

## 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup> 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.<sup>6</sup> 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).<sup>7</sup> 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.<sup>8-10</sup>

Recovery of communication usually occurs shortly after stroke.<sup>11-14</sup> Most likely, restoration of the perilesional network in the left hemisphere is the primary mechanism underlying this spontaneous recovery.<sup>15</sup> 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.<sup>4</sup> Hence SLT, and in particular CLT, is thought to contribute positively to spontaneous recovery of language.<sup>14, 15</sup>

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.<sup>14, 16</sup>

In this respect, several clinical studies suggest that therapy provided immediately after stroke results in more beneficial effects than deferred treatment.<sup>11</sup> 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.<sup>10</sup> 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.<sup>17</sup> Intensive training, for instance, massed practice, is thought to trigger remodeling and consolidation of neural networks.<sup>15</sup> Efficacy of SLT is considered to be related to intensity.<sup>8</sup> 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.<sup>3</sup> 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.<sup>18</sup> 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.<sup>19</sup> 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.<sup>8-10</sup>

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.

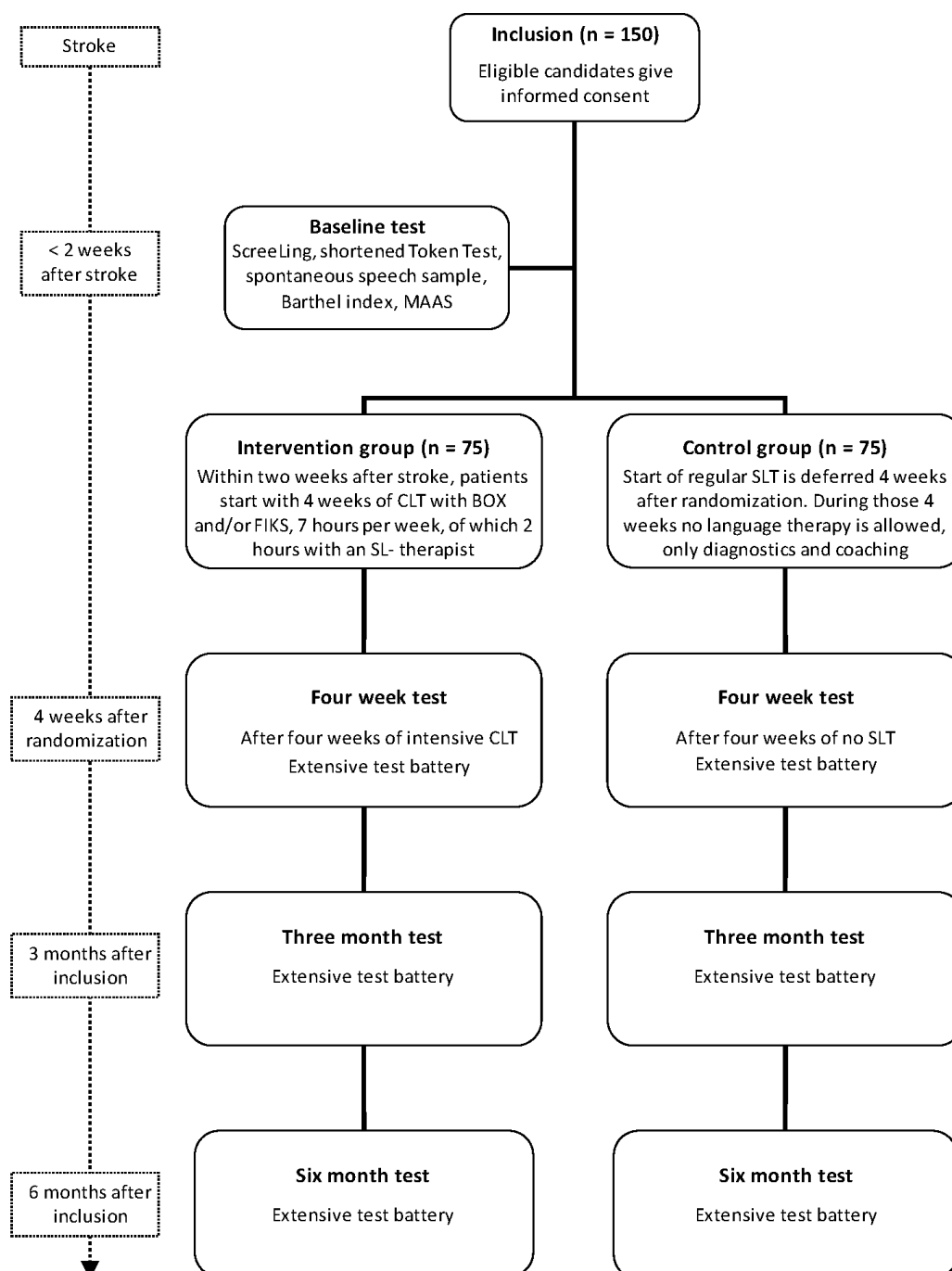
### **Objective**

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



### Participant 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

<b>Inclusion criteria:</b>	
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 <sup>20</sup>
4.	Aphasia ascertained with shortened Token Test <sup>21</sup> and/or a score <5 on Aphasia Severity Rating Scale <sup>22</sup>
5.	Age between 18 and 85 years
6.	Language near native Dutch
7.	Life expectancy of more than six months
<b>Exclusion criteria:</b>	
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.<sup>20</sup> Aphasia is ascertained with the shortened version of the Token Test<sup>21</sup> and a sample of spontaneous speech assessed with the Aphasia Severity Rating Scale<sup>22</sup>. Activities of daily life will be reported with the Barthel Index<sup>23</sup> and observational data on social and (neuro)psychological functioning and wellbeing will be collected with the MAAS (Multi-axial Aphasia System<sup>24</sup>).

### 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<sup>22</sup> 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<sup>25</sup> and/or FIKS<sup>26</sup>. 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.<sup>6</sup> 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.<sup>3, 8</sup> 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

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**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

*Which word does not match?*

Ruler

Musical scale

Gauge

Balance

Measuring tape

Sentence level

*Is this sentence correct?*

The balloon flies in the air.

Correct.

The candle is burning embittered.

Incorrect. *Please correct the sentence.*

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**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?*

*Read it out loud please.*

tion	trans	la	= translation
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– ...

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*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<sup>7</sup>
- ▶ Semi-standardized interview for spontaneous speech rated with the Aphasia Severity Rating Scale<sup>22</sup>
- ▶ Sabadel: connected speech<sup>27</sup>
- ▶ ScreeLing: screening of three linguistic components: semantics, phonology and syntax<sup>20, 28</sup>
- ▶ Token Test, short version: measures severity of aphasia<sup>21</sup>
- ▶ Boston Naming Test: identifies word finding difficulties<sup>29</sup>

#### Specific semantic tests

- ▶ Semantic Association Test, verbal version (SAT)<sup>30</sup>
- ▶ Comprehensive Aphasia Test, word comprehension (CAT)<sup>31</sup>
- ▶ Semantic Word Fluency<sup>32</sup>

#### Specific phonological tests

- ▶ Nonword repetition, PALPA<sup>33</sup>
- ▶ Auditory Lexical Decision, PALPA<sup>33</sup>
- ▶ Letter Fluency<sup>34</sup>

#### General

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

Aphasia type will be determined with the Aachen Aphasia Test (AAT)<sup>38</sup> 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.<sup>39</sup> 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<sup>7</sup> 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.<sup>40</sup> 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<sup>30</sup>; Semantic Word Fluency<sup>32</sup>, Psycholinguistic Assessment of Language Processing in Aphasia (PALPA), Nonword repetition<sup>33</sup>; PALPA, Auditory Lexical Decision<sup>33</sup>; and Letter Fluency<sup>34</sup> 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<sup>36</sup> (quality of life) and modified Rankin Scale (functional outcome)<sup>37</sup>.

#### **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<sup>22</sup> 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)<sup>41</sup>.

### Trial status

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

### Acknowledgements

We thank Mieke van de Sandt-Koenderman, Marion Smits, and Carolina Mendez Orellana for their suggestions and collaboration. We appreciate the help of Hester Lingsma with methodological and statistical issues. We would like to thank all local SL-therapists who will actively participate in this trial.

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