aphasia due to stroke. The model was derived from the dataset of the Sequential Prognostic Evaluation of Aphasia after stroKe (SPEAK) study, and performed well.[13] Aim of the current study was to externally validate the SPEAK model in an independent, yet comparable cohort of stroke patients with aphasia.

METHODS

The SPEAK model

SPEAK was an observational prospective study in 147 patients with aphasia due to stroke conducted between 2007 and 2009 in the Netherlands.[13] Demographic, stroke-related and linguistic characteristics of 130 participants, collected within six days after stroke, were used to construct a model predicting good aphasia outcome one year after stroke, defined by a score of 4 or 5 on the Aphasia Severity Rating Scale (ASRS) from the Boston Diagnostic Aphasia Examination.[17] This scale is often used for rating communicative ability in (semi-) spontaneous speech. The ScreeLing, an aphasia screening test designed to assess the core linguistic components semantics, phonology and syntax in the acute phase after onset, was also used in the model.[18-20] For detailed methods, results and discussion we refer to the original paper.[13] The final SPEAK model contained six baseline variables: ScreeLing Phonology score, Barthel Index score, age, level of education (high/low), infarction with a cardio-embolic source (yes/no) and intracerebral hemorrhage (yes/no) (Box 1). This model explained 55.7% of the variance in the dataset. Internal validity of the model was good, with an AUC (area under the receiver operation characteristic (ROC) curve) of 0.89.[13]

Box 1. The SPEAK model

$$P\ (\text{ASRS} = 4 \text{ or } 5) = e^{y} / (1 + e^{y})$$

y = 2.04 + 0.27(Phonology score) + 0.10(Barthel score) – 0.06(age) – 0.76(education level) + 0.27(cardio-embolic infarction) + 2.18(intracerebral hemorrhage)
e = 2.718 (constant)

Variables:
Phonology Score: score on ScreeLing subpart *Phonology* (score range: 0-24)
Barthel score: score on *Barthel Index* (score range: 0-20)
Age: age at stroke
Educational level: high = 0 (junior high school or middle vocational education up to university), low = 1 (unfinished elementary school up to sophomore high school or lower vocational education)
Cardio-embolic infarction: yes = 1, no = 0
Intracerebral hemorrhage: yes = 1, no = 0

Validation

For external validation of the SPEAK model we used data from the Rotterdam Aphasia Therapy Study (RATS) – 3, a randomized controlled trial (RCT) studying the efficacy of early initiated intensive cognitive-linguistic treatment for aphasia due to stroke, conducted between 2012 and 2014.[21, 22] RATS-3 was approved by an independent medical ethical review board. Details about the study design, methods and results have been reported elsewhere and a summary will be provided below.[21, 22]

Participants and recruitment

A total of 23 hospitals and 66 neurorehabilitation institutions across the Netherlands participated in RATS-3. The majority of participating institutions and local investigators (90%) differed from those involved in SPEAK. In- and exclusion criteria for both studies are presented in Table 1.

Table 1. In- and exclusion criteria for participants in RATS-3 and in the SPEAK cohort

	RATS-3	SPEAK
Inclusion	First-ever aphasia due to stroke	First-ever aphasia due to stroke
	Aphasia ascertained by a speech and language therapist using the 36-item Token Test[23] and a score <5 on the ASRS	Aphasia ascertained by a neurologist and a speech and language therapist
	Testable with the ScreeLing	A score below the cut-off point of the Token Test and/or the ScreeLing
	Within two weeks of stroke onset	Within two to six days of stroke onset
	Age between 18 and 85	Adult
	Language near-native Dutch	Language near-native Dutch
	A life expectancy of >six months	
	Able to tolerate intensive treatment	
Exclusion	A subarachnoid or subdural hemorrhage	
	Success or feasibility of intensive language treatment was severely threatened by:	Presence of one of the following criteria:
	▸ Severe dysarthria	▸ Severe dysarthria
	▸ Premorbid dementia	▸ Pre-stroke dementia (suspected or confirmed)
	▸ Illiteracy	▸ Illiteracy
	▸ Severe developmental dyslexia	▸ Developmental dyslexia
	▸ Severe visual perceptual disorders	▸ Severe perceptual disorders of vision and hearing
	▸ Recent psychiatric history	▸ Psychiatric history

Prognostic variables

Patients with aphasia due to stroke were included in RATS-3 within two weeks of stroke. At inclusion, the following baseline variables were recorded: age, sex, education level, stroke type (cerebral infarction or intracerebral hemorrhage) and ischemic stroke subtype (with or without a cardio-embolic source). Level of independence was estimated with the Barthel Index, a questionnaire containing ten items about activities of daily life.[24] All participants were tested with the ScreeLing to detect potential deficits in the basic linguistic components.[19, 25] Spontaneous speech samples were collected with semi-standardized interviews according to the Aachen Aphasia Test manual.[26] Aphasia severity was assessed by scoring the spontaneous speech samples with the ASRS.

Outcome

In SPEAK, ASRS scores were used to assess aphasia outcome.[17] This six-point scale is used to rate spontaneous speech and ranges from 0: "No usable speech or auditory comprehension" to 5: "Minimal discernible speech handicaps; the patient may have subjective difficulties which are not apparent to the listener". The SPEAK model predicts the occurrence of 'good outcome', i.e. an ASRS score of 4 or 5 after one year. In RATS-3 follow-up was at four weeks, three and six months after randomization. ASRS scores from the RATS-3 cohort at six months after randomization were used as outcome in the analysis, as this was closest in time to the original model.

Statistical analyses

Outcome in the RATS-3 cohort was divided in good (ASRS of 4 or 5) or poor (ASRS <4). To validate the SPEAK model we assessed discrimination and calibration.[3, 12, 27-29] For both analyses predicted probability of a good outcome was calculated using the SPEAK model (Box 1).

Discriminative properties of the model were summarized with the *c* index, similar to the AUC. Good discrimination means that the model is able to reliably distinguish patients with good aphasia outcome from those with poor outcome.

We assessed the calibration properties of the model by studying to what extent the predicted probability of aphasia outcome corresponded with the observed outcome. To construct a calibration plot, we ordered the predicted probabilities of good aphasia outcome ascendingly and formed five equally large groups. Per group, the mean probability of a good outcome at six months was calculated, resulting in five predicted risk groups. Subsequently, in each risk group, proportions were calculated of participants with an observed good outcome. These proportions were plotted against the mean probability of a good outcome predicted by the SPEAK model. Outcomes of the linear predictor *y*, calculated with the SPEAK model, were used to fit a logistic regression model predicting the dichotomous outcome of good versus poor outcome to assess calibration-in-the-large and the calibration slope. If calibration of a model is optimal, the calibration-in-the-large α equals 0 and the calibration slope β equals 1. In case of insufficient calibration we will recalibrate the prognostic model by adjusting the intercept.

Handling of missing data

For participants with missing outcome scores at six months, scores at three months after randomization were used. If no scores were available at three months, patients were excluded. Missing data for the other variables were imputed using simple imputation: for binary and categorical variables the mode was imputed and means were used for continuous variables.

RESULTS

No outcome data at six months were available in 28 of 153 participants, and one participant was excluded because aphasia was later found to be caused by a brain tumor. Reasons for missing outcome data were death (n = 7), serious illness (n = 4), refusal (n = 16) and emigration abroad (n = 1). Of these 28 patients, 21 participants were excluded because outcome at three months was also not available. For 7 participants we used ASRS scores at three months to impute missing values at six months. Baseline data of patients in the validation sample (n = 131), as well as those from the SPEAK cohort (n = 147) are provided in Table 2. Groups differed slightly with respect to the baseline variables sex, level of education, type of stroke and aphasia severity.

Table 2. Baseline model parameters of participants in the original SPEAK cohort and in RATS-3

	SPEAK cohort (n = 147) Derivation cohort	RATS-3 cohort (n = 131) Validation cohort
Age in years, mean (SD)	67 (15)	65 (12)
Female sex, n (%)	78 (53%)	56 (43%)
Level of education, n (%)		
High◊	55 (42%)	60 (46%)
Low△	74 (57%)	71 (54%)
Unknown○	2 (2%)	0
Type of stroke, n (%)		
Non-cardio-embolic infarction	84 (57%)	81 (62%)
Cardio-embolic infarction	42 (29%)	23 (18%)
Intracerebral hemorrhage	21 (14%)	24 (18%)
Unknown○	0	3 (2%)
Time since onset to inclusion in days, mean (range)	4 (2-6)	8 (1-18)
Barthel Index, median (IQR) ○	15 (8-20)	16 (6-20)
ScreeLing Phonology score, mean (SD) □	14 (6)	15 (6.5)
ASRS scores at baseline, n (%)		
Score 0	18 (12%)	17 (13%)
Score 1	28 (19%)	21 (16%)
Score 2	33 (22%)	28 (21%)
Score 3	26 (18%)	38 (29%)
Score 4	27 (18%)	27 (21%)
Score 5	3 (2%)	0
Missing	12 (8%)	0

Abbreviations: n = number; SD = standard deviation; IQR = interquartile range; ASRS = Aphasia Severity Rating Scale.

◊ High = senior vocational education, higher education or university.

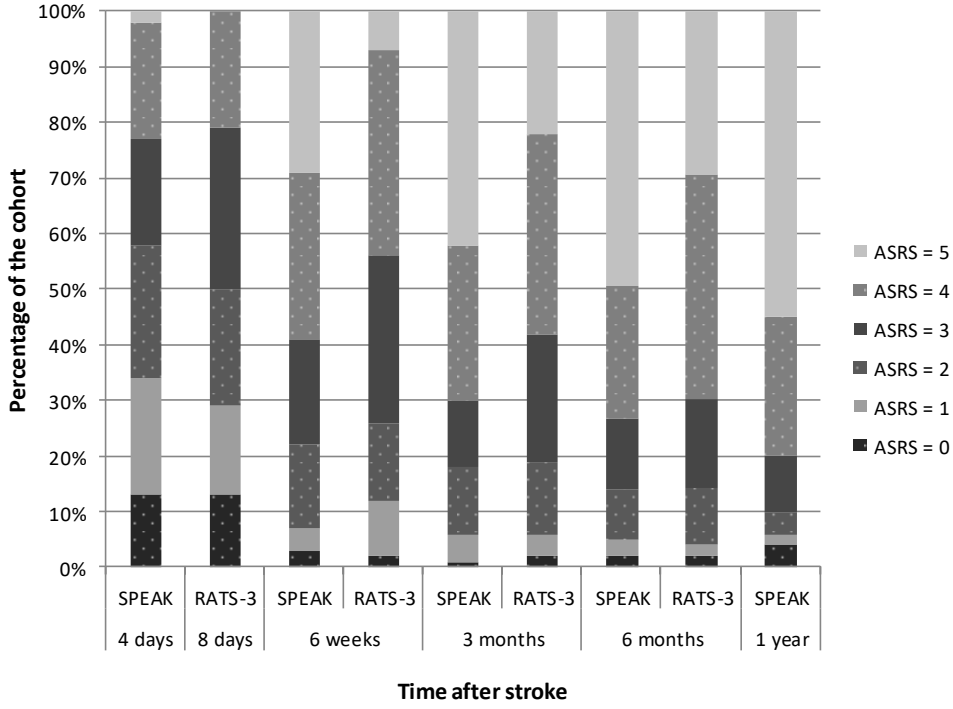
△ Low = no/unfinished elementary school, elementary school, unfinished junior secondary vocational education or junior secondary vocational education.

□ ScreeLing Phonology scores range from 0 to 24.

○ Imputed scores used for analysis: level of education = low; type of stroke = non-cardio-embolic infarction; Barthel Index score (n = 14) = 13.

In the derivation SPEAK cohort (n = 130), 11% of the patients had an ASRS score of 4 or 5 at baseline (four days after stroke) and 78% had a good outcome after one year. In the RATS-3 cohort we found a proportion of 21% with a score of 4 or 5 at baseline (eight days after inclusion) and 68% at six months. This is comparable to the 74% in SPEAK at six months. The course of ASRS scores in the RATS-3 and SPEAK cohort over time is presented in Figure 1.

Figure 1. ASRS scores over time in SPEAK and RATS-3

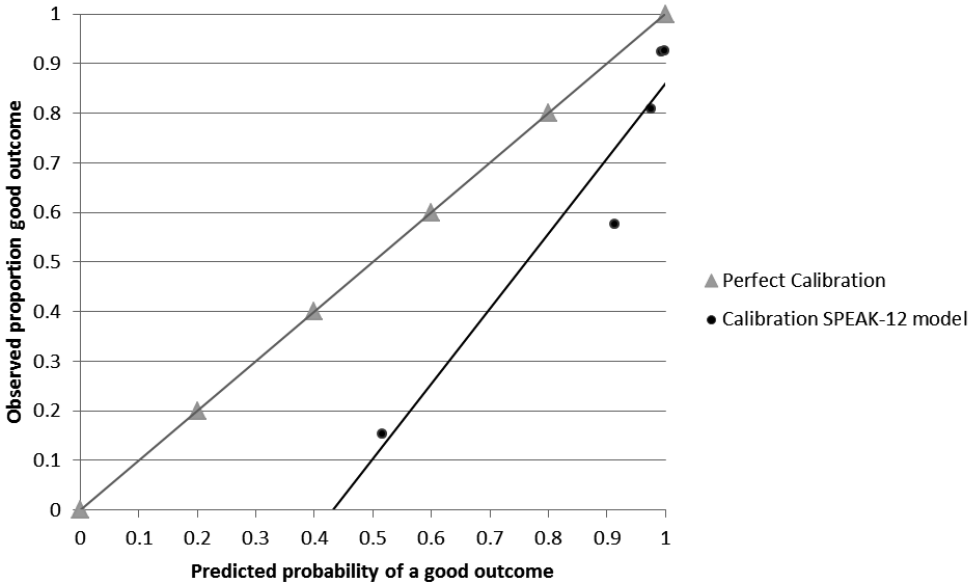


ASRS scores: 5 = minimal discernible speech handicap, some subjective difficulties that are not obvious to the listener; 4 = some obvious loss of fluency in speech or facility of comprehension, without significant limitation in ideas expressed or form of expression; 3 = able to discuss almost all everyday problems with little or no assistance, reduction of speech and/or comprehension; 2 = conversation about familiar topics is possible with help from the listener, there are frequent failures to convey an idea; 1 = all communication is through fragmentary expression, great need for inference, questioning and guessing by listener, limited information may be conveyed; 0 = no usable speech or auditory comprehension.

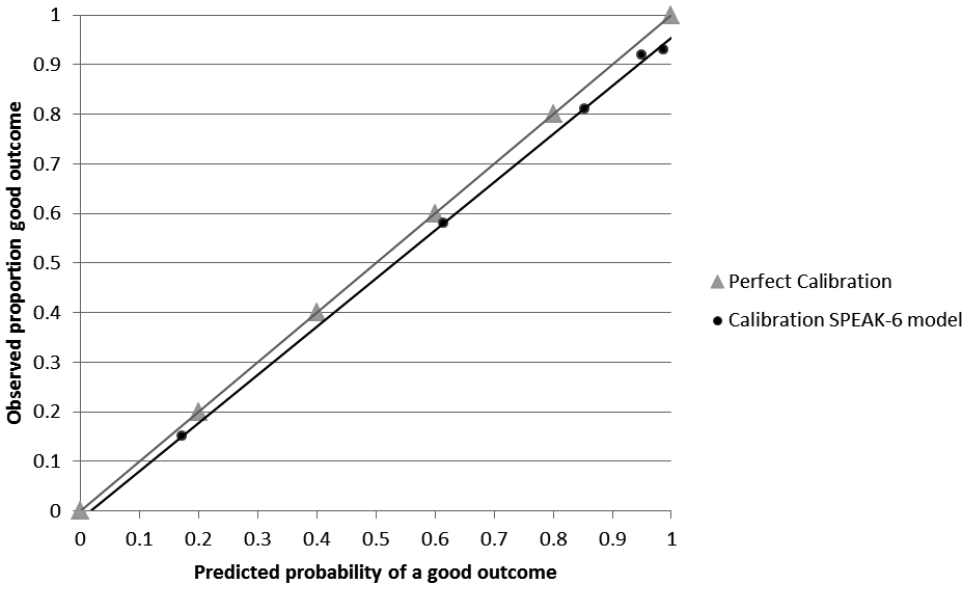
Discrimination of the SPEAK model was good, with an AUC of 0.87 (95% confidence interval, 95% CI: 0.81 to 0.94). In Figure 2A, the grey line depicts calibration of a hypothetically perfect model and the 5 dots represent calibration values in the five subgroups of patients, ordered by increasing predicted probabilities and plotted against the actual proportions of good outcome. The mean predicted probability of good aphasia outcome at one year was 88%, while the observed percentage was 68%, but this was measured at six months. The SPEAK model was too optimistic in predicting good aphasia outcome, with calibration-in-the-large of α = -1.98. The calibration slope of β = 0.88 indicated that the predictor effects were slightly weaker in the validation data than in the derivation data.

Figure 2. Calibration plots of the SPEAK model and updated SPEAK model with predicted probabilities and observed proportions of good aphasia outcome

A. Calibration plot of the original SPEAK model, SPEAK-12



B. Calibration plot of the updated SPEAK model, SPEAK-6



As Figure 1 shows that there is still improvement after six months, we assume that the poor calibration-in-the-large is at least partly due to the different timing of the outcome measurement; six months versus one year. Thus, we updated the SPEAK model to predict outcome at six months, instead of one year, by adapting the intercept (Box 2). After revising the SPEAK model, the calibration slope remained β = 0.88, but calibration-in-the-large improved considerably: α = -0.24 (Figure 2B). We suggest renaming the original SPEAK model predicting outcome at one year after stroke into SPEAK-12 and naming the updated model SPEAK-6.

Box 2. The updated SPEAK model, SPEAK-6

$$P\ (\text{ASRS} = 4 \text{ or } 5) = e^{y} / (1 + e^{y})$$

y = 0.06 + 0.27(Phonology score) + 0.10(Barthel score) – 0.06(age) – 0.76(education level) + 0.27(cardio-embolic infarction) + 2.18(intracerebral hemorrhage)
e = 2.718 (constant)

Variables:
Phonology Score: score on ScreeLing subpart *Phonology* (score range: 0-24)
Barthel score: score on *Barthel Index* (score range: 0-20)
Age: age at stroke
Educational level: high = 0 (junior high school or middle vocational education up to university), low = 1 (unfinished elementary school up to sophomore high school or lower vocational education)
Cardio-embolic infarction: yes = 1, no = 0
Intracerebral hemorrhage: yes = 1, no = 0

DISCUSSION

We aimed to externally validate the published SPEAK model for the long-term prognosis of aphasia due to stroke using data from an independent cohort of stroke patients with aphasia, RATS-3. The SPEAK model performed very well in terms of discrimination. However, calibration was suboptimal, as it was overoptimistic in predicting good aphasia outcome, partly due to the difference in timing of the outcome which was one year in SPEAK and six months in RATS-3. Therefore, we proposed an updated version of the SPEAK model for the prediction of outcome at six months.

Prognostic models are used in clinical practice to predict possible outcomes or risks of acquiring certain diseases. To our knowledge, apart from the SPEAK model, only three other models to predict recovery from aphasia due to stroke have been published.[14-16] One logistic regression model predicting early clinical improvement in stroke patients with aphasia was constructed based on findings from CT-angiography and CT-perfusion.[15] Clinical applicability of this model is limited, as these detailed CT-data are rarely available in daily practice. Another logistic regression model addressed the effect of speech and language therapy (SLT) on aphasia recovery.[14] The authors found that the amount of SLT, added to baseline aphasia severity and baseline stroke disability significantly affected communication four to five weeks after stroke. Baseline variables were recorded within two weeks of stroke. Recently, a model was published predicting everyday communication ability (Amsterdam-Nijmegen Everyday Language Test; ANELT) at discharge from inpatient rehabilitation based on

ScreeLing Phonology and ANELT scores at rehabilitation admission.[16] These models predict outcome of aphasia recovery only in patients treated with SLT, but do not predict outcome before treatment is initiated. Furthermore, in both studies the cohort included only patients eligible for intensive treatment.

In order for a prognostic model to be completely valid and reliable, it is important to evaluate the clinical applicability and generalizability of the model.[30] Inclusion criteria in SPEAK and RATS-3 were not strict, so that both cohorts can be considered representative of acute stroke patients with aphasia in general. The SPEAK model is valuable for predicting aphasia outcome early after stroke in clinical practice, as it includes easily available baseline variables.[13] It requires only the Barthel Index score and the ScreeLing Phonology score to be collected outside clinical routine. The Barthel Index is commonly assessed in the acute phase, allowing for application of this model without much effort.[31]

Our study is the first to validate a model for the prognosis of aphasia outcome in an independent cohort. Determining whether a model generalizes well to patients other than those in the derivation cohort, is crucial for the application of that model in daily practice.[12, 27, 28, 30] We found that the SPEAK model is able to adequately distinguish stroke patients with aphasia who will recover well with respect to functional verbal communication from patients who will not. The model appears less accurate when it comes to the comparison of predicted and actual good outcome.

A first possible explanation may be the different intervention in the two studies. In SPEAK, patients received usual care and researchers did not interfere with the treatment provided. In RATS-3, treatment was strictly regulated, as in this RCT patients were randomly allocated to four weeks of either intensive cognitive-linguistic treatment or no treatment, starting within two weeks after stroke. After this period both groups received usual care, as in SPEAK. In RATS-3 we found no effect of this early intervention and both intervention groups scored equally on all outcomes. Thus, we believe treatment does not explain the poor calibration.

Second, there was a difference between SPEAK and RATS-3 with respect to the interval between stroke onset and inclusion of patients. In SPEAK, patients were included on average four days after onset and in RATS-3 after eight days. This seemingly small difference might in fact have caused substantial differences in the prognostic effect of the baseline ScreeLing and Barthel Index scores. Recovery can occur rapidly early after stroke, as was shown in the SPEAK cohort, with a statistically significant improvement on the ScreeLing Phonology score between the first and second week after stroke.[32] Hence, these predictors might have different effects in the RATS-3 cohort, as represented in the suboptimal calibration slope.

Third and most importantly, calibration may likely have been influenced by a different follow-up duration, which was six months in RATS-3 versus one year in SPEAK. In SPEAK, ASRS scores improved significantly up to six months after aphasia onset, but no significant improvement was found between six and twelve months.[32] We used this finding for the design of the present study to justify the earlier time point for the outcome in RATS-3. Although in SPEAK no statistically significant improvement on the ASRS was found between six and twelve months after stroke, some improvement still occurred.[32] Of the participants from SPEAK 74% had an ASRS score of 4 or 5 at six months after stroke, which is fairly similar in RATS-3 at that time point (68%). It is likely that calibration would have been better if the outcome was determined at twelve months in the RATS-3 cohort, because of the small, but apparent recovery between six and twelve months after stroke. We therefore suggest an

updated version, SPEAK-6, to predict outcome at six months. More extensive updating could imply refitting the models to the new dataset, to obtain new model coefficients. [33-35] However, as the model discrimination was good, we updated only the intercept to make the model applicable to predict outcome at six months, when the average probability of a good outcome is lower than at one year. We recommend that the updated SPEAK-6 is validated in the future in new independent datasets.

This study shows again that the external validity of prognostic models in new settings should always be carefully assessed. However, it should also be noticed that perfect calibration might in fact be impossible, as it implies that a model perfectly predicts outcome for all patients.[36]

Strengths and limitations

The major limitation of this validation study is the difference in time post onset at which predictor and outcome data were collected. Strength is that the RATS-3 and SPEAK cohorts are comparable, due to similar inclusion criteria. However, whereas participation in SPEAK merely involved periodic language evaluations, RATS-3 was an intervention trial, with either early intensive treatment or no early treatment. Due to these experimental interventions many patients refused participation. Also, selection criteria for RATS-3 were slightly stricter than in SPEAK regarding the potential to receive early intensive treatment. Consequently, the SPEAK and RATS-3 cohorts might represent slightly different populations of stroke patients with aphasia, albeit closely related.[27] Therefore, as in all clinical trials, one must be careful in generalizing the results to all stroke patients with aphasia.[37]

Although both the derivation cohort and the validation cohort consist of well over a hundred participants, sample sizes may be considered rather small for adequate modelling.[29, 37] This is reflected in the slight imbalance of baseline characteristics between both study cohorts. This imbalance may underpin the necessity of larger sample sizes to better reflect the population of stroke patients with aphasia.

A much debated issue is the potential lack of sensitivity of rating scales for analyses of spontaneous speech in aphasia.[38] In the current study, we dichotomized outcome, further reducing sensitivity. It can be argued that the definition of “good outcome” with an ASRS of 4 or 5 is somewhat optimistic. A score of 4, or sometimes even 5, does not imply full recovery. Patients with a score of 4 still experience difficulties with word finding or formulating thoughts into language.

The ScreeLing is currently only available in Dutch, which severely limits the applicability of the prediction model. However, translation into other languages should not be very complicated as the ScreeLing Phonology subscale contains well-known tasks to measure phonological processing, e.g. repetition, discrimination of minimal pairs, and phoneme/grapheme conversion.[20]

Finally, the RATS-3 database contained several missing values. Of the participants who refused evaluation at six months, three had fully recovered, which may have introduced a slight bias. Missing values for other variables in the model mostly resulted from inconsistencies in reporting the scores. We used generally accepted methods for imputation of the data and for most variables few data were missing (<5%).[28] For the Barthel Index 10% had to be imputed, which is a fairly large proportion. There were no clear reasons for these missing values, other than clinicians sometimes just forgot to fill out the score form, which in our view justifies imputation.

CONCLUSION

The original SPEAK model, renamed SPEAK-12, performs well in predicting language recovery after one year in patients with aphasia due to stroke. As calibration was initially unsatisfactory, we propose an updated version of SPEAK-12 for the prediction of the probability of good language outcome at six months: SPEAK-6. Further external validation of SPEAK-12 and SPEAK-6 is recommended. Special attention should be given to timing, as time after stroke onset at which predictors and outcome data are collected appears crucial for adequate model validation. Our results show that SPEAK-6 may be used in daily practice to discriminate between stroke patients with good and patients with poor language recovery at six months after stroke.

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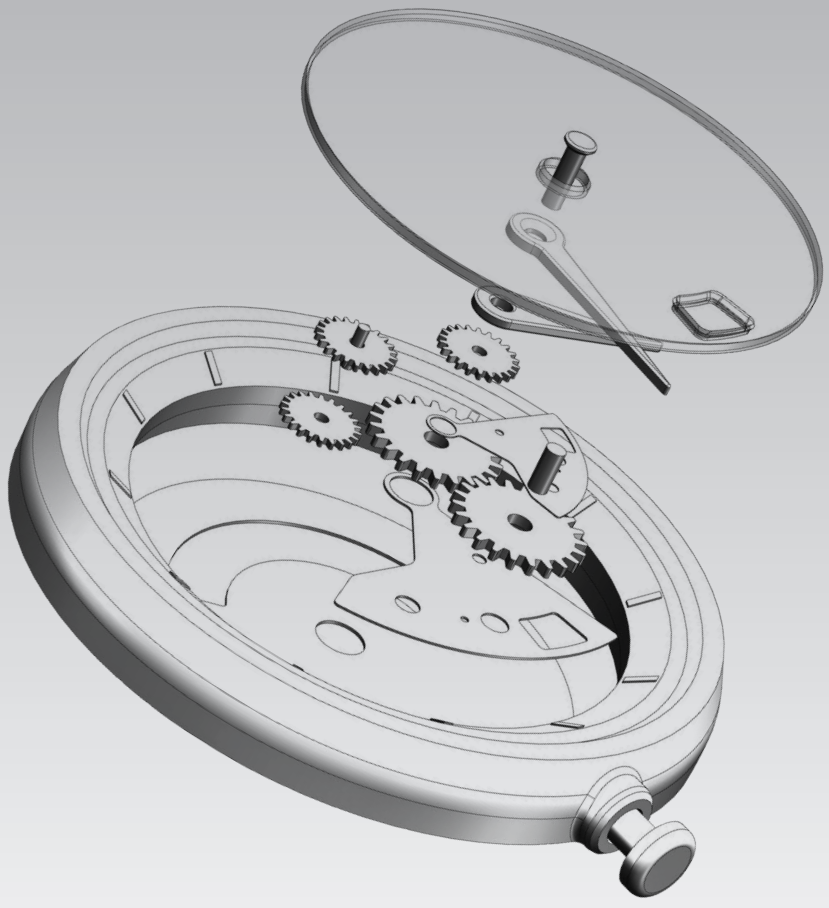
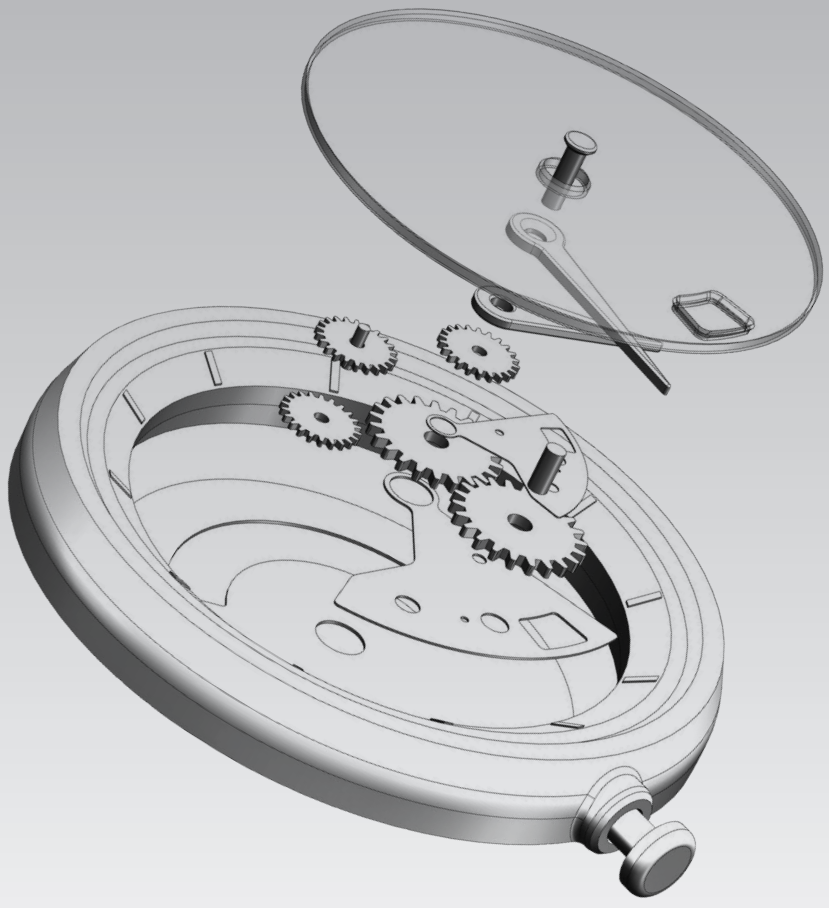


Chapter 4

Treatment of aphasia



Chapter 4.1

Optimal timing of speech and language therapy for aphasia after stroke; more evidence needed

Nouwens F, Visch-Brink EG, van de Sandt-Koenderman WME, Dippel DWJ, Koudstaal PJ, de Lau LML.
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ABSTRACT

Background

Aphasia due to stroke affects communication and quality of life. Most stroke survivors with aphasia receive speech and language therapy. Although an early start of treatment is advocated in clinical practice, evidence for "The earlier, the better" in aphasia rehabilitation is weak.

Hence, clinicians are faced with the dilemma when to initiate intensive treatment: as early as possible, when most of the spontaneous recovery occurs but when patients are often ill, or later, when the patients' condition is more stabilized.

Methods

In this literature-based overview, we discuss whether aphasia outcome is affected by timing of treatment in relation to stroke onset and whether there is evidence for an optimal window of time during which language therapy should be provided. Findings from various rehabilitation research fields are discussed and combined to provide principles for future research.

INTRODUCTION

Approximately one-third of stroke patients have aphasia, a deficit potentially affecting all language modalities.[1] People with aphasia (PWA) generally receive speech and language therapy (SLT) to enhance their communication. A recent large survey among stroke survivors, their caregivers and health professionals, placed treatment of aphasia as third in the top ten priorities in stroke research. This underlines the dramatic consequences of aphasia for communication and quality of life.[2]

When studying the efficacy of SLT, many factors need to be taken into account, because SLT comprises many different therapeutic interventions and strategies, not all of which have been thoroughly studied.[3] When to start SLT after stroke, i.e. timing of treatment, is an important clinical issue.

In general, the field of stroke rehabilitation tends to promote early initiation of treatment.[4-9] Well-known, often expert-based statements about rehabilitation advocate "The earlier, the better" and "Use it or lose it". Supposedly, early therapy is more effective than treatment initiated at a later stage, because of the interaction between spontaneous and learning-dependent neural recovery processes.[10, 11] However, there is no conclusive evidence supporting these notions.[4, 12, 13]

Also for SLT, evidence supporting immediate treatment is weak, since as yet timing of treatment has received little attention in aphasia research. The authors of the latest Cochrane review are unable to draw any conclusion regarding optimal timing of SLT.[1] They found a wide variation between stroke onset and initiation of treatment in trials, ranging from two days to 22 years, hampering comparison across studies. None of the trials directly studied the effect of timing on the efficacy of SLT by comparing early initiated treatment with later initiated treatment. In fact, the authors, as well as other experts in the field, call upon future researchers to study the effect of timing of aphasia treatment.[1, 4, 14]

Hence, clinicians are faced with the dilemma whether they should provide treatment as soon as possible after stroke, or initiate therapy later. Some patients are physically weak immediately after stroke and the treating physician may consider SLT not feasible or even hazardous in this stage. Physicians have to take patient related factors into account, but are also faced with changing health care policy and budget cutbacks.

We conducted a literature search in PubMed and Embase with the search terms: early, treatment, aphasia and stroke; and found no trials primarily studying the effect of timing of SLT for aphasia due to stroke on treatment efficacy in the acute stage. Hence, we aim to explore the evidence for current recommendations in clinical practice by summarizing what we do know about aphasia treatment in different stages after stroke and by using recovery models derived from neuroimaging studies, animal studies and studies on motor rehabilitation.

What exactly do we mean by timing of post-stroke rehabilitation? Definitions of early and late stages in the recovery process of language.

In order to evaluate the influence of timing of SLT on language recovery, agreement is required about the terminology used to describe stages of recovery after stroke. There is a difference between fields regarding the terms used to define stages in recovery from stroke. Clinicians often identify three stages: the acute, sub-acute and chronic stage, a distinction that seems to coincide with availability of rehabilitation resources. The acute stage is the

phase of hospitalization and the sub-acute phase the period of active rehabilitation after discharge from the hospital or acute stroke unit. The chronic stage is the final phase, when treatment intensity gradually diminishes and treatment is often focused on compensation, rather than restoration of function.[4, 12, 15]

Authors reporting randomized controlled trials (RCT) on aphasia treatment use a variety of terms referring to different stages after stroke onset. These terms are usually related to phases in the rehabilitation process rather than changing neurophysiological processes. In an RCT on *very early SLT,* Laska et al. start therapy within two days after stroke,[16, 17] whereas Bowen and colleagues define *early* as the first four months after stroke.[14] Godecke et al. published on the efficacy of *early initiated* SLT, defining the *very early* phase as within two weeks after stroke and the *early* phase as the period from two to six weeks after stroke.[18]

Commonly used terms in neuroimaging literature on aphasia recovery are the hyper-acute, acute, sub-acute and chronic phase.[19-25] There is a lack of consensus on the differentiation between stages and the duration of each of these phases. Some denominate the first hours after stroke as the acute stage, but others claim this phase lasts up to a week. The same holds for the outset of the chronic stage, which may be from two months up to more than six months after stroke.[19, 20, 22, 24, 26, 27]

Despite this large variety and seemingly arbitrariness in using these different terms, there is a certain consensus on differentiating at least between an *early* or *acute* stage in which spontaneous recovery occurs and a *late* or *chronic* stage in which spontaneous recovery has virtually ceased. Based on the fact that several studies indicate that the first three months, and specifically the first six weeks, after stroke are the most dynamic period in the recovery process, we suggest using *acute stage* for the first three months after stroke and *chronic stage* for the period after three months.[24, 25, 28-30]

What do we know about recovery processes in the language system of PWA? Evidence from neuroimaging studies.

Continuously improving imaging techniques have increased our understanding of the brain, its functions and its response to acute focal damage occurring after stroke.[24, 31, 32] Results from studies using fMRI, CT and PET-scans have shown that distinct stages can be recognized in the process of post-stroke language recovery.[19-21, 33, 34]

fMRI studies support the existence of at least three phases.[20, 21, 26] Immediately after stroke, not only functions of brain areas that are involved in the lesion are disrupted. Unaffected areas, functionally connected to the lesion, become dysfunctional as well, as a consequence of edema or reduced metabolism; a condition called diaschisis.[19-21, 26] This may result in a general breakdown of the language system, often manifesting as global aphasia.

In the next phase, diaschisis resolves and unaffected brain regions regain their function. In hours to days after stroke, vulnerable tissue of the penumbra (partly) recovers as a result of reperfusion.[19, 21, 26] In this phase language activation is observed in preserved areas in the left hemisphere, but there may also be increased activation in homologue regions in the right hemisphere.[19, 21, 34, 35] This latter activation might occur as a result of disinhibition of the right, non-dominant, hemisphere.[35] If persistent, this might be interpreted as a, possibly maladaptive, compensation mechanism.[26, 36] The size of the lesion likely plays a role in this activation shift, simply because in case of a large lesion in the left hemisphere there is not much tissue left to form a new language network.[26] Until now it is unknown whether activation in the right hemisphere enhances or disturbs language processing.[21]

The third phase is characterized by further reorganization of functional networks and compensation.[26] Activation in this chronic stage is observed in unaffected areas in the left hemisphere, perilesional tissue and homologue regions in the right hemisphere. In this final phase, activation favorably might shift back to the left hemisphere.[20, 21, 37]

Given these different phases, each with specific ongoing recovery processes, it is very likely that the efficacy of various therapeutic strategies will interact with these processes, and thus with the time elapsed after stroke.

Does timing of SLT in post-stroke aphasia matter in relation to neural reorganization and language recovery? Hypotheses derived from observations of recovery processes.

After a stroke, patients spontaneously learn new behavior as a result of natural adaptation to their impairments.[38] Consequently, if PWA adapt to language deficits by using alternative language production strategies, such as telegraphic speech, remaining neural networks for language processing are less intensively triggered, causing 'learned non-use'. This learned non-use may prompt new neural networks, so-called 'experience-driven plasticity', that function suboptimally compared to the original language network.[38-40] To prevent these maladaptive processes from occurring, it seems crucial to start early with SLT.

Generally spoken, SLT can be aimed at restoration of function or at compensation.[41] Restorative treatment focusses on regaining language processing by using the remaining linguistic network.[40, 42] Compensational treatment is aimed at learning new verbal or nonverbal strategies to compensate for language deficits, for instance by integrating alternative methods of communication with residual language capacities.[43]

It has been suggested that these two approaches should be timed differently after stroke, because they compete for available plasticity.[23, 44] Code describes language recovery processes after stroke in a theoretical framework, taking into account different levels and stages of recovery as result of restoration and compensation.[23] According to this framework, restorative treatment is specifically effective when spontaneous recovery takes place, i.e. when the neural network is able to restore. Impairment-based restorative treatment is directed at specific linguistic processes such as phonology, semantics or syntax. This supposedly triggers the premorbid, yet weakened, language network and prevents the formation of new networks at the cost of the original one.[45] However, one may question whether it will ever be possible to restore such a complex system as the language system after stroke and whether the language system will ever function normally again.

Only after true restoration has stabilized, compensational treatment should be applied, triggering plasticity or treatment induced reorganization to further enhance communication.[23] Yet, this hypothesis was not confirmed by results from an RCT comparing six months of restorative cognitive-linguistic treatment to compensatory, communicative treatment, started within three weeks of stroke onset.[41] The authors found no statistically significant difference in the recovery of functional communication between the two treatment types.

Some widely applied principles for effective treatment, such as massed practice, behavioral relevance and focusing principles, are derived from 'Hebbian learning', based on the idea that "Cells that fire together, wire together".[39, 40, 46] Treatment intensity plays an important role in these principles. However, in the latest Cochrane review on efficacy of SLT in aphasia, the authors conclude that "The potential benefits of intensive SLT over conventional SLT were confounded by a significantly higher dropout from intensive SLT".

This raises questions about the feasibility of intensive SLT, especially shortly after aphasia onset.

Language reorganization may occur in the dominant left hemisphere or in homologous regions in the right hemisphere.[23, 25, 47, 48] The explanation for this recruitment of the non-dominant hemisphere has been subject to debate; it occurs either as a result of 'transcallosal disinhibition', or language processing is incorporated by the right hemisphere, the so-called 'laterality-shift'.[35] It has been argued that persistence of the spontaneously occurring increased activation of the right hemisphere shortly after stroke onset is suboptimal.[19, 26, 35, 36] Hence, the dominant hemisphere should be triggered, either through sensory or motor routes or by inhibition of the contralateral hemisphere.[35, 37]

Several authors suggest that activating the left hemisphere is especially achieved by cognitive-linguistic treatment (CLT). CLT supposedly activates cortical networks involved in language processing, such as networks dedicated to phonology, semantics and syntax. [23, 49, 50] Functional MRI-scans revealed that specific language tasks activate distinct parts and networks of the brain.[20, 31] One may hypothesize that when metabolic demands increase through activation of cortical language areas, adjacent penumbral tissue will benefit, especially when circulation is already restored by reperfusion therapy.

The penumbra in ischemic strokes comprises the region around the core lesion in which blood flow is decreased, but can still be revived if blood flow has not decreased more than 90%, as was shown in animal studies.[33] Several techniques have been used to increase blood flow to the penumbra to save brain tissue and support recovery in the acute stage of ischemic stroke, such as intravenous or intra-arterial thrombolysis or mechanical thrombectomy.[33] The therapeutic window for reactivating the penumbra is yet unknown and it is unclear whether early SLT might save or rather damage penumbral tissue.[33]

It seems beneficial to speed up the process of the activation shift back to the left hemisphere, since that shift is associated with better language outcome, as was shown in language tests and MRI-scans.[26, 34, 37] Background of these propositions is that language is left lateralized and that language processing is optimal if it is performed by the dominant left hemisphere. However, more and more it is recognized that language is a function of a complex bilateral network, so this hypothesis might be too simplistic and needs modification.[35, 51]

What do we know about the importance of timing of SLT in post-stroke aphasia? Evidence from RCTs on early SLT.

The efficacy of SLT has been studied extensively in the chronic phase after stroke, presumably because recruiting of subjects is easier in this, more stable, phase and ethical issues concerning not providing therapy as a control condition are no longer a potentially limiting factor.[1] Furthermore, spontaneous recovery has ceased, which enables researchers to compare treatment effects with a stable control condition.

A systematic review showed that time since onset did not affect response to treatment in subjects with aphasia existing for more than one year.[52] In a meta-analysis of 55 studies on aphasia treatment, the authors found that the effect of language treatment started in the first three months after stroke was larger than when treatment was initiated beyond three months.[30] However, the methodological quality of included studies was not assessed, many of the studies were not controlled or randomized and, more importantly, the meta-analysis did not contain any study directly comparing early with later initiated treatment.

Nevertheless, some support for the authors' conclusion comes from an RCT on the efficacy of Melodic Intonation Therapy (MIT), showing that MIT initiated before three months post onset was more effective than MIT initiated after three months.[25]

Recently, several trials have been published on the efficacy of *early* initiated SLT for aphasia due to stroke.[14, 16, 17, 53-56] None of these studies directly compared early with later initiated SLT. Again terminology is confusing, because the starting point of the treatment denominated as 'early' in these studies varies from two to thirty days after stroke. We will only discuss trials truly starting early after stroke; i.e. within the first week.

Laska et al. randomized 123 PWA to either 21 days of 45 minutes SLT per weekday, initiated within two days after stroke, or no therapy until three weeks after randomization.[17] No significant differences were found between groups on the primary outcome measure Amsterdam-Nijmegen Everyday Language Test[57] (ANELT) after three weeks (median ANELT score in the early group was 1.3 versus 1.2 in the control group; p = 0.37) and after six months (median ANELT score in the early group of 1.8 versus 3.0 in the control group; p = 0.49). This suggests that early therapy has no advantage over therapy started after three weeks. Yet, it is unclear whether the intended treatment intensity was reached in all subjects and whether this was sufficient to add a therapy effect on top of spontaneous recovery.

Positive results were found in two pilot RCTs studying the efficacy of very early initiated, daily SLT. In the first study, PWA benefitted more from daily therapy started on average three days after stroke than from usual care, which was not more than one therapy session per week.[54] Furthermore, the dropout rate was not higher in the early intensive group. The authors conclude that early intensive SLT is both feasible and beneficial early after stroke.

A second pilot RCT comparing SLT every workday, initiated two days after stroke, with no SLT for two weeks, found similar results.[56] After two weeks and after six months, the early SLT group showed better performance on the Aachen Aphasia Test and fMRI-scans showed different activation patterns after two weeks. In the early SLT group, recruitment of the left hemisphere, especially the inferior frontal gyrus, was greater than in the no SLT group. The authors claim that early SLT triggers early recruitment of language related areas in the left hemisphere, resulting in better language performance.

Although these trials show promising results, due to the paucity of large well-designed RCTs it remains impossible to decisively determine whether PWA tolerate intensive SLT shortly after stroke and whether it is beneficial to start language therapy very early after stroke.[1, 17, 54, 56]

What do we know about the importance of timing of treatment after stroke? Lessons to be learned from studies on motor rehabilitation in animals.

To obtain clues about the optimal timing of SLT, it may be useful to also consider what is known about the effect of timing of therapy in motor recovery. Prior to studying rehabilitation techniques in humans, many studies have been performed on mice, rats and primates. Timing of treatment has been one of the topics of interest.

In an overview of studies on forced-use therapy in animals with an induced stroke, the authors conclude that early initiated therapy results in increased cortical reorganization and improved recovery, and that the effect of therapy attenuates with a longer delay between stroke and start of treatment.[10] However, they also mention that treatment initiated too soon after stroke might be detrimental, probably due to changes in neurotransmitter levels that might exacerbate brain injury. For instance, in a study performed in rats with induced

infarcts, lesion size increased due to hyperthermia in the perilesional area after constraint-induced movement therapy (CIMT; restraining the unaffected limb in order for the affected limb to be used), initiated 24 hours after stroke.[58] In another study, rats with induced brain infarcts were placed either in standard cages with no training, or were provided with early training (24 hours post onset) or late training (seven days post onset) in enriched environment cages.[59] Both groups of rats placed in the enriched environments performed significantly better than rats in standard cages, with the late training group performing best overall. Infarct sizes were significantly larger in the early group compared to both other groups, indicating that starting too early might be harmful.[10]

Research on recovery of motor functioning in animal models has shown that after a stroke brain regions around the infarct become temporarily hyperexcitable, due to neurotrophic changes.[10, 24, 32, 37, 44, 60] In most cases, stroke causes a loss of innervation and an imbalance of network activation and inhibition, which triggers positive adaptation.[32] Animal studies have shown that levels of genes and proteins involved in neuronal and dendritic growth, and synaptogenesis early in life also increase after a stroke.[37, 60, 61] This offers an ideal condition for neuroplasticity and pleads for an early start of rehabilitation to optimally profit from these temporary changes.[61]

A limited window of time for optimal rehabilitation is suggested by results from a study comparing three starting points of Enriched Rehabilitation (ER) for rats with induced ischemia.[62] Rats exposed to ER five days after stroke performed best on functional outcomes, and rats exposed after 14 days also improved, but less pronounced. The benefit of ER diminished in rats that were exposed to ER after 30 days, as they performed equally to rats receiving no training.

As mentioned above, it has been suggested that early treatment should aim at regaining normal functioning. An example of training focused on normal functioning is CIMT. Evidence for this form of forced-use therapy is equivocal.[10, 32, 37, 63] Some authors report that with CIMT cortical representations are retained, but others report increased cell-loss due to hyperthermia and changed neurotransmitter levels by which the lesion size increases.[10, 32, 37, 60, 61, 63] The authors of a review and meta-analysis conclude that there is no evident benefit of CIMT on neurobehavioral measures, and state that they cannot draw any conclusions about the optimal time to start CIMT.[63]

The effect of task-specific training regimens such as CIMT may be augmented by placing animals in an enriched environment, since animals are thereby challenged to engage in normal behavior. This supposedly enlarges spontaneous recovery processes, by triggering original neural networks.[44, 60]

In conclusion, animal studies on motor rehabilitation have provided us with three findings: (1) there is a critical window of time in a relatively early stage after stroke in which the brain is more sensitive to rehabilitation, (2) starting intensive treatment very early after stroke may be detrimental due to extended damage to the penumbra, and (3) a challenging, enriched environment augments spontaneous recovery.[10] Evidently, results from these studies on motor recovery in animals do not necessarily translate to language recovery in humans.[61, 63]

What do we know about the importance of timing of treatment after stroke? Lessons to be learned from studies on motor rehabilitation in humans.

More than a decade ago the importance of timing of motor rehabilitation was addressed in an observational study in stroke patients with matched controls (n = 135).[64] Allocation depended on an administrative waiting list. Three rehabilitation start intervals were compared: early (<20 days after stroke), intermediate (21 to 40 days) and late (41 to 60 days). An early start was associated with better outcome, but it is unclear whether inclusion and attrition bias may have confounded these results.

In a large prospective observational cohort study (n = 969), the relationship between several factors in the rehabilitation process and clinical outcomes was studied.[65] A significant association was found between an earlier start of rehabilitation and better functional outcomes. This association was strongest in severely affected patients. A longer time interval between stroke onset and start of rehabilitation was correlated with lower total scores on the Functional Independence Measure at discharge and lower functional motor independence scores in a subset of participants with moderate and severe strokes (n = 830).[13] These results must be confirmed in an RCT in order to rule out selection bias, control for patient differences and to study causality instead of association.

In a study based on a retrospective chart review (n = 435), significantly better functional outcome scores were found in patients who were admitted to rehabilitation within 30 days after stroke, than in those starting after 30 days.[66] An early start was also associated with earlier discharge from the rehabilitation center. The group with deferred rehabilitation improved also, but not as much as the early group and it took them longer to recover. Findings such as these were summarized in a European evidence-based guidance document for stroke rehabilitation, in which the authors conclude that early initiated rehabilitation seems beneficial in medically stable patients.[4]

However, Teasell et al. have argued that many observational studies perhaps wrongly conclude that an early start is causally related to better outcome, as findings might in fact be explained by the underlying reason why the rehabilitation process is delayed in some patients.[12] If a patient is seriously ill after stroke it is logical that rehabilitation is postponed until the patient is physically or mentally able to receive treatment. The relationship between timing of treatment and treatment efficacy should ideally be studied in well-constructed RCTs, taking into account general factors concerning the medical status of the patients after stroke.

In an RCT comparing an early start of CIMT (within three to nine months after stroke; n = 106) with a late start (15 to 21 months after stroke; n = 116), both groups showed significant improvement immediately after two weeks of CIMT and after twelve months, but there was a statistically significant difference in favor of the group that started CIMT earlier after stroke.[67] Another RCT (n = 52) comparing high-intensity CIMT to either standard-intensity CIMT or standard treatment for two weeks, initiated approximately ten days after stroke, showed no benefit of high-intensity CIMT over standard treatment or standard-intensity CIMT measured on the Action Research Arm Test (ARAT).[68] At the primary endpoint, 90 days after stroke, the intensive CIMT group even showed significantly less improvement on the ARAT than the control groups. This suggests that very intensive restrictive treatment might be detrimental, when initiated too early after stroke. This might be due to disturbed homeostatic mechanisms regulating excitability in neural networks, but it is still unclear whether this is a valid explanation, since activation is already low around the infarct.[37]

Studying improvement of function is no sinecure, because it is very difficult to rightfully distinguish improved function as a result of true recovery, from gains through compensation.[60, 61] It is important to differentiate between these processes while providing treatment and measuring treatment efficacy in RCTs, because supposedly rehabilitation is most successful when restoration of function is accomplished.[60, 61]

In summary, an early start of motor rehabilitation after stroke seems beneficial for functional outcome, but there are also signs indicating that intensive treatment might be harmful if initiated too early after stroke.[68] It is unclear whether these findings can be extrapolated to language rehabilitation, because recovery from aphasia might have a different course than motor recovery and other processes might interfere with recovery.[69, 70] We believe that, in contrast to motor functioning, language processing not only addresses an intricate network of cortical and subcortical networks, but relies more on cognitive systems also. Besides, motor rehabilitation is not only focused on regaining function, but also on preventing complications such as contractures, which do not affect language functioning.[10, 71]

EXPERT COMMENTARY

The currently available evidence is inconclusive and therefore insufficient to answer the question of when to start SLT in aphasia due to stroke. Studies on post-stroke language recovery using neuroimaging techniques provide some arguments favoring an early start, such as stimulating the penumbra to salvage function, making use of a hyperexcitable brain, facilitating an activation shift from right to left and preventing learned non-use. On the other hand, studies on motor recovery in animals and humans have suggested that starting too early might be detrimental because of damage to the penumbra, metabolic changes or overheating, which might increase lesion size.

Most evidence supporting the importance of an early start comes from the field of motor rehabilitation. Cohort studies show a relationship between early initiated interventions and better recovery. Yet, without results from RCTs directly comparing early with later treatment, the observed association might merely reflect the fact that patients who can tolerate treatment early after stroke probably recover better.

In this stage of the research on the relationship between timing of aphasia treatment and its efficacy, we cannot conclude that early initiated treatment is more beneficial for the recovery of aphasia than later initiated treatment. However, two smaller RCTs have shown that early SLT is tolerated and report better language functioning and recruitment of language related brain areas than in the control condition. This urgently calls for further research on this topic.

Considering the important implications for clinical practice, more research is needed to clarify the relationship between timing of SLT and response to treatment. In the next paragraph, we will provide some minimal requirements for conducting research in the early phase after stroke to which researchers should adhere.

FIVE-YEAR VIEW AND PRINCIPLES FOR FUTURE RESEARCH

Currently, we lack solid evidence linking efficacy of SLT to the stage of aphasia recovery. Experience has taught us that recruitment for large RCTs with PWA is challenging and time-

consuming, especially when recruiting early after stroke. Hence, we do not expect evidence will accumulate rapidly in the upcoming five years. At the moment, there are some research groups dedicated to studying the topic of timing. A search in clinical trial registries revealed two ongoing RCTs studying the efficacy of early initiated intensive SLT for the recovery of aphasia, so we do expect more insights soon into this component of timing.[72, 73]

RCTs are considered as the golden standard for unbiased research. However, the group of PWA is very heterogeneous and aphasic characteristics are unstable shortly after stroke, observed by rapid changes in behavior and often dramatic improvement in the hours and days after stroke. As a result, it is impossible to form adequate subgroups this early on. Therefore, in order to allow for stratified analyses, sample sizes ought to be large, a criterion that can be met by collaborations, either in multicenter or cross-national trials. Next to sample size, sound RCTs should adhere to the CONSORT statement and make use of and transparently report accurate methods for selection, randomization, blinding and analyses.[74]

The second, and possibly most important principle, is choosing proper interventions. In the critical phase after stroke, all experiences and actions trigger plasticity, some of it maladaptive.[35, 37, 38] It is therefore of the utmost importance and our obligation to participants to carefully select aphasia treatment. It still has to be confirmed whether in an early stage of treatment restorative SLT is preferred over compensational treatment because of the supposed interaction with the recovery of language-specific neural circuits.

To study an interaction between treatment and recovery, it would be ideal to compare an intervention to no intervention, hence to spontaneous recovery. It has often been argued that it is very difficult to distinguish improved functioning as a result of true neural recovery from improvement due to compensation. Interventions should therefore be very task-specific and impairment focused, e.g. CLT.[60]

It should be noted that a control condition with no specific language treatment does not mean that participants do not receive some form of colloquial communication training in normal daily life. It is therefore sensible to take into account the social environment of the participants. We suggest to monitor language or communication related activities in the control group, but also in the intervention group. It might even be possible to study social environment as a variable in RCTs, for instance by only placing the intervention group in an enriched communication environment.

If the intervention will be studied over a longer period ethical issues may prevent scientists from using a control group without treatment. In these cases, the chosen control intervention should contrast the study intervention maximally. A paradigm like this is ideal to compare the efficacy of task-specific restorative training to that of compensational training early after stroke. For instance, it would be clinically relevant to compare CILT training using 'normal' grammatical sentences (restoration), with training of agrammatic sentences, so-called ellipses (compensation).[75] Both training methods may have a direct effect on the quality of verbal communication in daily life, but are supposed to be different in their effect on neural repair and optimal timing in the rehabilitation course.

Treatment intensity is also of great importance, because insufficiently intensive treatment is ineffective. To reproduce results from animal studies, we must force up treatment intensity in studies on SLT. We suggest that participants at the least receive daily training. The question remains which stroke patients with aphasia, to which extent, tolerate highly intensive training shortly after stroke.

CONCLUSION

Although studies on motor recovery in animals and humans more and more show benefits of early initiated rehabilitation, it is unclear whether this also holds for SLT for recovery of aphasia. A robust foundation for the current strategy in clinical practice to start SLT as early as possible still requires methodologically sound research to test hypotheses about the relationship between timing of SLT and its efficacy.

Key issues

- Although it is often advocated that speech and language therapy should start as soon as possible after a stroke, evidence supporting this notion is weak.
- Animal studies have shown that there is a limited critical treatment window during which the brain is optimally responsive to rehabilitation training.
- Cohort studies have shown that there is a relationship between an early start of rehabilitation and better recovery, but in absence of evidence from RCTs it is unclear whether this relationship might merely reflect that stroke survivors who can tolerate early intensive training have a better potential for recovery anyway.
- Animal and human studies have shown that too early initiated and too intensive motor training might be detrimental.
- More solid evidence is needed to determine the relationship between timing of speech and language therapy and its efficacy in patients with aphasia due to stroke.

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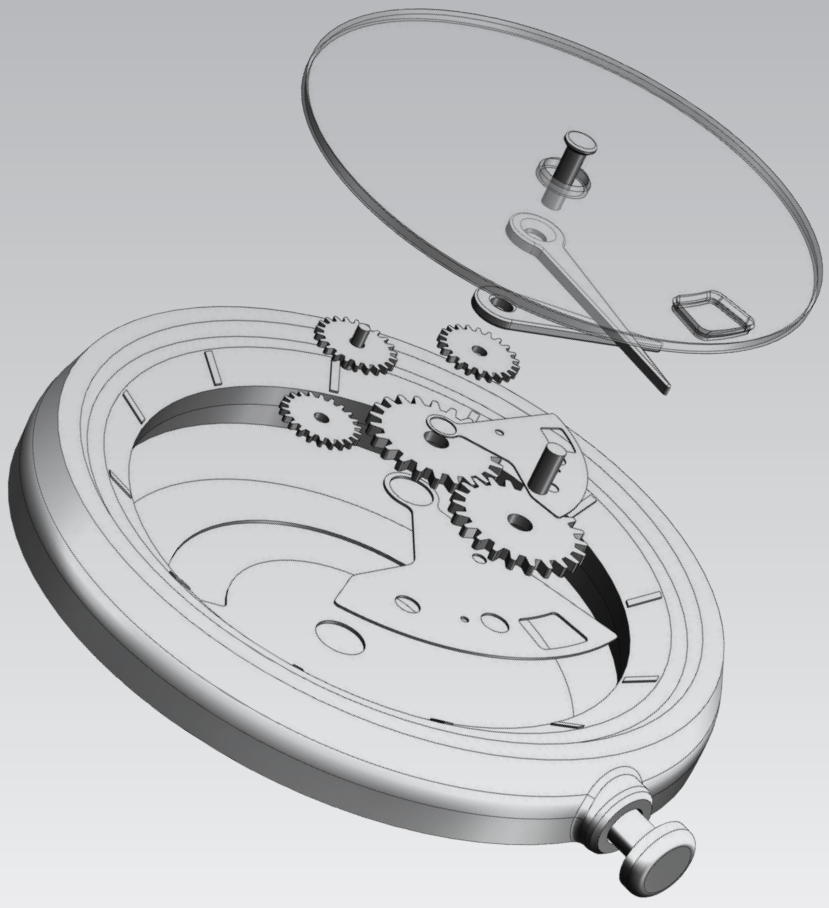


Chapter 4.2

Rotterdam Aphasia Therapy Study (RATS) – 3: "The efficacy of intensive cognitive-linguistic therapy in the acute stage of aphasia"; design of a randomized controlled trial

Nouwens F, Dippel DWJ, de Jong-Hagelstein M, Visch-Brink EG, Koudstaal PJ, de Lau LML.
Trials. 2013, vol. 14, issue24, pages: 1-8.

ABSTRACT

Background

Aphasia is a severely disabling condition occurring in 20 to 25% of stroke patients. Most patients with aphasia due to stroke receive speech and language therapy. Methodologically sound randomized controlled trials investigating the effect of specific interventions for patients with aphasia following stroke are scarce. The currently available evidence suggests that intensive speech and language therapy is beneficial for restoration of communication, but the optimal timing of treatment is as yet unclear.

In the Rotterdam Aphasia Therapy Study (RATS) – 3 we aim to test the hypothesis that patients with aphasia due to stroke benefit more from early intensive cognitive-linguistic treatment than from deferred regular language therapy.

Methods

In a single blinded, multicenter, randomized controlled trial, 150 patients with first-ever aphasia due to stroke will be randomized within two weeks after stroke to either early intensive cognitive-linguistic treatment (intervention group) or deferred regular therapy (control group). The intervention group will start as soon as possible, at the latest two weeks after stroke, with a four week period of one hour a day treatment with cognitive-linguistic treatment. In the control group professional speech and language therapy is deferred for four weeks. After this period, patients will follow the conventional procedure of speech and language therapy. Participants will be tested with an extensive linguistic test battery at four weeks, three months and six months after inclusion. Primary outcome measure is the difference in score between the two treatment groups on the Amsterdam-Nijmegen Everyday Language Test, a measure of everyday verbal communication, four weeks after randomization.

INTRODUCTION

About one fifth to a quarter of all stroke patients suffer from aphasia.[1] Aphasia after stroke is a major health problem with dramatic consequences for the quality of life of affected individuals. Communication is essential in daily life and may influence the outcome of rehabilitation, since different forms of therapy are usually instructed verbally.[2] Hence, speech and language therapy (SLT) is considered very important in the acute phase after stroke.

The effectiveness of SLT has been evaluated in a variety of studies, many of which relied on small samples and were of limited methodological quality. Recently, the Cochrane Collaboration has published a review of 39 trials on the efficacy of language therapy for aphasia after stroke.[3] The authors conclude that there is some evidence that SLT is more effective than no SLT for recovery of communication after stroke and that efficacy of SLT seems to be influenced by intensity of therapy. However, they emphasize that these results should be interpreted cautiously, as many studies lack proper methodology and comparison across studies is hampered by a large degree of heterogeneity regarding characteristics of the study population, applied treatment methods, timing and duration of therapy, and outcome assessments.

There are two main approaches in aphasia treatment: cognitive-linguistic treatment (CLT) and communicative or functional therapy.[4] CLT focuses on deficits in linguistic components, such as semantics (word meaning), phonology (speech sounds) and syntax (sentence level), and aims at restoring linguistic processes that are the foundation of language. Communicative therapy focuses on compensation by making use of all communicative channels; patients learn to utilize preserved verbal as well as nonverbal communicative functions. Communicative therapy is provided in a realistic everyday environment and uses gestures, communication aids, such as an icon board, role-plays and the Promoting Aphasics' Communicative Effectiveness (PACE) method.[5] CLT is mostly applied in early stages after stroke and communicative therapy later on.

Our group previously studied the efficacy of CLT, aimed at semantic and phonological processing, in comparison to communicative therapy in the acute stage of aphasia in the Rotterdam Aphasia Therapy Study (RATS) – 2.[6] A total of 80 aphasic patients were randomized to either CLT or communicative therapy for six months, starting within three weeks after stroke. We found no significant difference between groups on the primary outcome measure, the Amsterdam-Nijmegen Everyday Language Test, A-scale (ANELT-A).[7] However, the majority of the secondary outcome measures on semantics and phonology were in favor of CLT. Perhaps the treatment intensity of both interventions, on average 2.1 hours per week, was insufficient to generate a significant treatment effect on top of spontaneous recovery.[8-10]

Recovery of communication usually occurs shortly after stroke.[11-14] Most likely, restoration of the perilesional network in the left hemisphere is the primary mechanism underlying this spontaneous recovery.[15] Therapeutic strategies to restore cerebral blood flow, such as thrombolysis, enhance spontaneous recovery. SLT is aimed at stimulating cortical networks involved in language, hence increasing blood flow to these damaged areas. CLT especially stimulates the linguistic cortical network through specific exercises for linguistic components, such as semantics, phonology and syntax.[4] Hence SLT, and in particular CLT, is thought to contribute positively to spontaneous recovery of language.[14, 15]

Some, therefore, claim that the focus of speech and language therapists (SL-therapists) in the acute stage of aphasia, when restoration of the linguistic network is still plausible, should be on CLT.[14, 16]

In this respect, several clinical studies suggest that therapy provided immediately after stroke results in more beneficial effects than deferred treatment.[11] In a review article that was not restricted to randomized trials but also included studies with other designs, the authors conclude that SLT in the acute stages of aphasia following stroke is almost twice as effective as natural recovery alone.[10] This assumes the presence of a 'critical period' after stroke during which the brain is more susceptible to rehabilitation. Furthermore, it implies that SLT should be initiated as soon as possible after stroke. This assumption also suggests that if SLT is initiated too late, recovery might be restricted. The length of this supposed 'critical period', however, is unclear and optimal timing of therapy remains uncertain.

A second mechanism of recovery is neural plasticity.[17] Intensive training, for instance, massed practice, is thought to trigger remodeling and consolidation of neural networks.[15] Efficacy of SLT is considered to be related to intensity.[8] In the Cochrane systematic review of randomized controlled trials on SLT for stroke patients with aphasia, it was shown that efficacy of SLT positively correlated with treatment intensity, although this was related to more therapy dropouts.[3] However, a recently published pilot study on intensive SLT in 59 acute stroke patients with aphasia suggests that early intensive SLT is feasible in the acute stage after stroke.[18] The number of dropouts or deaths reported in the intervention group with daily therapy was not higher than in the control group with usual care therapy.

Another trial, in which 123 aphasic patients were randomized for intensive SLT (three weeks of daily SLT for 45 minutes on workdays, starting within two days after stroke) or control (no SLT for three weeks) in the acute stage of aphasia, showed no significant differences between groups on the primary outcome measure ANELT-A.[19] The authors conclude that not all patients with aphasia after stroke benefit from early intensive SLT, but it can be questioned whether therapy in this study was sufficiently intensive.[8-10]

Based on the currently available evidence, we suggest an optimal regimen of early initiated intensive CLT for aphasia after stroke. This regimen will be studied in the Rotterdam Aphasia Therapy Study (RATS) – 3.

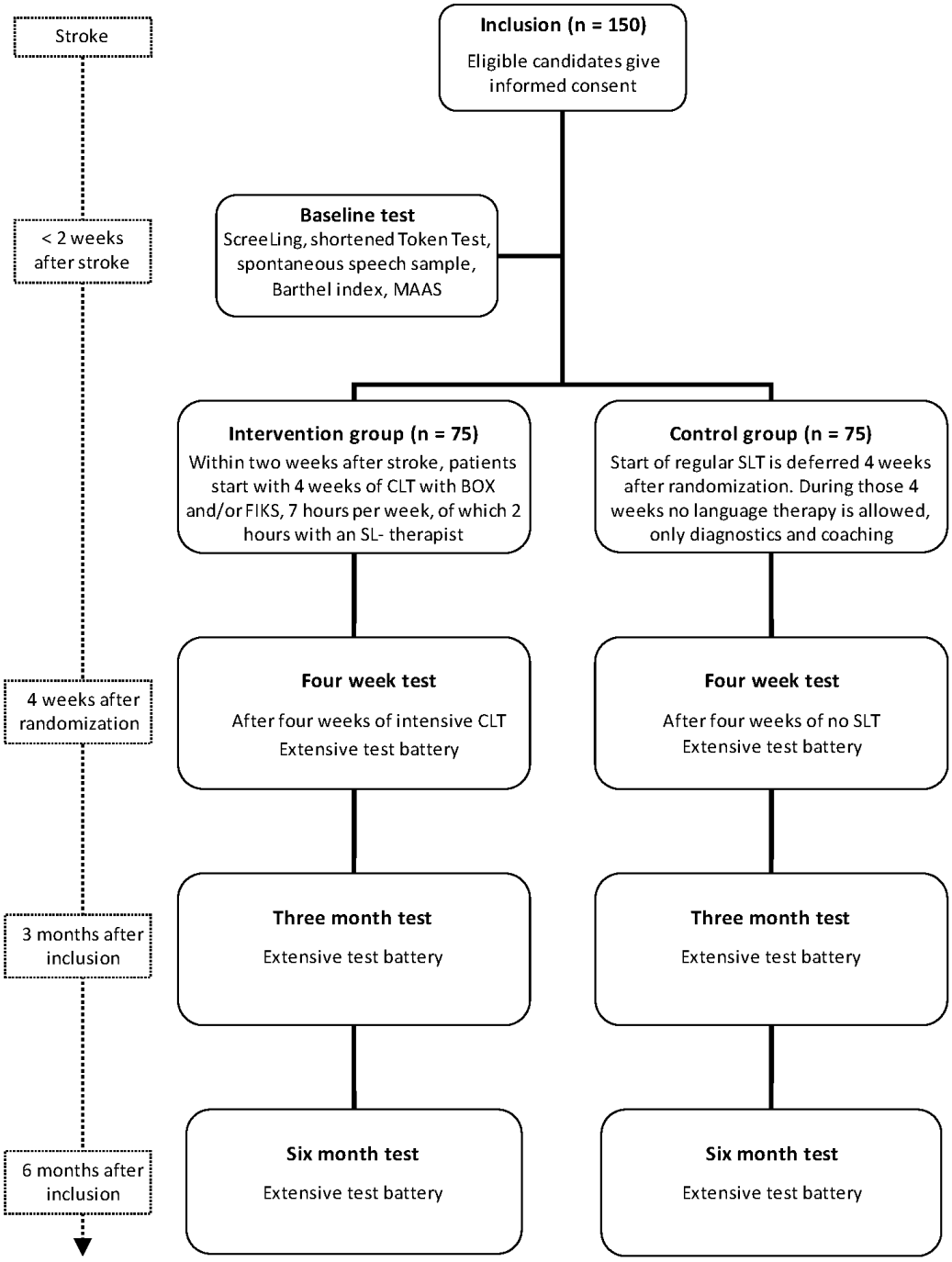
Objective

The objective of this study is to test the hypothesis that patients with aphasia after stroke benefit more from early initiated intensive cognitive-linguistic treatment than from deferred regular SLT.

METHODS

RATS-3 is a multicenter, stratified (for center of inclusion and severity of aphasia) single-blinded randomized controlled trial with parallel groups (Figure 1).

Figure 1. Flow diagram of the RATS-3 study design



Participants and recruitment

RATS-3 is coordinated by the Erasmus MC – University Medical Center Rotterdam, and over 40 hospitals, nursing homes and rehabilitation centers in the Netherlands participate. SL-therapists in participating centers are trained and supervised by the trial team.

Hospitalized patients with aphasia due to stroke are screened by the local SL-therapist for eligibility with the inclusion and exclusion criteria within two weeks after stroke (Table 1).

Table 1. Eligibility criteria for the Rotterdam Aphasia Therapy Study (RATS) – 3

Inclusion criteria:
1. Aphasia after stroke, determined by a neurologist or rehabilitation physician and speech and language therapist
2. Within two weeks after stroke
3. Testable with ScreeLing[20]
4. Aphasia ascertained with shortened Token Test[21] and/or a score <5 on Aphasia Severity Rating Scale[22]
5. Age between 18 and 85 years
6. Language near native Dutch
7. Life expectancy of more than six months
Exclusion criteria:
1. Pre-existing aphasia
2. Subarachnoid/subdural hemorrhage/hematoma
3. Severe threats to success and/or feasibility of language therapy:
▸ Severe dysarthria
▸ Premorbid dementia
▸ Illiteracy
▸ Severe developmental dyslexia
▸ Severe visual perceptual disorders
▸ Recent psychiatric history

Written informed consent is acquired by the local SL-therapist from eligible patients and/or their family. Patient information and consent forms are approved by the Medical Ethical Committee of the Erasmus MC – University Medical Center Rotterdam. Local SL-therapists will inform the RATS-3 team of every new participant.

Baseline tests

All candidates will be tested with the ScreeLing, a screening instrument for aphasia.[20] Aphasia is ascertained with the shortened version of the Token Test[21] and a sample of spontaneous speech assessed with the Aphasia Severity Rating Scale[22]. Activities of daily life will be reported with the Barthel Index[23] and observational data on social and (neuro)psychological functioning and wellbeing will be collected with the MAAS (Multi-axial Aphasia System[24]).

Randomization

Each participant is assigned to either the intervention group or the control group by restricted randomization via stratification for severity of aphasia and center of inclusion. The allocation sequence is computer generated and concealed in consecutively numbered, opaque, sealed envelopes. The trial coordinator randomizes participants to treatment groups after severity of aphasia is assessed. A score on the Aphasia Severity Rating Scale[22] of 0 to 2 is considered to reflect severe aphasia and a score of 3 to 5 reflects moderate to mild aphasia.

Intervention

As soon as possible after randomization the intervention period of four weeks starts, during which the intervention group receives early intensive CLT and the control group receives no SLT.

Intervention group (n = 75)

Participants allocated to the intervention group receive intensive CLT with the treatment programs BOX[25] and/or FIKS[26]. The BOX and FIKS programs are commonly used in the Netherlands and aim at the improvement of word finding (Table 2). BOX focuses on semantics and FIKS on phonology. Both interventions are well outlined, which ensures homogeneity of treatment in this group.[6] BOX and FIKS consist of several subparts that provide a large number of specific exercises, to treat various layers of semantic and phonological processing. Exercises can be presented visually and/or orally and require receptive and productive skills. Each subpart contains different levels of complexity, which makes these programs suitable to all types and severity levels of aphasia. Both programs are also available on computer (eBOX and eFIKS) to facilitate homework.

Therapy will start at the latest two weeks after stroke. However, as soon as participants are included and randomized, therapy can be started.

Recent findings on intensity of treatment suggest that one hour of language therapy per day is sufficiently intensive to generate an effect of therapy on top of the effect of spontaneous recovery.[3, 8] This high intensity is uncommon in the Netherlands. Therefore SL-therapists will treat participants at least two hours a week, supplemented with homework using paper or digital versions of the therapy programs. The SL-therapists register all therapy sessions in minutes on special registration forms. These forms will be handed to the patient and/or his caretaker also for homework registration.

The trial coordinator contacts SL-therapists every week to check whether the allocated treatment is adequately applied and ask if any problems arise complying with the protocol.

Table 2. Illustration of CLT with the semantic therapy program BOX and the phonological program FIKS

Semantic therapy program BOX
Subject: word meaning
Objective: consolidate the internal semantic network to improve word finding
Presentation: oral, visual or by computer (eBOX)

Examples:

Word level	Sentence level
Which word does not match?	*Is this sentence correct?*
Ruler	The balloon flies in the air.
Musical scale	Correct.
Gauge	
Balance	The candle is burning embittered.
Measuring tape	Incorrect. *Please correct the sentence.*

Phonological therapy program FIKS
Subject: processing and production of speech sounds
Objective: consolidate the internal phonological network and improve production of speech, to improve word finding
Presentation: oral, visual or by computer (eFIKS)

Examples:

Word level				
Which word is printed here?	tion	trans	la	= translation
Read it out loud please.	ment	ta	tes	= testament
Sentence level				
Please finish the sentence with a rhyming word:		The enthusiastic amateur cook, read the recipe carefully in his cooking– …		

Control group (n = 75)

Language therapy is deferred in the control group. Regular language therapy will start four weeks after randomization. During these four weeks no SLT is allowed. SL-therapists, however, will be attentive to participants in the control group. They may inform the patient and his caretakers about aphasia and its consequences and provide advice to avoid severe communication distress. Additional diagnostic tests and specific observations on communicative functioning may be performed to set detailed therapy goals.

Therapy after four weeks by an SL-therapist will be arranged if the patient is discharged home. The trial coordinator will keep in contact with the patient during these four weeks. If the patient is released to a rehabilitation center or nursing home, the coordinator will contact the SL-therapist after two weeks to evaluate whether the protocol can be followed correctly.

Follow-up measurements

Verbal communicative abilities of participants will be evaluated four weeks after randomization, three months after inclusion and six months after inclusion, using an extensive linguistic test battery (Table 3). Tests requiring a verbal response are recorded digitally. All SL-therapists receive a manual for the administration of the linguistic tests. Results will be scored in a booklet containing all score forms per test moment. The trial team will score all tests and report results to the SL-therapists.

Table 3. Linguistic test battery in RATS-3

General communication tests

- ANELT-A: communicative functioning in daily life[7]
- Semi-standardized interview for spontaneous speech rated with the Aphasia Severity Rating Scale[22]
- Sabadel: connected speech[27]
- ScreeLing: screening of three linguistic components: semantics, phonology and syntax[20, 28]
- Token Test, short version: measures severity of aphasia[21]
- Boston Naming Test: identifies word finding difficulties[29]

Specific semantic tests

- Semantic Association Test, verbal version (SAT)[30]
- Comprehensive Aphasia Test, word comprehension (CAT)[31]
- Semantic Word Fluency[32]

Specific phonological tests

- Nonword repetition, PALPA[33]
- Auditory Lexical Decision, PALPA[33]
- Letter Fluency[34]

General

- Barthel Index: activities of daily life[23]
- Multi-axial Aphasia System (MAAS)[24]
- Partner ANELT: partner's perspective on communicative functioning[35]
- Self-evaluation of communicative functioning on a 0 to 10 scale
- EQ-5D-3L : quality of life[36]
- Modified Rankin Scale: activities of daily life (mRS)[37]

Aphasia type will be determined with the Aachen Aphasia Test (AAT)[38] between the four week and three month test. This period after spontaneous recovery is chosen because we assume aphasia type will then be stabilized.

Sequel after the four week test

Regular language therapy will start in the control group and the intervention group continues with regular therapy after the four week test. Regular therapy in the Netherlands

comprises a combination of CLT and communicative therapy and focuses mainly on therapy goals set by the patient. Regular therapy intensity is on average approximately two hours per week.[39] Registration of therapy sessions and therapy type (either CLT or communicative or a combination) will be continued, although not as meticulously as during the four weeks of intervention.

Primary outcome

The primary outcome measure in RATS-3 is the difference in score on the ANELT-A[7] at the four week test moment (after intervention) between the two groups. CLT aims at improving linguistic skills, which theoretically results in better daily communication. The A-scale of the valid and reliable ANELT measures verbal communicative ability.[40] Participants' verbal responses to ten everyday communicative scenarios are scored on a five-point scale for information content.

Secondary outcomes

The difference in scores between groups at the four week test on the Semantic Association Test (SAT), verbal version[30]; Semantic Word Fluency[32], Psycholinguistic Assessment of Language Processing in Aphasia (PALPA), Nonword repetition[33]; PALPA, Auditory Lexical Decision[33]; and Letter Fluency[34] will be used as secondary outcome measures. Other secondary outcomes are differences in all test scores at three months, and differences in scores on the EQ-5D-3L [36] (quality of life) and modified Rankin Scale (functional outcome)[37].

Tertiary outcomes

Scores on the above mentioned tests at six months after inclusion, including ANELT-A, will be used as tertiary outcome measures.

Sample size

A sample of 75 participants in each treatment group, a total of 150 participants, is estimated to provide 84% power to detect a statistically significant difference between groups on the primary outcome measure at a 5% two-sided significance level. An inclusion period of two years is estimated to be required for recruitment.

Blinding

Due to the intervention type, therapy or no therapy, it is impossible for participants and SL-therapists to be blinded for intervention. Assessment of the primary outcome, however, will be blinded. Two experienced independent observers, who are blinded for treatment allocation and test moment, will score the primary outcome measure ANELT-A. The mean score of both independent observers will be used in the analyses. Interobserver agreement will be assessed by means of a plot of differences between scores versus their mean. The mean difference between observers will be calculated with a 95% confidence interval (95% CI).

Statistical analyses

Difference in score on ANELT-A between groups will be compared with analysis of covariance (ANCOVA) with a 95% CI, adjusted for baseline severity. Baseline severity is

determined according to the Aphasia Severity Rating Scale[22] in a sample of spontaneous speech.

This method will also be used for the additional linguistic tests in the secondary and tertiary outcome measures.

Ethics

The RATS-3 study protocol is approved by the independent Medical Ethical Committee of the Erasmus MC – University Medical Center Rotterdam (MEC-2005-347), and registered in the Dutch Trial Register (NTR3271)[41].

Trial status

The trial started January 2012. We estimate that inclusion will be finished in January 2014.

Acknowledgements

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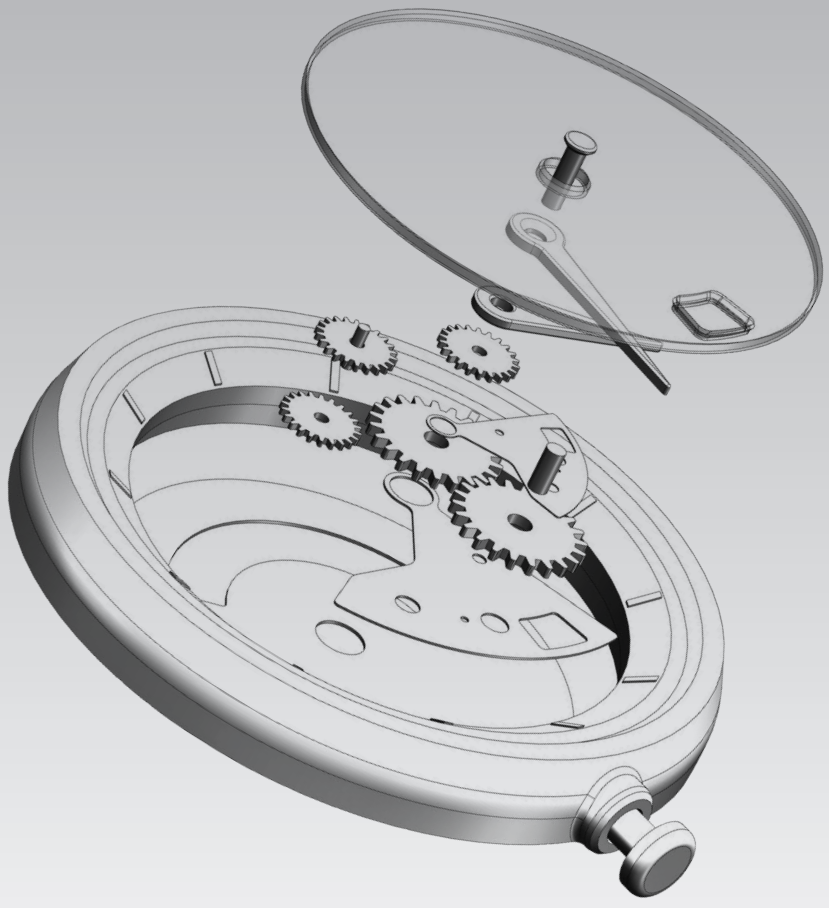

Chapter 4.3

Efficacy of early cognitive-linguistic treatment for aphasia due to stroke; a randomized controlled trial (Rotterdam Aphasia Therapy Study – 3)

Nouwens F, Lau LML, Visch-Brink EG, van de Sandt-Koenderman WME, Lingsma HF, Goosen S, Blom DMJ, Koudstaal PJ, Dippel DWJ, on behalf of the RATS-3 investigators (Appendix I).
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ABSTRACT

Background

One third of patients with acute stroke have aphasia. The majority receive speech and language therapy (SLT). There is evidence for a beneficial effect of SLT on restoring communication, but it is unknown whether and how efficacy of SLT is influenced by timing of treatment. We studied whether SLT early after stroke by way of intensive cognitive-linguistic treatment (CLT) is more effective than no SLT in the Rotterdam Aphasia Therapy Study (RATS) – 3, a multicenter randomized single-blind trial.

Methods

Stroke patients with first-ever aphasia were randomized within two weeks of onset to either four weeks of early intensive CLT (one hour/day) or no language treatment. Hereafter, both groups received regular SLT. Primary outcome was the score on the Amsterdam-Nijmegen Everyday Language Test (ANELT), measuring everyday verbal communication, four weeks after randomization. Secondary outcomes were ANELT at three and six months. The study was powered to detect a clinically relevant difference of four points on the ANELT.

Results

Of the 152 included patients, 80 patients were allocated to intervention. Median treatment intensity in the intervention group was 24.5 hours. The adjusted difference between groups in mean ANELT scores four weeks after randomization was 0.39, 95% CI: -2.70 to 3.47, $p = 0.81$. No statistically significant differences were found at three and six months after randomization either.

Conclusion

Four weeks of intensive CLT initiated within two weeks of stroke is not more effective than no language treatment for the recovery of aphasia due to stroke. Our results exclude a clinically relevant effect of very early CLT on everyday language.

INTRODUCTION

Aphasia occurs in about one third of stroke patients and has severe consequences for verbal communication and quality of life.[1, 2] Several randomized controlled trials (RCT) have reported a benefit of speech and language therapy (SLT) over no treatment for patients with aphasia due to stroke.[3] Hence, most patients receive SLT as part of their rehabilitation program.

The relationship between timing of SLT, i.e. the interval between stroke onset and start of treatment, and its efficacy is unclear.[4] In a meta-analysis comparing studies with different starting points of SLT, the average effect size in studies evaluating treatment initiated in the first three months after stroke was larger than that in studies performed in a later stage.[5] However, this analysis was mainly based on uncontrolled and non-randomized studies. The efficacy of early initiated SLT has been studied in four trials with contradictory findings; two large studies were neutral, but two smaller studies suggested an effect of early treatment.[6-9] The need for more research on the effect of timing of SLT was explicitly accentuated in a Cochrane review on efficacy of SLT for aphasia due to stroke.[10]

In the early phase after stroke, impairment-based cognitive-linguistic treatment (CLT) is often preferred over other types of SLT, as it targets specific linguistic functions, supposedly stimulating functional neural networks.[11-13] As most recovery occurs within the first three months after stroke,[5, 14-16] standard practice early after stroke often comprises CLT.[17] When linguistic performance reaches a plateau, SLT may be continued with compensatory treatment instead of CLT.

There is some evidence suggesting that high-intensity treatment may be more effective than less frequent therapy.[3, 18, 19] However, the feasibility of high-intensity treatment is questionable, as in several trials compliance with treatment was significantly lower in intervention groups with intensive language treatment.[3]

Experts in language rehabilitation suggest a best practice regimen of early initiated intensive CLT.[13, 17] Scientific evidence underpinning this recommendation is frail. The objective of the Rotterdam Aphasia Therapy Study (RATS) – 3 was to study whether early intensive CLT for four weeks is more effective than no language treatment in the first four to six weeks after stroke, and whether this approach generates a long-lasting benefit.

METHODS

Essential elements of the study design are described below. Detailed methods were published elsewhere.[20] RATS-3 is a prospective multicenter controlled clinical trial with randomized treatment allocation, open label treatment and blinded evaluation of the primary outcome measure (PROBE design).[21] Thus, after randomization both patients and therapists were aware of the allocated treatment. Fourteen regional networks for integrated stroke care comprising a total of 23 hospitals and 66 rehabilitation facilities across the Netherlands participated (Appendix I). Within two weeks of stroke onset, patients were randomized to four weeks of either intensive CLT or no language treatment. After the four weeks, both groups received regular SLT.

The study protocol was approved by the Medical Ethical Committee of the Erasmus MC (MEC-2005-347) and the study was registered in the Netherlands Trial Register (NTR3271).

Participants

Speech and language therapists (SL-therapists) from participating centers checked eligibility criteria (Table 1) and requested informed consent from patients and/or their proxy. Information about RATS-3 was provided to patients and their relatives orally and on paper, including simplified information leaflets adapted to people with aphasia.

Patients who were not eligible or who did not consent to participation were not registered.

Table 1. Eligibility criteria for RATS-3

Inclusion criteria:	
1.	Aphasia after stroke, diagnosed by a neurologist or rehabilitation physician and SL-therapist
2.	Aphasia ascertained with shortened Token Test (score<29) or Aphasia Severity Rating Scale (score<5)
3.	Testable with ScreeLing
4.	Treatment can be started within two weeks after stroke onset
5.	Age 18-85 years
6.	Language near-native Dutch
7.	Life expectancy of more than six months
Exclusion criteria:	
1.	Pre-existing aphasia
2.	Subarachnoid/subdural hemorrhage/hematoma
3.	Language therapy is not feasible because of:
	▸ Severe dysarthria
	▸ Premorbid dementia
	▸ Illiteracy
	▸ Severe developmental dyslexia
	▸ Severe visual perceptual disorders
	▸ Recent psychiatric history

Randomization

The trial coordinator verified inclusion criteria and, after written informed consent was obtained, included and randomized participants within two weeks of stroke onset. Independent trial assistants concealed computer-generated allocation sequences in consecutively numbered, opaque, sealed envelopes. Randomization was stratified according to baseline aphasia severity (Aphasia Severity Rating Scale: ASRS score 0 to 2 = severe; ASRS score 3 to 4 = moderate/mild) and including center.

Baseline tests

At baseline, a short test battery was conducted including the ScreeLing, the 36-item Token Test and a semi-standardized interview for eliciting spontaneous speech, which was rated with the ASRS.[20] An experienced SL-therapist blinded to treatment allocation classified the

spontaneous speech samples as fluent or non-fluent. Baseline characteristics and the Barthel Index were recorded, as well as treatment with intravenous alteplase, as this is associated with rapid recovery from stroke.[22]

Intervention

Patients in the intervention group were to receive at least one hour of CLT every day of the week for a period of four weeks. The hour of treatment could be delivered in more than one session per day, if preferable. We chose an intervention period of four weeks for three reasons. First, intervention in the control group had to reflect usual care in the Netherlands, where SLT for aphasia starts on average three to six weeks after onset. Second, we specifically aimed to study the effect of early initiated treatment. With a maximal inclusion period of two weeks and a four-week intervention period this early phase was not exceeded. Lastly, we expected that a longer intervention with high intensity would be too burdensome for many patients.

Treatment was directed at semantics using the therapy program BOX[23] and/or phonology using the therapy program FIKS[24], to improve word finding deficits. Participating SL-therapists had ample experience in using both Dutch therapy programs and carefully selected exercises for face-to-face treatment and homework, registered as part of the total amount of treatment provided. Treatment could be delivered at the local treatment facility or at home, whatever was most convenient for patients.

The control group received no language treatment during the first four weeks after randomization. Minimal counseling was allowed, aimed at preventing communication problems and included elaborate information about aphasia and providing communication advice. Concise diagnostics for therapy goal setting was allowed also.

The trial coordinator had at least two-weekly contact with the SL-therapists to ensure no treatment was provided in the control group and to monitor compliance in the intervention group. After four weeks, further SLT was left to the discretion of the local SL-therapist in both groups.

Assessments

An extensive linguistic test protocol was conducted at three time points; four weeks, three months and six months after randomization, with the following tests for language and communication: Amsterdam-Nijmegen Everyday Language Test (ANELT) for everyday functional verbal communication,[25] a semi-standardized interview from the Aachen Aphasia Test (AAT) rated with the reliable and valid ordered categorical six-point ASRS; the ScreeLing, the Token Test, and the Boston Naming Test. The battery also included tests for semantic processing: Semantic Association Test (SAT), verbal version; Comprehensive Aphasia Test (CAT), word comprehension; and Category Fluency; and for phonological processing: Nonword repetition and Auditory Lexical Decision from the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) and Letter Fluency. In addition, we assessed general functional outcome with the EQ-5D-3L for quality of life, and the modified Rankin Scale (mRS) and Barthel Index for level of independency.

Outcomes

Primary outcome was the ANELT-A score 'understandability' (score range: 10 to 50, higher scores equal better performance), measuring the adequacy of verbal communication, four

weeks after randomization. This valid and reliable test was chosen to verify whether the impairment-based CLT generalizes to everyday communication.[25] All ANELTs were audio-recorded and rated by five experienced and additionally trained independent assessors, blinded to intervention and time point. Each ANELT was scored by two assessors. If scores of the two assessors differed more than six points, they were asked to rate the test again without providing them details about the direction of the differences. The mean of these two scores was used for analyses. In case of persistent differences between assessors, the scores were averaged with the score of a third independent assessor, who was unaware of other scores. Secondary outcomes were scores on the linguistic tests, EQ-5D-3L and mRS at four weeks, and scores on the ANELT-A, the linguistic tests, EQ-5D-3L, and mRS at three and six months after randomization.

Sample size

We considered a four-point difference between both groups on the ANELT-A a clinically worthwhile treatment effect. This is 50% of the critical difference for individual improvement and half a standard deviation of average ANELT-A scores in previous RATS trials.[25-27] We estimated that a sample of 150 participants would provide 84% power to find a statistically significant treatment effect at a 5% two-sided significance level.

Blinding and data safety

To ensure data safety and blinding, the primary outcome for each patient was scored by two of the five independent assessors, who were blinded to treatment allocation and time point. Furthermore, data were collected in four separate anonymized databases, which were merged after patient inclusion and data collection were completed. Hence, during data collection the trial coordinator could only access individual patient data. Scores on the primary outcome measure remained masked for the entire RATS-3 investigator team until data collection was completed.

An independent assessor verified a random sample of 10% of all participants' files, by comparing all data points in the databases with the original source files. Apart from minor inaccuracies, no critical errors endangering data quality were found. Yet, all data points were checked against source data again by the study coordinator, further minimizing errors.

The trial was not overseen by a data monitoring committee, as this concerned a non-medical intervention study without anticipated adverse events.

Statistical analyses

Primary analyses were performed on intention-to-treat basis. In addition, on-treatment analyses were performed, with on-treatment being defined for the intervention group as having accomplished at least the intended intensity of 28 hours in four weeks and for the control group as having received no language treatment during four weeks after randomization. We used linear regression to analyze the treatment effect as a mean difference in ANELT-A scores between the intervention and control group four weeks after randomization, adjusted for age (years), sex, education (high or low), baseline aphasia severity (ASRS score), type of stroke (ischemic or hemorrhagic), location of stroke (right or left hemisphere) and baseline Barthel Index score. Linear regression was also used to analyze the effect of treatment on the specific linguistic measures and measures of general functional outcome at four weeks, three months and six months after randomization, with

the same adjustments as in the primary analysis. For the ordered categorical variable mRS we used multivariable ordinal logistic regression.

Handling of missing data

Standard simple imputation techniques were used to impute missing baseline variables; study mean for continuous variables and study mode for binary and categorical data. Patients who died during the intervention period were assigned the worst score on all outcome measures and this score was carried forward during follow-up. Subjects with missing values at a certain time point were excluded from analyses at that time point. Statistical analyses were performed using IBM SPSS software version 23.0.

Post-hoc subgroup analyses

Post-hoc subgroup analyses were conducted with the ANELT-A four weeks after randomization per covariate used for baseline adjustment in the regression analyses. We also compared treatment effects in patients treated with intravenous alteplase and those who were not, and in patients with and without a cardiac source of emboli.

Synthesis of evidence

In order to put our findings into perspective we have performed a concise meta-analysis of the available evidence on the topic of early initiated SLT. In December of 2015, we searched PubMed and the Cochrane Library for studies published between 1990 and 2015 with the search terms: aphasia, stroke, treatment, therapy, rehabilitation, acute, early and timing. We selected randomized controlled trials on early initiated SLT for aphasia due to stroke, i.e. the largest part of the treatment was provided within four weeks of stroke onset. Only RCTs comparing early treatment to no treatment, or early intensive treatment to no treatment or usual care were selected. We have used results from the primary outcomes reported in the selected studies and our primary outcome for the meta-analysis by standardizing the mean differences between study arms.

RESULTS

From 1 January 2012 until 2 December 2014 we included 153 participants with first-ever aphasia due to stroke, of whom 80 were allocated to the intervention group (Figure 1). One participant in the control group was excluded after randomization, because more detailed assessment revealed that a brain tumor had been misdiagnosed as hemorrhagic infarct. The baseline distribution of clinical characteristics was similar for both groups (Table 2).

In the intervention group, two patients died in the intervention period, and in the control group one patient died in the intervention period and one just afterwards, before testing could be performed (Figure 1). During follow-up, in each group two patients died. Five participants from the intervention group did not receive the allocated treatment; one was very ill and four refused intensive treatment. In the control group, ten participants refused deferred treatment and received regular SLT. The trial coordinator did not interfere with treatment, and details on the content of SLT provided to these patients were not recorded.

Figure 1. Flow-chart Rotterdam Aphasia Therapy Study – 3

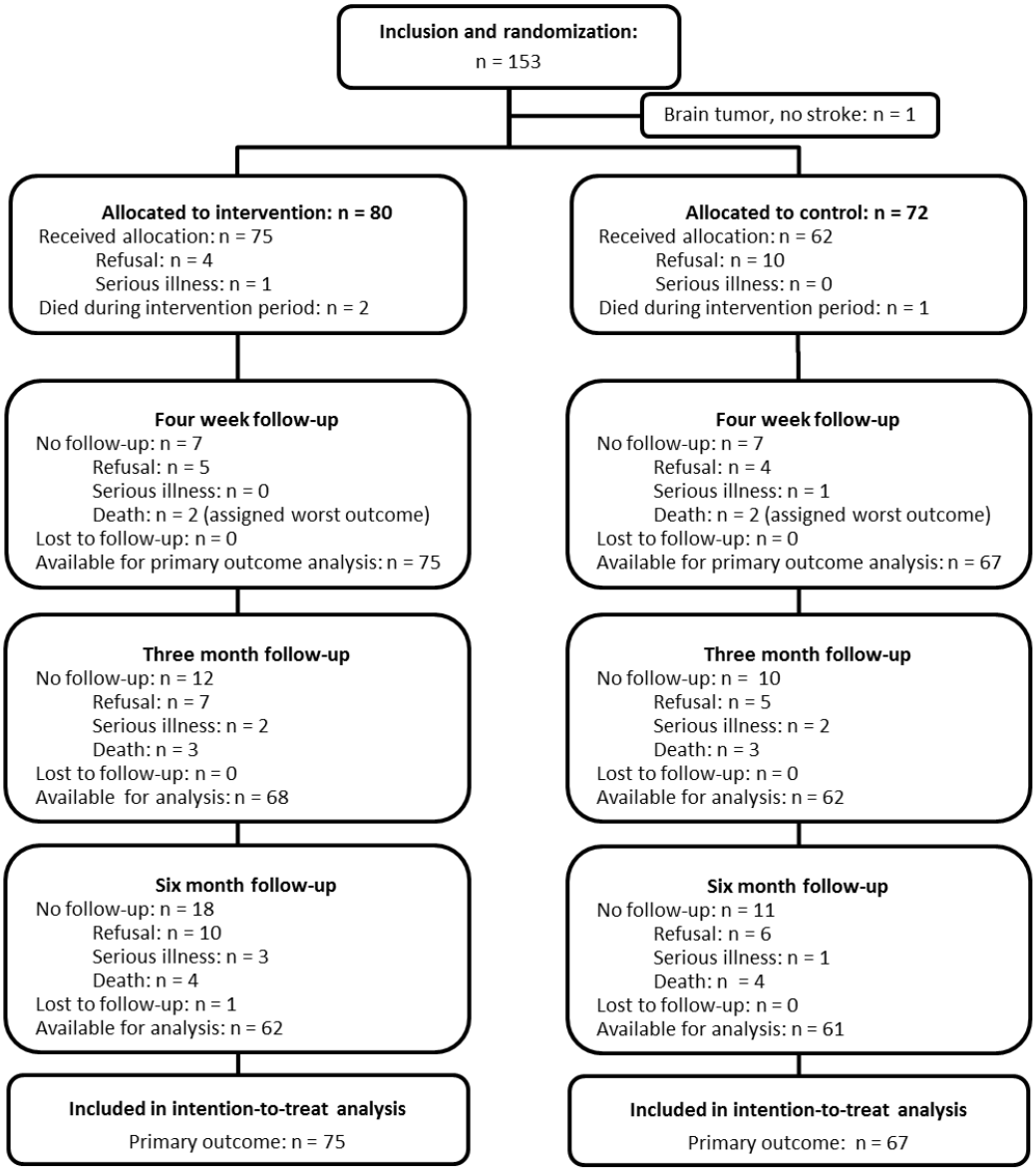


Table 2. Baseline characteristics of participants in RATS-3

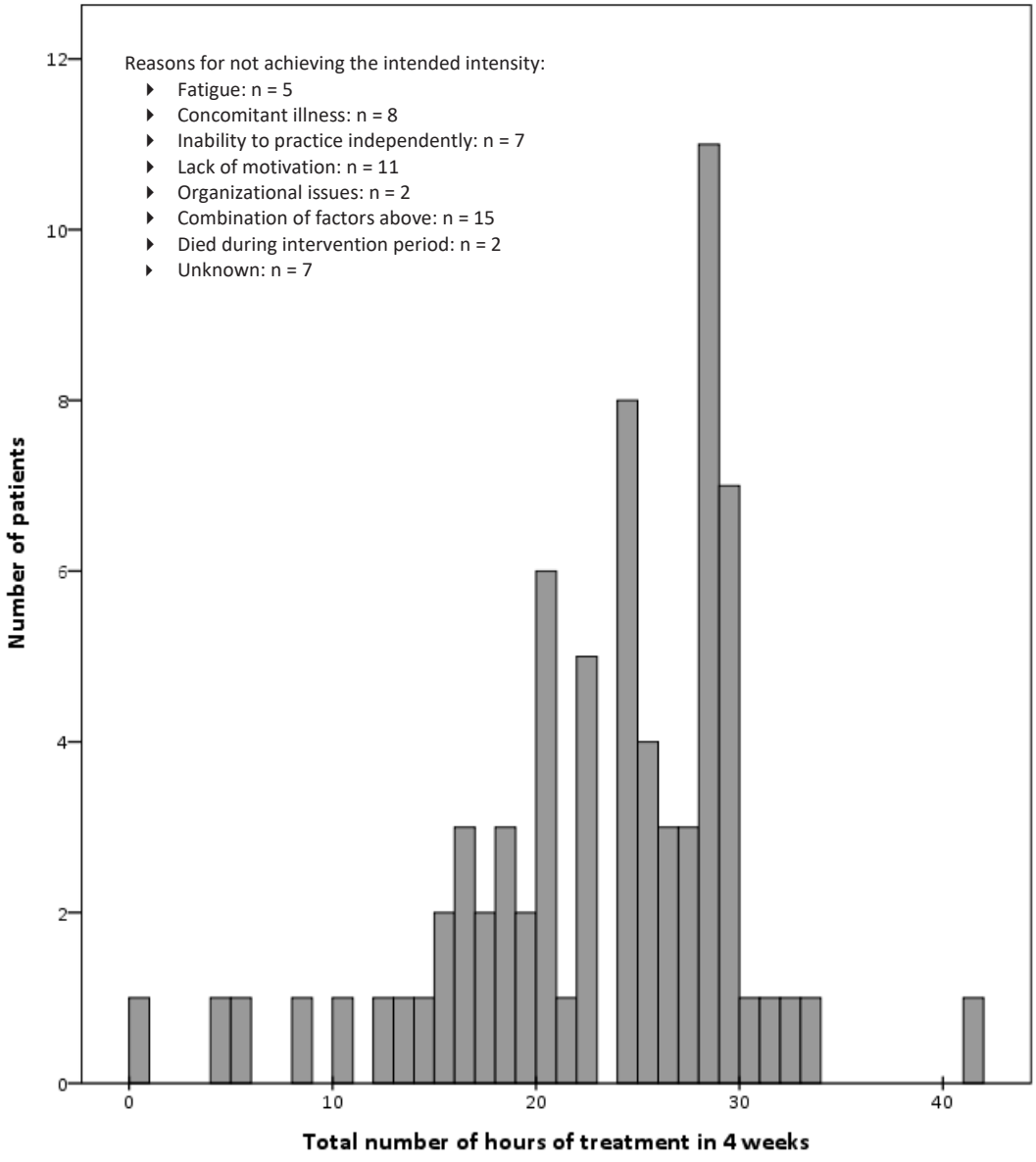
	Intervention group (n = 80)	**Control group (n = 72)**
Age in years, mean (SD)	66 (12)	66 (12)
Male sex, n (%)	48 (60%)	37 (51%)
Handedness, n (%)		
Right	63 (79%)	61 (85%)
Left	6 (8%)	7 (10%)
Ambidextrous	5 (6%)	1 (1%)
Unknown	6 (8%)	3 (4%)
Level of education, n (%)		
No/unfinished elementary school	3(4%)	0
Elementary school	13 (16%)	11 (15%)
Unfinished junior secondary vocational education	4 (5%)	8 (11%)
Junior secondary vocational education	27 (34%)	13 (18%)
Total low education	47 (59%)	32 (44%)
Senior vocational education	17 (21%)	16 (22%)
Higher education	13 (16%)	18 (25%)
University	2 (3%)	3 (4%)
Total high education	32 (40%)	37 (51%)
Unknown	1 (1%)	3 (4%)
Type of stroke, n (%)		
Ischemic	60 (75%)	61 (85%)
Hemorrhagic	20 (25%)	11 (15%)
Location of lesion, n (%)		
Left hemisphere	77 (96%)	69 (96%)
Right hemisphere	3 (4%)	3 (4%)
Treatment with intravenous alteplase, n (%)		
Yes	28 (35%)	16 (22%)
No	50 (63%)	55 (76%)
Unknown	2 (3%)	1 (1%)
Time between stroke and randomization in days, mean (range)	8 (1-18)	8 (2-15)
Time between stroke and start treatment in days, mean (range)	12 (5-22)	n.a.
Barthel Index score, median (IQR)	15 (6-20)	17 (7.5-20)
Aphasia severity, n (%)		
Severe (ASRS score = 0 to 2)	44 (55%)	30 (42%)
Mild-moderate (ASRS score = 3 to 4)	36 (45%)	42 (58%)
Fluency, n (%)		
Fluent aphasia	26 (33%)	30 (42%)
Non-fluent aphasia	52 (65%)	42 (58%)
Missing	2 (3%)	0

Abbreviations: n = number; SD = standard deviation; IQR = Interquartile Range; ASRS = Aphasia Severity Rating Scale; n.a. = not applicable.

Compliance

A treatment intensity of 28 hours in four weeks in the intervention group was achieved by 23 of 80 patients (29%). The median treatment intensity was 24.5 hours in four weeks (IQR: 19 to 29) (Figure 2).

Figure 2. Distribution of treatment intensity in the intervention group



Intention-to-treat analysis

The mean score on the primary outcome, the ANELT-A at four weeks, was 33.2 in the intervention group and 36.2 in the control group, with a difference of -3.01; 95% CI: -7.15 to 1.14. Baseline aphasia severity and baseline Barthel Index were strong prognostic factors in the regression model (Table 3). The adjusted mean difference in scores on the ANELT-A was 0.39; 95% CI: -2.70 to 3.47, p = 0.81 (Figure 3). There were also no statistically significant differences on the ANELT-A between groups at three months (adjusted difference = 0.54, 95% CI: -3.04 to 4.12, p = 0.77) and six months after randomization (adjusted difference = -0.41, 95% CI: -3.70 to 2.89, p = 0.81) (Figure 3).

Table 3. Prognostic factors in the linear regression model with ANELT-A at four weeks as outcome

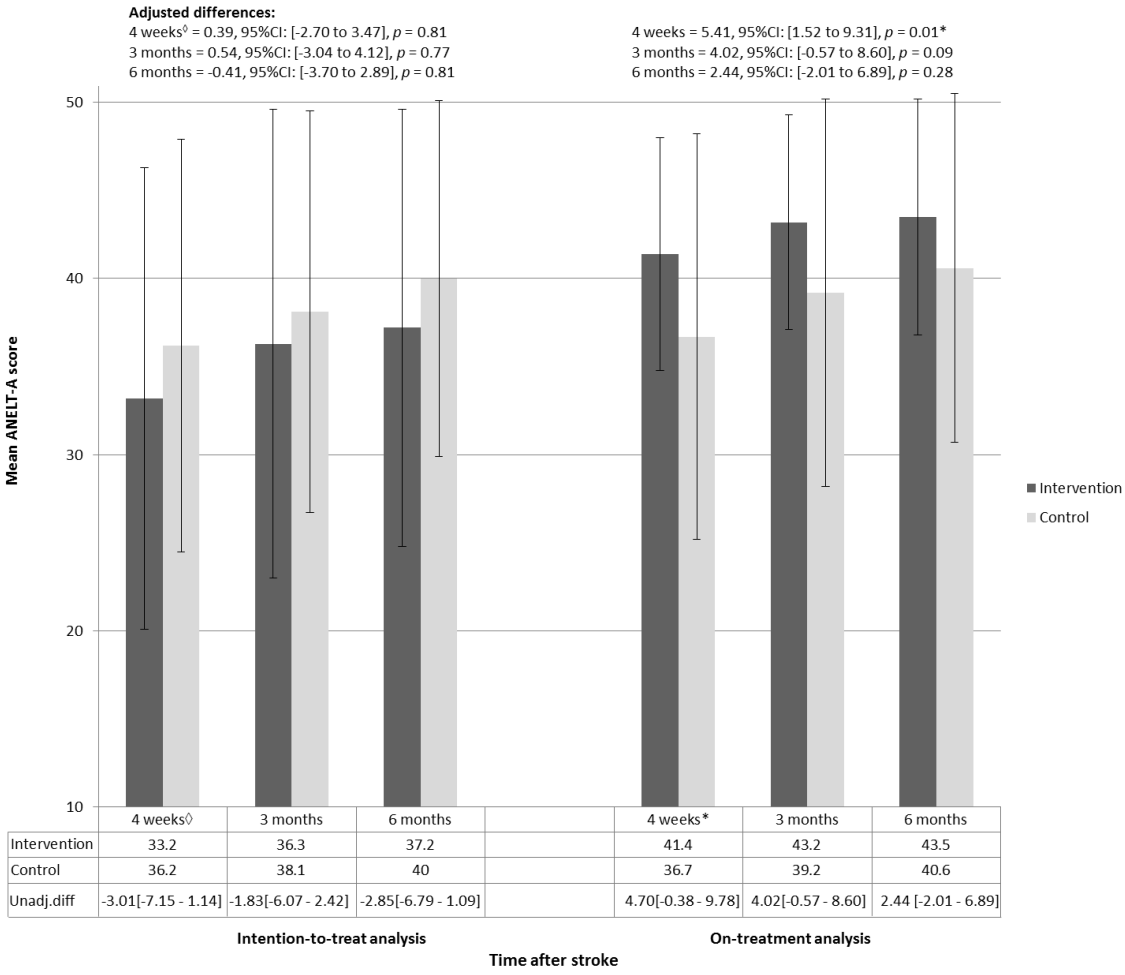
	β	**95% CI**	***p*-value**
Sex (female or male)	-2.08	[-5.17 – 1.02]	0.19
Age	0.02	[-0.10 – 0.15]	0.74
Type of stroke (hemorrhagic or ischemic)	1.46	[-2.39 – 5.31]	0.45
Location stroke (right or left hemisphere)	0.35	[-7.16 – 7.85]	0.93
Education (high or low)	2.64	[-0.47 – 5.75]	0.10
Barthel Index score (0-20)	0.37	[0.11 – 0.62]	0.01*
Aphasia Severity Rating Scale score (0-5)	5.90	[4.58 – 7.23]	<0.01*

Abbreviations: *β* = unstandardized difference; 95% CI = 95% confidence interval.

* Statistically significant at a 95% confidence level.

No statistically significant treatment effects were observed on the linguistic tests and on the measures for general functional outcome, at any time point (Table 4).

Figure 3. Differences in outcome and treatment effect between intervention and control on the ANELT-A



	4 weeks◊	3 months	6 months		4 weeks*	3 months	6 months
Intervention	33.2	36.3	37.2		41.4	43.2	43.5
Control	36.2	38.1	40		36.7	39.2	40.6
Unadj.diff	-3.01[-7.15 - 1.14]	-1.83[-6.07 - 2.42]	-2.85[-6.79 - 1.09]		4.70[-0.38 - 9.78]	4.02[-0.57 - 8.60]	2.44 [-2.01 - 6.89]

Abbreviations: 95% CI = 95% Confidence Interval; ANELT = Amsterdam-Nijmegen Everyday Language Test; unadj. diff = unadjusted differences.
* Statistically significant at a 95% confidence level.
◊ Primary outcome.

Table 4. Differences in outcome and treatment effect between intervention and control on secondary outcomes: intention-to-treat analyses

		Intervention mean (SD)	Control mean (SD)	Unadjusted difference [95% CI]	Adjusted difference [95% CI]	*p*-value
SAT verbal (0-30)	4 weeks	21.2 (7.9)	22.1 (7.8)	-0.86 [-3.50 – 1.78]	1.09 [-1.27 – 3.45]	0.36
	3 months	22.7 (7.6)	24.1 (6.2)	-1.41 [-3.81 – 0.99]	-0.34 [-2.58 – 1.91]	0.77
	6 months	23.0 (7.3)	24.2 (6.6)	-1.25 [-3.70 – 1.20]	-0.12 [-2.41 – 2.18]	0.92
Category Fluency (no. words/ minute)	4 weeks	12.6 (11.0)	15.9 (11.9)	-3.32 [-7.13 – 0.50]	-0.06 [-3.09 – 2.96]	0.97
	3 months	16.2 (11.0)	20.3 (12.8)	-4.13 [-8.26 – 0.00]	-1.50 [-4.86 – 1.86]	0.38
	6 months	16.5 (11.7)	21.1 (13.3)	-4.56 [-8.98 – -0.13]	-1.77 [-5.47 – 1.93]	0.35
CAT (0-30)	4 weeks	25.0 (6.9)	24.9 (7.4)	0.12 [-2.26 – 2.50]	1.40 [-0.93 – 3.72]	0.24
	3 months	25.5 (6.6)	26.4 (6.0)	-0.96 [-3.11 – 1.20]	-0.10 [-2.20 – 2.01]	0.93
	6 months	25.8 (7.0)	27.0 (5.4)	-1.18 [-3.40 – 1.05]	-0.45 [-2.66 – 1.76]	0.69
PALPA Nonword repetition (0-24)	4 weeks	16.6 (7.6)	18.3 (6.3)	-1.76 [-4.10 – 0.58]	-0.39 [-2.46 – 1.67]	0.71
	3 months	16.9 (7.6)	19.1 (6.0)	-2.15 [-4.52 – 0.22]	-1.02 [-3.04 – 0.99]	0.32
	6 months	16.7 (7.5)	18.6 (5.7)	-1.90 [-4.26 – 0.46]	-0.79 [-2.91 – 1.34]	0.47
Letter Fluency (no. words / minute)	4 weeks	11.4 (9.6)	14.0 (10.9)	-2.62 [-6.04 – 0.80]	-0.29 [-3.25 – 2.67]	0.85
	3 months	12.8 (9.7)	17.1 (12.6)	-4.33 [-8.19 – -0.47]	-2.19 [-5.65 – 1.28]	0.21
	6 months	15.0 (10.4)	17.3 (12.5)	-2.35 [-6.39 – 1.69]	0.04 [-3.56 – 3.64]	0.98
PALPA Auditory Lexical Decision (0-80)	4 weeks	67.2 (18.4)	70.8 (14.6)	-3.61 [-9.18 – 1.97]	-1.46 [-6.91 – 3.99]	0.60
	3 months	68.1 (17.6)	72.3 (14.2)	-4.23 [-9.78 – 1.32]	-2.18 [-7.57 – 3.22]	0.43
	6 months	68.7 (18.4)	72.3 (14.3)	-3.64 [-9.50 – 2.22]	-1.79 [-7.63 – 4.05]	0.55

BNT (0-60)	4 weeks	28.6 (17.9)	31.4 (20.4)	-3.08 [-9.44 – 3.29]	1.40 [-3.99 – 6.78]	0.23
	3 months	33.0 (17.7)	37.5 (18.3)	-4.42 [-10.61 – 1.76]	-1.46 [-6.85 – 3.94]	0.59
	6 months	34.9 (18.0)	39.5 (17.9)	-4.56 [-10.86 – 1.74]	-1.29 [-6.85 – 4.28]	0.65
Token Test (0-36)	4 weeks	20.9 (10.4)	23.7 (10.3)	-2.84 [-6.30 – 0.62]	-0.10 [-2.98 – 2.78]	0.94
	3 months	23.3 (10.6)	26.0 (9.3)	-2.75 [-6.17 – 0.67]	-0.86 [-3.68 – 1.95]	0.55
	6 months	23.7 (10.9)	26.7 (9.1)	-3.00 [-6.57 – 0.57]	-0.83 [-3.92 – 2.25]	0.59
EQ-5D-3L (0-1)	4 weeks	0.79 (0.11)	0.81 (0.11)	-0.02 [-0.06 – 0.02]	-0.01 [-0.05 – 0.02]	0.48
	3 months	0.82 (0.12)	0.81 (0.13)	0.01 [-0.03 – 0.05]	0.02 [-0.02 – 0.06]	0.32
	6 months	0.82 (0.13)	0.82 (0.13)	-0.01 [-0.05 – 0.04]	-0.01 [-0.05 – 0.04]	0.78
mRS◊ (5-0)	4 weeks	3	3	-0.22 [-0.80 – 0.36]	-0.01 [-0.62 – 0.62]	0.99
	3 months	2	2	-0.23 [-0.82 – 0.36]	0.06 [-0.57 – 0.70]	0.85
	6 months	2	2	-0.23 [-0.83 – 0.38]	-0.07 [-0.70 – 0.57]	0.84

Abbreviations: SD = standard deviation; 95% CI = 95% confidence interval; SAT = Semantic Association Test; CAT = Comprehensive Aphasia Test; PALPA = Psycholinguistic Assessment of Language Processing in Aphasia; BNT = Boston Naming Test; mRS = modified Rankin Scale.
◊ Mode is reported for this categorical variable.

On-treatment analysis

In the on-treatment analysis we included all patients of the intervention group who received at least the prespecified intensity of 28 hours in four weeks (n = 23, 29%) and all subjects in the control group who did not receive any treatment (n = 62, 86%). Baseline characteristics of the intervention and control group included in the on-treatment analyses were similar (Table 5).

When on-treatment criteria were applied, the intervention group reached significantly higher scores than the control group after four weeks on the primary outcome ANELT-A (adjusted difference = 5.41, 95% CI: 1.52 to 9.31, p = 0.01); SAT verbal (adjusted difference = 3.57, 95% CI: 0.36 to 6.78, p = 0.03) and CAT word comprehension (adjusted difference = 3.64, 95% CI: 0.58 to 6.69, p = 0.02) (Figure 3, Table 6). On all other outcome measures and time points results did not differ from those of the intention-to-treat analyses.

Table 5. Baseline characteristics of participants in the on-treatment analyses

	Intervention (n = 23)	**Control (n = 62)**
Age in years, mean (SD)	64 (11)	66 (12)
Male sex, n (%)	17 (74%)	31 (50%)
Handedness, n (%)		
Right	20 (87%)	53 (86%)
Left	2 (9%)	7 (11%)
Ambidextrous	1 (4%)	1 (2%)
Unknown	0	1 (2%)
Level of education, n (%)		
No/unfinished elementary school	1 (4%)	0
Elementary school	3 (13%)	9 (15%)
Unfinished junior secondary vocational education	1 (4%)	7 (11%)
Junior secondary vocational education	7 (30%)	10 (16%)
Total low education	12 (52%)	28 (45%)
Senior vocational education	4 (17%)	15 (24%)
Higher education	6 (26%)	16 (26%)
University	1 (4%)	3 (5%)
Total high education	11 (48%)	34 (55%)
Unknown	0	2 (3%)
Type of stroke, n (%)		
Ischemic	18 (78%)	53 (86%)
Hemorrhagic	5 (22%)	9 (15%)
Location of lesion, n (%)		
Left hemisphere	22 (96%)	59 (95%)
Right hemisphere	1 (4%)	3 (5%)
Treatment with intravenous alteplase, n (%)		
Yes	9 (39%)	16 (26%)
No	14 (61%)	45 (73%)
Unknown	0	1 (2%)
Time between stroke and randomization in days, mean (range)	7 (2-14)	8 (2-15)
Time between stroke and start treatment in days, mean (range)	11 (6-19)	n.a.
Barthel Index Score, median (IQR)	20 (7.5-20)	17 (6-20)
Aphasia severity, n (%)		
Severe (ASRS score = 0 to 2)	12 (52%)	25 (40%)
Mild-moderate (ASRS score = 3 to 4)	11 (48%)	37 (60%)

Abbreviations: n = number; SD = standard deviation; IQR = Interquartile Range; ASRS = Aphasia Severity Rating Scale; n.a. = not applicable.

Table 6. Differences in outcome and treatment effect between intervention and control on secondary outcomes: on-treatment analyses

		Intervention mean (SD)	Control mean (SD)	Unadjusted difference [95% CI]	Adjusted difference [95% CI]	*p*-value
SAT verbal (0-30)	4 weeks	24.8 (4.1)	22.1 (8.0)	2.67 [-0.81 – 6.14]	3.57 [0.36 – 6.78]	0.03*
	3 months	26.1 (2.5)	24.1 (6.3)	1.93 [-0.92 – 4.77]	1.92 [-0.88 – 4.73]	0.18
	6 months	26.3 (2.5)	24.2 (6.8)	2.04 [-1.23 – 5.30]	2.17 [-0.99 – 5.33]	0.18
Category Fluency (no. words/ minute)	4 weeks	17.6 (11.4)	16.4 (12.0)	1.25 [-4.48 – 6.99]	1.61 [-3.12 – 6.33]	0.50
	3 months	22.5 (10.0)	21.1 (13.0)	1.41 [-4.85 – 7.66]	1.03 [-4.49 – 6.55]	0.37
	6 months	24.1 (12.4)	21.6 (13.6)	2.46 [-4.72 – 9.63]	1.74 [-4.77 – 8.26]	0.60
CAT (0-30)	4 weeks	28.0 (2.5)	25.0 (7.3)	3.01 [-0.08 – 6.10]	3.64 [0.58 – 6.69]	0.02*
	3 months	28.1 (1.8)	26.3 (6.1)	1.80 [-0.92 – 4.52]	1.99 [-0.72 – 4.70]	0.15
	6 months	28.4 (1.9)	27.0 (5.6)	1.44 [-1.26 – 4.14]	1.50 [-1.27 – 4.27]	0.28
PALPA Nonword repetition (0-24)	4 weeks	20.0 (3.3)	18.3 (6.5)	1.73 [-1.11 – 4.56]	1.79 [-0.86 – 4.43]	0.18
	3 months	20.6 (2.6)	19.4 (5.9)	1.27 [-1.37 – 3.91]	0.85 [-1.52 – 3.21]	0.48
	6 months	20.6 (2.4)	18.6 (5.8)	2.05 [-0.76 – 4.86]	1.35 [-1.34 – 4.04]	0.32
Letter Fluency (no. words / minute)	4 weeks	15.0 (10.7)	14.3 (11.2)	0.67 [-4.70 – 6.03]	0.93 [-3.85 – 5.72]	0.70
	3 months	17.0 (10.4)	17.4 (13.0)	-0.49 [-6.77 – 5.80]	-1.12 [-6.99 – 4.75]	0.71
	6 months	21.0 (11.1)	17.5 (12.8)	3.51 [-3.19 – 10.21]	2.70 [-3.46 – 8.87]	0.39
PALPA Auditory Lexical Decision (0-80)	4 weeks	73.7 (5.9)	70.6 (15.2)	3.07 [-3.43 – 9.56]	3.31 [-3.24 – 9.86]	0.32
	3 months	75.3 (3.9)	71.9 (14.9)	3.46 [-3.12 – 10.04]	3.39 [-3.31 – 10.09]	0.32
	6 months	75.5 (3.6)	72.0 (14.9)	3.48 [-3.62 – 10.58]	3.06 [-4.21 – 10.34]	0.40

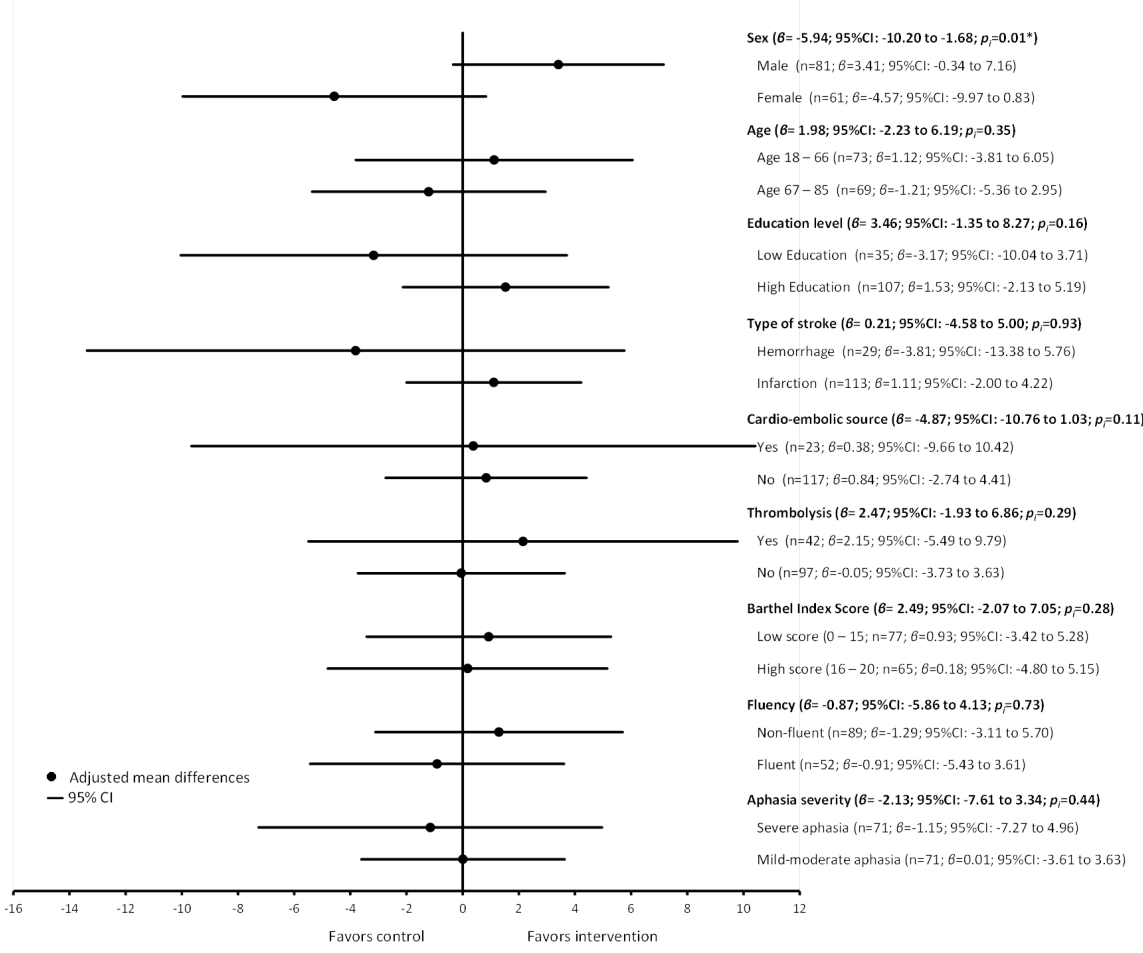
BNT (0-60)	4 weeks	37.3 (14.6)	31.7 (20.0)	5.52 [-3.57 – 14.61]	6.27 [-1.38 – 13.93]	0.11
	3 months	41.9 (13.7)	38.0 (17.9)	3.82 [-4.74 – 12.38]	4.65 [-3.39 – 12.69]	0.25
	6 months	42.7 (14.7)	40.0 (17.5)	2.69 [-6.39 – 11.76]	3.19 [-4.96 – 11.34]	0.44
Token Test (0-36)	4 weeks	24.4 (8.0)	24.1 (10.2)	0.35 [-4.35 – 5.04]	1.12 [-2.83 – 5.08]	0.57
	3 months	27.8 (7.4)	26.5 (9.2)	1.30 [-3.14 – 5.75]	1.33 [-2.57 – 5.24]	0.50
	6 months	29.4 (6.7)	26.9 (9.1)	2.59 [-2.06 – 7.25]	2.29 [-1.79 – 6.36]	0.27
EQ-5D-3L (0-1)	4 weeks	0.83 (0.12)	0.81 (0.11)	0.02 [-0.04 – 0.08]	0.01 [-0.04 – 0.06]	0.72
	3 months	0.86 (0.11)	0.81 (0.12)	0.05 [-0.02 – 0.11]	0.03 [-0.03 – 0.09]	0.29
	6 months	0.87 (0.11)	0.83 (0.13)	0.04 [-0.03 – 0.11]	0.02 [-0.05 – 0.09]	0.53
mRS◊ (5-0)	4 weeks	3	2	0.45 [-0.43 – 1.33]	0.64 [-0.31 – 1.59]	0.19
	3 months	2	2	0.35 [-0.55 – 1.24]	0.41 [-0.54 – 1.37]	0.39
	6 months	2	2	0.50 [-0.39 – 1.39]	0.62 [-0.32 – 1.57]	0.20

Abbreviations: SD = standard deviation; 95% CI = 95% confidence interval; SAT = Semantic Association Test; CAT = Comprehensive Aphasia Test; PALPA = Psycholinguistic Assessment of Language Processing in Aphasia; BNT = Boston Naming Test; mRS = modified Rankin Scale.
* Statistically significant at a 95% confidence level.
◊ Mode is reported for this categorical variable.

Post-hoc subgroup analyses

We also compared treatment effects per covariate used for baseline adjustment and we compared patients treated with intravenous alteplase and those who were not, and patients with and without a cardiac source of emboli. There was a statistically significant interaction between sex and intervention (adjusted β = -5.94; 95% CI: -10.20 to -1.68, p = 0.01), but not for other subgroups (Figure 4).

Figure 4. Subgroup comparisons for the ANELT-A at four weeks after randomization

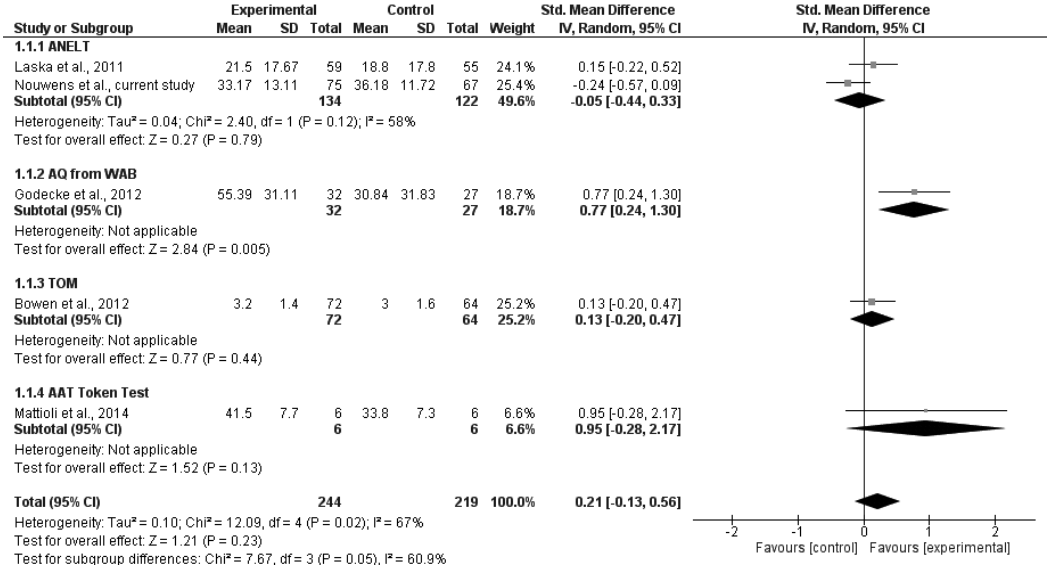


* Statistically significant interaction.

Synthesis of evidence

We found two RCTs comparing early intensive SLT to no treatment, one comparing early SLT to no SLT, and one comparing early intensive SLT to usual care.[6-9] We conducted a meta-analysis with the primary outcomes reported in these trials and our findings (Figure 5). The effect of early initiated SLT over deferred regular SLT or no treatment was small and not statistically significant (standardized mean difference = 0.21, 95% CI: -0.13 to 0.56).

Figure 5. Forest plot comparing standardized mean differences between early initiated intensive SLT and no treatment or usual care



Abbreviations: ANELT = Amsterdam-Nijmegen Everyday Language Test; AQ = Aphasia Quotient; WAB = Western Aphasia Battery; TOM = Therapy Outcome Measure, functional communicative ability; AAT = Aachen Aphasia Test.

Data derived from the Cochrane Systematic Review[10] and original manuscripts.

The figure was made using Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

DISCUSSION

Principal findings

In this multicenter RCT in 152 patients with aphasia due to stroke, we found that four weeks of early intensive CLT did not result in better everyday verbal communication than no early language treatment. The 95% CIs for the adjusted differences between groups did not include the prespecified clinically relevant difference of four points on the ANELT-A, which allows us to conclude that early intensive CLT is not effective.

This contradicts the findings from two smaller RCTs in which a benefit of early intensive treatment was reported. In 59 patients, 30 to 80 minutes of impairment-based SLT per workday for four weeks initiated three days after stroke, improved communication more

than usual care (<80 minutes per week).[7] Although nearly 20% of patients in the intervention group did not achieve the minimum treatment intensity of 150 minutes per week, the authors conclude that daily treatment is feasible early after stroke and, if tolerated, is effective for recovery of aphasia. In another study, 12 patients were randomly allocated to two weeks of either one-hour sessions of impairment-based SLT on workdays starting on average 2.2 days after stroke or no SLT.[8] In addition to statistically significant better scores in the early treatment group on the AAT subparts Naming and Written language processing, the authors report significant differences between groups in post treatment recruitment of brain areas on functional MRI-scans. However, this is a very small trial with only six participants per treatment arm.

Our findings are in line with those from two larger RCTs on early initiated SLT. In a trial among 123 patients, Laska et al. found no effect of three weeks of early intensive impairment-based SLT on ANELT-A scores three weeks and six months after stroke onset.[6] Bowen et al. randomly allocated 170 stroke patients with communication deficits to either agreed best practice SLT or social support provided by trained volunteers for 16 weeks starting on average two weeks after stroke onset.[9] They found no differences regarding functional communication at follow-up and conclude that SLT is not more effective than social support. This trial differs from ours, as stroke patients with either aphasia, dysarthria or both were included, which makes the results difficult to interpret. Furthermore, treatment intensity was tailored to the individuals' needs and possibilities. Consequently, treatment intensity was on average only 1.5 hours per week, which may not have been sufficient to reach a sizeable treatment effect.[3, 18, 19]

While the concept of early language rehabilitation after stroke is attractive, the summary of evidence in our meta-analysis shows that SLT, whether or not intensive, when started within four weeks after stroke onset, is not more effective in improving verbal communication or language functioning, than regular, less intensive or deferred treatment.

Strengths and weaknesses

Strengths of RATS-3 are its large size, multicenter design, a clearly defined clinically relevant intervention contrast, and representative cohort of patients with aphasia due to stroke. The treatment programs used in the intervention group are frequently applied in daily practice in the Netherlands and have good potential to generate an effect on language recovery, as exercises are directed at facilitating word finding, an essential problem in aphasia. Consequently, results of our trial are highly generalizable to daily practice. We could have opted for a more distinct intervention contrast by actively limiting all language related activities in the control group e.g. reading, writing and computer use, but that would not reflect daily reality. In fact, our aim was to study whether intensive CLT, added to language related activities people with aphasia engage in naturally, is effective for the recovery of aphasia.

Many efficacy studies on impairment-based treatment have used impairment-based language tests as outcome measures, e.g. naming or word comprehension, as these are closely related to the intervention being studied.[28] However, scores on linguistic tests are rather artificial and do not necessarily reflect adequate functional communication in daily life, which should be the ultimate goal of aphasia treatment.[3] Therefore, a relevant and reliable measure of communication, most closely reflecting the patients' sense of recovery and return to normal functioning, is preferable.[10] Hence, in line with our previous trials, both

in which we found that improvement on the ANELT-A was correlated with improvement at the impairment level, we used the ANELT-A as primary outcome measure.[16, 26, 27]

Our study has limitations. Although we accomplished a high median treatment intensity of 24.5 hours in four weeks, achieving the intended intensity of 28 hours appeared a major challenge. Even with a strictly protocolled treatment regimen and highly motivated SL-therapists who were frequently contacted by the trial coordinator, less than 30% of the intervention group achieved the requested intensity. Patients were often too tired or ill to practice one hour per day, even if treatment was spread over the day. Although poor adherence to the protocol was mainly caused by patient related issues, organizational problems such as limited availability of therapists, or priority given to motor rehabilitation also played a role, albeit minor. While this trial was no feasibility study, the results demonstrate that even if intensive treatment had been found more effective for selected patients, feasibility is improbable for all stroke patients with aphasia early after onset. This is in line with findings from the most recent Cochrane review.[3]

Patient selection seems essential to generate a potential beneficial effect of early intensive CLT on recovery of aphasia, as the on-treatment analyses did show a limited effect. However, this finding should be interpreted with great caution, as on-treatment analyses could only be performed in patients in the intervention group who could tolerate intensive treatment, whereas the control group comprised both patients who may and may not tolerate this intensive regimen.

Completeness of follow-up for the primary outcome was 93%, which is in line with other studies in this field.[3] At six months after stroke 19% of participants had refused follow-up testing. This may have reduced the validity of our findings, but the measurements at three and six month follow-up are secondary outcomes and are in line with the primary outcome.

Implications

Despite the lack of unequivocal proof for a beneficial effect of early SLT, deferring treatment in aphasia due to stroke has long been considered unethical.[29] However, early after stroke, patients may suffer from concomitant illness or fatigue and may not tolerate intensive impairment-based treatment. Our findings demonstrate that it is not detrimental to delay CLT in the first weeks after stroke onset in these vulnerable patients, which also occasionally happens unintentionally due to waiting lists or lengthy diagnostic pathways.

However, our findings do not justify the conclusion that the work of SL-therapists is redundant in the first weeks after stroke, as patients with aphasia and their proxies definitely need guidance and help in coping with their deficits early after stroke. In times of radical changes in health care policy and budget cutbacks, SL-therapists are urged to utilize their limited resources effectively for patients with acute stroke. Instead of focusing on impairment-based treatment, they might better put more emphasis on counseling and providing communication support, which are essential for coping with communication problems and prevention of social isolation. CLT may be more effective later in the course of this disabling condition.

Future research

Future studies should aim to find the optimal timing of commonly used treatment types, either impairment-based or functional approaches. New studies may be focused on patient selection also, as results from our on-treatment analyses indicate that some patients might

benefit from early intensive treatment. International cooperation is one way to conduct large aphasia trials that allow for more reliable prespecified subgroup analyses, which is of great importance to identify factors contributing to treatment success and may enable individualization of SLT.

CONCLUSION

Our study shows that four weeks of intensive CLT aimed at semantic and phonological processing started within two weeks after stroke onset does not improve the recovery of aphasia, either in the short or long-term.

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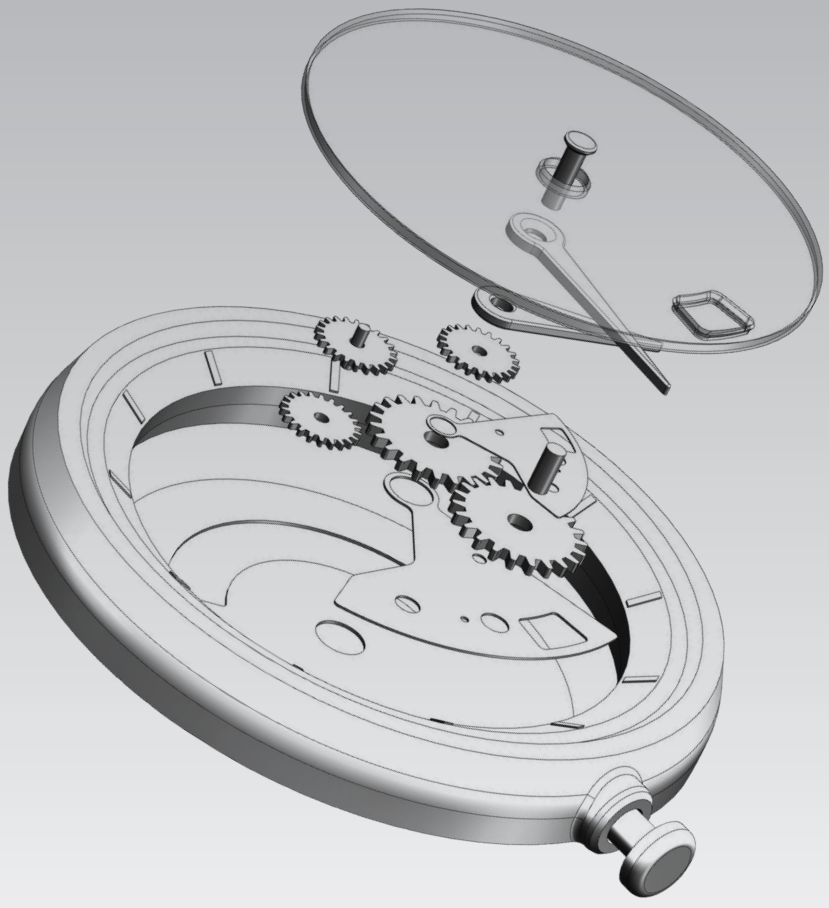

Chapter 4.4

Severity of aphasia and recovery after treatment in patients with stroke

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ABSTRACT

Background

Aphasia due to stroke is often very severe immediately after onset. However, knowledge about the impact of severity on therapeutic potential in the first months is scarce. The optimal therapeutic approach for patients with severe aphasia is still subject to debate.

Objective

To explore the recovery pattern of verbal communication in stroke patients with aphasia of varying degrees of severity receiving language therapy during the first six months post stroke.

Methods

We used data from our previous trial in which 80 patients with aphasia due to stroke were randomized within the first three weeks post onset for either cognitive-linguistic treatment or communicative therapy. All patients were tested at baseline and three and six months after aphasia onset. We formed three severity groups, based on baseline Amsterdam-Nijmegen Everyday Language Test scores. We used repeated measures ANOVA to compare test scores at baseline, three and six months post stroke onset for each of the three severity groups, stratified for the two treatments.

Results

Patients with severe or very severe aphasia improved substantially during follow-up; especially during the first three months post stroke. Improvement was less pronounced in the moderate to mild group. Although improvement did not differ significantly between the two treatment arms of the trial during the first six months post stroke, the very severe group seemed to benefit particularly from cognitive-linguistic treatment (mean difference between treatments was 4.1 points; 95% CI: -4.0 to 12.2).

Conclusion

Even in very severely aphasic patients, considerable improvement of functional communication is possible. These patients might benefit more from early initiated cognitive-linguistic treatment than generally assumed. Hence, speech and language therapists should not refrain from applying cognitive-linguistic treatment in the acute phase of rehabilitation of severe aphasia.

INTRODUCTION

Aphasia caused by stroke is often severe; between 26% and 61% of these patients have global aphasia at onset.[1, 2] Severity of aphasia is known to be an important prognostic factor for the recovery of stroke.[3-7] Few recovery studies concerning aphasia have provided specific data on severely affected patients in the acute stage and severely aphasic patients were excluded from several randomized controlled trials (RCT) investigating the effect of linguistic treatment in the acute stage.[7-9] The majority of the studies in severely aphasic people are conducted in the chronic stage. One reason for excluding patients with severe aphasia from acute therapy studies is obviously the challenge to obtain informed consent in patients with severe comprehension deficits.[7] Nevertheless, the lack of research data possibly also reflects some clinicians' pessimistic view on treatment induced language recovery from severe aphasia, despite some reports of patients regaining language function beyond expectation.[5-8, 10-12]

The influence of treatment on language processing of people with severe aphasia in the acute stage is as yet unclear. Roughly, there are two main approaches to aphasia treatment; cognitive-linguistic treatment (CLT) and communicative treatment.[13] The first is directed at restoration of the affected linguistic function and the latter at compensation strategies.

In the first weeks after stroke, speech and language therapist (SL-therapists) often focus their treatment on functional communication in patients with severe aphasia. Treatment in this vulnerable stage is usually aimed at enhancing communicative abilities using verbal and nonverbal channels.

CLT may be applied in later stages, although it has been suggested that recovery is hampered by the extensive neural damage in these severely affected patients.[6, 11] Furthermore, because of the widespread damage to the language system in severe aphasia, it may be difficult to determine which linguistic deficit(s) should be treated with CLT.[14] Studies on the efficacy of CLT in patients with severe aphasia are scarce, whereas communicative therapy for severe aphasia has been evaluated in quite a number of studies.[15-21] However, this paucity of reports on the efficacy of treatment in patients with severe aphasia may be the result of bias in research studies and does not necessarily reflect true clinical practice. Some case studies and studies in small samples do suggest that a cognitive-linguistic approach might be beneficial for severely affected people.[22-26]

Given the high incidence of severe aphasia in acute stroke, the impact of this disorder, the burden on healthcare, and the association between aphasia and the success of rehabilitation,[27, 28] more knowledge about recovery and the potential effect of treatment in severely aphasic patients is needed.

We therefore explored the recovery pattern of verbal communication in stroke patients with aphasia of varying degrees of severity who received either CLT or communicative therapy during the first six months post stroke.

METHODS

All patients included in the present study participated in the Rotterdam Aphasia Therapy Study (RATS) – 2, a multicenter, single blinded RCT on the efficacy of CLT among 80 patients with aphasia due to stroke.[13] RATS-2 was approved by the Medical Ethical Committee of the

Erasmus MC – University Medical Center Rotterdam, the Netherlands. Written informed consent was obtained from all patients and/or their proxy before inclusion.

The design and main results have been described elsewhere.[13] In brief, stroke patients aged between 18 and 85 years with impaired verbal communication and an overt semantic and/or phonological disorder were randomized within three weeks after stroke to six months of either CLT or communicative therapy. Mean treatment intensity was 2.1 hours per week.

CLT was directed at two basic language components, lexical semantics using BOX[29, 30] and phonology using FIKS[30, 31]. BOX and FIKS are well described verbal treatment programs targeting lexical semantic and phonological processing on word, sentence and text level. Strengthening the semantic relations between words is the focus of the BOX therapy. Within each task the patient is required to deny or confirm the semantic relationship between written and/or auditory presented content words, either presented separately or within the context of a sentence or text. FIKS is directed to the phonological in- and output routes with word discrimination tasks indicating phonemic (dis)similarities (auditory presentation) and word production tasks (repetition, reading aloud and producing phonemic similar words). To enhance the generalization effect, both programs offer a great variety of tasks. Moreover, a considerable number of items on different levels of difficulty is included to ensure that the SL-therapist is able to spend enough time on tasks that correspond to the patients' needs. Consequently, these treatment methods are appropriate for all aphasia types and severity degrees. For each patient, based on the test results, the participating SL-therapists determined which parts of BOX and/or FIKS were suitable to meet the individual needs.

Communicative therapy was directed at functional communicative behavior using all verbal and nonverbal strategies available to the subject. Treatment was tailored to the requirements in daily life, for instance to enhance the ability to bring the message across using the Promoting Aphasics' Communicative Effectiveness.[32] In deliberation with the patient and their proxies, treatment was focused on actions relevant in everyday life via role-playing and conversational coaching (if necessary together with the partner), guided discussions about actual topics and written diaries. The SL-therapist used the test results to determine the level of treatment in terms of the nature of the support during the activities. No impairment-based linguistic treatment, such as semantic or phonological treatment was allowed.

Meetings were organized regularly for SL-therapists to discuss the progress of the trial and the content of treatment and to establish compliance to treatment. At any time during the study, the trial team could be consulted for advice.

At baseline, as well as three and six months post aphasia onset, patients were tested with the Amsterdam-Nijmegen Everyday Language Test (ANELT), a test for everyday verbal communication with scores ranging from 10 to 50.[33, 34] Subjects are presented with ten everyday situations, for instance "You have a doctor's appointment, but for some reason you cannot make it. So you call the doctor and what do you say?". Two practice items are used to familiarize participants with the task and to instruct them to respond verbally, using direct speech. Verbal responses are audio recorded and rated for informational content on "Understandability" (ANELT-A scale), a five-point scale, by two independent experts, blinded to test moment and treatment allocation. A score of 1 is given when a response is not understandable at all, a score of 3 reflects a partial message and a score of 5 reflects a fully understandable and adequate response. For instance a response like "I have an

appointment, but I cannot make it. Can I make another appointment?" to the scenario presented above, is rewarded a score of 5, but "I need an appointment" gets a score of 3 and "Yesterday today going away yes no you know" gets a score of 1.

The average scores of both independent experts were used for the analysis if they did not deviate more than seven points. If the difference between scores of the two judges exceeded seven points, both experts were requested to score the test a second time. If the difference between experts was again larger than seven points, a third expert scored the test. The average score of the three judges was used for the analysis.

For the present study, we used the baseline ANELT scores to form three severity groups; very severe aphasia (ANELT-A score 10 to 15), severe aphasia (ANELT-A score 16 to 30) and moderate to mild aphasia (ANELT-A score 31 to 50). Our severity groups are based on adjusted severity levels from the test manual.[35] According to the manual very severe aphasia is defined as ANELT scores between 10 and 19, severe as 20 to 29, moderate as 30 to 39 and mild as 40 to 48. Because these criteria resulted in skewed data and a gap between the lowest score of 10 and higher scores, we adjusted severity group cut-off values. The adjusted categorization results in a more evenly distributed number of subjects per severity group and matches daily practice in a better way.

Baseline characteristics such as handedness assessed by means of the Edinburgh Handedness Inventory,[36] educational level (low = junior vocational education or lower), stroke type (ischemic or hemorrhagic) and location of the lesion were collected. In addition, the Token Test, a general measure for severity of aphasia was administered at baseline.[37] Correlation between baseline Token Test scores and baseline ANELT scores was calculated to confirm the ANELT as a valid measure for severity of aphasia in our patient group.

Scores at baseline, three and six months post stroke onset were compared between severity groups, stratified for the two treatment types, using repeated measures ANOVA with 95% confidence intervals (95% CI).

RESULTS

Table 1 shows the baseline characteristics of the study population for each severity group. Baseline tests were administered on average 19 days post stroke onset. Pearson's correlation between the two blinded raters of ANELT-A scores at baseline was $r = 0.975$, $p < 0.05$, at the three month test $r = 0.978$, $p < 0.05$ and $r = 0.971$, $p < 0.05$ for the six month test. The ANELT scores at baseline were strongly correlated with the Token Test scores ($r_s = 0.589$, $p < 0.01$).

Table 1. Baseline characteristics of the study population, by severity of aphasia

	Very severe (n = 35)	**Severe (n = 26)**	**Moderate to mild (n = 19)**
ANELT score, range	10-15	16-30	31-50
ANELT score, mean (SD)	11.0 (1.4)	23.2 (4.6)	37.3 (3.5)
Therapy group:			
CLT, n (%)	16 (46%)	13 (50%)	9 (47%)
Communicative therapy, n (%)	19 (54%)	13 (50%)	10 (53%)
Age in years, mean (SD)	68 (11)	65 (18)	70 (13)
Male sex, n (%)	19 (54%)	10 (38%)	9 (47%)
Right-handedness, n (%)	28 (80%)	20 (77%)	18 (95%)
Low educational level, n (%)	23 (66%)	20 (77%)	12 (63%)
Stroke type:			
Ischemic stroke, n (%)	29 (83%)	22 (85%)	16 (84%)
Hemorrhagic stroke, n (%)	5 (14%)	2 (8%)	2 (11%)
Missing, n (%)	1 (3%)	2 (8%)	1 (5%)

Abbreviations: ANELT = Amsterdam-Nijmegen Everyday Language Test scale A (understandability); SD = standard deviation; CLT = cognitive-linguistic treatment.

Figure 1 displays mean ANELT scores of the three severity groups at baseline, three months and six months post aphasia onset. In patients with very severe aphasia the mean improvement on ANELT was 12 points from baseline to three months and 2 points from three to six months, regardless of therapy type (Table 2). This improvement was statistically significant from baseline to three months and from three months to six months. For the severe group the mean improvement from baseline to three months was 14 points and from three to six months 1 point. The mean improvement in the moderate to mild group from baseline to three months was 6 points and from three to six months 2 points. The severe and moderate to mild group significantly improved during the first three months, but not between three and six months post onset.

Figure 1. Scores on the Amsterdam-Nijmegen Everyday Language Test (ANELT) in the three severity groups for cognitive-linguistic (CLT) and communicative therapy at baseline, three months and six months after aphasia onset

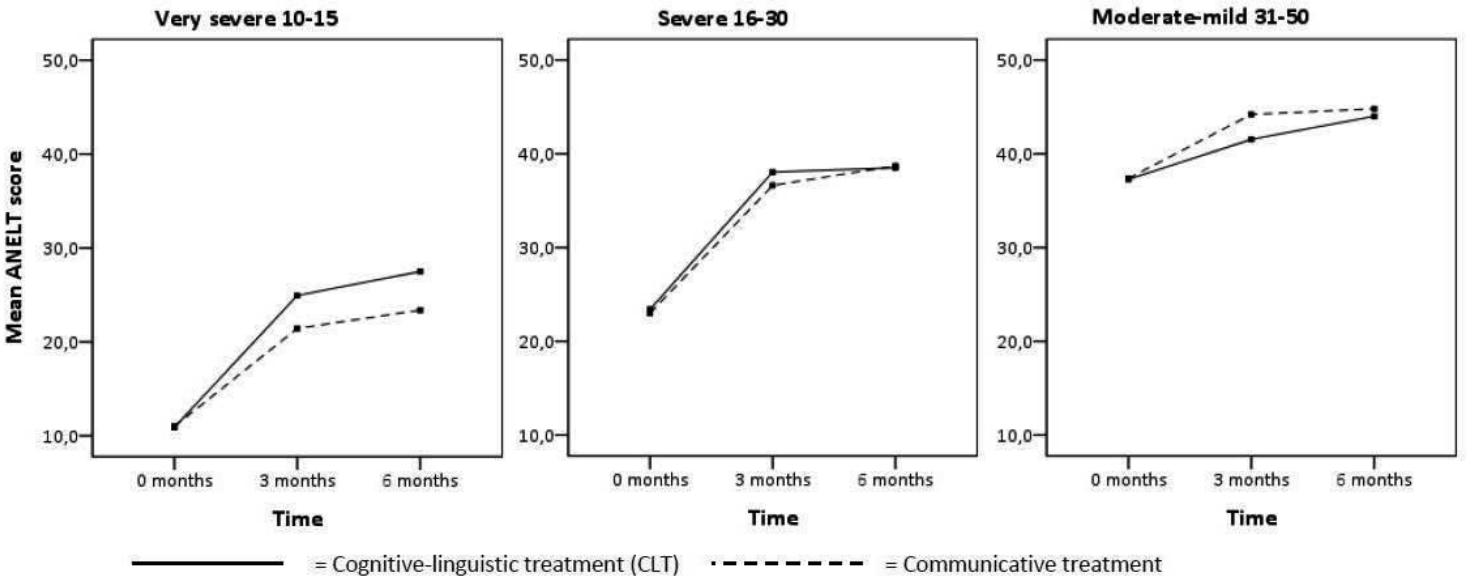

Table 2. Improvement on ANELT during the first six months post stroke, by severity of aphasia

	Mean improvement [95% CI]	***F* (df)**	***p*-value**
Baseline to three months post stroke			
Very severe aphasia	12.2 [7.4 – 17.1]	*F* (1,33) = 40.93	0.00
Severe aphasia	14.1 [10.2 – 18.1]	*F* (1,24) = 84.97	0.00
Moderate to mild aphasia	5.5 [2.6 – 8.5]	*F* (1,17) = 25.44	0.00
Three to six months post stroke			
Very severe aphasia	2.2 [0.2 – 4.3]	*F* (1,33) = 7.64	0.01
Severe aphasia	1.3 [-1.2 – 3.7]	*F* (1,24) = 1.75	>0.05
Moderate to mild aphasia	1.5 [-1.0 – 4.0]	*F* (1,17) = 2.63	>0.05

Abbreviations: ANELT = Amsterdam-Nijmegen Everyday Language Test scale A (understandability); 95% CI = 95% confidence interval; *F* = test of within subjects contrasts; df = degrees of freedom.

The mean difference in ANELT scores at six months post aphasia onset between CLT and communicative therapy in the very severe group was 4.1 points (95% CI: -4.0 to 12.2), in the severe group -0.2 points (95% CI: -5.7 to 5.3) and in the moderate to mild group -0.8 points (95% CI: -5.4 to 3.8). The differences between ANELT scores in both types of treatment were not statistically significant in all severity groups. Yet, the difference in ANELT scores between CLT and communicative therapy at six months post stroke in the very severe group suggests a trend favoring CLT for the rehabilitation of very severe aphasia in the acute stage.

DISCUSSION

Our study shows that in the first three months after stroke verbal communication improved significantly in patients of all severity groups who received therapy. Most progress was observed in the patients with a severe and in patients with a very severe aphasia. The latter group made a statistically significant progress also in the second period of follow-up. Overall, there was no difference in the benefit from CLT or communicative therapy. Only the very severely aphasic patients showed a trend to benefit more from CLT than from communicative therapy.

Strength of our study is that it was conducted within the setting of a randomized controlled clinical trial with standardized assessments by well-trained experts. Furthermore, patients were included from over twenty institutions in the Netherlands, which increases generalizability. All experts were trained and closely monitored by the trial team to assure protocol compliance. The use of the standard treatment programs BOX and FIKS and the regular discussions about the communicative treatment approach during the meetings with the participating SL-therapists further diminishes inter-site and inter-therapist variability.

Drawbacks of the present study are that it concerns post-hoc analyses in relatively small groups. Moreover, the number of subjects per group in this study was not equal; fewer patients were categorized in the severe and moderate to mild groups than in the very severe group. The finding that the improvement between three and six months post stroke was not significant in the severe and moderate to mild group may have been due to insufficient statistical power.

We chose to adjust the severity levels of the ANELT manual to have a better distribution of subjects per severity group. Applying the severity levels from the manual in the current study, with a larger cohort containing all severity levels, resulted in a vast gap between a large number of subjects scoring lowest on ANELT (a score of 10) and a more even distribution of subjects in the higher range of scores. Adjusting the severity levels resulted in a better distribution of subjects over the groups, although the number of subjects per group was still uneven.

It is increasingly recognized that treatment intensity may be related to outcome.[38] The relatively low treatment intensity of on average 2.1 hours per week in our study may thus have influenced our findings. However, our results are clinically relevant, because the treatment intensity of our study reflects general daily practice in the Netherlands. A higher intensity is often not feasible in rehabilitation settings.

The significant correlation in our data between ANELT and Token Test at baseline is of particular interest. All patients scoring low on the ANELT are diagnosed with severe aphasia by means of the Token Test as well, showing that this high occurrence of low scores cannot be attributed to a prominent disorder in speech production.

Several researchers have indicated that substantial improvement may be expected in patients with severe aphasia, because low baseline scores provide more room for improvement.[8, 12, 39] On the other hand, previous findings suggest that greater initial severity is associated with poorer outcomes.[6] Both notions are confirmed in our study. The results show that the moderate to mild group scored highest on the ANELT and reached on average a good level of functional communication. Both severe groups did not reach such a high level of functional communication, but did show the largest improvement. We cannot rule out the possibility that the relatively small increase in the moderate to mild group is caused by a ceiling effect. However, the moderate to mild group reached an average ANELT-A score of 44. None of the participants in the moderate to mild group reached a normal score of 49 to 50, which leaves some room for improvement, although not as large as in both severe groups.

Our results challenge the assumption that people with severe aphasia are unlikely to benefit from restorative CLT and that functional communicative therapy is preferable for this aphasic subgroup.[11, 14] Patients with very severe aphasia appeared to particularly benefit from CLT as compared with communicative therapy, whereas in the other two groups this difference between therapy types was absent. This finding is in contrast with the assumption that extensive neural damage is a contra-indication for the application of restorative impairment-based therapy. In patients with severe aphasia, CLT might trigger specific linguistic neural networks in order to restore linguistic functions, more than is generally assumed.[11] Some basic linguistic content is required to compensate for the reduced language behavior in severe aphasia. This can be regained through CLT, as was also observed in a recent study in which naming therapy seemed to be more effective than gesture learning.[40]

The debate on aphasia treatment does not only concern therapy type, but also the optimal duration of treatment. All groups showed improvement up until six months after stroke onset. Interestingly, the positive slope of the line of the very severe group in Figure 1 suggests a possibility of ongoing recovery beyond six months after stroke. This finding is valuable in the light of changing stroke care policies that seem to continuously limit resources to treat stroke patients. Rehabilitation facilities beyond six months post stroke are

usually restricted or even unavailable for aphasic patients. Our results suggest that the rehabilitation period perchance might be prolonged beyond the usual six months to realize optimal recovery.

The claim that CLT could be effective in an early stage of severe aphasia needs to be confirmed in future studies, preferably in a randomized controlled trial controlling for severity.

CONCLUSION

We conclude that very severely aphasic patients, although they achieve a lower outcome level than milder cases, do have the capacity to significantly regain communicative abilities during the first six months after stroke. There is a trend for very severely aphasic patients to benefit more from CLT than from communicative treatment. This suggests that aphasia therapy, especially restorative treatment, should not be postponed or withheld in this group of patients. We also plead for the inclusion of very severe and severe patients in future trials.

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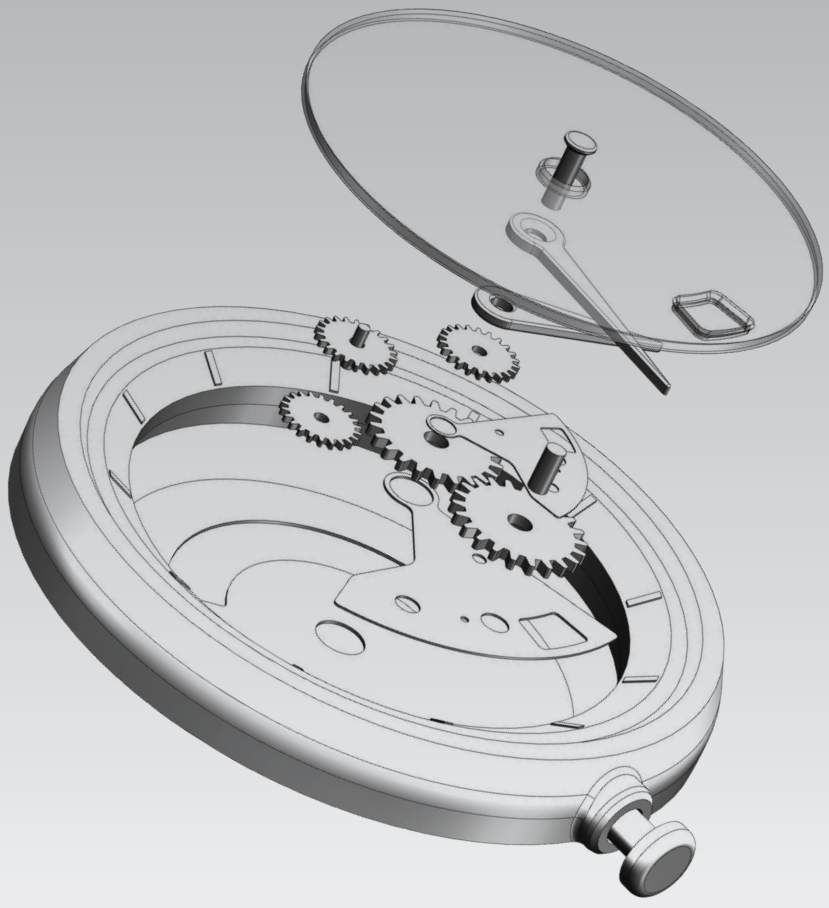

Chapter 5

General discussion

The aim of this thesis was to study language rehabilitation of stroke patients with aphasia, with a main focus on timing of speech and language therapy (SLT). In this concluding chapter I will recapitulate and discuss the main findings of this thesis. Methodological limitations and implications for clinical practice will be discussed also, as well as directions for future research.

MAIN FINDINGS

The following three questions were addressed in this thesis:

- How accurately can we diagnose the presence of aphasia in the early stage after stroke?
- Which factors are of importance for an accurate prediction of aphasia outcome in stroke?
- Is there a relationship between the timing of aphasia treatment and its efficacy?

I will start with discussing findings from the cornerstone of this thesis: the Rotterdam Aphasia Therapy Study (RATS) – 3, a randomized controlled trial (RCT) on the efficacy of early initiated intensive cognitive-linguistic treatment (CLT) in aphasia due to stroke. After that, I will discuss the two other questions.

Efficacy of early intensive CLT

In RATS-3, we set out to answer the important clinical question of whether intensive SLT is effective early after stroke onset. We first wrote a literature-based narrative overview on what is known about the relationship between timing and efficacy of aphasia treatment, by exploring evidence from language rehabilitation, but also from motor rehabilitation and animal studies. Directly after stroke onset, increased neuroplasticity in the brain may help the brain to optimally benefit from SLT. Correlations between an early start of treatment and good recovery of motor function have been reported. Although these findings suggest that early treatment may be effective, most findings were not supported by RCTs. Thus, this may merely reflect that patients who can tolerate early treatment have greater potential for recovery.[1-13] There are also arguments against an early start of intensive rehabilitation. In animals with induced stroke, it was found that intensive training early after stroke onset increased the lesion size, and human stroke patients who started early after stroke with intensive constraint-induced movement treatment showed less improvement of motor function than those receiving early usual treatment or less intensive restrictive treatment. This infers that, when started early after stroke onset, intensive motor treatment is not only ineffective, but might even be detrimental.[14, 15]

We concluded from this literature-based review that there is still insufficient evidence to favor an early start of SLT for aphasia after stroke. Hence, we conducted a large multicenter RCT: RATS-3. In this RCT we included patients with first-ever aphasia within two weeks after stroke, and randomly allocated them to four weeks of either intensive CLT or no language treatment. The intention-to-treat analyses showed neither statistically significant, nor clinically relevant differences between groups on the primary outcome: the score on the ANELT after four weeks; adjusted difference = 0.39, 95% confidence interval (95% CI): -2.70 to 3.47. No effect of early treatment on everyday communication was found three months (adjusted difference = 0.54, 95% CI: -3.04 to 4.12) and six months (adjusted difference = -

0.41, 95% CI: -3.70 to 2.89) after randomization either. The 95% CIs did not include the predefined clinically relevant difference between groups of four points on the ANELT. In addition, no statistically significant differences between groups were found for the secondary outcomes, i.e. impairment-based linguistic tests and measures for general functional outcome, at all time points. Potential clinically relevant differences between groups on the secondary outcome measures were also ruled out by the corresponding 95% CIs.

These findings consistently exclude an effect of a boost of CLT initiated in the first two weeks after stroke onset on the recovery of aphasia due to stroke. A meta-analysis combining our primary outcome results with those of the only four published RCTs on early intensive treatment versus no SLT or usual care, convincingly showed no benefit of early intensive treatment. Hence, in general it is not necessary to start CLT as soon as possible after stroke onset and a waiting list or longer diagnostic phase are not detrimental.

Factors associated with efficacy of treatment

We additionally conducted on-treatment analyses including only the patients who actually adhered to the RATS-3 protocol, i.e. patients in the intervention group who received 28 hours of treatment or more (n = 23) and patients in the control group who received no treatment at all (n = 62). Results from these analyses suggest an effect of early intensive CLT, but this effect was restricted to only three linguistic tests, including the ANELT, only after the four week intervention period. No effects were observed on other tests and other time points. This might imply that the selected group of patients who tolerated early intensive CLT may benefit from this approach.

Although this finding seems promising, the effect was only short-term and had disappeared at three months after stroke, and we must be careful interpreting results of this subgroup analysis, as I will discuss later. Furthermore, characteristics of the patients included in the on-treatment intervention group must be identified first and subsequently a new trial may be designed specifically to confirm this potential effect.

Findings from these on-treatment analyses suggest that it is important to carefully select patients who might benefit from early SLT. Important factors for such a selection process are as yet unclear. Findings from the intention-to-treat regression analysis showed that everyday verbal language performance at four weeks after randomization was predominantly related to aphasia severity and stroke severity at baseline, suggesting that these two factors may affect early outcome more than SLT and may be relevant factors for patient selection.

To study the relationship between recovery of aphasia in patients receiving SLT and baseline aphasia severity, we plotted recovery profiles of three groups with different aphasia severity levels according to baseline ANELT scores in a post-hoc study using the data from RATS-2. The groups with severe and very severe aphasia showed comparable recovery profiles, with a steep increase from baseline to three months and further, yet less steep improvement from three to six months. Patients in the moderate to mild group showed a rather flat improvement curve during the entire six month follow-up period.

We also studied whether the severity groups would respond differently to type of treatment, permitted by the random allocation to either CLT or communicative treatment in RATS-2. Exclusively in the group with very severe aphasia we observed a trend of a greater effect of CLT than of communicative treatment on ANELT scores at follow-up. This

contradicts the general notion of severely aphasic patients not benefitting from CLT, and that they ought to be treated with compensatory communicative treatment.[6, 16]

Early diagnosis of aphasia

Available aphasia screening tests were evaluated in a systematic review to explore whether they are reliable and valid for detecting aphasia early after stroke. A systematic search was conducted to identify screening tests that were evaluated in validation studies. We found eight screening tests that fitted the prespecified criteria. Four tests had good sensitivity and specificity properties, but only three validation studies on two tests, i.e. the Language Screening Test (LAST)[17] and ScreeLing[18], had an intermediate or low risk of bias. Therefore, we concluded that the LAST and ScreeLing can be reliably used in clinical practice for diagnosing the presence of aphasia early after stroke. The ScreeLing was also used in RATS-3 for inclusion purposes.

Predicting aphasia outcome after stroke

We used data from RATS-3 to externally validate a previously published prognostic model, derived from the observational prospective study SPEAK (Sequential Prognostic Evaluation of Aphasia after StroKE).[19] In this model a limited number of baseline variables is used to predict long-term outcome of aphasia due to stroke and internal validation was good. The external validation process showed that the SPEAK model had good discriminative properties, but calibration was insufficient. This may have been caused by differences between the SPEAK and RATS-3 cohorts regarding timing of the collection of outcome variables. The SPEAK model predicts good outcome one year after stroke, but we collected outcome data in RATS-3 at six months after stroke. Although in SPEAK there was no statistically significant improvement in ASRS scores between six months and one year after stroke, there was some improvement. This apparent small improvement may have caused the insufficient calibration. We therefore suggest an update of the model to predict good aphasia outcome at six months after stroke.

Language recovery after intra-arterial treatment for ischemic stroke

Rapid changes in language functioning early after stroke were also demonstrated in the post-hoc analysis of patients with aphasia in the MR CLEAN trial. We found that intra-arterial treatment (IAT) added to usual care was more effective than usual care alone for the recovery of aphasia.[20] We also found that, in line with observations in the clinic, motor function recovers significantly faster than language function in the early stage after stroke. At 24 hours after IAT, motor function had recovered beyond that of language function, but this difference almost disappeared after a week.

METHODOLOGICAL LIMITATIONS

I will discuss the most important limitations of the research presented in this thesis, focusing on the most comprehensive study, RATS-3.

Ethical considerations

In RATS-1 and RATS-2 we did not include a control group without treatment, because we considered withholding treatment for more than six months to be unethical. In RATS-3 we

did introduce a control group that received no SLT for six weeks at maximum after stroke onset. This raised considerable stir in the Netherlands and abroad. Many clinicians asked whether depriving patients with aphasia of language treatment was ethically justifiable, as in clinical practice they often observe improvement during therapy and thus consider early treatment effective. However, at the time we initiated our trial solid evidence showing that starting treatment as soon as possible is more effective than initiating treatment in a later stage was lacking. Thus, there was clinical equipoise regarding the potential effect of early initiated SLT, and there were no ethical arguments against this trial design. Consequently, medical ethical approval was acquired.

We have carefully chosen for a duration of four weeks for the intervention phase. Our hypothesis was derived from the theory that especially CLT positively interacts with spontaneous neural recovery and therefore should be provided in the early phase after stroke, as in this phase most spontaneous recovery occurs.[6] However, there is no consensus in the literature on the duration of the spontaneous recovery phase, like there is no consensus on the definition of 'early phase' either. Therefore, we coincided with current clinical practice in the Netherlands, also for feasibility purposes. SL-therapists strive to start treatment as soon as possible after stroke, as this is recommended in the Dutch evidence-based clinical guideline on care for stroke patients.[21] In daily practice, patients generally start with impairment-based treatment after three to six weeks, due to transfer time from hospital to rehabilitation center, time needed for diagnostics and limited resources. We also presumed that a long intervention period with intensive treatment would not be feasible, as it is known that stroke patients are generally unable to tolerate intensive treatment early after stroke onset.[22]

Still, it would have been interesting to defer treatment for a longer period, as the contrast between both treatment groups would have been larger. Ideally, for a maximum contrast, deferred treatment in the control group should be started as soon as spontaneous neural recovery has ceased. The steep recovery curves in the first three months after stroke in the aphasia severity groups presented in *Chapter 4.4* and other studies indicate that three months may be an interesting deferral period.[23-25] Hereby, we may better disentangle spontaneous recovery and treatment induced recovery. Yet, I expect that recruiting sufficient SL-therapists and patients who would want to participate in such a trial would be very difficult, as the notion that starting treatment as soon as possible is beneficial is deeply embedded in rehabilitation medicine and public opinion.

Feasibility of intensive treatment

A major finding of RATS-3 is the limited feasibility of high-intensity treatment initiated early after stroke. Several studies suggest that more intensive treatment is more effective, but a threshold in hours of treatment per week between effective and ineffective treatment intensity is as yet unidentified.[26, 27] Some studies have suggested that treatment is effective if it is provided for nearly nine hours per week, but others showed a benefit of five hours weekly, whereas low-intensity treatment, i.e. two hours a week, was not effective.[26, 28, 29] There are also studies indicating that treatment distributed over a longer period (six hours per week for eight weeks or ten sessions in five weeks) is better for retaining newly learned skills than a short intensive treatment program (16 hours per week for three weeks or ten sessions in two weeks),[30, 31] while in other studies treatment intensity did not have an impact on the efficacy of treatment.[32, 33]

In line with available evidence we chose a fairly high target treatment intensity of 28 hours in four weeks, to at least provide sufficient therapy in the intervention group. Based on Godecke et al.'s pilot RCT we expected that one hour of treatment a day would be feasible.[34] However, mostly due to fatigue, comorbidities or illness, this turned out not to be viable in the majority of patients and despite all our efforts, only 29% of the intervention group reached the target intensity. This demonstrates that, although high-intensity treatment is often advocated by researchers and clinicians, patients are unable to or do not always want to adhere to such a protocol. This result is not surprising though, since in other trials higher dropout rates, either from intervention or follow-up, were reported for high-intensity treatment protocols than for regular SLT.[22] When treatment intensity was not prescribed in a study-protocol, but instead patients and therapists decided on intensity themselves, it was found that 1.5 hours of treatment per week was the preferred and tolerated intensity in the first four months after stroke.[35]

The fact that only a minority of patients in the intervention group received the intended treatment intensity may be considered a limitation of our trial. On the other hand, the 28 hours in four weeks were more or less arbitrary, and several studies have shown a benefit of less than six hours of treatment per week.[28, 34, 36] Moreover, in the few published evidence-based or best practice guidelines on SLT for aphasia the minimally recommended treatment intensity is two hours of treatment per week.[21, 37-39] When I look at the median treatment intensity in RATS-3 of 24.5 hours in four weeks, i.e. more than six hours per week, I am still convinced we provided sufficient therapy in order to demonstrate a treatment effect, if there would be one.

In general, a failure to demonstrate superiority of an intervention is not surprising if there is no strong contrast between the intervention and control.[40] The fact that we provided a median treatment intensity of six hours of impairment-based CLT per week to the intervention group and no SLT, but only minimal counseling to the control group created a large contrast between treatment groups in RATS-3, justifying our conclusion that intensive CLT is not superior to no SLT early after stroke onset.

Intervention

In research, the studied intervention must be standardized in order to adequately evaluate and interpret its efficacy.[41] Factors such as type of treatment, intensity of treatment, individual or group treatment, location where the treatment is provided and who is providing treatment have to be reported. Consequently, clinicians know which factors have been proven effective in trials and need to be included in their treatment regimen.[42] Downside of this strict demarcating of interventions is that we may end up with lab-conditions, not reflecting clinical practice, in which many factors and treatment types are combined in one therapy session.

In RATS-3 we have chosen a rather pragmatic approach by using two language treatment programs that were already frequently used in daily practice in the Netherlands and that were used in the two prior RATS trials. We may debate whether this type of treatment is most appropriate early after stroke. CLT presumes some form of meta-linguistic consciousness, as it is based on linguistic processing models and exercises target detailed semantic, phonological and syntactic operations.[43] While communicating, we normally do not intentionally process these actions separately. As many stroke patients are faced with cognitive impairments,[44] this type of treatment may be focused too much on details and too

complex, possibly explaining the lack of treatment effect in RATS-3.[44-47] However, in the post-hoc analysis of the RATS-2 cohort, we found that especially severely impaired patients seemed to benefit from CLT, refuting the notion that CLT would be too complicated to administer in the acute phase.

Outcome measures

The baseline test battery in RATS-3 was limited to the 36-item Token Test, ScreeLing and a recording of spontaneous speech and did not include the ANELT, our primary outcome measure. Consequently, we were unable to compare improvement in ANELT scores between groups from baseline to follow-up, i.e. improvement due to an early boost of CLT (intervention group) or due to spontaneous recovery (control group). Instead, we compared ANELT scores at follow-up with adjustment for baseline aphasia severity. Although evaluating improvement in ANELT scores would have been interesting, it has been shown that methods comparing change or delta scores introduce more variation in analyses than analyses of covariance with a correction for baseline severity.[48] We favor the more conservative method, and thus chose for the latter option.

Moreover, RATS-3 was set out to be a pragmatic trial and choices for baseline testing were made based on feasibility considerations. Conducting an ANELT very early after stroke is not standard practice, as most patients are faced with severe language deficits early after stroke. The design of the ANELT requires role-playing in routine situations, which is a difficult task for stroke patients in the acute stage.

The ANELT is designed to assess everyday verbal communication, which is clinically relevant as opposed to other rather artificial tests measuring detailed linguistic processing. We chose the ANELT as the primary outcome in all RATS trials based on the assumption that adequate impairment-based treatment should generalize to everyday communication.[49, 50] The lack of differences in ANELT scores between the intervention and the control group in RATS-3 could mean that there is no effect of early CLT, or it may imply that CLT does not directly generalize to everyday communication and that this process takes a while. Yet, this last explanation seems unlikely as we did not find an effect of early CLT on the ANELT six months after the start of treatment either.

The lack of differences between groups may also be attributed to the scoring of the ANELT-A scale. To get the maximum score of five points per item it is not necessary to produce semantically, phonologically and syntactically correct utterances. In line with normal everyday communication, ellipses or telegram speech are awarded with five points, as long as the assessor understands what the patient is expressing. The ANELT may therefore be insensitive to pick up improvement or differences in linguistic functioning, which is explicitly trained with CLT.[51] Yet, the other linguistic tests used in RATS-3 detected no differences between groups either, further supporting our conclusion that in fact there is no effect of early CLT on recovery of language function in aphasia due to stroke.

It is however possible to observe early changes in language recovery after stroke. To measure the effect of IAT added to usual care on language recovery we used the fairly coarse NIHSS Language scale. A detailed analysis of changes in language function would have enabled us to better understand language recovery in this very early phase after stroke. The ScreeLing would have been a suitable instrument for this, which was pointed out in our systematic review on screenings tests for aphasia.

Randomized controlled trials in aphasia research

SL-therapists should apply evidence-based practice and implement the highest levels of evidence in clinical practice, providing their patients with the best treatment possible. RCTs are considered the gold standard in efficacy research and are highly valued by policy makers.[52] There are two types of RCTs: explanatory trials and pragmatic trials. The first type studies whether an intervention is effective under strictly protocoled conditions, i.e. lab-conditions, and the latter studies whether an intervention is effective when it is applied in the real world.[53] Pragmatic trials are suitable for interventions that have been proven effective in explanatory trials. RATS-3 was a pragmatic trial, set out to study the effectiveness of early intensive CLT under clinical practice circumstances. Intensive treatment regimens and CLT-approaches have been found more effective than no SLT or other treatment approaches in several studies.[22, 54] However, when we applied this treatment regimen very early after stroke onset in RATS-3, we found that intensive CLT is not more effective than no SLT for recovery of aphasia and more importantly that intensive treatment is poorly feasible in the average patient with aphasia.

An ongoing debate in aphasia research is whether RCTs are the optimal study design for this group of patients and remarks such as: "Single case design is more appropriate than randomized controlled trials for studying treatment effects"[55 (p. 401)] or "Particular problems have arisen when randomized control trials are used to examine therapy provision for a client group"[56 (p.285)] are frequently heard in discussions on this topic.[55-57] People who oppose using RCTs in aphasia research claim that the group of people with aphasia and the treatment provided to them are too heterogeneous to be studied with this study design. They are of the opinion that each patient should receive personalized treatment, tailored to individual deficits and needs. In their view, this individual approach cannot be tested in an RCT, as results on an individual level are disregarded in RCTs. Alternatives for RCTs in aphasia research are single-case studies or non-randomized group studies.[55, 58] However, showing a benefit of an intervention in a small number of patients, does not reliably demonstrate that the treatment is effective, as those results in a selective group cannot be generalized to the population of people with aphasia and a selection bias is likely at play. Moreover, the only way to effectively rule out the effect of spontaneous recovery is by a controlled, preferably randomized design.

The power of an RCT lies in the fact that researchers are able to study the efficacy and effectiveness of the operational mechanism(s) underlying the intervention, by investigating a group of patients with a similar deficit. This common deficit in patients with aphasia is the underlying language disorder and the operational mechanism of SLT may be timing, treatment intensity or treatment type. Thus, RCTs are suitable for aphasia research, provided that they are properly executed.

To accurately execute an RCT, sufficient participants have to be recruited, as the precision of RCT designs relies heavily on the number of participants. Performing a power calculation is therefore an essential part of the methodology.[59] According to our calculations 75 participants in each experimental arm would provide 84% power to detect a clinically relevant treatment effect, defined as a four-point difference between groups on the ANELT four weeks after randomization. The inclusion rate in RATS-3 was lower than expected. On average, in the Netherlands a hospital admits approximately 300 stroke patients per year. Approximately a third of these patients has aphasia shortly after stroke, but less than half of them remain aphasic for a longer period of time.[60, 61] This comes down to around 45 patients

per including hospital that might fit the inclusion criteria. Yet, these patients had to be able to tolerate intensive treatment and had to provide informed consent, and that appeared more difficult than we anticipated. A considerable proportion of eligible stroke patients or their representatives refused participation, either because they wanted to start treatment as soon as possible, or because they expected the early intervention to be too burdensome. This has been reported previously and may be inevitable in RCTs early after stroke.[35] Still, by extending the inclusion period, we succeeded in recruiting more than 150 subjects for RATS-3. Nevertheless, this contrasts heavily with the estimated number of 3600 patients each year with stroke and lasting aphasia in the Netherlands.[62]

Frequently, post-hoc subgroup analyses are performed with data collected in RCTs. However, post-hoc analyses should be used for hypothesis generation only, especially those from RCTs with a neutral outcome, such as RATS-3. By selecting patients for subgroups, one disregards the essential element of RCTs; a reliable comparison of groups that were similar at baseline, as a result of the random allocation of intervention. In our on-treatment analysis we selected only those patients from the intervention group that apparently were able to tolerate high-intensity treatment, but in the control group such a selection was not made. Thus, the control group included patients that might and patients that might not tolerate early intensive treatment. In this way we compared groups that are actually no longer comparable. It might very well be that the results of the on-treatment analyses merely show that patients, who are able to start with intensive treatment early after stroke onset, may anyhow have more potential to improve, regardless of whether treatment is provided. Perhaps being able to tolerate intensive treatment is a predictor for recovery.

CLINICAL IMPLICATIONS

Early after stroke, patients, their family members or medical staff may be fiercely focused on impairment-based treatment, assuming that language deficits improve more rapidly when treatment is initiated as soon as possible. These notions are endorsed by literature, such as the Cochrane review, in which the authors conclude that SLT is more effective than no treatment, despite several restrictions.[22] Consequently stroke patients, who are often ill and exhausted shortly after stroke, are pushed to practice intensively.

With RATS-3 we have now shown that the urgency to initiate CLT quickly after stroke is unfunded. Hence, there is no need to stimulate all patients to start with CLT as soon as possible. Perhaps, in this phase it is better to focus on motor rehabilitation to prevent maladaptive processes from occurring, and to focus on counseling and guidance. It may also be good to take plenty of rest in order not to overload the brain and to let spontaneous recovery processes do their work first, as some animal studies have suggested.[3, 15, 63] Yet, our results also imply that early intensive treatment may not be detrimental in patients who are able to tolerate and are motivated for intensive CLT.

These findings are important in the light of changes in health care policy and budget restrictions. In those patients who seem unable to tolerate intensive treatment, SL-therapists may better focus on enhancing communication in order to prevent isolation, instead of training linguistic functioning. In a later phase in the stroke recovery process, this may be more effective.

The post-hoc analysis of RATS-2 on the impact of baseline aphasia severity on recovery of language function showed that in all severity groups most improvement occurred in the first

three months. Combining these results with other studies presenting similar findings,[4, 23-25] it appears that the window of opportunity during which most recovery is expected lasts until three months after stroke.

The longest period of improvement was found in the very severely impaired group. The recovery profiles in this group showed a positive slope until six months, implying that improvement might still be ongoing beyond six months after stroke. This suggests that very severely aphasic patients may have a more extended recovery period, and treatment resources should be available for a longer period to these patients than the commonly prescribed six months. In this group we also observed an unexpected benefit of CLT over that of communicative treatment. SLT for very severely affected patients is generally aimed at compensation, but our findings suggest that impairment-based CLT may also be a good treatment approach.

Results presented in *Chapter 3.2, Chapter 4.1* and *4.4* suggest that spontaneous language recovery is most pronounced in the first weeks after stroke, leading to an instable language function in this early phase. This implies that taking more time for detailed diagnosis of the language deficits before starting targeted treatment is not detrimental, and it may be even sensible to wait with detailed diagnostics until aphasia has more or less stabilized.

From the SPEAK model and its validation we know that baseline variables measured during the first week after stroke may provide a grounded prediction of aphasia outcome one year after stroke. We must keep in mind that when these baseline variables are collected in a later stage after stroke onset, the prognosis derived from the SPEAK model may be less accurate. Therefore a good cooperation between the SL-therapist and the neurologist is necessary, so that the neurologist is timely provided with essential information to provide the patient with an adequate personal prognosis. When the updated model is further externally validated, it may be used to predict good outcome six months after stroke.

Three of the studies I have presented showed a relationship between aphasia severity shortly after stroke onset and long-term outcome and recovery: severity of aphasia shortly after stroke was a predictor of outcome in the SPEAK model; in RATS-3, baseline aphasia severity was significantly associated with ANELT scores at follow-up; and in the post-hoc analysis of RATS-2 we found that very severely impaired patients improved for the longest period after stroke and seemed to benefit more from CLT than less severely impaired patients. These accumulated findings show that adequate estimation of aphasia severity shortly after onset is important for reliable prognostication and providing adequate individual treatment. The ScreeLing proved to be a valid and reliable instrument, very well suitable for this purpose.

FUTURE RESEARCH

With RATS-3 we have consistently demonstrated that starting intensive CLT within two weeks of stroke onset is not more effective than starting treatment later after stroke for the recovery of aphasia. It is important not to interpret this finding as SLT being of no use in the acute and post-acute phase of aphasia due to stroke. SLT comprises much more than CLT alone and there is still much more that has to be studied in order to identify which factors are of importance for effective rehabilitation of aphasia.

In our trial we compared the optimal treatment regimen as suggested by the available evidence (early intensive CLT), to usual care (later initiated, less intensive treatment). Using

this design, we did not merely study the effect of timing of therapy, as this would require a direct comparison between early initiated intensive treatment and later initiated intensive treatment. Neither did we distinctively study the impact of treatment intensity early after stroke, as this would imply comparing high-intensity to low-intensity treatment in the early stage after stroke.

Whenever the effect of both timing and intensity was to be studied in one single RCT, multiple treatment arms or a more complex method of analysis would be necessary. Consequently, large numbers of participants would have to be recruited in order to warrant sufficient statistical power. Recruiting sufficient participants for RATS-3 turned out to be rather difficult, and I therefore recommend international cooperation to increase feasibility of large RCTs. This is one of the reasons the Collaboration of Aphasia Trialists (CATs) was founded with funding from the European Cooperation in Science and Technology (COST).[64] The main aim of this collaboration is to improve international cooperation, resulting in joint goal setting for future large international multicenter trials, and to further improve quality of research on aphasia.

One project of the CATs is RELEASE (REhabilitation and recovery of peopLE with Aphasia after StrokE), aimed at accumulating data from various trials performed in stroke patients with aphasia.[64] Pooling of data will enable us to more reliably conduct subgroup analyses. These retrospective studies are apt for identification of gaps in aphasia research, to identify relevant subgroups and to generate hypotheses for future trials.

We could start by exploring the RATS-3 cohort to identify which factors are associated with rapid spontaneous recovery and factors associated with good response to early intensive treatment, as during data collection in RATS-3 I have noticed that participants could roughly be classified into four groups. I observed individuals in the intervention group that seemed to improve rapidly, but also patients from this group showing barely any clinical progress. In the control group I also observed patients recovering quickly and patients hardly showing any improvement. It would be clinically relevant to identify factors that predict which patients may benefit from early treatment and which patients will improve well spontaneously. Hereby SLT resources may be better directed to those patients who are expected to benefit from language treatment. In this way we can also identify which patients will likely not benefit from CLT, and thus may need a different type of intervention to improve communication ability, such as communicative treatment.

One of the factors that we did not take into account in RATS-3 is cognitive functioning before and after stroke. It would be meaningful to study whether cognitive functioning after stroke is associated with being ready for receiving language treatment, because an association between cognitive impairment and rehabilitation success has been reported previously.[44, 46, 65, 66] Clinical observations in the RATS-3 cohort suggested that patients who were less likely to cope with and respond to treatment also had cognitive impairments. However, adequate estimation of cognitive functioning will probably be challenging in patients with aphasia, as cognition and language are highly intertwined.[44, 67]

It is also unknown which types of treatment are effective for which patients. We have chosen to study CLT, based on the assumptions that recovery is optimal if the premorbid language system is restored and that linguistic functioning can be restored with CLT.[6] However, there are also researchers advocating to implement communicative treatment in the early phase after stroke to initiate effective communication as soon as possible.[68] Hereby, maladaptive processes are thought to be prevented and social interaction is

enhanced, keeping patients from feeling isolated. It would be interesting to test the effectiveness of one-to-one communicative treatment combined with structured education of the patients' social environment, creating a 'language enriched environment', in a well-designed RCT with for instance classical impairment-based SLT as control condition.

Most findings in this thesis show that the language system is extremely capricious in the first days to weeks after stroke. It would be meaningful to include neuroimaging measures in future trial designs, and it is important to continue improving neuroimaging techniques and our interpretation of the results in order to better understand post-stroke language recovery and its response to treatment. Questions such as '*Is the activity-shift to the right hemisphere maladaptive or supportive for language recovery?*' or '*Can early language treatment salvage penumbral tissue?*' remain unanswered still. In particular, we must further explore the effect of therapy principles e.g. massed practice, focusing principles, constraint-induced principles and enriched environments that allegedly are crucial for effective treatment.[69]

To study the effect of intensive CLT on the neural network dedicated to language in acute and chronic aphasia, our group conducted a second trial parallel to RATS-3; Functional Imaging in Aphasia Treatment (FIAT).[70] Patients were randomly allocated to either four weeks of intensive CLT or no language treatment at all, comparable to the RATS-3 treatment protocol. In addition to the linguistic test data collected in RATS-3, in FIAT functional MRI-data on language performance were collected. All patients eligible for RATS-3 without contra-indications for MRI were asked to participate in FIAT as well. Unfortunately, because of the additional MRI-scanning the few eligible candidates were very reluctant to consent and we did not succeed in recruiting sufficient participants with acute aphasia, i.e. within two weeks after stroke onset. We also aimed at including 40 patients with chronic aphasia, defined as aphasia due to stroke existing for at least one year, and eventually succeeded in including a number of 38 patients for this group. Results from FIAT in the chronic phase are analyzed, but are not yet published.

Furthermore, in order to better time language treatment, we need to verify the existence of a critical window of opportunity during which the brain is hyperexcitable and language treatment supposedly positively interacts with neural recovery.[2, 3, 71] Findings from RATS-3 justify longer periods without treatment early after stroke for future studies. However, 'doing nothing' will probably be highly unattractive to most patients, as the majority of patients is motivated for rehabilitation. One way to solve this problem is to introduce a control condition with other activities instead of SLT. One could think of an attention control group, with nonverbal exercises aimed at improving cognitive functioning, such as attention and memory.

Techniques for non-invasive brain stimulation, e.g. transcranial magnetic stimulation or transcranial direct current stimulation might also be explored in future studies, as they have shown promising results in restoring language function, though working mechanisms are as yet unclear.[72] In studies like these, a sham control condition is often used, which is a good alternative for 'doing nothing'.

CONCLUSION

In this thesis I showed that early screening for aphasia after stroke is feasible and can be done accurately, and I demonstrated that combining clinical information collected early after stroke onset improves prognostication in aphasia, while our large multicenter trial did not

show a beneficial effect of early initiated CLT. Taking the limitations into consideration, I can confidently conclude that we are able to adequately diagnose aphasia in the early phase after stroke and predict aphasia outcome. Furthermore, I provided solid evidence rejecting the hypothesis that intensive CLT is the optimal treatment approach early after stroke onset.

Considering that aphasia is a heterogeneous condition, it is unlikely that one therapeutic approach suits all patients. Hence, we still need well-designed large multicenter RCTs with multiple arms and stratification for at least stroke severity and aphasia severity, but also for instance for type of aphasia, and taking into account comorbidities. These future RCTs should aim to identify treatment parameters and patient related factors that can predict individual response to treatment. Ideally, this would result in a model that provides the parameters for an optimal individual treatment regimen, based on individuals' characteristics shortly after stroke onset.

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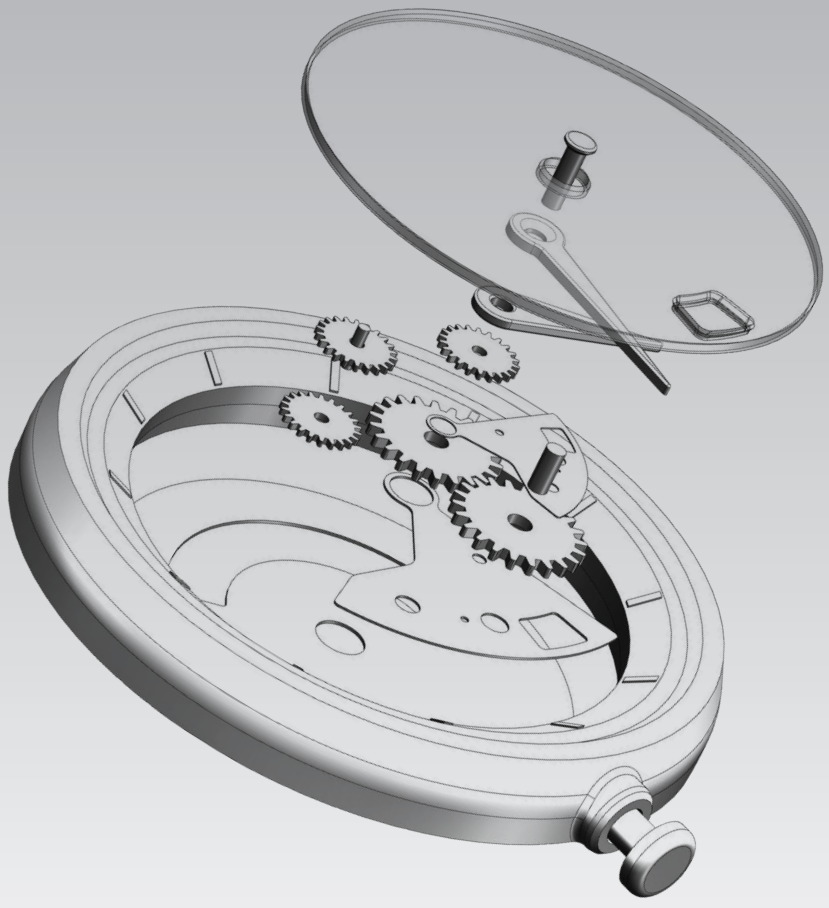
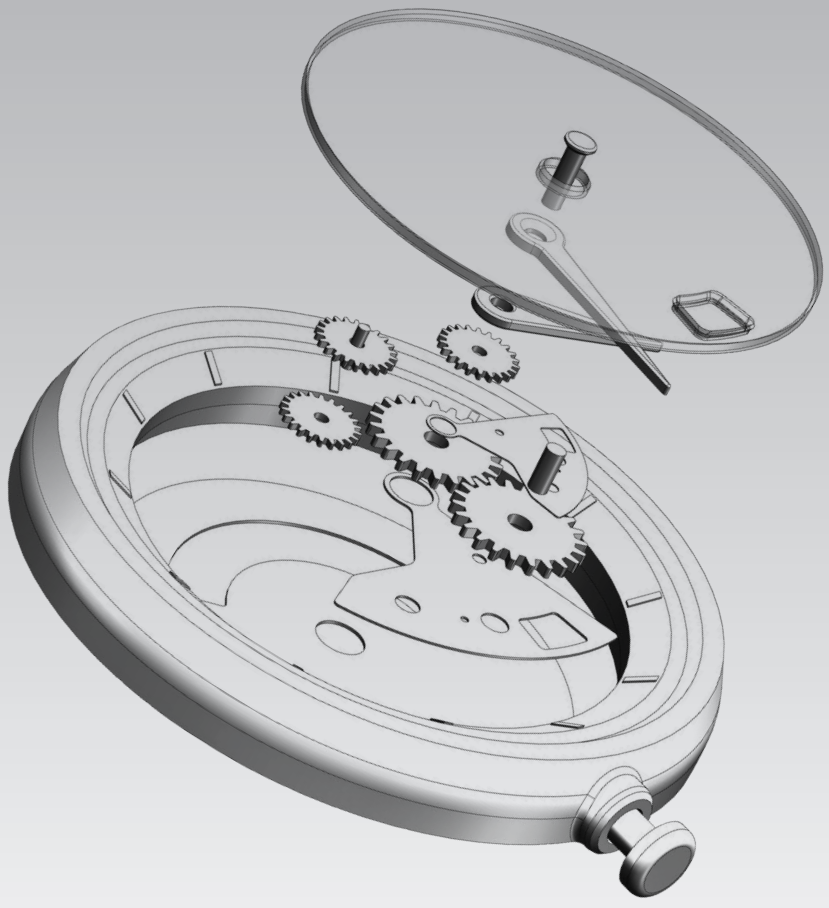


Chapter 6

Summary



Chapter 6.1

Summary

SUMMARY

In this thesis I discuss various aspects of the diagnosis and treatment of aphasia due to stroke. I address questions on adequate recognition and prognostication of aphasia, and I study the effect of medical and linguistic interventions on the recovery of language after stroke. I am using data from the *Rotterdam Aphasia Therapy Study (RATS) – 3* which I coordinated and three other studies. The most important findings are summarized in this closing chapter.

In *Chapter 1* I describe the general background of aphasia due to stroke and its consequences. I also address the importance of adequate and timely diagnosis, prediction of aphasia recovery and treatment for patients with aphasia.

I present a systematic review on screening tests for aphasia in *Chapter 2*. The systematic literature search yielded a total of 1021 abstracts. After careful selection, we identified 10 validation studies and one review paper that fitted our selection criteria, evaluating eight screening tests in total. We found that reporting was poor in the majority of studies; only three studies had an intermediate or low risk of bias. Two tests were found with the highest level of accuracy: the Language Screening Test (LAST) and the ScreeLing.

In *Chapter 3* I analyze aspects regarding the prognosis of aphasia recovery. I evaluate the effect of intra-arterial treatment (IAT) on the recovery of language function in ischemic stroke in *Chapter 3.1.* Patients with aphasia were selected from the MR CLEAN trial, a phase III randomized controlled trial on the effectiveness of IAT with retrievable stents compared to that of usual care. Language function was better in patients treated with IAT than in patients who received usual care, showing that this intervention improves the prognosis of aphasia recovery. A comparison of language function and motor arm function 24 hours and one week after intervention confirmed the thus far unverified clinical impression that motor function recovers more quickly than language function.

In *Chapter 3.2* I describe the external validation of a prognostic model for the prediction of good aphasia outcome one year after stroke, derived from the observational SPEAK study. Using data from RATS-3 we determined the sensitivity and specificity of this model. The model proved to be reliable in discriminating patients with good outcome from those with poor outcome. Calibration of the model was insufficient, meaning that the proportion of the observed outcomes was not similar to the predicted outcomes. This was most likely due to differences in timing of the collection of outcome variables between the derivation and validation cohort. Hence, we proposed an updated model.

In *Chapter 4*, I discuss aspects of aphasia treatment. I review several sources of evidence in search of a relationship between timing of language treatment and its efficacy for rehabilitation of aphasia in *Chapter 4.1.* I summarize results from research on aphasia rehabilitation, but also on animal studies and motor rehabilitation. There were arguments in favor of an early start of treatment, but also signals that early intensive treatment may be detrimental. Lack of randomized controlled trials and inconsistent results across all fields of research hampered drawing a conclusion on the effect of timing on efficacy of treatment.

In *Chapter 4.2* I describe the rationale and design of RATS-3. In this randomized controlled trial we compare the effect of intensive cognitive-linguistic treatment (CLT) primarily to that of no treatment in the acute phase after stroke, and secondarily to that of deferred regular treatment. A total of 152 stroke patients with aphasia were randomly

allocated to four weeks of either daily CLT or no language treatment within the first four to six weeks after stroke.

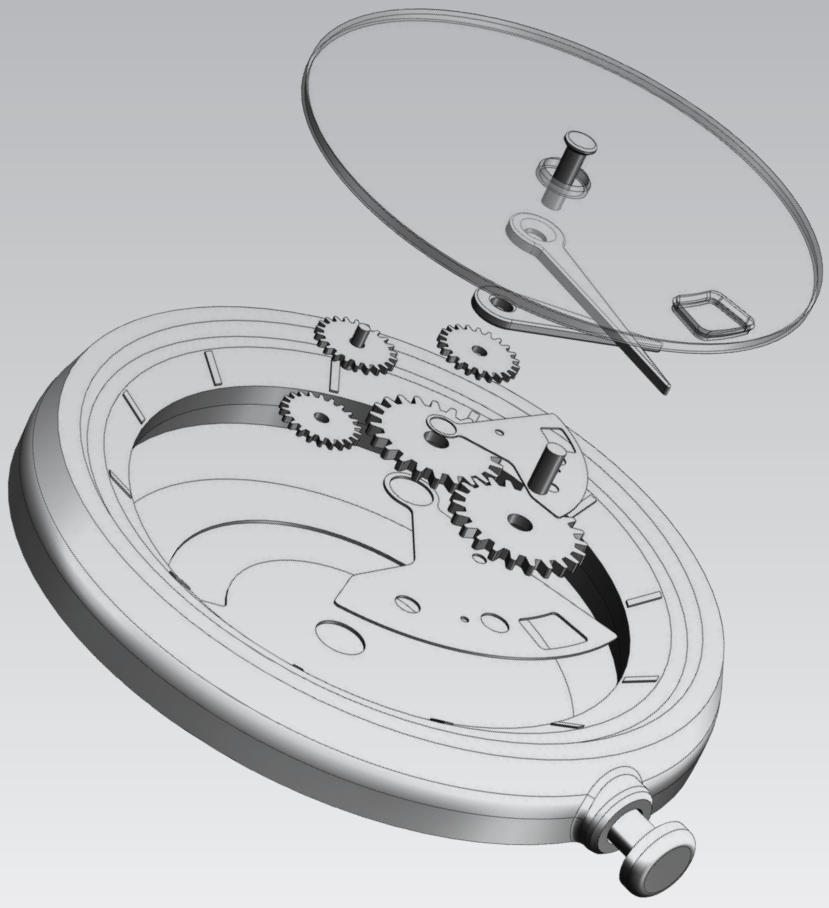
I present the findings from this trial in *Chapter 4.3.* With RATS-3 we showed that in general there is no effect of four weeks of intensive CLT when initiated within two weeks of stroke onset over spontaneous recovery. In the long-term, the early boost of CLT was not effective either. Hence, we conclude that there is no need to start impairment-based CLT as soon as possible after stroke. Our compliance results even showed that it may not be feasible to start this early with intensive CLT in the majority of stroke patients with aphasia.

When we restricted the analyses to the participants that had adhered to our protocol, we found a limited effect of early CLT on three tests measured four weeks after randomization. This implies that some patients may benefit from early intensive treatment and possibly that patient selection is important to determine who should start therapy early after stroke. However, we must be careful interpreting results from these post-hoc analyses.

Aphasia severity at onset may be one factor of importance for patient selection, and I explore this in *Chapter 4.4.* We compared three recovery profiles of different degrees of aphasia severity during the first six months after stroke. We observed statistically significant improvement during the first three months after stroke in all groups, but only in the very severe group we also found significant improvement in the period from three to six months after stroke. Interestingly, the very severe group seemed to benefit more from CLT than from communicative treatment.

In *Chapter 5* I discuss the major findings reported in this thesis. Methodological limitations are discussed and aims for future research are provided. I also describe the following implications of the findings for clinical practice:

- The ScreeLing is an adequate diagnostic tool for early screening of language function and to estimate initial aphasia severity shortly after stroke.
- Initial aphasia severity is an important factor for predicting the prognosis and recovery of language function.
- Variables collected in the first week after stroke can be used to estimate the expected outcome of aphasia one year after stroke.
- Language function is very capricious in the first weeks after stroke; hence it may be better to postpone detailed language diagnosis until language function has stabilized.
- Early after stroke it may be better to emphasize on restoring communicative abilities instead of starting with CLT, especially in those patients who are unable to tolerate intensive language treatment.
- Most language recovery is observed in the first three months after stroke, thus providing language treatment in this phase may be important to maximize recovery.
- In patients with very severe aphasia significant recovery is observed up to six months after stroke and maybe even longer, which justifies continuing treatment for six months or longer after stroke.
- Patients with very severe aphasia appeared to benefit more from CLT than patients with milder aphasia, hence this type of treatment may also be provided to patients with very severe aphasia, which is as yet uncommon.



Chapter 6.2

Nederlandse samenvatting

SAMENVATTING

In dit proefschrift behandel ik verschillende aspecten van de diagnostiek en behandeling van afasie ten gevolge van een beroerte. Ik bespreek het belang van het adequaat vaststellen van afasie en het geven van een gefundeerde prognose ten aanzien van het te verwachten herstel, evenals het effect van medische en logopedische interventies op het herstel van de taalfunctie na een beroerte. Hiervoor gebruik ik data uit de door mij gecoördineerde *Rotterdamse Afasie Therapie Studie (RATS) – 3* en drie andere studies. De belangrijkste bevindingen vat ik in dit laatste hoofdstuk samen.

Een algemeen kader over afasie ten gevolge van een beroerte en de gevolgen ervan schets ik in *Hoofdstuk 1*. Ik benadruk het belang van een adequate en tijdige diagnostiek van afasie en het geven van een gefundeerde persoonlijke prognose ten aanzien van het herstel van de afasie. Ook bespreek ik de dagelijkse praktijk van de behandeling van afasiepatiënten.

Ik beschrijf een systematische review over screeningstesten voor afasie in *Hoofdstuk 2*. De systematische literatuurstudie resulteerde in 1021 abstracts. Na zorgvuldig selecteren, bleken tien studies en één review waarin acht screeningstesten besproken worden te voldoen aan de gestelde criteria. De meerderheid van de studies was slecht gerapporteerd; slechts drie studies hadden een gemiddeld of laag risico op bias. Uiteindelijk bleken de Language Screening Test (LAST) en de ScreeLing de enige twee testen te zijn met het hoogste niveau van nauwkeurigheid.

In *Hoofdstuk 3* analyseer ik aspecten met betrekking tot de prognose van het herstel van afasie. Ik evalueer het effect van intra-arteriële therapie (IAT) op het herstel van de taalfunctie bij afasie als gevolg van een herseninfarct in *Hoofdstuk 3.1.* Patiënten met afasie werden geselecteerd uit de MR CLEAN studie, een fase III gerandomiseerd gecontroleerd onderzoek naar de effectiviteit van IAT met verwijderbare stents in vergelijking met die van de standaard behandeling. De taalfunctie van patiënten die behandeld waren met IAT bleek beter te zijn dan die van patiënten die de standaard behandeling hadden gekregen. Dit toont aan dat IAT het herstel van afasie bevordert en de prognose verbetert. Een vergelijking tussen de taalfunctie en de armmotoriek 24 uur en één week na de interventie bevestigde de tot dusver niet systematisch onderzochte klinische indruk dat motoriek sneller herstelt dan taal.

In *Hoofdstuk 3.2* beschrijf ik de externe validatie van een prognostisch model dat een goede uitkomst van afasie een jaar na de beroerte voorspelt. Het prognostisch model was afgeleid van data verzameld uit de observationele SPEAK studie. Met data verzameld uit RATS-3 werden de sensitiviteit en specificiteit van het model bepaald. Het SPEAK model bleek betrouwbaar in het onderscheiden van patiënten met een goede uitkomst van diegenen met een slechte uitkomst. Kalibratie van het model was matig, wat inhoudt dat een deel van de geobserveerde uitkomsten niet overeenkwam met de voorspelde uitkomsten. Dit is hoogstwaarschijnlijk het gevolg van een verschil in timing tussen de twee cohorten ten aanzien van het verzamelen van de uitkomst data. We stelden daarom een aanpassing van het model voor.

In *Hoofdstuk 4* bediscussieer ik diverse aspecten van de behandeling van afasie. Verschillende soorten wetenschappelijk bewijs betreffende de relatie tussen de timing van taaltherapie en de effectiviteit ervan bespreek ik in *Hoofdstuk 4.1.* Ik vat resultaten samen van onderzoek naar de revalidatie van afasie, maar ook van dierstudies en studies naar

motorische revalidatie. Er blijken meerdere argumenten voor een vroege start van de behandeling, maar er zijn ook signalen dat vroege therapie juist schadelijk zou kunnen zijn. Een gebrek aan gerandomiseerde gecontroleerde onderzoeken en inconsistente resultaten op alle gebieden van vroege revalidatie na een beroerte bemoeilijken het formuleren van een conclusie ten aanzien van het effect van timing op de effectiviteit van een behandeling.

In *Hoofdstuk 4.2* beschrijf ik de rationale en het design van RATS-3. In dit gerandomiseerde gecontroleerde onderzoek vergeleken we vroege intensieve cognitief-linguïstische therapie (CLT) primair met geen taaltherapie in de eerste weken na een beroerte, en secundair met uitgestelde reguliere taaltherapie. In totaal werden 152 patiënten met afasie door een beroerte willekeurig verdeeld over twee behandelgroepen. De ene groep kreeg gedurende vier weken dagelijks behandeling met CLT en de andere groep kreeg geen taaltherapie gedurende de eerste vier tot zes weken na de beroerte.

De resultaten van deze trial presenteer ik in *Hoofdstuk 4.3.* Met RATS-3 hebben we aangetoond dat er over het algemeen geen toegevoegd effect is van vier weken intensieve CLT bovenop dat van spontaan herstel, wanneer de therapie binnen twee weken na de beroerte gestart wordt. Op de lange termijn bleek een vroege boost van CLT ook niet effectiever dan later gestarte reguliere therapie. Daarom concluderen we dat er geen urgentie is om zo snel mogelijk na de beroerte te starten met stoornisgerichte CLT. De resultaten over de therapietrouw in de interventiegroep toonden zelfs aan het in de meerderheid van de patiënten met afasie door een beroerte niet haalbaar is om vroeg te starten met CLT.

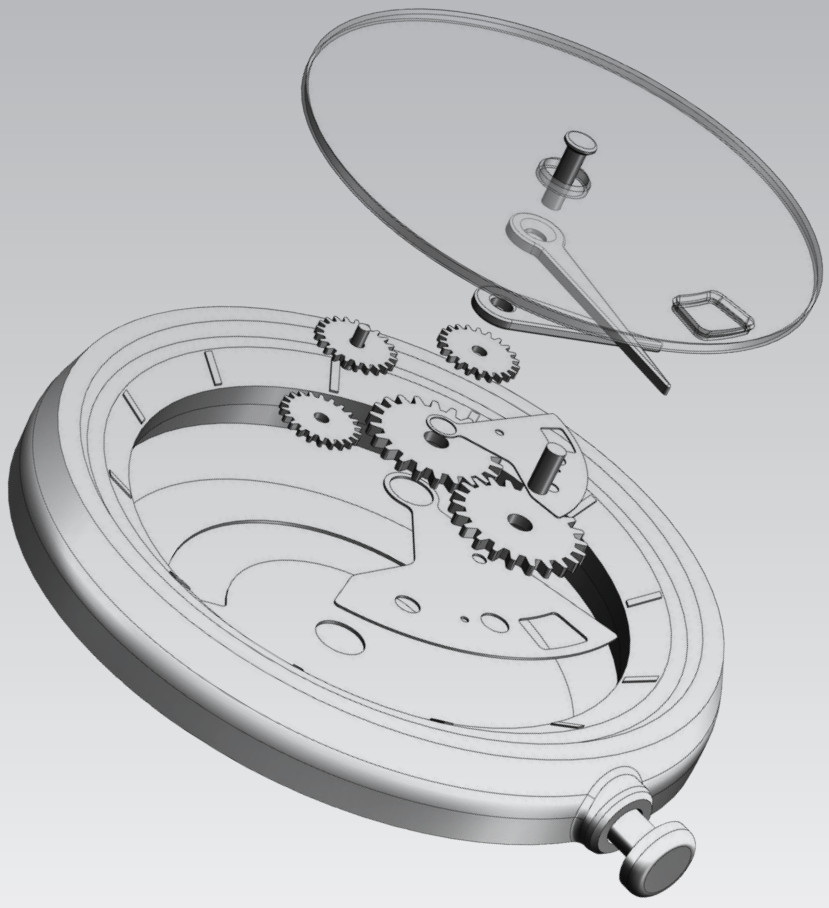
Wanneer we alleen de patiënten analyseerden die het onderzoeksprotocol trouw gevolgd hadden, vonden we een beperkt effect van vroege CLT op drie testen die vier weken na de randomisatie afgenomen waren. Dit impliceert dat sommige patiënten wel baat zouden kunnen hebben bij vroege intensieve therapie en dat patiëntselectie mogelijk belangrijk is bij het bepalen wie er wel en niet in aanmerking komt voor vroege taaltherapie. De resultaten van deze post-hoc analyse moeten echter met grote voorzichtigheid worden geïnterpreteerd.

Een factor die van belang zou kunnen zijn bij patiëntselectie is de ernst van de afasie kort na de beroerte en dit wordt in *Hoofdstuk 4.4* onderzocht. We vergeleken de herstelcurves gedurende de eerste zes maanden na de beroerte van drie patiëntgroepen met een verschillende ernstgraad van afasie. Statistisch significant herstel werd in alle groepen gevonden in de eerste drie maanden na de beroerte, maar uitsluitend de groep met zeer ernstige afasie herstelde nog aanzienlijk tussen drie en zes maanden na de beroerte. Tegen onze verwachting in, bleek de groep met zeer ernstige afasie, in tegenstelling tot de groepen met mildere afasie, meer te profiteren van CLT dan van behandeling gericht op functionele communicatie.

In *Hoofdstuk 5* bediscussieer ik de belangrijkste bevindingen van dit proefschrift. Methodologische tekortkomingen, evenals aanwijzingen voor toekomstig onderzoek worden besproken. In dit hoofdstuk beschrijf ik de volgende implicaties van de bevindingen voor de klinische praktijk:

- de ScreeLing is een geschikt diagnostisch instrument om de taalfunctie kort na de beroerte te screenen en een inschatting te maken van de initiële ernst van de afasie.
- De initiële ernst van de afasie is een belangrijke factor bij het voorspellen van de prognose en het herstelverloop van de taalfunctie.

- Variabelen die in de eerste week na de beroerte geregistreerd worden, kunnen gebruikt worden om een adequate inschatting te maken van de te verwachten ernst van de afasie na een jaar.
- In de eerste weken na de beroerte is de taalfunctie zeer instabiel, waardoor het mogelijk beter is om te wachten met gedetailleerde diagnostiek tot de taalfunctie gestabiliseerd is.
- In de vroege fase na een beroerte is het mogelijk beter om de nadruk te leggen op het herstellen van communicatiemogelijkheden dan te starten met CLT, met name bij die patiënten die intensieve taaltherapie (nog) niet aan kunnen.
- Het meeste herstel van taalfunctie treedt op in de eerste drie maanden na de beroerte, waardoor het geven van taaltherapie in deze fase belangrijk lijkt om herstel te maximaliseren.
- Bij patiënten met een zeer ernstige afasie is nog tot zes maanden, maar mogelijk langer significant herstel zichtbaar, wat ervoor pleit om deze patiënten langer dan zes maanden na de beroerte te behandelen.
- Patiënten met zeer ernstige afasie lijken meer baat te hebben bij CLT dan patiënten met een mildere afasie, dus deze vorm van therapie kan ook aan patiënten met zeer ernstige afasie aangeboden worden, wat tot dusver niet gebruikelijk is.



Appendices

Appendix I: List of participating centers in RATS-3

Appendix II: List of abbreviations

Appendix I. Participating centers with principal local investigators

Hospitals	Principal Local Investigator
Haven Ziekenhuis, Rotterdam	Ida Boas
Sint Franciscus Gasthuis, Rotterdam	Joyce van Dalen
Ikazia Ziekenhuis, Rotterdam	Mathanja Sibon
Maasstad Ziekenhuis, Rotterdam	Fabiënne Stok
Vlietland Ziekenhuis, Schiedam	Obbe de Roos
IJsselland Ziekenhuis, Capelle aan de IJssel	Ingrid Arp
Reinier de Graaf Gasthuis, Delft	Jolanda van Veldhuizen
MCH Westeinde, Den Haag	Marike Kamphuis
MCH Antoniushove, Leidschendam	Christa Kerkhof
Haga Ziekenhuis, Den Haag	Nienke Splinter
VUMC, Amsterdam	Antoinette Keulen
Diaconessenhuis, Meppel	Cock Meijs
Beatrix Ziekenhuis, Gorinchem	Tonny Methorst
Amphia Ziekenhuis, Breda	Sylvia Goosen
Onze Lieve Vrouwe Gasthuis, Amsterdam	Fleur Sickinghe
Sint Lucas Andreas Ziekenhuis, Amsterdam	Sofie van Wessel
Catharina Ziekenhuis, Eindhoven	Danielle Boer
Franciscus Ziekenhuis, Roosendaal	Nicole Dekkers
Isala Klinieken, Zwolle	Leonore Meilof
Kennemer Gasthuis, Haarlem	Astrid Vriend
Tergooi Ziekenhuizen, Blaricum	Marieke van Beek
Jeroen Bosch Ziekenhuis, Den Bosch	Linda Paulus
Erasmus MC, Rotterdam	Femke Nouwens

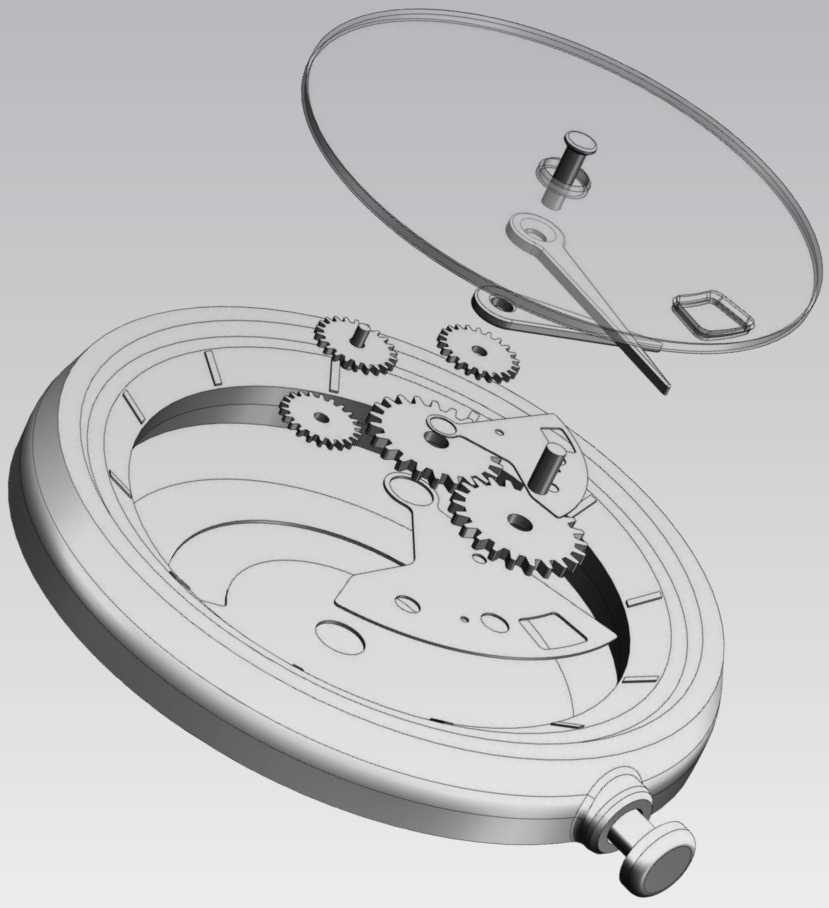
Rehabilitation centers	Principal Local Investigator
Laurens Antonius Binnenweg, Rotterdam	Janneke van Hemert
Laurens Antonius IJsselmonde, Rotterdam	Ankerien Gerretse
Rijndam Central clinic, Rotterdam	Mieke van de Sandt
Rijndam Central outpatient center, Rotterdam	Miranda de Waard
Rijndam SFG, Rotterdam	Merle Paterson
Rijndam Vlietland, Schiedam	Merle Paterson
Rijndam De Waarden, Gorinchem	Tonny Methorst
Vlietland Ziekenhuis outpatient center, Schiedam	Obbe de Roos
Centrum voor Reuma en Revalidatie, Rotterdam	Anke de Meij
Maasstad Ziekenhuis outpatient center, Rotterdam	Fabiënne Stok
Zonnehuis, Vlaardingen	Suzanne van Almenkerk
Sophia Revalidatie, Delft	Marjolein Zomerdijk
Stichting Pieter van Foreest, Delft	Margot van Vorstenbosch
Sophia Revalidatie, Den Haag	Elske van Egmond
Florence, Gulden Huis, Den Haag	Charlotte Schmitz
Florence, Huize Westhoff, Rijswijk	Charlotte Schmitz
Florence, Mariahoeve, Den Haag	Charlotte Schmitz
Zonnehuis, Amstelveen	Jan van Olsthoorn
Reade Revalidatie, Amsterdam	Laurien Sietsma
De Volckaert-SBO, Oosterhout	Marianne Slabbekoorn
Stichting Elisabeth, Breda	Judith van Bree
Thebe Aeneas, Breda	Cirsten Boon

De Riethorst-Stromenland, Geertruidenberg	Cirsten Boon
Stichting de Bilthuysen, Bilthoven	Melanie Swens
Zorgcombinatie Noorderboog Reggersoord, Meppel	Nelleke Loseman
Stichting Groenhuysen, Roosendaal	Saskia Aarts
Avoord Zorg en Wonen, Etten-Leur	Nancy Schuurman
Stichting SHDH Janskliniek, Haarlem	Annet Voogd
Stichting Afasietherapie, Amsterdam	Marieta Gerarts
Rivas Waerthove, Sliedrecht	Tonny Methorst
Rivas Lingesteijn, Leerdam	Tonny Methorst
Rivas Het Gasthuis, Gorinchem	Tonny Methorst
Aafje Zorghotel SFG, Rotterdam	Deanne de Brabander
Aafje Zorghotel Maasstad, Rotterdam	Deanne de Brabander
Aafje Schiehoven-Wilgenplan, Rotterdam	Deanne de Brabander
Aafje De Twee Bruggen, Rotterdam	Deanne de Brabander
Aafje De Vijf Havens, Rotterdam	Deanne de Brabander
Aafje 't Lichtpunt, Rotterdam	Deanne de Brabander
Aafje Afasietrainingscentrum, Rotterdam	Deanne de Brabander
De Zellingen Rijckehove, Rotterdam	Janine van der Plas
Saffier de Residentie Mechropa, Den Haag	Natasha Dinwiddy
Respect Zorggroep Scheveningen, Den Haag	Janneke van Zandbergen
Revant Revalidatie, Breda	Dineke Blom
Surplus Zorg, Zevenbergen	Annelies van Diepen
De Trappenberg, Huizen	Anne Punt
Careyn De Plantage, Brielle	Lianne Hartog
Careyn Mariaoord, Vinkeveen	Klaske van Sluis
Careyn De Vier Ambachten, Spijkenisse	Ingrid Muller
De Vogellanden, Zwolle	Elsbeth Boxum
De Hoogstraat, Utrecht	Hannelore van de Velden
Woonzorgconcern IJsselheem, Zwolle	Marleen van der Ploeg
Osira Leo Polak, Amsterdam	Tenise van de Ven
Osira Sint Jacob, Amsterdam	Tenise van de Ven
Stichting Sint Jacob, Jacobkliniek, Haarlem	Marlies van Nouhuys
Viattence De Wendhorst, Heerde	Agnes Kleine
Zonnehuisgroep IJssel-Vecht, Zwolle	Marjan Jager
Zorgbalans, Driehuis	Natascha Darlang
Novicare, Best	Renske Groenen
Libra Zorggroep Blixembosch, Eindhoven	Marloes Geraeds
Logopedie Zandvoort, Zandvoort	Ineke Schavemaker
Logopediepraktijk M.P. de Boer, Haarlem	Claudia Philippo
Brabantzorg, Ammerzoden	Marieke de Bruijn
Zorggroep Elde, Boxtel	Mariëlle van Boxtel
Van Neynselgroep, Den Bosch	Jannet Coppoolse
Tolbrug Revalidatie, Den Bosch	Nicole Verwegen
Vivent, Rosmalen	Sandra Jansen

Appendix II. List of abbreviations

AAT	Aachen Aphasia Test
acOR	adjusted common Odds Ratio
AIS	Acute Ischemic Stroke
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
ANELT	Amsterdam-Nijmegen Everyday Language Test
ANELT-A	Amsterdam-Nijmegen Everyday Language Test, A-scale for 'understandability'
ARAT	Action Research Arm Test
ASRS	Aphasia Severity Rating Scale
AUC	Area Under the ROC Curve
BDAE	Boston Diagnostic Aphasia Examination
CAT	Comprehensive Aphasia Test
CI	Confidence Interval
CIMT	Constraint-Induced Movement Therapy
CLT	Cognitive-Linguistic Treatment
CT	Computer Tomography
df	degrees of freedom
DOR	Diagnostic Odds Ratio
ER	Enriched Rehabilitation
exp.	expert assessment
F	Test of within subjects contrasts
FAST	Frenchay Aphasia Screening Test
FCP	Functional Communication Profile
fMRI	functional Magnetic Resonance Imaging
IAT	Intra-arterial Treatment
IQR	Inter Quartile Range, presented as the range from 25^{th} to 75^{th} percentile
IV	Intravenous
LAST	Language Screening Test
LR+	Likelihood Ratio of a Positive Test
LR-	Likelihood Ratio of a Negative Test
MAAS	Multi-axial Aphasia System
MAST	Mississippi Aphasia Screening Test
MAST*	Mobile Aphasia Screening Test
MCA	Middle Cerebral Artery
MIT	Melodic Intonation Therapy
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
mRS	modified Rankin Scale
n	number
n.a.	not applicable
n.f.s.	not further specified
NGA	Norsk Grunntest for Afasi
NIHSS	National Institutes of Health Stroke Scale
n.r.	not reported

PACE	Promoting Aphasics' Communicative Effectiveness
PALPA	Psycholinguistic Assessment of Language Production in Aphasia
PET	Positron Emission Tomography
PROBE	Prospective Randomized Open Blinded Endpoint
PWA	Person/People with Aphasia
RATS	Rotterdam Aphasia Therapy Study
RCT	Randomized Controlled Trial
ROC	Receiver Operation Characteristic
SAT	Semantic Association Test
SD	Standard Deviation
SLT	Speech and Language Therapy
SL-therapist	Speech and Language therapist
SPEAK	Sequential Prognostic Evaluation of Aphasia after stroKe
sS	short Schuell
SST	Sheffield Screening Test for Acquired Language Disorders
STAND	Screening Test for Aphasia and Neurologic-Communication Disorders
SVF	Semantic Verbal Fluency
tPA	tissue Plasminogen Activator
TT	Token Test
UAS	Ullevaal Aphasia Screening Test



Epilogue

ABOUT THE AUTHOR

Femke Nouwens was born on December 2nd 1982 in 's-Hertogenbosch. She received her *Athenaeum* diploma in 2001 from the Lingecollege in Tiel. In 2001 she started the Bachelor *Speech and Language Therapy* at the Fontys University of Applied Sciences in Eindhoven and she graduated in 2005. During the final internship at Sophia Rehabilitation Institute in Delft, Femke's interest in aphasia was triggered. Directly after graduating she started working as a speech and language therapist at Sophia Rehabilitation Institute in The Hague and Delft.

In 2006 Femke started the Master's program *Language and Speech, processing and deficits* at the Faculty of Linguistics at the Utrecht University. She focused on language processing and acquired deficits in adults. In addition to the standard curriculum, Femke did an internship at the Erasmus MC – University Medical Center with Evy Visch-Brink and Marjolein de Jong-Hagelstein, who were conducting the Rotterdam Aphasia Therapy Study (RATS) – 2. After successfully finishing her thesis titled "*Adverb Distribution in Broca's Aphasia"* Femke graduated in 2008.

Just before graduating, Femke started working as a speech and language therapist at Respect Health Care Institution in 2007. After having worked fulltime as a speech and language therapist for four years, Evy Visch-Brink contacted Femke in the summer of 2011 for the position of coordinator of the Rotterdam Aphasia Therapy Study (RATS) – 3. In January 2012, Femke changed her jobs at Sophia Rehabilitation Institute and Respect Health Care Institution for a fulltime position at the Erasmus MC as research coordinator of RATS-3.

During the RATS-3 period Femke became a working group member of the Collaboration of Aphasia Trialists (CATs), an EU funded collaboration of researchers in the field of aphasia. Femke was also a member of the working group that wrote the Dutch evidence-based guidelines titled "*Diagnosis and Treatment of Aphasia"*.

In 2015 she continued working on RATS-3 part-time and started working again as a speech and language therapist at the outpatient center of Rijndam Rehabilitation in the Erasmus MC. Currently, she is working at this location still.

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PHD PORTFOLIO

Name PhD student: F. Nouwens	PhD period: 01-01-2012 to 31-12-2016
Erasmus MC Department: Neurology	Promotor(s): Prof. Dr. D.W.J. Dippel
Research School: COEUR	Supervisor: L.M.L. de Lau, PhD

PhD TRAINING	**Year**	**Workload ECTS**
General academic skills		
Basis cursus Regelgeving en Organisatie van Klinische trial (BROK)	2012	1.0
Mini-course Methodology Patient oriented research (CPO)	2013	0.3
Integrity in scientific research	2013	2.0
Biomedical English Writing and Communication	2014	3.0
Research skills		
Biostatistics for clinicians	2013	0.7
Basic Introduction Course on SPSS	2012	0.8
COST CATs◊ training Malta (2x)	2014, 2016	2.5
In-depth courses		
Aphasia Clinics (3x)	2012, 2013, 2014	0.9
Vascular Clinical Epidemiology, COEUR	2012	1.5
Presentations		
Start-up meeting RATS-3	2012	0.3
Congress of Aphasia	2012	0.3
Congress NVSST	2012	0.3
Hosting and presenting update meeting RATS-3	2013	0.5
COEUR PhD day	2013	0.1
Afasie Jongerendagen (2x)	2013, 2014	0.6
Congress IARC	2014	0.3
CATs Conference London	2015	0.3
Dag van de Logopediewetenschap	2015	0.3
Congress DCRM	2015	0.3
Congress ECNR	2015	0.3
Clinical Aphasiology Conference (CAC)	2016	0.3
Keynote Congress of Aphasia (Afasienet)	2016	0.3
National conferences		
Congress of Aphasia (3x)	2012, 2013, 2014	1.5
Congress NVSST	2012	0.3
Dag van de Logopediewetenschap	2015	0.3
International conferences		
Science of aphasia	2012	1.2
Congress IARC	2014	0.9
CATs◊ Conference London	2015	0.6
Congress DCRM	2015	0.3
Congress ECNR	2015	1.2
Clinical Aphasiology Conference	2016	1.2

Seminars and workshops		
PhD Day (2x)	2012, 2016	0.4
COEUR PhD Day	2013	0.2
Afasiejongerendagen (3x)	2013, 2014, 2016	2.4
Miscellaneous		
Lecture Language and the brain	2013	0.1
CATs◊ seminar Nice, Dublin, Tampere, Rotterdam	2014-2016	3.2
TEACHING ACTIVITIES		
Lecturing		
Guest class Neurology for Nurses	2012	0.3
Guest lecture, NTSS Artevelde Gent	2015	0.3
Guest lecture Timing SLT, AIOS EMC	2015	0.3
Guest lecture Timing SLT, AIOS Sophia Rehabilitation	2015	0.3
Guest lecture RATS-3, VRA Brabant	2016	0.3
Trainer CATs◊ training school	2016	0.8
Supervising Master's theses		
Aafke Ruiter (Neuropsychology)	2013	0.6
Anke Harbers (SLP)	2015	0.4
Wieke de Boer (SLP)	2015	0.4
Yvette Crijnen (Medical Faculty)	2015	0.4
Supervising Bachelor's theses		
Sabadel group (SLT; 4 students)	2013	1.0
Lokke Walstra (Linguistics)	2015	0.4
Ryanne van Maldegem (Linguistics)	2015	0.4
Lisanne Groen (Linguistics)	2016	0.4
Supervising internships		
Leanda Bosschaart (Neuropsychology)	2012	0.6
Liset Bergevoet (SLT)	2012	0.6
Rosemary Nieuwenhuize (Linguistics)	2012-2013	0.7
Karlijn Pols (SLT)	2012-2013	0.3
Nienke Wolthuis (Linguistics)	2013	0.4
Birgitte Grootscholten (Neuropsychology)	2014	0.3
TOTAL WORKLOAD		**39.9 ECTS**

◊ CATs = Collaboration of Aphasia Trialists

DANKWOORD

Ook al staat mijn naam op de omslag van dit proefschrift, ik ben zeker niet de enige geweest die dit proefschrift mogelijk heeft gemaakt. Gedurende de totstandkoming van dit boek ben ik door veel mensen geholpen en gesteund. En eindelijk kan ik jullie dan nu bedanken. Ik hoop dat jullie de trots, die ik voel als ik naar het eindresultaat kijk, met mij delen.

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