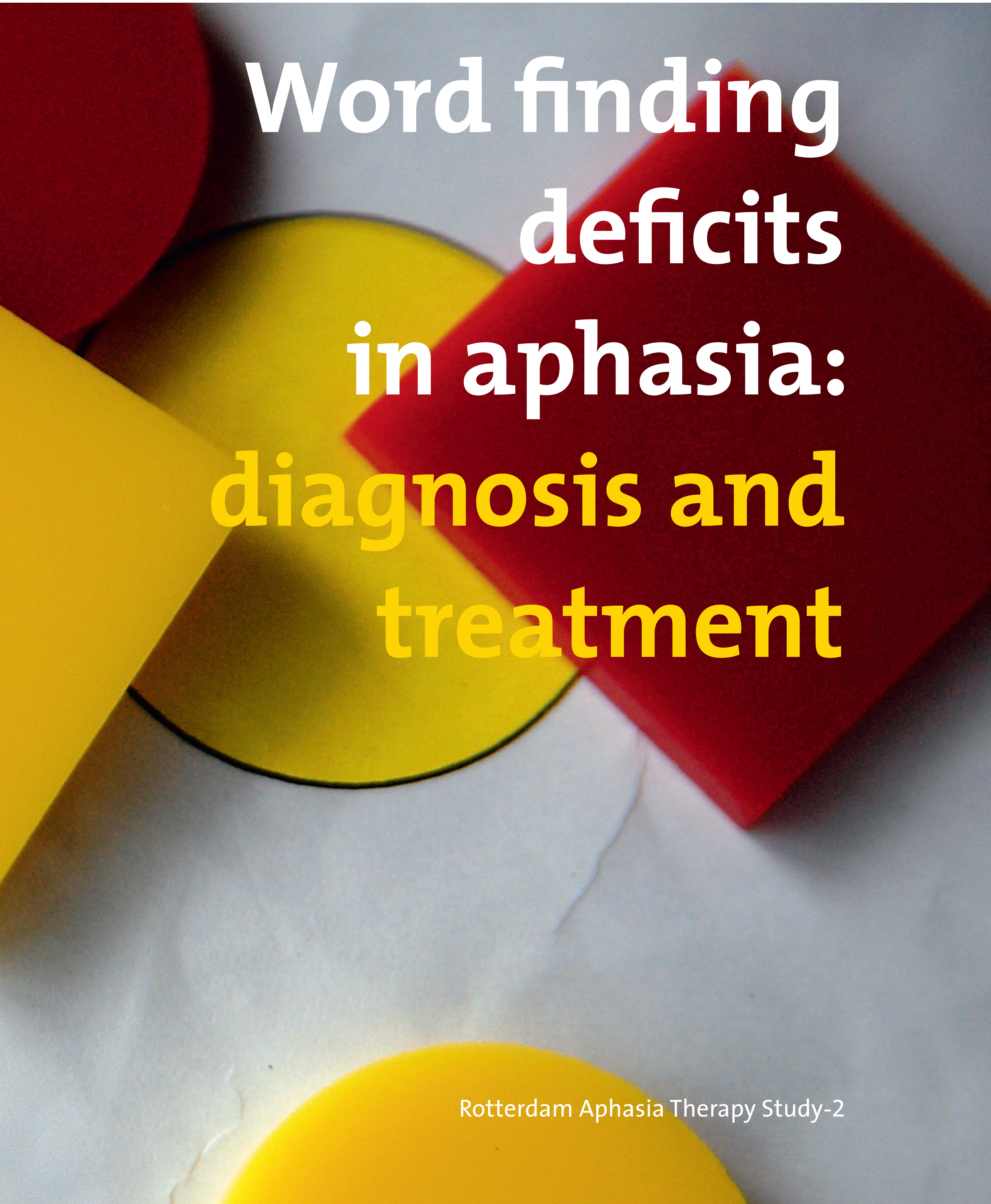
Marjolein de Jong-Hagelstein



Word finding deficits in aphasia: diagnosis and treatment

Rotterdam Aphasia Therapy Study-2

WORD FINDING DEFICITS IN APHASIA: DIAGNOSIS AND TREATMENT

Marjolein de Jong-Hagelstein

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Word finding deficits in aphasia: diagnosis and treatment

Rotterdam Aphasia Therapy Study-2

Woordvindstoornissen in afasie: diagnose en behandeling

Rotterdamse Afasie Therapie Studie-2

Proefschrift

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Aan Loes (1958-2011),
mijn allerliefste tante

Contents

General introduction

Aphasia

Imagine finding yourself all of a sudden alone in a Chinese city and not speaking or understanding Chinese. How do you ask for the way or read the signs, buy food and other necessities, watch TV or listen to the news, let alone have a social conversation with someone? This thought experiment might shed some light on how it must be for people to have a stroke and suddenly have lost the ability to communicate.

The term aphasia is used to describe an acquired loss or impairment of the language system following brain damage. Damage to the brain can be caused by trauma, a tumor, infection or neurodegenerative disease such as Alzheimer's disease. But the most frequent cause of aphasia is a stroke, mainly to the left hemisphere, where the language function of the brain is located in nearly all right-handed people and half of the left handers.

In the Netherlands, approximately 40,000 people per year experience a stroke.[1] About one-third of these patients develop aphasia, with higher frequencies in the early stages after stroke onset. It is estimated that there are about 30,000 people with aphasia in the Netherlands (www.afasie.nl).

The severity of aphasia varies from occasional word-finding difficulties to having no means of communication at all. Individual aphasia profiles also vary regarding the degree of involvement of the modalities of language processing: speaking, comprehension of speech, writing and reading. A central problem for nearly all aphasic people is word finding, which requires intact semantic and phonological processing.

During the first year following the stroke event, aphasia tends to improve.[2] A recent study found that 74% of patients presenting with aphasia in the hyperacute stage have completely recovered after six months and that aphasia improved in 86% of the patients.[3] Most of the recovery occurs in the first three months after which the speed of spontaneous recovery slows, and little additional recovery can be expected after 12 months. Spontaneous recovery of cognitive functions is considered to be associated with the reduction of edema and the reperfusion of previously hypoxic tissue in the perilesional area.[4] Neuroplasticity might also underlie some degree of functional recovery after stroke and has been shown to occur in perilesional areas and in areas distant from the lesion in both the acute and chronic phase.[5]

The most powerful predictor of recovery is initial aphasia severity.[6–9] Greater initial stroke severity and lesion volume are associated with greater initial aphasia severity which in turn is associated with poorer outcome. Studies examining other factors including age, sex, handedness and level of education provided conflicting results.

As already mentioned, Alzheimer's disease – the most common form of dementia in the elderly – is another cause of brain damage that often leads to aphasia. Unlike the often focal lesions caused by a stroke, the pathology due to Alzheimer's disease is often diffuse. Alzheimer dementia (AD) usually starts with memory impairment and progresses steadily until there is global cognitive decline, affecting motor activities (apraxia), perception (agnosia), executive functioning and language (aphasia). A frequently observed language problem in AD patients is a naming disorder. It is assumed that the global cognitive deterioration equally affects naming and the underlying verbal and visual semantic processing, the interpretation of words and pictures respectively.

Aphasia has far reaching consequences: it is reported to have an adverse effect on mood, functional outcomes, social outcomes and quality of life.[10–11] Aphasic patients may get a different role in their relationship and family, are often unable to maintain their job or education, experience a reduction of their social contacts and activities, and often suffer from depression.

Aphasia therapy

Most aphasic patients receive therapy from a speech-language therapist (SLT). There are three approaches in aphasia therapy: the disorder-oriented, the functional and the social approach. This section will deal with linguistic interventions, not with pharmacological therapy. There is no evidence that medications are effective in the absence of language therapy.[12]

The *disorder-oriented approach* aims at restoring linguistic processing by providing cognitive-linguistic therapy (CLT), i.e. exercises for the linguistic level affected. The levels are phonology (word sound), morphology (inflections – e.g. single/plural – and derivations – e.g. 'independently' from 'depend', compound words), semantics (word meaning) and syntax (understanding and building sentences).

The *functional approach* aims at optimizing the level of communication in daily life, given the linguistic deficits. This includes teaching the patient to use word finding strategies or an Augmentative and Alternative Communication aid (e.g. a communication book). In this thesis, the functional approach will be called communicative therapy.

The *social approach* focuses mostly on the social network of the patient in order to enable or facilitate participation of the patient in society. The aim of aphasia therapy, no matter what approach is used, is always "functional": to maximize individuals' ability to communicate in daily life.

Disorder-oriented therapy is mostly applied in the acute and post-acute stages after stroke. There is some indication that treatment should be started as early as possible[13–15] in order to take advantage of spontaneous neural recovery occurring in the first weeks or months. Disorder-oriented therapy is generally applied until improvement plateaus and therapy becomes more and more communicative; the focus is then on using residual linguistic skills as effectively as possible and/or compensating for the linguistic deficit. Finally, the patient's social context is increasingly involved in the therapy in order to guide a return to work or a sports club or enable participation in other recreational activities. The sequence of CLT followed by communicative therapy might not be appropriate for every patient; this depends on the presence or absence of specific deficits, the severity of the disorder and the needs of the patient.

Besides the type of treatment, it is recognized that severity of aphasia is a factor that strongly influences treatment effects. Since the degree of spontaneous or therapy-induced recovery can be highly variable across individuals[4], it is evident that there is a call for more studies with specific subgroups of patients such as severely aphasic stroke patients.[16–17] To conclude, it is difficult to make general statements about the effectiveness of treatment in these subgroups before the cumulative evidence on the effect of aphasia therapy in general is considered conclusive. This will be discussed in the next paragraph.

Efficacy research

Randomized controlled trials (RCTs) represent the gold standard in clinical research. Only a minority of studies on the efficacy of aphasia therapy is an RCT. The Cochrane Library publishes reviews on health care and the previous review from 2000 on speech and language therapy for aphasia following stroke included 12 RCTs[18], whereas the latest update from 2010[19] included 30 RCTs, which is still not impressive. The Cochrane conclusion is that there is some indication of the effectiveness of aphasia therapy, both cognitive-linguistic and communicative, compared with no aphasia therapy. No substantial difference was found between professional therapy and volunteer facilitated therapy – the volunteers were trained and guided by the professionals. In the review it was concluded that it contained insufficient data to answer the question if one treatment approach is better than another. Finally, there was very limited evidence that social support and stimulation may be beneficial.

In a review of evidence-based cognitive rehabilitation[20], CLT is recommended during acute and post-acute rehabilitation after stroke (Practice Standard). Also, it is concluded that group based interventions and computer-based interventions as an adjunct to clinician-guided treatment may be considered in these aphasic patients.

An important issue in any clinical trial is the outcome measure. Since the ultimate goal of aphasia therapy is to maximize individuals' ability to communicate within day-to-day interactions, it is important to use a functional outcome measure.[21] In addition to spontaneous speech analysis[22], which is time-consuming, the Amsterdam-Nijmegen Everyday Language Test[23] (ANELT) was the only adequate test available in the Netherlands before the recently published Scenario Test.[24] Since gathering information about aphasic patients' abilities in natural communication from patients themselves is hampered by their language deficits, it is an option to rely on a person familiar with the patient, such as a partner, friend or caregiver. This so-called proxy rating provides indispensable insights into how aphasia affects the individual patient's daily living.

Outline of the thesis

In *Chapter 1* an overview of aphasia therapy is provided, focused on therapy for word finding problems on the semantic and phonological level (CLT) and on communicative therapy. The level of evidence for the efficacy of both therapeutic approaches is also discussed.

In *Chapter 2* the results of a pilot study aimed at exploring the semantic system in patients with Alzheimer's disease are described. This study reports on naming and the underlying semantic processing and reveals if these two abilities degrade to the same extent.

Chapter 3 reports on a multicenter RCT, RATS-2, in which six months of CLT versus communicative therapy was evaluated in the (post)acute stages of aphasia after a stroke. The aim was to study whether the efficacy differed between the two treatment approaches as measured with both a functional and disorder-oriented outcome assessment.

In *Chapter 4* I focus on the spontaneous and therapy-induced recovery of aphasia in the most severely affected patients with the aim to unravel whether these patients can profit from acute treatment.

The final study in this thesis, described in *Chapter 5*, explored the level of agreement between expert and proxy ratings of verbal communicative ability. In this study, factors that could influence the level of agreement, such as the type of relation between patient and proxy, were investigated.

The *General Discussion* provides a summary of the main results and a discussion of some methodological issues. After a description of the clinical implications of the findings, several essential aspects of aphasia therapy other than type of treatment are discussed. Lastly, suggestions for future research are provided.

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SONY
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VOLUME
Panasonic
Blu-ray Disc
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LUNDI • MONTAG • MAANDAG
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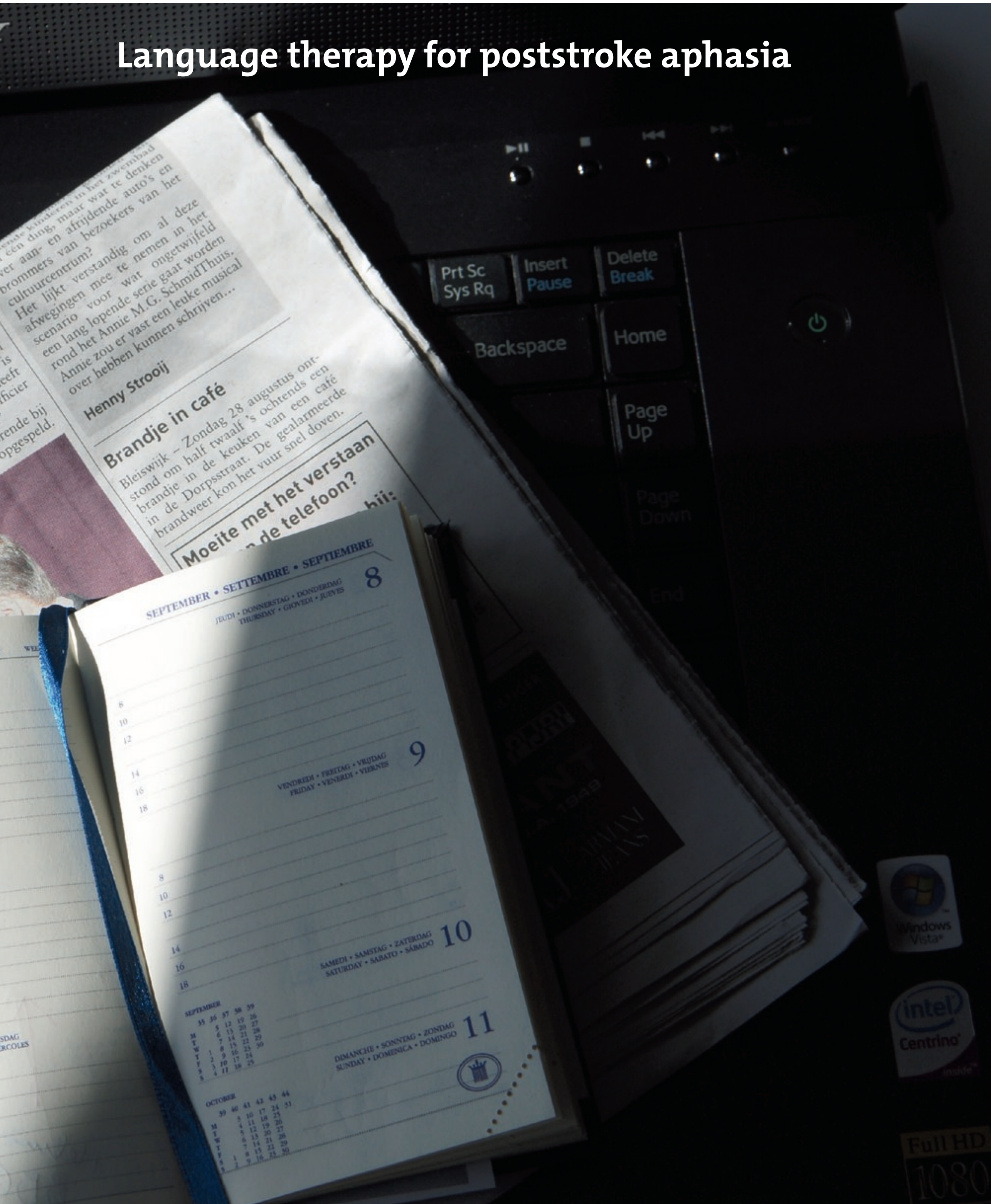
TUESDAY • MARTEDI • MARTES

Chapter 1

Language therapy for poststroke aphasia



Introduction

Speech-language therapists (SLTs) in the Netherlands have many therapy methods, programs and materials at their disposal for the treatment of aphasia. Their professional task is to choose those with the highest potential benefit for each individual patient, taking into account how evidence-based a treatment is, what the specific needs of the patient are in terms of linguistic deficits and personal preferences, and how experienced the SLT is in applying the treatment. In this chapter, I provide an overview of the two main approaches in aphasia therapy, i.e. cognitive-linguistic therapy (CLT) and communicative therapy. Therapy methods belonging to both approaches are described, as well as the extent to which their efficacy has been proven. Within the cognitive-linguistic approach, two therapy methods are discussed in particular: BOX[1] and FIKS.[2] Both programs are directed to the improvement of word finding deficits, a central problem in aphasia with a large impact on the quality of verbal communication. The evaluation of both therapy programs is the subject of the Rotterdam Aphasia Therapy Studies. First, some information is given on the background of CLT and communicative therapy and the difference between the two.

The ultimate goal of aphasia therapy is to improve the patients' daily communication. How this goal is achieved differs fundamentally between CLT and communicative therapy. CLT focuses on the impairment and aims to improve linguistic processing at the linguistic levels affected, e.g. semantics (word meaning), phonology (word sound) or syntax (understanding and building sentences). It is assumed that improvement on these linguistic levels has a direct influence on the quality of verbal communication. Communicative treatment focuses on the participation restriction: patients are trained to use their residual language skills combined with compensatory strategies in order to optimize information transfer. The ability to receive or convey a message in a given situation as efficiently and independently as possible, irrespective of the modality, is the aim of this approach. One could view CLT as working on the building blocks of language and communicative therapy as going straight for the target: communicating. Or to compare it to agoraphobia: communicative therapy would train the phobic person to cross an increasingly large public square, whereas CLT would target the fundamental issues underlying or causing the fear.

It is proposed that therapeutic activities are aligned along a continuum with on the one end disorder-oriented therapy and on the other communicative therapy. The amount of context involved in the treatment determines how disorder-oriented or communicative the treatment is.

Aphasia therapy

Some prominent examples of CLT and communicative therapy applied in The Netherlands as well as internationally are presented.

CLT

Semantics

- *Semantic feature analysis*[3] is thought to improve retrieval of conceptual information by accessing semantic networks. During semantic feature analysis treatment, the patient is guided to produce words semantically related to the target. According to the spreading activation theory of semantic processing, activating the semantic network surrounding the target should activate the target itself above its "threshold" level, thus facilitating retrieval of the word.
- *Training atypical exemplars.*[4] Patients are trained in naming pictures of atypical exemplars of various categories, for example "fuchsia" for colors and "spades" for shapes. In studies on manipulating typicality of category exemplars during treatment of naming deficits, it is shown that training atypical exemplars generalizes to untrained typical examples but not vice versa.
- *Neurolinguïstische Afasietherapie*[5] (Neurolinguistic Aphasia Therapy). The eBook "Visual-semantic disorders" contains 250 sheets with one to six pictures combined with word stimuli. It aims at treating lexical-semantic disorders in combination with the processing of pictures or visual perception of objects. It covers the semantic aspects of part-whole relationships, semantic fields, situative relationships, homonyms and cohyponyms.
- *BOX*. This lexical-semantic therapy method is described in detail below.

Phonology

- *Phoneme-based rehabilitation of anomia.*[6] First, the patient learns to connect the following phonemic information: the correct articulation of a phoneme through a drawing of a mouth; proprioceptive and visual feedback from their own production of the phoneme; and verbal descriptions of the distinctive oral-motor features of each phoneme. Then phonological and orthographic sequence knowledge is enhanced by training patients to recognize, distinguish and manipulate nonexistent words and words composed of these phonemes in the form of heard, read, seen and orally produced phonological sequences. The goal is to improve naming via a phonological route.
- *Phonological and orthographic cueing therapy.*[7] Participants were presented with a picture to name and if unable to do so within five seconds, they were given a phonological or orthographic cue. Four types of cue were used: CV spoken, CV written, rhyme, and repetition. For example, when the patient was unable to name a picture of a cage, he was shown the letters CA and told "It begins with this".
- *FIKS*. This phonological therapy method is described in detail below.

Syntax

- *Visuele Cue Programma*[8] (Visual Cue Programme). This syntactic treatment aims at increasing the patient's awareness of the sentence structure by an external visual scheme: nouns are symbolized by a square, verbs by a horizontal rectangle and a preposition by a triangle. The program contains 172 sentences to be trained.

- *Mapping therapy*[9] is a general approach to the treatment of sentence processing deficits. It explains the 'sentence semantics' (who does what to whom). The focus is on the difficulties patients have in interpreting and producing noun-verb relational structures in sentences.
- *Werkwoordproductie op woord- en zinsniveau*[10] (Verb production at the word and sentence level) is a treatment program for training the correct use of verbs in sentences, which requires three processes: retrieval of the right verb from the lexicon, positioning the verb correctly in the sentence and applying the correct inflection. The program consists of four steps, all using action pictures to elicit the target verb.

Semantics and phonology

- *Auditief Taalbegripsprogramma*[11] (Auditory language comprehension program). This treatment program aims at training comprehension of nouns and verbs. Spoken words must be matched with one of four pictures: the correct response and three distracters which can be related to the target. The process of word comprehension is subdivided into steps of increasing difficulty.

All levels

- *Logotherapia*[12] is a book with many exercises on different levels of difficulty, all linguistic levels and in all modalities. The exercises are suitable for people with a moderately-severe or mild aphasia and should be selected on the basis of the patients' specific disorders. Examples are selecting out of four pictures the one depicting an exemplar of an orally presented category (e.g. "show me the animal"), forming words with given word stems and pre- and suffixes (e.g. "depend" with "in-" and "-ent"), word fluency (e.g. "name words associated with *fast*") or writing a letter to a friend with the use of some key phrases.

Communicative therapy

Training communicative strategies

- *Promoting Aphasic's Communicative Effectiveness (PACE).*[13] PACE was one of the first therapy methods that were called "pragmatic". It introduces a number of pragmatic aspects of conversation into clinical practice. Combining four principles makes the interaction in therapy resemble natural conversation: (1) the exchange of new information, (2) equal participation of patient and therapist, (3) free choice of communicative channels – the SLT can apply modeling to encourage certain strategies, (4) functional feedback – the SLT tells whether the message was understood. The rationale of PACE is that the patient discovers the most efficient ways of communicating himself. The content of messages becomes more complex and abstract as therapy progresses, e.g. from cards of objects to newspaper articles.
- *Total communication therapy.* The patient is trained in using all means of communication to convey a message, e.g. gesturing, facial expression, drawing, pointing, indicating the size or using a communication aid. Word meanings are activated and if possi-

ble linked to word form. The difference between total communication therapy and PACE is that the former applies an overt learning strategy.

Augmentative and Alternative Communication aid

- *Gespreksboek*[14] (conversation book). The so called Gespreksboek contains sections with words and pictures that can be used to support conversation. It is applied by the conversation partner of the aphasic person: the partner poses questions in a structured order, each time pointing to the words or pictures concerned and writing down the answers of the aphasic person.
- *TouchSpeak*.[15] TouchSpeak is a computerized communication aid consisting of a pocket pc with touch screen and dynamic communication software. The Topic Vocabulary is a personal, coherently organized set of interactive pages which contain all the symbols, images, photos and text of the aphasic user. The aphasic user can also type text and have it spoken by an artificial voice.

Communication in everyday situations

- *Role playing*. Role plays enable the patient to practice communication situations from everyday life in a therapeutic setting. The SLT can select appropriate communicative strategies or channels through which the patient must try to communicate. Role plays can vary from asking the nurse for a cup of coffee to calling a telephone company with a technical complaint.
- *Conversational coaching*.[16] The aim of conversational coaching is that the patient can apply the practiced strategies outside the clinical setting. The patient must first communicate a script, a short text containing some sentences or a combination of pictures and words, to the SLT. This difficult task provokes the patient to apply the strategies they trained before. As a next step, the patient does the same with another familiar person while being coached by the SLT. The video recording of the conversation is then analyzed and discussed with the people involved. Next steps are practicing with unfamiliar persons and other scripts.
- *Form an opinion*. The SLT can try to find out what the patient's opinion is about a current or controversial issue. The patient can prepare extensively at home by collecting information, discussing with a family member, and writing down notes or respond to statements that the SLT provided. All arguments and counterarguments must become clear and finally a conclusion can be formulated.
- *Retelling a movie*, short video, TV program or story. Internet is a very useful source for these exercises. The level of difficulty can be increased by varying the material, the conversation partner, amount of support, and use of communication channels.
- *Situation-specific training*.[17] Various personally relevant communicative situations can be trained with the patient, such as telephoning, shopping, receiving visitors, or visiting the dentist.

Other therapies

Some treatment methods fall in between CLT and communicative therapy or combine the principles of both approaches.

- *Melodic Intonation Therapy (MIT).*[18] MIT is an intonation-based treatment method for nonfluent or dysfluent aphasic patients, aiming to elicit spontaneous speech production. It is a hierarchically structured treatment that uses intoned (sung) patterns that exaggerate the normal melodic content of speech and exploits the rhythmic feature of speech across three levels of increasing difficulty.
- *Speaking in ellipses.*[19] An opposite approach to training the production of syntactically correct sentences is to stimulate agrammatic production in conversation. Speaking in ellipses is a Dutch and adapted version of Reduced Syntax Therapy (REST)[20], intended to stimulate and automatize the production of ellipses. An ellipse is a syntactic frame that contains fewer grammatical morphemes than a full sentence, e.g. "everybody inside" or "out for lunch".
- *Multicue*[21] is a computer program that offers a variety of cues for improving word finding. It stimulates the users' independence by encouraging them to discover themselves which cues are most helpful. In a naming task, the patient can choose from a list which one of nine types of cues he or she wants to be shown. Cues all have a distinct function for the retrieval process.
- *Constraint-induced aphasia therapy (CIAT)*[22] is a relatively new method for the treatment of aphasia, which practices language in a communication context. CIAT is based on the principle from brain science that learning requires repeated practice of skills – hence, CIAT is applied very intensely; and that brain systems for language and action are heavily interwoven – hence, language is practiced in the context of actions, that is playing language games, often card games. It contains exercises on the different linguistic levels and is directed to conversational formulas. Specific exercises and level of difficulty are tailored to the patients' needs.

Efficacy research

With all these possibilities in aphasia therapy, it is essential to establish which approaches and methods actually benefit aphasic persons. As early as the 1860s, single case studies were conducted, suggesting that therapy for patients with chronic aphasia can lead to substantial improvement.[23–24] It was only since the 1970s that groups of researchers have attempted to apply the methodology of the 'randomized clinical trial', which was mainly developed to assess the efficacy of drug treatment, to the study of aphasia therapy. Since then, only about 30 RCTs have been conducted.

RCTs are considered the most robust methodology for assessing the effectiveness of an intervention. Nevertheless, some advocate case studies or focused rehabilitation trials with small homogeneous samples. Their arguments are that large-sample RCTs in rehabilitation are resource-intensive and expensive, that a cognitive disorder like aphasia is a complex condition and that patients have multiple cognitive and physical problems due to a stroke that vary significantly in pattern and severity across patients, making a tailored therapy difficult. However, because aphasia is a condition in which the natural course is improvement, case-studies generally cannot provide strong evidence of efficacy without a control group. In addition, generalization of results is much more difficult from case-studies or small homogeneous samples than from RCTs.[25]

In evidence-based systematic reviews, it is common to assign studies to one of three classes:

I well designed, prospective RCTs
II prospective, nonrandomized cohortstudies or retrospective, nonrandomized case-control studies
III clinical series without concurrent controls or studies with results from one or more single cases that used appropriate single-subject methods.

There are different stages in therapeutic research, each of which requires a specific study design. The first is *discovery*: treatment approaches are developed and assessed in the context of whether they show promise of being efficacious. A suitable type of study for this stage is a single-subject study. The second stage is *efficacy* in which promising interventions are tested in a rigorous way under ideal, highly controlled conditions to determine the outcome. Here randomized controlled trials (RCTs) apply. The third stage is *effectiveness*: the intervention is tested in a "real-world" clinical setting. The final stage is cost *effectiveness*. In aphasia therapy, studies at stage three and four are scarce.

Probably the most widely used source of information about evidence-based aphasia therapy is the Cochrane Database of Systematic Reviews: Speech and language therapy for aphasia following stroke.[26] A recent update showed that there is some indication of the effectiveness of aphasia therapy for people with aphasia following stroke; that there is a consistency in the direction of results which favored intensive aphasia therapy over conventional aphasia therapy, though significantly more people withdrew from intensive than from conventional therapy; that aphasia therapy facilitated by a therapist-trained and supervised volunteer appears to be as effective as the provision of aphasia therapy by a professional; and that there is insufficient evidence to draw any conclusions in relation to the effectiveness of one approach over another.

The conclusions in the Cochrane Review are based on 30 RCTs. But there are reviews that included more studies, on various levels of evidence, such as the two described below. Although the evidence from these reviews is less strong, they are important for clinicians to base their therapeutic decisions on and they provide directions for new RCTs.

The first is the Evidence-Based Review of Stroke Rehabilitation: Aphasia (13th edition).[27] For each conclusion, one key reference is shown that I selected from the studies on which the conclusion is based. Also, the level of evidence is provided (Strong: a meta-analysis or multiple RCTs; Moderate: a single RCT; Limited: at least one controlled trial).

- Language therapy is most effective in treating aphasia when provided intensely; less intensive therapy given over a longer period of time does not provide a statistically significant benefit, although some clinical benefit may be achieved[28] – *Strong*.
- Trained volunteers can provide an effective adjunct to SLTs' treatment[29] – *Strong*.
- Participation in group therapy may result in communicative and linguistic improvements[30] – *Moderate*.
- Supported conversation for adults with aphasia improves conversational skill. In addition, training communication partners may result in improved access to conversation and increased social participation[31] – *Moderate*.
- Computer-based aphasia therapy results in improved language skills measured at the impairment level[32] – *Strong*.
- Constraint-induced aphasia therapy may result in improved language function and everyday communication in individuals with chronic aphasia[22] – *Moderate*.
- Task-specific semantic therapy and task-specific phonological therapy improves semantic and phonological language activities respectively in aphasia[33] – *Moderate*.
- Phonological and semantic cueing may improve naming accuracy in aphasics with word-finding deficits[34] – *Limited*.

The second is a review of evidence-based cognitive rehabilitation[35] that recommends CLT during acute and post-acute rehabilitation for language deficits secondary to left hemisphere stroke (Practice Standard: at least one good-quality RCT, supported by lower-level studies). Also, cognitive interventions for specific language impairments such as reading comprehension and language formulation are recommended (Practice Guideline). Besides, group based interventions may be considered for remediation of language deficits, and computer-based interventions as an adjunct to clinician-guided treatment may be considered in the remediation of cognitive-linguistic deficits (both Practice Option, nonrandomized or uncontrolled studies).

The conclusion that CLT is Practice Standard is questionable: two of the six RCTs on which it is based, involved communicative therapy and one involved CIAT instead of CLT; and the results were not consistently in favor of CLT.

Specific aphasia therapy: BOX and FIKS

It is clear that there is an urgent need of well-designed and well-reported RCTs on specific aphasia therapy. In the Rotterdam Aphasia Therapy Studies we focus on CLT because word finding difficulties are a central problem for practically all people with aphasia and result from semantic and/or phonological processing deficits. Therefore, CLT on the word level is an indispensable part of aphasia rehabilitation. A hypothesis is that CLT in particular can boost aphasia recovery in the early stages after stroke; the specific linguistic (semantic and phonological) exercises could promote natural recovery of the neural circuits that are involved in semantic and phonological processing.[36–37] For instance, a substantial part of the treatment methods used for disorders in semantic processing are comprehension tasks, which are assumed to bring about changes in the semantic system with a positive influence on word retrieval.[37] According to these authors, such a restitutive strategy would be suitable for early therapy because of the interaction with the neurophysiologic processes of recovery. Besides, CLT is suited as an intervention in trials because it is well controllable and relatively demarcated. In this thesis, BOX and FIKS occupy a special place and are described in more detail below.

The lexical semantic therapy program BOX aims at stimulating lexical semantic processing by applying the odd-word-out technique in a context of increasing difficulty. It focuses on improving recognition of the semantic features of content words and strengthening the semantic relations between words rather than regaining semantic items; strategies are trained which are assumed to generalize to word retrieval in everyday communication, noticeable in an increase in the number of adequate content words in spontaneous speech. It is assumed that verbal and visual semantics are relatively separate entities, requiring a modality-specific therapeutic approach.[38] Therefore, no pictures are included in the program, making it also possible to include abstracts concepts. The items can be read silently by the patient, read aloud by the patient and/or by the therapist, presented in an additional mode and elaborated with new material. Strengths of BOX are the variety of exercises and the variation in levels of difficulty, which keeps the patient alert in semantic processing. The SLT should choose items that can be performed correctly but with some effort in order to optimize internalization of the learned strategies.

The phonological therapy program FIKS aims at facilitating selection and seriation of phonemes in speech production. By making patients aware of word forms and of their phonological processing, the effect of FIKS should be a decreased frequency and severity of phonemic paraphasias. Like BOX, it contains a large amount of exercises in various forms. Both receptive and productive exercises are provided but the emphasis is on productive phonology. Receptive tasks can be applied when the patient has problems with the input route or needs a change to prevent blocking in the production tasks.

Both BOX and FIKS have an impact on language comprehension and language production, and both work via the training of strategies rather than regaining concepts. The purpose of the programs is to give the patients insight into their disorder and to activate strategies by confronting the patient under pressure with basal components of semantics and phonology. It is assumed that the results generalize to everyday language use.

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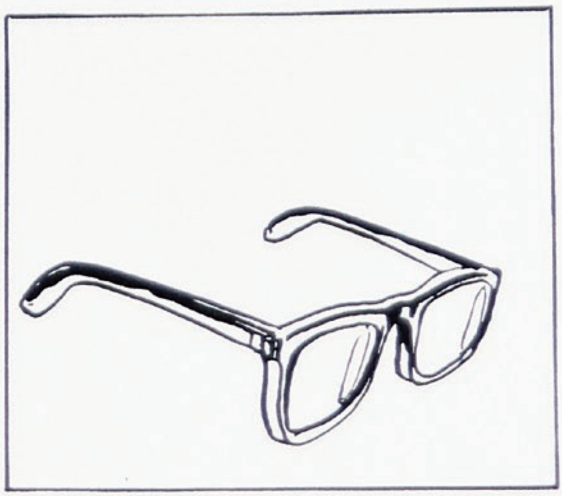
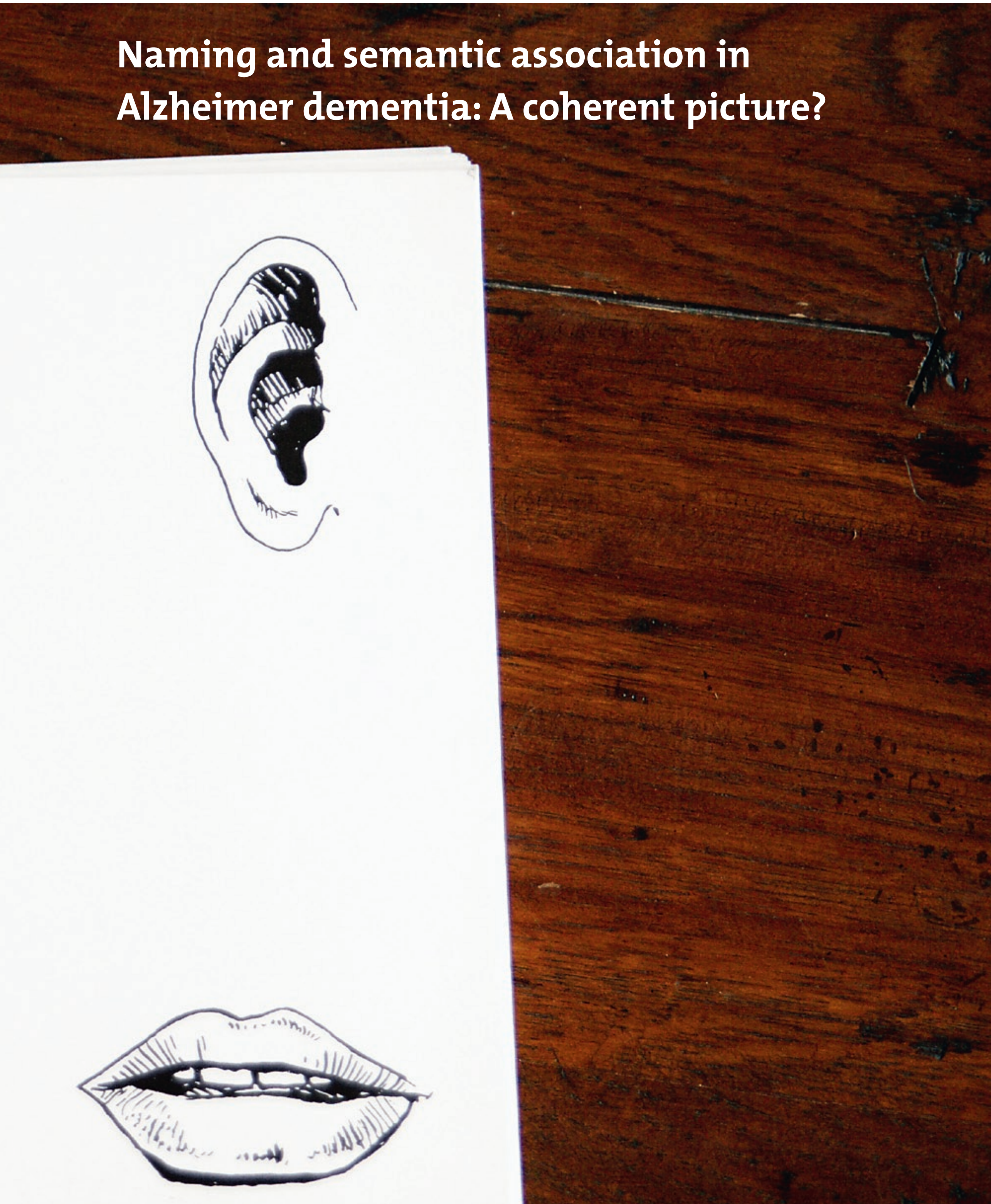


Chapter 2

Naming and semantic association in Alzheimer dementia: A coherent picture?



Abstract

Aims

Alzheimer dementia (AD) is characterized by global cognitive decline. Naming problems occur frequently and are reported to result from a breakdown in semantic processing. We examined if there is a homogeneous deterioration of naming and the underlying verbal and visual semantic processing.

Methods

Results on a naming test and a verbal and visual semantic association test of 19 AD patients were compared with those of 19 matched controls.

Results

Patients' naming was within the normal range and better than verbal and visual semantic processing. Three patients showed selectively intact naming, three others selectively intact verbal semantics. Living items were easier to name than non-living items, whereas the reverse pattern held for visual semantics.

Conclusion

We found heterogeneous deterioration in naming and the underlying verbal and visual semantic processing, which contradicts a global conceptual degradation forming the background of linguistic problems and fits the assumption that AD selectively affects regions of the brain. Naming appears insufficient as a single task to measure language disorders in AD.

Introduction

Alzheimer dementia (AD) is the most common form of dementia in the elderly, accounting for about 70% of dementia cases.[1] The clinical syndrome of AD is thought to be caused by neurofibrillary tangles and neuritic plaques, although evidence is accumulating that vascular pathology intertwines with the Alzheimer-type pathology. AD presents with progressive cognitive decline of insidious onset, usually starting with memory impairment and progressing steadily until there is global cognitive decline, affecting language (aphasia), motor activities (apraxia), perception (agnosia) and executive functioning. A magnetization transfer imaging (MTI) study[2] showed that not only selective damage to the temporal and frontal lobes was associated with global cognitive decline and impairment in specific cognitive domains, but also widespread damage to the whole brain. These findings were claimed to agree well with clinical reality: AD is not characterized by specific cognitive impairment but rather by global cognitive decline resulting from impairment in multiple cognitive functions. In this view, it is evident that this is not caused by selective brain damage. From post-mortem studies it is known that diverse neuropathological changes underlying the global cognitive decline in AD can be found in large parts of the brain even in the earliest stages.[2]

Much research has been conducted on memory function, which is often selectively impaired in early stages of AD. We examined language function and questioned if language as a whole degrades, being a linguistic component of memory. A frequently observed language problem in AD patients is a naming disorder[3], which is clinically apparent in a progressive decline of lexical richness of spontaneous speech.[4] In structural language tasks, AD patients are impaired in their capacity to name objects and actions on visual confrontation: they show lower accuracy and longer latencies in naming tasks than healthy control subjects.[5–7]

Naming problems can arise from various stages of processing: visual perception, semantics, lexical retrieval, selection of phonemes, and articulation. In AD, the severity of the disease seems to influence the background of the naming disorder. Phonology and articulation are preserved until the final stages.[8–9] In contrast, a selective disorder in lexical access might be observed in early AD; patients might present with difficulties in selecting the correct lexical-phonological response after activation of an intact semantic field.[10] A high-level visuo-perceptual impairment is mentioned as a major contributor only in the late stages of the disease. Just occasional atypical cases presenting with prominent visual deficits from the beginning have been reported.[11–12]

The main linguistic problem for most AD patients is a breakdown in semantic processing.[13–14] Semantic deficits have already been detected early in the course of the disease process.[15–16] A disruption of the semantic field is indicated by semantic paraphasias in naming[17], semantic priming effects[18–19] and disorders in semantic association.[20] Semantic associations and attributes of low typicality (e.g., pyramid – palm tree) are reported to erode first, followed only later by highly typical semantic associations (e.g., baker – bread).[21] The breakdown often follows the hierarchy of semantic features from most specific to most general.[22] Knowledge of the details of an object, e.g., that a shoe has laces, you wear it on your foot, is lost earlier then the superordinate category, i.e., that a shoe is a type of clothing.[23] This is reflected in the tendency of patients to name the category instead of the object pictured.[7]

Impairments in specific categories of concepts are frequently observed, in particular loss of knowledge of living relative to non-living things.[5, 24–26] Category-specific deficits are reported to be multimodal: independent of the input modality there is a loss of knowledge about the impaired category.[27] For example, recognition, identification and naming of famous faces were equally impaired in AD patients.[28] It is more a conceptual deficit than a language deficit[29]; the cognitive process of sharing ideas through language is impaired.[30–31]

A central task to investigate semantic processing is a semantic association task, in which patients are required to analyze and combine concepts by selecting shared and neglecting unshared features. The Pyramids and Palm Trees Test[32], a well-known semantic association test, is sensitive to early changes in semantic processing in AD, even in patients with minimal severity.[33] The test is widely used in patients with aphasia as a consequence of brain damage and is unique in the sense that semantic association is required between the same concepts, presented in different modalities.[34] We examined patients with probable AD with the Semantic Association Test[35] (SAT), a Dutch, modified version of the Pyramids and Palm Trees Test that also comprises a naming task.

Purpose of the study

In order to further elucidate the clinical aspects and pathophysiology of AD, we performed an exploratory study to detect disorders in naming and in verbal and visual semantic processing in AD patients. The hypothesis was that bad performance in naming would be accompanied by disorders in both verbal and visual semantic processing. We expected AD patients to score lower than controls on all three parts of the SAT, and performance to worsen with increasing decline of cognitive function. Concerning the naming errors, we expected predominantly semantic errors in patients with moderate cognitive function and relatively more perceptual errors in patients with more severe cognitive impairment. The performance on living relative to non-living items was expected to be equal in all three parts of the SAT with a predominance of errors on living items.

Methods

Subjects

Patients (n = 19) from the geriatric out-patient clinic and the geriatric department of the Erasmus Medical Center were referred by their geriatrician after full comprehensive geriatric assessment, including history and informant history, medication history, and physical and neurological examination. Inclusion criteria were probable Alzheimer's disease (AD), adequate hearing and visual acuity, relatively intact lexical reading and visual perception, and Dutch as native language. Patients had to be capable of undergoing linguistic assessment. The diagnosis of dementia was verified according to a standard protocol and consistent with the DSM-IV criteria.[36] The subdiagnosis of probable AD was based on the NINCDS-ADRDA criteria.[37]

Written informed consent was obtained in all patients and their primary representative and the study protocol was approved by the ethics committee of Erasmus MC. Sex, date of birth and education were registered.

Data of healthy controls were available. Nineteen controls were matched for age, sex and education level.

Measures

We administered the Semantic Association Test[35] (SAT), a standardized instrument that is developed to detect disorders in naming as well as verbal and visual semantic processing. The SAT is based on the principles of the Pyramids and Palm Trees Test[32] and consists of three parts. Each part of the SAT contains the same 30 items, but in a different order. Half of the targets are living, half are non-living. Test results of the SAT are expressed in terms of number of correct responses.

The first part, SAT-naming, contains 30 black-and-white line drawings of objects that the subjects have to name. Exposure time was not limited. Responses were tape recorded and errors were later classified as either semantic error, phonological error, omission or perceptual error. A score below 26 points means impairment. SAT-naming is a reliable test (Cronbach's alpha = 0.91), the sensitivity and specificity for distinguishing AD patients from healthy controls are low (around 65%).[35]

The second part, SAT-verbal, is composed of 30 written target words encircled by four words: three distracter words and the correct response. Two of the distracter words are semantically related to the target, but more distant than the correct response. One distracter is not semantically related. SAT-verbal is used to measure verbal semantic processing. The third part, SAT-visual, has the same format as SAT-verbal but consists of pictures and is used to measure visual semantic processing. For both parts, a score below 25 points means impairment. The reliability is good (Cronbach's alpha = 0.85), sensitivity and specificity for distinguishing AD patients from healthy controls are 54% and 88% for SAT-verbal and 71% and 75% respectively for SAT-visual.[35]

We also administered the Dutch version of the Mini-Mental State Examination (MMSE).[38] The score ranges from 0 to 30 points, higher scores representing better cognitive function.

Statistical methods

Statistical analyses were conducted using SPSS version 15. Differences between AD patients and controls on the three parts of the SAT were tested using an Independent-Samples T Test. Differences between performance on the three parts of the SAT within the AD patients group and within the control group were tested using Paired-Samples T Tests. Differences between living and non-living items were tested using the Wilcoxon Signed Ranks Test. Multiple Linear Regression Analysis was used to investigate whether SAT-naming, SAT-verbal and SAT-visual could serve as relevant predictors of cognitive function as measured by the MMSE. We calculated Pearson correlations to examine the relation between cognitive function and semantic and perceptual naming errors. In all analyses an alpha of .05 was employed.

Results

Patients with probable Alzheimer's disease (AD) from the geriatric out-patient clinic (n = 15) and the geriatric department (n = 4) with a mean age of 76 years (SD = 11) were included in the study and compared with 19 healthy controls with a mean age of 76 years (SD = 3), matched for age, sex and level of education. MMSE scores of the patients ranged from 9 to 28. The four patients from the geriatric department were admitted because of somatic problems and then appeared to also have dementia. In Table 1, demographic and clinical characteristics of patients and controls are summarized. There were no differences in age, sex or level of education between the two groups.

Table 1. Demographic and clinical characteristics of patients and controls

		AD patients (n = 19)	**Controls (n = 19)**	**P value**
Sex (male)	n	9 (47%)	9 (47%)	1.00
Age (years)	mean (SD)	76.1 (11.3)	75.5 (3.1)	0.82
	range	53-94	71-80	
	median	2	1	1.00
Level of education*	1 or 2 or 3	15 (79%)	14 (74%)	
	4 or 5 or 6	0 (0%)	2 (10%)	
	7 or 8	4 (21%)	3 (16%)	
MMSE	mean (SD)	18.4 (5.3)		
	range	9-28		

* 1 = elementary school, 2 = technical and vocational training for 12-16 years old,
3 = lower general secondary education, 4 = higher general secondary education, 5 = pre-university education,
6 = intermediate vocational education, 7 = higher vocational education, 8 = university
MMSE: Mini-Mental State Examination

The scores of all patients on the tests that were administered are shown in Table 2.

Table 2. Scores of each AD patient on the three parts of the Semantic Association Test (SAT) and MMSE (maximum score is 30)

Patient number	**SAT-naming**	**SAT-verbal**	**SAT-visual**	**MMSE**
1	23	(28)	18	22
2	22	(26)	20	18
3	(29)	(26)	(26)	21
4	(28)	21	21	16
5	(30)	(28)	(27)	20
6	(28)	(28)	(27)	17
7	21	19	15	15
8	25	18	18	16
9	20	22	19	14
10	(29)	(26)	(27)	(26)
11	(27)	(27)	(26)	18
12	23	21	20	9
13	(29)	(26)	(28)	(26)
14	23	14	14	9
15	(28)	(27)	(28)	(28)
16	22	(26)	23	18
17	(29)	(25)	(28)	19
18	22	17	21	13
19	(30)	(28)	(29)	24

Figures between brackets are within the normal range.

Group SAT results

AD patients scored significantly lower than controls on all three parts of the SAT (Table 3). Within the AD group the mean score on SAT-naming, which fell within the normal range, was significantly better than the mean score on SAT-verbal (difference = 1.9, 95% CI = 0.01 to 3.8) and on SAT-visual (difference = 2.8, 95% CI = 1.5 to 4.2). There was no significant difference between the mean score of the patients on SAT-verbal and SAT-visual (difference = 0.95, 95% CI = -0.6 to 2.5, Table 3).

Table 3. Mean (SD) scores of patients and controls on the three parts of the Semantic Association Test (SAT, maximum score is 30)

	AD patients (n = 19)	**Controls (n = 19)**	**Difference (95% CI)**	**P value**
SAT-naming, mean (SD)	25.7 (3.4) a,b	28.4 (1.8) c,d	2.7 (0.9 to 4.5)	0.006
SAT-verbal, mean (SD)	23.8 (4.3) a	27.7 (1.2) c	3.9 (1.8 to 6.0)	0.001
SAT-visual, mean (SD)	22.9 (4.8) b	27.4 (2.5) d	4.5 (1.9 to 7.0)	0.001

Within groups, significantly differing means (at the .05 level) are indicated using corresponding subscripts.
Normal scores: naming ≥26, verbal and visual ≥25.

Individual SAT results

In individual patients, selective disorders were observed (see Table 4). A selective disorder means that the score on one subpart is substantially higher than the scores on the other subparts. There were three patients with (relatively) selectively intact naming; in case 4, 8, and 14 naming was (relatively) preserved in contrast with verbal and visual semantic processing. Three other patients showed selectively intact verbal semantic processing; case 1, 2, and 16 had a normal performance on SAT-verbal in contrast with SAT-naming and SAT-visual.

Table 4. Performance of patients with selective disorders

	SAT-naming relatively intact	**SAT-verbal**	**SAT-visual**
Patiënt 4	(28)	21	21
Patiënt 8	25	18	18
Patiënt 14	24	14	14
	SAT-naming	**SAT-verbal intact**	**SAT-visual**
Patiënt 1	23	(28)	18
Patiënt 2	22	(26)	20
Patiënt 16	22	(26)	23

Normal scores SAT (between brackets): naming >25, verbal and visual >24.

Cognitive function and naming errors

Correlations between MMSE score and the three SAT parts were all positive and significant. Thus, the more severe the cognitive impairment, the lower the performance on all SAT parts. The model in total accounted for 55% of the variance in MMSE score (p = .002). However, SAT-verbal was the only significant predictor in the model (p = .049), accounting for 52% of the variance in MMSE score.

On average, the number of naming errors was small. AD patients made slightly more semantic errors on SAT-naming (mean = 1.1, SD = 1.4) than controls (mean = 0.7, SD = 1.3), but not significantly so (p = .4). Neither patients nor controls produced phonological errors. AD patients showed significantly more perceptual errors (mean = 2.1, SD = 1.9) than controls (mean = 0.6, SD = 0.9, p = .005). This also held for omissions (AD patients: mean = 1.1, SD = 1.6; controls: mean = 0.3, SD = 0.5; p = .04). Within the AD group, patients made significantly more perceptual than semantic naming errors (p = .03).

Within the AD group, the correlation between MMSE score and semantic errors was negative but not significant (r = -.39, p = .1). The correlation between MMSE score and perceptual errors was also negative and nearly significant (r = -.43, p = .066). Thus, there was a trend that the more severe the cognitive impairment, the more perceptual errors patients made on the naming task.

Living versus non-living items

The scores on living versus non-living items are given in Table 5. In SAT-naming, the mean performance of AD patients on living items was significantly better than on non-living items (z = -2.3, p = .02). In SAT-verbal, there was no significant difference (z = -1.2, p = .22). In SAT-visual, the mean performance on living items was significantly worse than on non-living items (z = -2.1, p = .04). Controls also showed a significantly better performance on non-living items in SAT-visual (z = -3.1, p = .002). Controls performed equally on living and non-living items in SAT-naming (z = -1.0, p = .31) and SAT-verbal (z = -0.6, p = .57).

Table 5. Mean (SD) scores on living and non-living items of the three parts of the Semantic Association Test (SAT, maximum score is 15) for patients and controls.

	AD patients		**Controls**	
	Living	**Non-living**	**Living**	**Non-living**
SAT-naming	13.2 (1.5)	12.5 (2.1)	14.1 (0.9)	14.3 (1.1)
SAT-verbal	12.3 (2.4)	11.6 (2.6)	14.0 (1.1)	13.8 (0.5)
SAT-visual	10.8 (3.0)	12.1 (1.3)	13.0 (1.9)	14.4 (0.8)

Discussion

This pilot study provides no support for the hypothesis that AD patients show a global breakdown of meaning as the underlying deficit of a prominent naming disorder: we found a heterogeneous deterioration in naming and verbal and visual semantic processing. Although AD patients performed worse than controls on all three parts of the Semantic Association Test (SAT), we found several discrepancies. First, naming was within the normal range and better than verbal and visual semantic processing. Second, three patients showed selectively intact or relatively intact naming and three other patients selectively intact verbal semantic processing. Finally, the proportion between the scores on living and non-living items was different in the three SAT parts: in the naming task, performance was better for living items than for non-living items, whereas the reverse pattern was found in SAT-visual.

Selective preservation of naming in the context of impaired semantic processing was already observed by others in some AD patients and labeled as 'automatic naming'[39] or 'nonoptic aphasia'.[40] A direct pathway for picture naming, through visuo-phonological connections bypassing semantic processing, is assumed to account for this phenomenon.[41] This is analogous to the direct lexical pathways for the reproduction of isolated words and the often reported finding that demented patients are capable of reading words aloud without understanding their meaning.[42] Because of the rarity of occurrence of this phenomenon we did not expect to find such a discrepancy between naming and semantic processing in our pilot study both in the group and individual results. The fact that the (relatively) good naming in our three cases is observed in the context of a poor overall cognitive function as measured with the MMSE and a moderate to severe disorder in both verbal and visual semantic association might contribute to the relevance of our finding.

In addition to the automatic naming hypothesis, a causal factor for their bad performance on the association tasks might be the complexity of these tasks. SAT-verbal and SAT-visual demand that patients combine words or pictures in order to elicit the shared features and to select the combination with the narrowest semantic relationship. The critical feature is present implicitly and patients have to consider at least three combinations simultaneously in order to make the correct choice. Besides semantic processing, completing this complex task requires a certain level of executive functioning. However, the intactness of verbal semantic processing in contrast with visual semantic processing in three other patients challenges the complexity hypothesis.

The finding that verbal semantic processing could be preserved in contrast with naming and visual semantic processing is in line with the acknowledged fact that verbal abilities are preserved longer than non-verbal abilities in healthy elderly adults.[43] In the three cases of disturbed naming and intact verbal semantic association, the word finding deficit might be explained by problems with lexical access, a less severe naming problem than a semantic disorder. These patients appeared to be less severely cognitively impaired than the patients with semantic disorders. An additional explanation for the three cases of intact verbal semantics could be a visuo-perceptual impairment: 3 out of 7, 3 out of 8 and 5 out of 8 naming errors respectively were visual-perceptual in nature. Since both the naming task and the visual semantic association task consist of pictures it cannot be ruled out without thorough investigation that subtle problems with visual perception – the standard clinical examination did not reveal a visuo-perceptual disorder – were to some extend impeding the patients' performance on these tasks.

The results of the error analysis in the categories living and non-living things are also not in line with a global deterioration of language: on the three parts of the SAT there was no parallel error distribution concerning living and non-living items. In addition, the better performance on the living items in the naming task does not agree with the generally assumed preservation of processing non-living things in AD. Perceptual properties are reported to weigh more heavily in living things and functional attributes in non-living things.[44] Possibly, perceptual properties of a depicted concept facilitate naming the object, making living concepts easier to name than non-living concepts. Functional attributes might be more crucial when one has to make a semantic association with a target object by grouping the relevant information of the distracters – a more advanced processing of concepts than just naming them – making non-living items easier in an association task. Irrespective of an explanation, the finding does not support our hypothesis that category-specific deficits are multimodal.

Concerning the error pattern in the naming task, our hypothesis was partly confirmed. As expected, neither healthy controls nor AD patients made phonological naming errors. However, the number of semantic errors did not significantly differentiate the AD patients from the controls, in contrast with the number of perceptual errors and omissions. Consequently, no relation was found between the number of semantic naming errors and cognitive function as measured with the MMSE, whereas the number of perceptual naming errors seemed to increase with progression of the disease. The latter finding supports our hypothesis that a high-level visuo-perceptual impairment is a major contributor only in the late stages of the disease. It should be noted that the number of naming errors was so small that the results should be interpreted with caution.

Our expectation that performance on all three parts of the SAT would worsen with increasing cognitive decline was confirmed, but only SAT-verbal proved to contribute significantly to the prediction of cognitive function. Exactly the same was found in a study on semantic processing in aphasic stroke patients.[45]

The finding that certain subparts of language were preserved and others were impaired might point to different ways the brain is affected by pathological changes. One hypothesis is that there are more neurofibrillary tangles and neuritic plaques, and possibly vascular pathology, in certain brain areas than in others. Another possibility is that certain brain areas are more susceptible for the negative effects of pathological changes than others. The results suggest that there are inter-individual and intra-individual differences in the presence of, or susceptibility for, pathology in the brain areas involved in naming and verbal and visual semantic association, underlying the clinical pictures of selectively intact naming and selectively intact verbal semantics. This is in line with the recent finding that different cognitive profiles in AD are associated with specific types of EEG abnormalities[46]: apparently there is biological support for variability in the cognitive and linguistic profile in AD.

Memory and language deficits are a core problem in AD patients and naming is a widely used diagnostic task. But in individual patients a naming test alone appears to be insufficient to diagnose language deficits in AD, considering the not at all coherent picture we found: automatic naming proved to exist.

Studies that compare performance on tasks requiring naming and verbal and visual semantic association with the same set of items and with an equivalent distribution of living and non-living objects are rare. We did so in a pilot study with a relatively small number of patients. Consequently, the results should be considered preliminary. For future research we would recommend using a larger sample size, extensive neuropsychological assessment and thorough examination of visuo-perceptual ability. Besides, a neuropathological substrate of our functional findings should be sought in order to link behavioral and biological manifestations of AD.

In conclusion, our findings of selectively preserved subparts of language do not support the notion that a global conceptual degradation forms the background of linguistic problems. Also, the linguistic assessment of AD patients should include, besides naming, a verbal and visual semantic association task. The results fit the assumption that AD selectively affects regions of the brain.

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Chapter 3

The efficacy of early cognitive-linguistic treatment and communicative treatment in aphasia after stroke – A randomized controlled trial (RATS-2)

Abstract

Background
The two main approaches in aphasia treatment are cognitive-linguistic treatment (CLT), aimed at restoring the linguistic levels affected, semantics, phonology or syntax, and communicative treatment, aimed at optimizing information transfer by training compensatory strategies and use of residual language skills. We tested the hypothesis that CLT is more effective than communicative treatment in the early stages after stroke.

Methods
In this multi-center, randomized, parallel group trial with blinded outcome assessment, 80 patients with aphasia after stroke were included within three weeks post-stroke. Patients received six months of CLT, comprising semantic and/or phonological training, or communicative treatment for at least two hours per week. They were assessed before treatment and at three and six months with the Amsterdam-Nijmegen Everyday Language Test (ANELT-A, primary outcome) and semantic and phonological tests (secondary outcomes). The intervention effect was evaluated by means of analysis of covariance, with adjustment for baseline scores.

Results
There was no difference between the mean ANELT-A score of the CLT group (n = 38) and the communicative treatment group (n = 42), neither at three (adjusted difference: 1.5, 95% confidence interval: -2.6 to 5.6) nor at six months post-stroke (adjusted difference: 1.6, 95% confidence interval: -2.3 to 5.6). On two of six specific semantic and phonological tests the mean scores differed significantly, both in favor of CLT.

Conclusion
This study does not confirm our hypothesis that patients with aphasia after stroke benefit more from CLT, aimed at activation of the underlying semantic and phonologic processes, than from general, nonspecific communicative treatment (ISRCTN67723958 Current Controlled Trials).

Introduction

Aphasia is present in about 30% of all acute stroke patients and affects their daily communication and social participation. There are two main approaches in aphasia treatment: cognitive-linguistic treatment (CLT) and communicative treatment. The ultimate goal of both approaches is to improve patients' everyday communication. They differ fundamentally in how they achieve this: CLT focuses on the impairment and aims at improving the underlying linguistic processing at the linguistic levels affected, e.g. semantics (word meaning)[1], phonology (word sound)[2] or syntax (understanding and building sentences).[3] Communicative treatment focuses on the disability: patients are trained to use their residual language skills combined with compensatory strategies in order to optimize information transfer.[4]

It is unclear which of both approaches is best for which patients in which period of recovery. In the extensive literature about the efficacy of aphasia treatment there is more evidence for the efficacy of CLT – recommended as Practice Standard in 2005[5] – than of communicative treatment, which has been evaluated less frequently. However, a meta-analysis and recent reviews on cognitive rehabilitation have emphasized the need for well-designed trials on aphasia treatment in general and on specific treatments[5–8] with a sufficient sample size, a functional outcome measure and well-defined methods of intervention.[6] In the last three decades 11 randomized controlled trails (RCTs) were conducted on a specific treatment method for aphasic stroke patients delivered by a speech-language therapist (SLT). To date, no RCTs have been conducted in which the benefits of both approaches, in the form of individual treatment, are compared.

A factor that may influence the efficacy of treatment is timing. Meta-analyses of uncontrolled studies and RCTs suggested that the largest improvements after language treatment occur within one year post-injury[8–9] and mainly when treatment was started within the first three months.[8] In these analyses the type of treatment was not controlled. It is very well possible that CLT and communicative treatment differentially interact with time post-onset.

Code[10] poses that treatment aimed at restoration of impaired cognitive processes is probably more appropriate in acute stages when natural recovery occurs. Addressing specific neural networks, involved in semantics and phonology, by specific treatment activities (CLT) might facilitate or speed up neural recovery processes. Hence, starting early may be crucial for the efficacy of CLT, but less important for communicative treatment. This view is reflected in the current preference in many centers to give CLT in the acute stage followed by communicative treatment when a plateau in improvement has been reached.

In our previous RCT, RATS-1[11], semantic treatment (BOX)[12] was compared with phonological treatment (FIKS)[13], applied 4-12 months post-stroke. The two treatments appeared to be equally effective in improving verbal communication (Amsterdam-Nijmegen Everyday Language Test, ANELT-A).[14] In the current study, RATS-2, we therefore combined BOX and FIKS and compared this CLT with communicative treatment to evaluate their efficacy in an earlier stage of aphasia.

Our objective was to measure the efficacy of CLT, applied in the first six months starting within three weeks post-stroke, on everyday verbal communication and on semantic and phonological processing. We hypothesized that CLT would be more effective than communicative treatment and that its effect would be the largest in the first three months.

Methods

Participants

All patients with aphasia after intracerebral hemorrhage or ischemic stroke of less than three weeks duration were screened for eligibility by the local speech-language therapist (SLT) of 15 hospitals in the Netherlands and Belgium. We included patients aged 18-85 with a life expectancy of more than six months.

Apart from a disorder in verbal communication as measured with the ANELT-A (score <44/50), a semantic and/or phonological disorder had to be present. A semantic disorder implied a score on Semantic Association Test-verbal[15] of less than 26/30 and/or a score on Semantic Association (PALPA)[16] of less than 12/15. A phonological disorder implied a score on Nonword Repetition Task[16] of less than 20/24 and/or on Auditory Lexical Decision[16] of less than 76/80.

Exclusion criteria were severe dysarthria, developmental dyslexia or visual perceptual disorder; pre-existing aphasia, premorbid dementia and recent psychiatric disorder.

Interventions

Experimental treatment

Cognitive-linguistic treatment (CLT) consisted of BOX, a semantic treatment program, and/or FIKS, a phonological treatment program (paper and computer versions). BOX contains many semantic decision tasks using written words, sentences and texts that may also be presented orally. BOX aims to enhance semantic processing. FIKS has a similar structure but is directed at the phonological input and output routes. The SLT determined which treatment program(s) and which subparts the patient needed.

Control treatment

Communicative treatment aimed at improving communicative ability using all verbal and nonverbal strategies available to the patient, e.g. written choice communication and communication books. By definition, exercises are personally relevant and embedded in a communicative setting. Examples of methods used are PACE[17] (Promoting Aphasics' Communicative Effectiveness), role playing and conversational coaching.

Assessment

Baseline measures, including patient demographics and date and type of stroke, were recorded before randomization. The assessment at baseline and at three and six months post-stroke consisted of various linguistic measures and a measure of disability (Box 1).

Box 1. Reported assessments

Linguistics
Semantic measures

- Semantic Association Test (SAT)[15], verbal version. The SAT is based on the principles of the Pyramids and Palm Trees Test.[18] The patient chooses from four written words (three semantically related words and an unrelated word) the word that is semantically closest to the target word.
- Semantic Association with low-imageability words (PALPA).[16]
- Semantic Word Fluency: animals and professions.

Phonological measures

- Nonword Repetition Task (PALPA).
- Auditory Lexical Decision (PALPA). The patient decides if words are existing or nonexisting.
- Letter Fluency: D, A and T.

Other linguistic measures

- Amsterdam-Nijmegen Everyday Language Test (ANELT).[14] Verbal responses to ten everyday language scenarios are scored on a 5-point scale for informational content (scale A).
- Aachen Aphasia Test[19] (only at 6-8 weeks post-stroke).

Disability

- Modified Rankin Scale.[20] This scale captures in one number the level of limitation of activities and ranges from 0 (no symptoms at all) to 5 points (severe disability: bedridden and requiring constant nursing care).

The Amsterdam-Nijmegen Everyday Language Test (ANELT) consists of ten scenarios to which the patient has to respond verbally. For example: You are in a store and you want to buy a television. I am the salesperson here. "Can I help you?". Patients' verbal responses are rated for informational content on scale A "understandability", and for articulation on scale B (intelligibility"). The scales are from 1 (bad) to 5 (good) so the total score on both scales ranges from 10 to 50. The ANELT is both a valid test (ecological validity is strong, criterion-related validity is .81, construct validity is good) and a reliable test (inter-rater reliability is .92, test-retest reliability is .92, goodness of fit is >0.91).[21]

Procedure

This trial was approved by the Ethical Committee of Erasmus MC and is registered (ISRCTN67723958). Written informed consent was obtained from all patients and their proxy before enrollment.

Patients were assessed as soon as possible as from day three. Subsequently, they were included in the study and the allocated treatment was started three weeks post-stroke at the latest. Treatment was provided for six months or shorter if the patient had completely recovered. Patients were retested at three and six months. The assessment and treatment took place in patients' subsequent treatment settings or at home.

Treatment was applied with a minimum of two and preferably for five hours per week, partly individual and partly as homework. The SLTs wrote down the content and amount of treatment their patients received on registration forms that were returned to us and discussed this with us every two to three weeks.

Outcomes

The primary outcome was the ANELT scale A (understandability) at six months. This scale measures functional verbal communication. The ANELT-A was scored from audiotapes by two independent, experienced SLTs, blinded to test moment and treatment allocation. The means of both raters' scores were used in the analyses. In case of a difference between two scores of ≥7 points, the raters were asked, without giving further information, to score the particular test again. In the few cases in which the difference was still ≥7 points, the scores were averaged with that of a third rater.

The secondary outcome measures were the ANELT-A at three months, three semantic tests: Semantic Association Test-verbal, Semantic Association with low-imageability words and Semantic Word Fluency; and three phonological tests: Letter Fluency, Auditory Lexical Decision and Nonword Repetition Task.

The primary effect measure was the difference between the two treatment groups in mean score on the ANELT-A at six months. This difference at three months was a secondary effect measure. The other secondary effect measures were the following: the difference in proportion of patients who improved ≥7 points, the clinically relevant change for individual patients on the ANELT (critical difference) according to the test manual[14]; the difference in proportion of patients who, after treatment, fell in the ANELT category "moderate" or "mild/no communication disorder", score 30-50; and finally, the difference in score on the three semantic and three phonological tests, all at three and six months.

The assessments were done by members of the research group, of a supporting aphasia team, trainees, or involved or uninvolved colleagues of the treating SLT. In the minority of cases it was unavoidable that the tests were administered by the treating SLT. One hundred of 158 follow up assessments were carried out by a person who was blind for treatment allocation. The assessors were instructed both orally and through a manual on how to administer the tests. In addition, they were trained specifically in administering the ANELT.

Statistical analyses

Analyses were performed on the basis of intention to treat. We also performed an on treatment analysis by limiting the analysis to patients who had completed treatment. We used ANCOVA and adjusted for baseline severity[22] to test group differences in score on the ANELT-A and on the semantic and phonological tests at three and six months, with 95% confidence interval (CI). Beside baseline severity, we planned to adjust for age, sex, level of education, aphasia type, and intensity of treatment. The proportion of patients in each group who improved ≥7 points after three and six months, and the proportion of patients in each group who fell in the ANELT category "moderate" or "mild/no communication disorder" were compared by Odds Ratio with 95% CI by means of multiple logistic regression. All analyses were performed in SPSS 15.0 for Windows.

Sample size

We calculated that a sample of 70 patients would provide a power of 0.87 to detect a difference of seven points, the clinically relevant change for individual patients, on the ANELT between the two treatment groups at a 5% 2-sided significance level. To compensate for non-evaluable patients we randomized 80 patients.

Randomization and blinding

Treatment allocation was stratified by center. An independent statistician provided the computer-generated random allocation sequence per center. An uninvolved secretary put the assignments per center in sequentially numbered, opaque envelopes that were sealed and stored in a locked drawer. The research coordinator wrote the research number of the patient on the next appropriate envelop and then opened it to assign the intervention.

The patients and SLTs could not be blinded to individual treatment allocations, but the assessment of the primary outcome was blinded. Patients' responses on the ANELT were tape-recorded and scored by two independent raters, blinded to test moment and treatment allocation.

Results

From September 2006 to April 2008, 85 patients were enrolled in 27 treatment centers in The Netherlands and Belgium. In 3 of 41 patients assigned CLT and in 2 of 44 patients assigned communicative treatment only baseline assessment was obtained and no follow-up due to serious concomitant illness, death or refusal to further participate. Because no outcomes could be determined in these five patients, we do not report on them. The intention-to-treat group therefore consisted of 80 patients who had received at least one follow-up assessment and in whom outcomes could be determined. For the on-treatment analyses we excluded 5 of 80 patients who prematurely aborted treatment (see details in Figure 1).

Figure 1. Flow chart of enrolled patients

85 stroke patients with aphasia enrolled

CLT		No-CLT
41 randomly assigned CLT 41 received allocated intervention	Allocation n = 85	44 randomly assigned no-CLT 44 received allocated intervention
0 lost to follow-up 4 discontinued intervention 3 concomitant illness 1 refusal by SLT 3 no assessment 2 concomitant illness 1 refusal	3-month follow-up	0 lost to follow-up 3 discontinued intervention 1 concomitant illness 2 refusal 3 no assessment 1 concomitant illness 2 refusal
0 lost to follow-up 0 discontinued intervention 3 no assessment 2 concomitant illness 2 death 1 refusal	6-month follow-up	0 lost to follow-up 3 discontinued intervention refusal 2 no assessment 1 death 1 refusal
38 assessed for the primary outcome*	Intention to treat analysis n = 80	42 assessed for the primary outcome
37 completed therapy	On treatment analysis n = 75	38 completed therapy

* In one patient the ANELT-A score at six months could be extrapolated from the 3-month score.

Baseline characteristics were well balanced (Table 1), except for sex: there were more men in the control group (57% versus 37% in the CLT group).

Table 1. Baseline characteristics of enrolled patients

	CLT (n = 38)	Communicative treatment (n = 42)
Age ±SD, y	68 ±13	67 ±15
Sex, n: male	14 (37%)	24 (57%)
Handedness (EHI), n:		
• right	31 (82%)	36 (86%)
• left	5 (13%)	2 (5%)
• ambidextrous	2 (5%)	4 (9%)
Level of education, n:		
• no/unfinished elementary school	0 (0%)	1 (2%)
• elementary school	7 (18%)	9 (21%)
• unfinished junior secondary vocational education	1 (3%)	2 (5%)
• junior secondary vocational education	17 (45%)	18 (43%)
• senior vocational education	9 (24%)	8 (19%)
• higher education	4 (10%)	2 (5%)
• university	0 (0%)	2 (5%)
Type of stroke, n:		
• ischemic	33 (87%)	38 (90%)
• hemorrhagic	5 (13%)	4 (10%)
Location of lesion, n:		
• left hemisphere	36 (95%)	39 (93%)
• right hemisphere	2 (5%)	3 (7%)
Time post stroke to start of treatment, mean in days (range)	22 (11-37)	23 (9-49)
Rankin score (0-5), median (range)	3 (0-5)	3 (2-5)
ANELT A-scale (10-50), mean ±SD	21.4 ±11.0	21.0 ±11.1
Severity category ANELT-A, n		
• very severe-severe (score 10-29)	27 (71%)	30 (71%)
• moderate-mild-normal (score 30-50)	11 (29%)	12 (29%)
Disorder at inclusion, n		
• semantic	3 (8%)	2 (5%)
• phonological	4 (10%)	4 (9%)
• semantic and phonological	31 (82%)	36 (86%)
AAT classification at 8 weeks, n:		
• residual aphasia	5 (13%)	2 (5%)
• not classifiable	4 (10%)	3 (7%)
• global	2 (5%)	4 (9%)
• Wernicke	8 (21%)	16 (38%)
• Broca	4 (11%)	2 (5%)
• Anomic	12 (32%)	12 (29%)
• Unknown	3 (8%)	3 (7%)

EHI indicates Edinburgh Handedness Inventory.
ANELT indicates Amsterdam-Nijmegen Everyday Language Test.
AAT indicates Aachen Aphasia Test.

Primary outcome
In both treatment groups the average ANELT-A scores improved. There was no significant difference in the mean ANELT-A scores between the two treatment groups, neither at three nor at six months post-stroke (Table 2). Almost all improvement occurred in the first three months. In total, four ANELT scores were lacking, two in the CLT group and two in the control group, due to loss of the audiotape, death, residence abroad and refusal. We replaced these lacking scores by the sum of the patient's ANELT-A score on the previous assessment and the mean improvement of the whole group in the previous period.

There was also no difference in improvement of ≥7 points on the ANELT-A. At three months 22/38 patients (58%) in the CLT group improved ≥7 points, compared with 26/42 (62%) in the communicative treatment group (OR = 0.85, 95% CI = 0.35 to 2.07). At six months 27/38 patients (71%) in the CLT group improved ≥7 points, compared with 31/42 (74%) in the communicative treatment group (OR = 0.87, 95% CI = 0.33 to 2.33).

At three months there was a trend regarding the proportion of patients in each group who fell in the ANELT category "moderate" or "mild/no communication disorder": 27/38 patients (71%) from the CLT group, versus 23/42 (55%) in the communicative treatment group (OR = 2.0, 95% CI = 0.80 to 5.13). But this trend was not present anymore at six months (29/38 [76%] in the CLT group versus 30/42 [71%] in the communicative treatment group, OR = 1.3, 95% CI = 0.47 to 3.52).

In the on-treatment analyses, with five patients less than in the intention to treat group, the treatment effects were much the same. Adjustment for neither the baseline characteristics age, sex, and level of education, nor for the variables aphasia type and intensity of treatment changed the results of the main outcomes.

The intraclass correlation coefficients between the two independent raters of the ANELT indicated excellent agreement (at baseline 0.95, at three months 0.97 and at six months 0.96).

Table 2. Primary outcome measure: mean ANELT-A scores for the CLT and the communicative treatment group

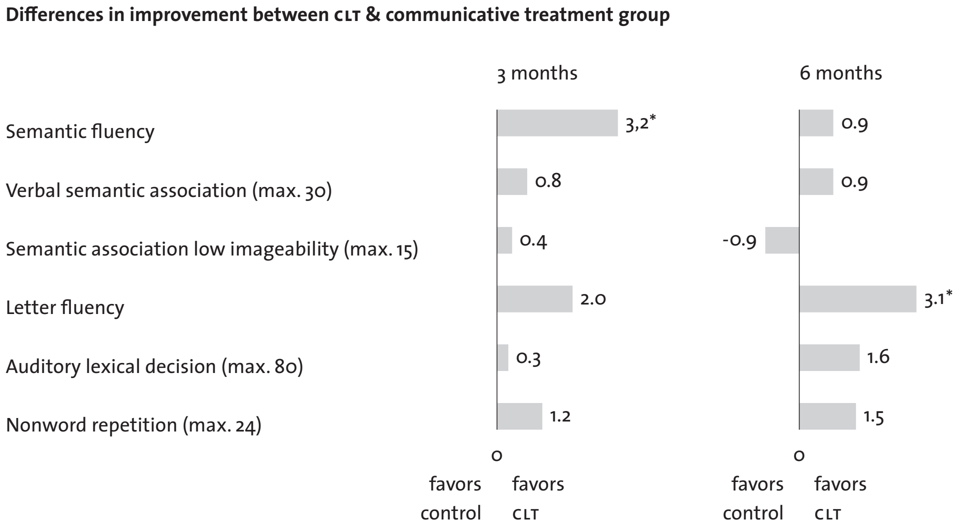
	CLT (n = 38)	Communicative treatment (n = 42)	Difference (95% CI)	Adjusted difference (95% CI)*	P value
3 months post-stroke	33.4	31.6	1.8 (-2.6 to 5.6)	1.5 (-3.8 to 7.4)	0.48
6 months post-stroke†	35.2	33.2	1.9 (-3.4 to 7.3)	1.6 (-2.3 to 5.6)	0.42

* Adjusted for baseline score; † Primary effect measure

Secondary outcome measures

Both treatment groups improved on all secondary tasks. There was a statistically significant difference between the groups on the fluency tasks, in favor of CLT: on Semantic Word Fluency at three months (adjusted difference = 3.2, 95% CI = 0.4 to 6.0) and on Letter Fluency at six months (adjusted difference = 3.1, 95% CI = 0.3 to 6.0). On the remaining secondary tasks, Semantic Association Test-verbal, Semantic Association with low imageability words, Auditory Lexical Decision and Nonword Repetition Task, there was no significant difference in improvement between the groups (Figure 2).

Figure 2. Difference between the mean improvement on the secondary outcome measures of the CLT (n = 38) and the communicative treatment group (n = 42)



* Indicates significant difference ($p < 0.05$)
Between brackets: the maximum score on the test

Treatment intensity

The mean intensity of treatment was 2.1 hours per week. The mean number of hours of therapy was 45.4 hours of which 33.8 hours were face-to-face with an SLT and 11.6 hours were spent on homework. More details are given in Table 3.

Table 3. Data on treatment intensity for both treatment groups

	0-3 months CLT (n = 38)	 Communicative (n = 41)	3-6 months CLT (n = 38)	 Communicative (n = 41)
Mean intensity (SD)	2.4 (0.9)	2.0 (1.0)	2.1 (1.2)	2.0 (1.2)
Number of patients who had ≥ 2 hours of therapy	25 (66%)	21 (51%)	21 (55%)	15 (37%)
Number of patients who had ≥ 5 hours of therapy	2 (5%)	1 (2%)	2 (5%)	2 (5%)

Intensity did not differ significantly between the two treatment groups (0-3 months: $p = 0.2$; 3-6 months: $p = 0.5$). A smaller percentage of patients in the communicative treatment group received the minimum treatment intensity of two hours compared with patients in the CLT group. However, this difference was not statistically significant (0-3 months: $\chi^2 = 1.7$, $p = 0.2$; 3-6 months: $\chi^2 = 2.8$, $p = 0.1$).

Discussion

We compared the efficacy of CLT (semantic and phonological treatment) and communicative treatment, applied in the first six months post-stroke. The two groups showed an equal improvement on the ANELT-A at three and six months with the largest increase in the first three months. The proportion of patients who fell in the ANELT category "moderate" or "mild/no communication disorder" showed a trend in favor of CLT at three months, but not at six months. This difference at three months might be due to chance: more patients in the CLT group than in the control group scored near the cut-off and thus were more likely to shift from the severe to the moderate category. The scores on nearly all specific semantic and phonological tests were higher after CLT than after communicative treatment, but the difference was only significant for the semantic and letter fluency tasks.

This treatment effect in favor of CLT could be meaningful. Both fluency tasks are explicitly related to the aim of CLT, i.e. to improve semantic and phonological processing, which has a positive influence on word finding. The fluency tasks are productive tasks that require self generation of words, a stage in the pursuit of adequate verbal communication in general, measured by the ANELT. Although there was no significant overall treatment effect on our primary outcome measure, nearly all differences between groups were in favor of the CLT group and therefore the efficacy of CLT remains to be evaluated in future studies.

Some methodological aspects of our study should be discussed. To our knowledge, RATS-2 is the first RCT that has evaluated aphasia treatment started in the acute stage, with everyday language use as primary outcome. Other strengths were the relatively large sample size (n = 80), very good compliance and minimal loss to follow-up.

In line with recommendations for efficacy research on cognitive rehabilitation[5], we used a functional communication measure as primary outcome. In the Netherlands, the ANELT, in origin Dutch, was the only adequate test available. It has a high ecological validity[21] and is increasingly applied as primary outcome in treatment studies, both in the Netherlands[11, 23–24] and elsewhere.[25] It is considered a weakness if, as in most studies, the outcome measure is trained material. Fewer studies considered generalization to untrained material. The ultimate result is generalization of the intervention to everyday communication, which we aimed to show. Therapy-specific findings in our previous trial[11] support the view that improving the underlying linguistic processing results in improved verbal communication.

Although we could not avoid that about one third of the outcome assessments was non-blinded, the final judgment of all ANELT samples, the primary outcome measure, was blinded.

A limitation is that we did not include a control group without language treatment. Therefore, we are not able to specify the potential effect of treatment over natural recovery. Because our aim was to measure the efficacy of a 6-months treatment period, we considered it both unethical and impracticable to withhold treatment from patients with a recent stroke for such a long period. Also, one may question whether the contrast between both treatments was large enough. Although only one patient in our study received less than 75% of treatment according to protocol, it is obvious that in any communicative exercise, semantic and phonological processes are implicitly addressed. Therefore, we cannot exclude that overlap between the two treatments may have played a role. Finally, treatment intensity is currently an important issue in efficacy research and is assumed to be vital for the efficacy of treatment.[5, 8, 26] Possibly, the intensity in our study did not reach the threshold necessary to exceed natural recovery and find potential treatment effects[27] as we did not succeed in achieving the preferred intensity of five hours per week (the mean was 2.1 hours). A meta-analysis[28] suggested that 8.8 hours of treatment per week is needed to obtain a treatment effect and that two hours per week is insufficient. Recommendations in the remaining literature on treatment intensity range from 1.5 to two hours per week as being too little[8, 29], to two or three hours as the minimum to obtain positive results.[8, 30–31]

Of the few well-designed RCTs on the efficacy of aphasia treatment, the one of Wertz et al.[32] is most comparable to ours. These authors compared treatment of specific language deficits with communicative treatment, started at four weeks post-onset, and found that the two were equally effective. Communicative treatment, however, was provided in a group instead of individually. In most other studies, conventional treatment was used, so approaches were mixed. Constraint-induced Aphasia Therapy[33], a treatment that is to date evaluated best, also combines a cognitive-linguistic and communicative approach. Elman&Bernstein-Ellis[4] examined the efficacy of group communication treatment separately, and found higher scores on communicative and linguistic measures compared to no treatment. CLT directed to semantic and phonological processing, which are crucial to word finding, has not been contrasted with no treatment in an RCT.

Our study does not support the widespread notion that CLT is more appropriate in an early stage and that communicative training is more suitable at a later stage.[10] Nor do the results support the recommendation that, in cognitive rehabilitation, clinicians should focus on training cognitive skills directly rather than broad interventions with the expectation of subsequent generalization to broader use in daily life.[9] The results also do not support the hypothesis that treatment of communication via the activation of the underlying processes, i.e. semantics and phonology, would be more effective in early aphasia, when natural recovery takes place, than a direct training of the communication itself. Because of the possible overlap between the two treatments and the low treatment intensity, the question whether CLT is efficacious particularly in the acute stage remains open. Therefore, in our next study, RATS-3, we aim to compare the effect of intensive CLT in aphasia patients very early post-stroke, with deferred treatment.

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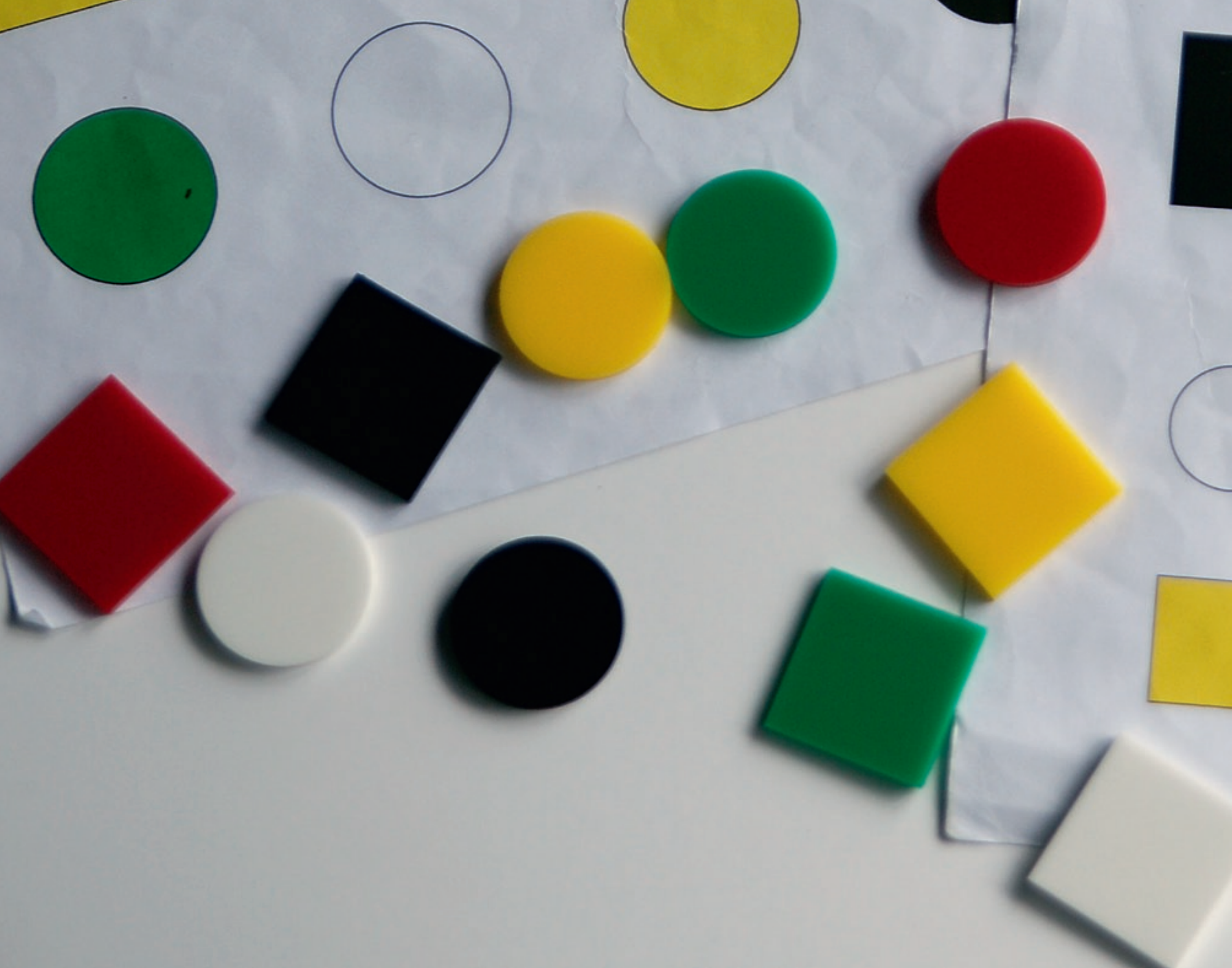
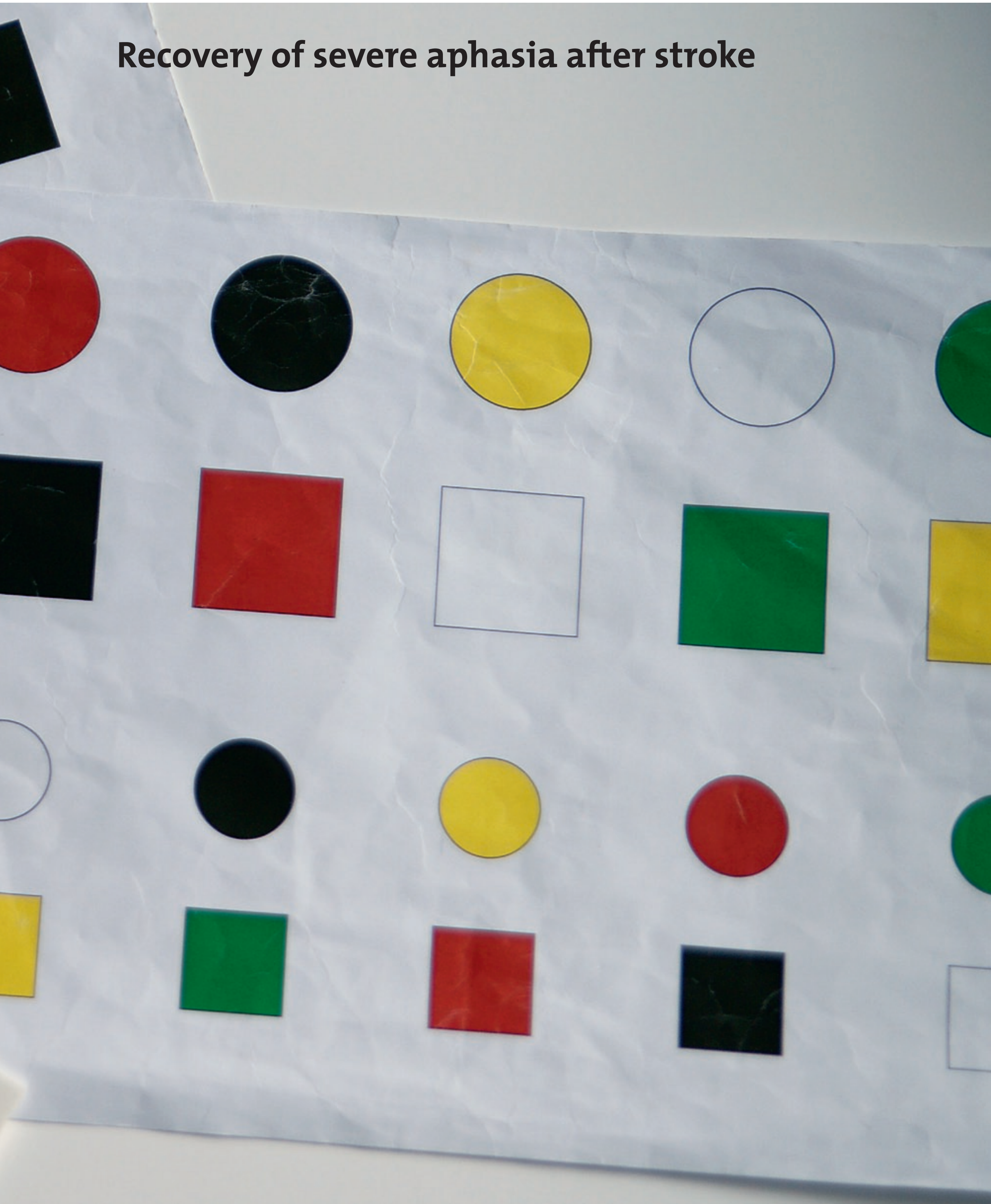


Chapter 4

Recovery of severe aphasia after stroke



Abstract

Background
Severe aphasia is common after stroke. However, knowledge about recovery and therapeutic potential in severely aphasic patients is scarce.

Aim
To explore the recovery pattern of verbal communication in aphasia from acute stroke of varying degrees of severity during 6 months of therapy.

Methods
Patients were allocated to cognitive-linguistic or communicative therapy. Three equally large groups were formed, based on baseline Amsterdam-Nijmegen Everyday Language Test scores. Outcomes at baseline, 3 and 6 months after stroke onset were compared between the three severity groups, stratified for the two treatments using ANCOVA.

Results
Patients with severe or moderate aphasia improved the most, particularly after cognitive-linguistic therapy.

Conclusions
Severely aphasic stroke patients showed significant improvement of verbal communication and might benefit more from acute treatment than generally assumed.

Introduction

Aphasia caused by stroke is often severe; between 26% and 61% of these patients have global aphasia.[1] Yet few recovery studies on aphasia have provided data on severely affected patients.[2, 3] Moreover, severely aphasic patients were excluded from about 30% of randomized controlled trials (e.g., Katz and Wertz[4], Berthier et al[5]). This reflects the clinicians' generally pessimistic view on recovery from severe aphasia, despite some reports of patients regaining language skills beyond expectation.[6] 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,[7] more knowledge about recovery and therapeutic potential of severely aphasic patients is necessary.

We explored the recovery pattern of verbal communication in (sub)acute aphasic stroke patients of varying degrees of severity during 6 months of therapy.

Methods

All patients included in the present study participated in the Rotterdam Aphasia Therapy Study-2 (RATS-2, n = 80), a multicenter, randomized controlled trial on the efficacy of cognitive-linguistic therapy (CLT). RATS-2 was approved by the ethics committee of Erasmus MC and written informed consent was obtained from all patients and their proxy before inclusion.

The design and main results have been described elsewhere.[8] In brief, stroke patients aged 18-85 years with disruption of everyday verbal communication and an overt semantic and/or phonological disorder were assessed within 3 weeks after stroke onset and at 3 and 6 months. They were allocated to either CLT or communicative therapy. CLT was directed at two basic language components: semantic therapy for word meaning and phonological therapy for word sound. Communicative therapy was directed at functional communicative behavior using all verbal and nonverbal strategies available to the patient.

Primary outcome measure was the Amsterdam-Nijmegen Everyday Language Test (ANELT)[9] for functional verbal communication with scores ranging from 10 to 50. Responses were scored from audio recording by two independent experts, blinded to test moment and treatment allocation.

For this study, we formed three equally large severity groups based on baseline ANELT score. Scores at baseline, 3 and 6 months were compared between the severity groups, stratified for the two treatment types, using ANCOVA with 95% confidence interval (CI) and adjustment for baseline severity.

Results

Table 1 shows the range of ANELT scores and number of patients in each severity group.

Table 1. Grouping of the study population by severity of aphasia

	Baseline ANELT score	Type of therapy CLT	Communicative	Total
Severe aphasia	10 – 12	11	15	26
Moderate aphasia	13 – 26	13	14	27
Mild aphasia	27 – 43	14	13	27

There were no striking differences in baseline characteristics between the three severity groups (Table 2).

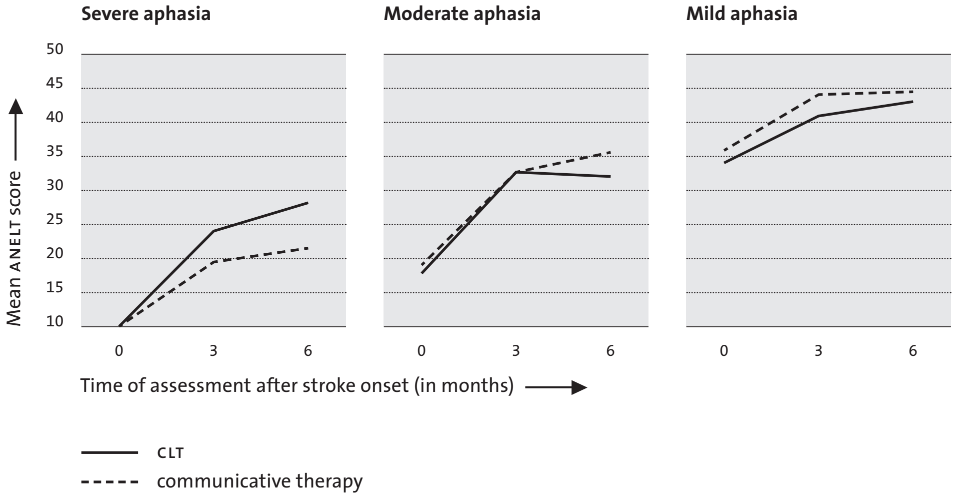
Table 2. Baseline characteristics of patients with acute aphasia, included in RATS-2, by severity of aphasia.

Aphasia severity	**Severe (n = 26)**	**Moderate (n = 27)**	**Mild (n = 27)**
Age in years (mean, SD)	67 (12)	67 (14)	68 (16)
Male **sex**	14 (54%)	14 (52%)	10 (37%)
Right-**handedness**	21 (81%)	21 (78%)	25 (92%)
Low **educational level**	19 (73%)	17 (63%)	19 (71%)
Stroke type			
• Ischemic stroke	22 (85%)	24 (89%)	25 (93%)
Location of lesion			
• Left hemisphere	25 (96%)	24 (89%)	26 (96%)
Time post stroke to **start of treatment** in days (mean, range)	21 (9-32)	24 (13-38)	22 (11-49)
Barthel Index score (mean, SD)	11.6 (6.5)	13.7 (6.3)	16.1 (5.2)
Type of aphasia (AAT classification)			
• Global	6 (23%)	0	0
• Wernicke	10 (38%)	13 (48%)	1 (4%)
• Broca	3 (12%)	2 (7%)	1 (4%)
• Anomic	5 (19%)	8 (30%)	11 (41%)
• Residual aphasia	0	1 (4%)	6 (22%)
• Not classifiable	0	2 (7%)	5 (18%)
• Unknown	2 (8%)	1 (4%)	3 (11%)
ANELT score (mean, SD)	10 (0.6)	18 (4.4)	35 (5.0)

AAT indicates Aachen Aphasia Test
ANELT indicates Amsterdam-Nijmegen Everyday Language Test scale A (understandability)

In patients with severe aphasia the mean improvement on ANELT was 12 points from 0-3 months and 3 points from 3-6 months, in patients with moderate aphasia 15 points from 0-3 months and 1 point from 3-6 months, and in patients with mild aphasia 7 points from 0-3 months and 2 points from 3-6 months (Figure 1). In severely aphasic patients, the mean adjusted difference between CLT and communicative therapy at 6 months was 8 points (95% CI: -1 to 17).

Figure 1. Improvement on the Amsterdam-Nijmegen Everyday Language Test (ANELT) for the cognitive-linguistic (CLT) and communicative therapy group in the 3 severity groups.



Discussion

We found substantial improvement of verbal communication in patients with severe aphasia due to stroke, both in the first and second 3-months period. There was a trend for severely aphasic patients to benefit more from CLT than from communicative therapy.

This study was conducted within the setting of a randomized clinical trial with standardized assessments by well trained experts. Furthermore, patients were included by over 20 centers, increasing the generalizability. Drawback of the present study is that it concerns post-hoc analyses and the subgroups are relatively small.

Some previous studies reported that great improvement may be achieved in patients with severe aphasia,[6, 10] but that greater initial severity is associated with poorer outcomes.[11] Both are reflected in our study: improvement in patients with severe and moderate aphasia was comparable, but their outcome at 6 months differed considerably.

Patients with severe aphasia appeared to particularly benefit from CLT compared with communicative therapy. Our results challenge the theory that people with extensive neural damage are unlikely to benefit from restorative treatment[12] and that functional communicative therapy is preferable for this aphasic subgroup.[13]

We conclude that severely aphasic patients, although they reach a lower outcome than milder cases, do have the capacity to significantly regain communicative abilities during the first 6 months. This suggests that aphasia therapy does not need to be postponed in these patients, and that they could particularly benefit from CLT.

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Chapter 5

Expert versus proxy rating of verbal communicative ability of aphasic stroke patients

Abstract

In randomized clinical trials of aphasia treatment, a functional outcome measure like the Amsterdam-Nijmegen Everyday Language Test (ANELT), administered by speech-language therapists, is often used. However, the agreement between this expert rating and the judgement of the proxy about the quality of the person with aphasia's daily life communication is largely unknown. We examined the association between ANELT scores by speech-language therapists and proxy judgements on the Partner Communication Questionnaire both at 3 and 6 months in 39 people with aphasia after stroke. We also determined which factors affected the level and nature of disagreement between expert and proxy judgement of the communicative ability at 6 months in 53 people with aphasia. We found moderate agreement (at 3 months $r = .662$; $p = <.0001$ and at 6 months $r = .565$; $p = .0001$), with proxies rating slightly higher than experts. Less severe aphasia, measured with the Aphasia Severity Rating Scale, was associated with less overestimation by the proxy compared with the expert. In conclusion, although proxies were slightly more positive than experts, we found moderate agreement between expert and proxy rating of verbal communicative ability of people with aphasia after stroke, especially in milder cases.

Introduction

People with aphasia are known to communicate better in daily life than would be anticipated by results of standardized language tests, administered by professionals.[1–2] This indicates the importance of information on the daily functioning of the person with aphasia by a proxy: a significant other who is familiar with the person with aphasia, such as a partner, friend or caregiver. To broaden our understanding of the impact of aphasia on everyday communication, data from multiple sources – such as the affected people themselves, proxies and clinicians – should be gathered. A proxy has knowledge of the person with aphasia's premorbid functioning, and spends substantially more time with the person with aphasia in various situations than the professional, providing ample opportunity for daily observations. A professional has encountered many people with aphasia in various degrees of severity and in a diversity of personalities; a professional therefore is experienced in anticipating the impact of aphasia on different affected persons and different proxies, also in various stages after stroke onset.

Several factors may influence the proxy's perception of the person with aphasia's communicative ability. The age of the person with aphasia is generally associated with the type and number of social and communication situations in which the patient still participates. The relation with the proxy (e.g. spouse, child or friend) determines how much time they spend together. The severity of the aphasia noticeable in spontaneous speech and the profile of aphasic impairment, e.g. verbal versus nonverbal communicative abilities and productive skills versus language comprehension level, may influence proxies' assessment of verbal communication. Neurological and neuropsychological impairments apart from aphasia are often related to the level of dependence and quality of life of the person with aphasia, and influence how the proxy views the affected partner. The time elapsed since onset is also considered to have an impact on proxies' perception because adaptation to and acceptance of possible changes in the person with aphasia's daily functioning is a process that evolves over time.[3] The psychological coping mechanisms used by relatives and their personality characteristics may also influence their estimation of the person with aphasia's communicative ability. Finally, a significantly better agreement between expert and proxy rating was found among spouse pairs of whom the person with aphasia was receiving aphasia treatment.[2, 4]

Obviously, the judgments of professionals are also influenced by various factors. Experts have worked with many people with aphasia and this reference might introduce a bias when rating an individual with aphasia. Also, experts have little knowledge of the individual's premorbid functioning and possibly rate harshly by comparing communication to an ill-defined ideal of 'normal' behaviour.[5] Finally, experts might tend to rate harshly as they know how to recognize and categorize linguistic errors.

Most studies comparing experts' and proxies' perception of the activity limitations and participation restrictions of aphasia have concluded that family members make valid and reliable evaluations of both the linguistic and the communicative abilities of people with aphasia.[6–10] However, a difference between experts' and proxies' perceptions of aphasia was also found.[11] As for the nature of this disagreement, various authors reported that proxies overestimated the linguistic ability of their aphasic partner compared with speech-language therapists (SLTs).[12–14] The opposite, an underestimation of linguistic ability by proxies was also observed.[15–16]

In conducting trials and planning and providing care for people with aphasia, it is crucial to have insight into the extent to which the judgments of experts and proxies align. It determines for example the guidance and information SLTs can best provide to family members. The first aim of this study was to examine the association between the rating of everyday communication by the SLT (expert) and by the proxy of people with aphasia due to stroke, and the influence of time post onset (three versus six months) on this association. The second aim of this study was to determine if aphasia severity, quality of life, level of independence, age, and relation with the proxy influence the level and nature of disagreement between both ratings at six months, a more stable point in time.

Method

The people included in the present study participated in the Rotterdam Aphasia Therapy Study-2 (RATS-2, *n* = 80), a multicenter, randomized controlled trial on the efficacy of cognitive-linguistic therapy (CLT) in the acute stage of aphasia after stroke. The design and results of RATS-2 have been published elsewhere.[17] RATS-2 was approved by the ethics committee of Erasmus MC and completed in accordance with the Helsinki Declaration (http://www.wma.net/e/policy/17-c_e.html). Written informed consent was obtained from all participants and their proxy before inclusion in the study.

Participants

Participants were between 18 and 85 years and had aphasia due to acute stroke. Aphasia resulted in disruption of everyday verbal communication and an overt semantic and/or phonological disorder. All participants were assessed within three weeks after stroke and at three and six months. This study centers on the three and six month outcomes only.

Measurements

ANELT

The Amsterdam-Nijmegen Everyday Language Test (ANELT)[18] measures functional verbal communication, an important clinical outcome measure in RCTs. It was the only Dutch test available at that time. The ANELT scale A (understandability) was scored from audio recording by two independent, experienced SLTs, blinded to test moment and treatment allocation. The means of both raters' scores were used in the analyses. More details have been published elsewhere.[17] The ANELT was administered by a member or trainee of the RATS team, of the Aphasia Team in Rotterdam, a colleague of the treating SLT, or the treating SLT at that time. It consists of ten scenarios to which the person with aphasia is asked to respond verbally (see Appendix for examples). The verbal responses are rated for informational content on a scale from 1 (bad) to 5 (good) so the total score ranges from 10 to 50 points. The ANELT is both a valid test, with strong criterion-related, construct and ecological validity (no differences between expert ratings and ratings by naive persons without any experience with aphasia), and a reliable test with high inter-rater and test-retest reliability.[19] It is increasingly applied as outcome measure in treatment studies, both in The Netherlands[20–23] and elsewhere.[24–25]

PCQ

One of the few assessment tools for functional communicative performance that are designed to be used by proxies is the Partner Communication Questionnaire (PCQ).[26] The PCQ is an observational instrument with which partners can assess the verbal communicative abilities of their aphasic partner everyday situations (see Appendix for examples). The partners are asked to indicate to what extent they think the person with aphasia is able to handle verbally every situation on a 5-point scale ranging from 1: never succeeds to 5: always succeeds. The PCQ consists of 46 questions so total score ranges from 46 to 230 points, with a higher score indicating better verbal communication. The partner is instructed to take into account only the ability to verbally convey a message, without the help of hand gestures and facial expressions. In case they did not actually experience the given situation, the partner is instructed to imagine the verbal ability of his partner in such a situation.

Aphasia Severity Rating Scale

We used the (Goodglass) Aphasia Severity Rating Scale from the Boston Diagnostic Aphasia Examination[27] to rate the person with aphasia's communicative behaviour. Since functional verbal communication – measured with the ANELT and PCQ – was the focus of this study, we selected a similar measure (communication) to explore the influence of its severity on agreement of ratings. Spontaneous speech is collected through a conversation in which the person with aphasia is encouraged to speak for ten minutes, guided by standard questions about what happened, the person with aphasia's family, occupation and hobbies. The person with aphasia's capacity for oral communication is rated on a 6-point scale, ranging from 0: no comprehensible speech production to 5: no or minimal noticeable speech difficulty. The rating was performed by a member or trainee of the RATS team or of the Aphasia Team in Rotterdam.

EQ-5D

The European quality of life-5 dimensions (EQ-5D)[28] was used to assess self-reported health status of the person with aphasia at the time of completion. The EQ-5D is widely used in stroke populations, available in Dutch and relatively simple. It was administered together with the participant by the treating SLT at that time, a member or trainee of the RATS team, of the Aphasia Team in Rotterdam, or by a colleague of the treating SLT. All cues were used to help the person with aphasia understand the items. The EQ-5D consists of five subscales that assess mobility, self-care, usual activities, pain, and anxiety/

depression. Each subscale is scored on a 3-point scale: no problems, some problems or severe problems. A utility score was calculated with population-based preference weights for combined health scores.[29] Utility scores range from -0.33 to 1.00; a score of 1 represents perfect health, a score of 0 represents death, and negative scores represent health states considered worse than death.

Barthel Index

The Barthel Index[30] was used to measure the degree of physical activity limitations and the level of independence in activities of daily living (ADL). The scale was filled out by a nurse within three weeks after stroke (standard procedure in hospitals) or by the SLT together with the participant and often with help from a proxy. It consists of 10 items all representing physical abilities, e.g. climbing the stairs, using the toilet, getting dressed. The rater is asked to evaluate the person with aphasia's dependency on others for each activity on a 3-point scale with 0 indicating complete dependence and 2 indicating complete independence. Scores range from 0 to 20, with a higher score indicating more independence in ADL.

Statistical analyses

For comparability we rescaled the ANELT-A and PCQ by dividing the ANELT-A scores by 10 and the PCQ scores by 46 (the number of scenarios/questions) so that total scores on both measures range from 1 to 5.

First aim

The association between the rating of the SLT (expert) and the rating of the proxy both at three and at six months after stroke was examined through scatter plots of the data and with Pearson correlation coefficients. We labelled the points in the scatter plots in order to explore agreement between both ratings as a function of aphasia type.

Second aim

To determine which factors affect the discrepancy (level of disagreement) between expert and proxy judgement at six months after stroke, we first performed linear regression analysis with the absolute difference between ANELT and PCQ scores (range 0 to 4) as dependent variable. This provides us with information about the influence of the factors on the extent to which both ratings align. Nothing can be said about the direction of the disagreement, that is, if the expert or proxy scores higher. Therefore, as a next step, we performed linear regression analysis with PCQ minus ANELT (range -4 to 4) as dependent variable to determine whether the discrepancy at six months was due to underestimation or overestimation by the proxy compared with the expert. Combining the results of the two models allows for a detailed interpretation.

For readability we describe the nature of the discrepancy as "under- or overestimation by the proxy compared with the expert". This by no means suggests that the expert scores were the standard or true scores.

The predictors considered were (Goodglass) Aphasia Severity Rating Scale, Barthel Index, EQ-5D, age of the person with aphasia and type of relation with the proxy (whether the proxy was the partner or a non-partner, i.e. child, parent or friend of the person with aphasia). Those factors with a value of $p < .2$ in the univariable regression analysis were entered into a multivariable regression model to determine which independent factors were associated with (i) the discrepancy between the expert and proxy rating of the person with aphasia's verbal communicative ability and (ii) the amount of under- or overestimation by the proxy compared with the expert. Analyses were performed in SPSS 17.0 for Windows.

Results

For 53 of 80 participants, data on all the predictor variables (Aphasia Severity Rating Scale, Barthel Index, EQ-5D, age of the person with aphasia and type of relation with the proxy) and ANELT and PCQ were complete at six months after stroke. For 39 of these 53 people, ANELT and PCQ were obtained both at three and six months after stroke (not all proxies returned both questionnaires). Baseline characteristics of the 53 people included in this study are summarized in Table 1. The intraclass correlation coefficients between the two independent raters of the ANELT indicated excellent agreement (at baseline 0.95, at three months 0.97 and at six months 0.96).

Table 1. Baseline characteristics of the participants (n = 53)

Mean (SD) **age** (years)	67 (14)
Sex (male)	29 (55%)
Handedness	
• Right-handed	44 (83%)
• Left-handed	4 (8%)
• Ambidextrous	5 (9%)
Educational level	
• Low	37 (70%)
Stroke type	
• Ischemic stroke	47 (89%)
Location of lesion	
• Left hemisphere	49 (93%)
• Right hemisphere	4 (7%)
Mean (SD) **ANELT-A**[a] score (scale 1-5)	2.2 (1.1)
Mean (SD) **PCQ**[b] score 3 months after stroke (scale 1-5)	3.6 (1.1)
(Goodglass) **Aphasia Severity Rating**	
• 0	2 (4%)
• 1	4 (7%)
• 2	9 (17%)
• 3	16 (30%)
• 4	16 (30%)
• 5	3 (6%)
• unknown	3 (6%)
Mean (SD) European quality of life-5 dimensions (**EQ-5D**) score	0.68 (0.25)
Mean (SD) **Barthel Index** score	14.3 (6.5)
Type of aphasia (AAT[c] classification) 8 weeks after stroke	
• Global	5 (9%)
• Wernicke	12 (23%)
• Broca	4 (8%)
• Anomic	19 (36%)
• Residual aphasia[d]	6 (11%)
• Not classifiable	4 (7%)
• Unknown	3 (6%)
Type of relation person with aphasia-proxy	
• Partner	38 (72%)
• Non-partner (child, parent or friend)	15 (28%)

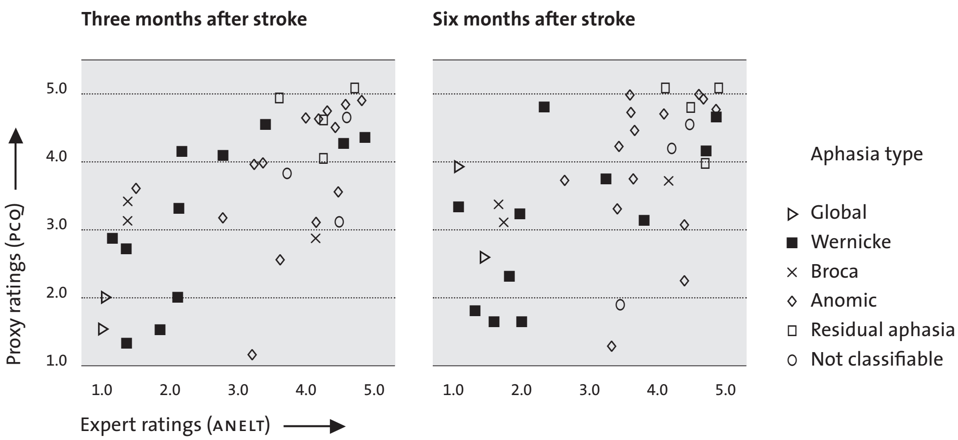
a Amsterdam-Nijmegen Everyday Language Test, scale A (understandability)
b Partner Communication Questionnaire; not suitable in acute stroke, thus only used 3 and 6 months after stroke
c Aachen Aphasia Test31; not suitable in acute stroke, thus administered 8 weeks after stroke
d Recovered aphasia with mild deficits

Association ***ANELT – PCQ***

The first question concerned the association between the rating of SLTs on the ANELT and the rating of the proxies on the PCQ. Figure 1 shows scatter plots of expert versus proxy ratings at 3 and 6 months. It appears that the higher the scores (both on ANELT and PCQ), the better the agreement. Figure 1 also shows that proxies tended to rate the person with aphasia's verbal communicative ability somewhat higher than experts. We tested this by means of paired samples t-tests: mean difference = .38 (95% CI = .05 to .71) and p = .023 at 3 months; mean difference = .35 (95% CI = .005 to .71) and p = .053 at 6 months. The correlation was moderate: at three months r = .662 (p = <.0001) and at six months r = .565 (p = <.0001). The mean improvement from 3 to 6 months on the ANELT was 0.155 points (3.9% of the maximum improvement of 4 points), the mean improvement on the PCQ was 0.124 points (3.1% of the maximum improvement of 4 points). Neither measure showed a statistically significant improvement (ANELT: p = .074; PCQ: p = .188).

Points in the scatter plots are labelled for aphasia type (classification according to the Aachen Aphasia Test). It appears that for all aphasia types, proxies more often give higher ratings than experts than vice versa. Also, the forementioned effect of severity is reflected in the aphasia types: in the more severe types (Global, Wernicke and Broca), ratings diverge more strongly than in less severe types.

Fig. 1. Scatter plots of the ratings by the proxy (PCQ) and the expert (ANELT) of the person with aphasia's verbal communicative ability 3 and 6 months after stroke (n = 39)



PCQ: Partner Communication Questionnaire; ANELT: Amsterdam-Nijmegen Everyday Language Test, scale A

Predictors of the discrepancy

The second aim was to examine which factors influenced the level and nature of disagreement between both ratings at six months.

Discrepancy between the expert and proxy rating

We first considered the absolute difference between ANELT and PCQ scores (range 0 to 4). Univariable regression analysis showed that a higher (more favourable) Aphasia Severity Rating was significantly associated with a smaller discrepancy between proxy and expert judgement of the everyday verbal communicative ability (B = -0.271; p = .001) (Table 2A). Also, there was a trend indicating that a higher quality of life (EQ-5D) of the people with aphasia was associated with a smaller discrepancy between proxy and expert judgement (B = -0.539; p = .12). In our dataset, we found no indications of an association between the remaining variables (Barthel Index, person with aphasia's age and type of relation with the proxy) and the discrepancy between proxy and expert judgement. Therefore, only Aphasia Severity Rating and EQ-5D were entered as predictors in a multivariable regression analysis.

Table 2. Prediction of the discrepancy between proxy and expert rating of a person with aphasia's verbal communicative ability (absolute difference between ANELT and PCQ) at six months, range 0 to 4 (n = 53)

A *Univariable*

Predictor	B (SE)	P value	R^2
(Goodglass) Aphasia Severity Rating (0 – 5)	-.248 (.073)	.001	.192
EQ-5D (-0.330 – 1)	-.539 (.341)	.12	.049
Barthel Index (0 – 20)	-.006 (.026)	.826	.001
Age of the person with aphasia (years)	-.004 (.007)	.568	.006
Type of relation person with aphasia-proxy: non-partner (reference is partner)	-.110 (.206)	.595	.006

B Multivariable

Predictor	B (SE)	P value	R^2
(Goodglass) Aphasia Severity Rating (0 – 5)	-.239 (.075)	.003	.231
EQ-5D (-0.330 – 1)	-.463 (.326)	.162	

EQ-5D: European quality of life-5 dimensions; B: unstandardized regression coefficient; SE: standard error; R^2: measure of explained variance.
Constant = 1.899
Example: the predicted discrepancy between proxy and expert in a person with an Aphasia Severity Rating of 3 and an EQ-5D of 0.6 is: 1.899 + 3*-0.239 + 0.6*-0.463 = 0.9042. One point higher on the Aphasia Severity Rating in this person results in a predicted discrepancy of 0.6652.

Multivariable regression analysis showed that Aphasia Severity Rating and EQ-5D together explained 22% of the variance in the discrepancy between proxy and expert rating (Table 2B). This discrepancy was predicted best by Aphasia Severity Rating: a higher communication level of the person with aphasia was significantly associated with a smaller discrepancy (B = -0.264; p = .001). EQ-5D did not significantly predict everyday verbal communicative ability of the people with aphasia anymore (B = -0.402; p = .225).

Amount of under- or overestimation by the proxy compared with the expert
We also examined the influence on PCQ minus ANELT (range -4 to 4). A positive coefficient B in the present analysis indicates a larger value for this variable in case of an increase in a predictor. Since the above regression analysis showed that an increase in all the predictors resulted in a decrease of the discrepancy, the larger value implies a shift from -4 to 0, so less underestimation of everyday verbal communicative ability by the proxy compared to the expert. In contrast, a negative coefficient B in the present analysis indicates a smaller value of this variable in case of an increase in a predictor, which, in combination with the above finding, implies a shift from +4 to 0, so less overestimation by the proxy.

Univariable regression analysis showed that a higher Aphasia Severity Rating of the person with aphasia was significantly associated with less overestimation by the proxy compared with the expert in judging everyday verbal communicative ability (B = -0.427; p = .001) (Table 3A). There was a trend indicating that a higher level of independence in activities of daily living (Barthel Index) was associated with less underestimation by the proxy compared with the expert (B = 0.053; p = .199). Also, there was a trend indicating that non-partners (a child, parent or friend of the person with aphasia) overestimated less than partners (B = -0.473; p = .142). In our dataset, we found no predictive value for the variables EQ-5D and person with aphasia's age on the amount of under- or overestimation by the proxy compared with the expert. Therefore, the remaining variables (Aphasia Severity Rating, Barthel Index and type of relation with the proxy) were entered as predictors in a multivariable regression analysis.

Table 3. Prediction of the amount of under- or overestimation by the proxy compared with the expert at six months, range -4 to 4 (n = 53)

A Univariable

Predictor	B (SE)	P value	R^2
(Goodglass) Aphasia Severity Rating (0 – 5)	-.381 (.115)	.002	.185
EQ-5D (-0.330 – 1)	.299 (.547)	.587	.006
Barthel Index (0 – 20)	.053 (.041)	.199	.033
Age of the person with aphasia (years)	.001 (.011)	.953	.000
Type of relation person with aphasia-proxy:			
non-partner (reference is partner)	-.473 (.317)	.142	.042

B Multivariable

Predictor	B (SE)	P value	R^2
(Goodglass) Aphasia Severity Rating (0 – 5)	-.458 (.117)	.000	
Barthel Index (0 – 20)	.07 (.037)	.065	
Type of relation person with aphasia-proxy:			.305
non-partner (reference is partner)	-.361 (.307)	.246	

EQ-5D: European quality of life-5 dimensions; B: unstandardized regression coefficient; SE: standard error; R2: measure of explained variance.
Constant = 0.404
Example: the predicted amount of under- or overestimation by the proxy compared with the expert in a person with an Aphasia Severity Rating of 3, a Barthel Index of 18 and a PCQ filled in by the partner is: 0.404 + 3*-0.458 + 18*0.07 + 0*-0.361 = 0.329. This means a small amount of overestimation by the proxy compared with the expert. One point higher on the Aphasia Severity Rating in this person results in an amount of -0.168. This means a very small amount of underestimation by the proxy compared with the expert.

Multivariable regression analysis showed that the model in total explained 28% of the variance in the amount of under- or overestimation by the proxy compared with the expert (Table 3B). This discrepancy was predicted best by Aphasia Severity Rating: a higher communication level of the person with aphasia was significantly associated with less overestimation by the proxy compared with the expert (B = -0.49; p = .000). Like in the univariable regression analysis there was a trend indicating that a higher level of independence in activities of daily living (Barthel Index) was associated with less underestimation by the proxy compared with the expert (B = 0.053; p = .189). Type of relation with the proxy did not significantly predict the amount of under- or overestimation anymore (B = -0.403; p = .218).

Discussion

In this study of people with aphasia after stroke we found moderate agreement between the rating by the SLT and by the proxy of the everyday verbal communicative ability of the person with aphasia, both at 3 and 6 months. A higher Aphasia Severity Rating of the person with aphasia was associated with less overestimation by the proxy compared with the expert at 6 months.

This study was conducted within the setting of a randomized clinical trial. An advantage of this setting is that all study assessments were standardized and performed by well trained and motivated SLTs. Furthermore, participants were included by over 20 centers, both rural and metropolitan, which increases the generalizability of the results. Drawbacks of the study are that we could not collect all the predefined assessments for each person with aphasia at 3 and 6 months after stroke and that the sample size is relatively small.

Several previous studies have compared the judgements of people with aphasia and their partner about the communication of the person with aphasia on the level of participation restrictions, but not primarily on the level of activity limitations. We compared the judgement of the expert (SLT) and the partner, the two persons having the best opportunities to monitor the communication of the person with aphasia in the rehabilitation stage. We used the Partner Communication Questionnaire, which very well matches the ANELT-A, the expert assessment. Both measure the level of activity limitations of the person with aphasia.

The only comparable study using the same test and questionnaire is that of Blomert.[26] Although this study used a 20-item precursor of the current PCQ, the correlation between the ANELT-A and the PCQ in the chronic stage (r = .69) very well accords with our correlation at 3 and 6 months (.66 and .57). Blomert found that 71% of the ratings (n = 28) concurred and that in case of a discrepancy, 62% of the proxies underestimated and 38% overestimated the verbal communication of people with aphasia compared with the expert. In contrast, we found that only 26% of the ratings concurred and that of the remaining 74%, only 41% of the proxies underestimated and 59% overestimated. A difference between our study and that of Blomert is the time elapsed since onset: the proxies in our sample had had less time to obtain sufficient rating expertise than those in Blomert's study. Still, the correlation between the ANELT and the PCQ in both studies are similar, which does not support the assumption that a minimum of 5 months post onset might not be enough time for proxies to adapt.[4]

We found no conclusive evidence for the influence of time post onset on the association between expert and proxy rating. The correlations at 3 and 6 months were comparable (though little less strong at 6 months), whereas the discrepancy between both ratings slightly decreased: the difference was statistically significant at 3 months and (just) not at 6 months. Possibly, in a more chronic stage of aphasia, e.g. one year or more after stroke onset, better acceptance by proxies might lead to higher agreement between proxies' and experts' view on the communicative abilities of the people with aphasia.

Our finding that the proxies rated the verbal communicative ability of people with aphasia slightly higher than the SLTs is in line with previous studies[12, 14] and confirms the notion that people with aphasia communicate better in natural contexts than would be anticipated by results of standardized tests.[1–2] It is unknown whose judgement most accurately appraises the person with aphasia's actual communication, the expert's or the proxy's. For readability we use the phrases "under- and overestimation by proxies compared with experts" but imply by no means that expert ratings are the true or standard scores. There are several explanations for the finding that expert ratings were on average slightly below proxy ratings. First, SLTs might be more sensitive to the linguistic deviations than proxies because proxies probably do not recognize and label formal deviations in the verbal communication such as phonemic paraphasias. Also, proxies probably cannot disentangle verbal and nonverbal communication as efficiently as experts and therefore rate the verbal communicative ability higher than experts. In addition, the SLT does not witness the person with aphasia during communication in everyday situations, like the proxy does. Also, the ANELT contains ten selected scenarios that are played – it is an artificial measure –, in contrast to the many scenarios in the PCQ which are easy to imagine for the proxy. Finally, the ANELT requires some level of abstraction by the people with aphasia; they have to imagine being in the given situation.

A possible explanation for the finding that a lower Aphasia Severity Rating of the person with aphasia was associated with a larger discrepancy between proxy and expert judgement is that in more severely impaired aphasics, nonverbal communication may play a larger role. Another explanation might be that people with a less severe aphasia are involved in more communicative situations than people with worse communicative abilities, which could make a realistic rating easier for their proxy.

Our finding that a better ADL score of the person with aphasia leads to better agreement between ratings, namely less underestimation by the proxy compared with the expert, seems plausible as the person with aphasia is likely to have more communicative abilities if he is capable to undertake other activities in daily living independently. A similar result was found in a study on overprotection by spouses and conversational participation of their aphasic spouse: the less severe the motor impairments, the less overprotection was reported by spouses.[32] Apparently, more physical independence of the person with aphasia increases a proxy's confidence in the communicative ability of the partner.

A possible explanation for the finding that a higher quality of life (QOL) of the person with aphasia was associated with better agreement between the judgements of proxy and expert is that people with a higher QOL probably participate in more social situations than people with severe impairments and therefore the rating of the proxy could be more reliable. It seems obvious that the worse the person with aphasia's QOL, the more the proxy underestimates the verbal communicative ability compared with the SLT, who is much less aware of the person with aphasia's QOL than the partner. However, the results of the EQ-5D should be interpreted with caution because the scores in our sample appeared unlikely high (mean score at 6 months: 0.72) compared to other studies that assessed post stroke quality of life (e.g. mean score at 6 months: 0.33[33] and 0.57).[34] The reliability of the EQ-5D in an aphasic population remains questionable.

The finding that non-partners tended to overestimate less than partners compared with the expert seems obvious: proxies other than the (marital) partner probably have a more objective, realistic view on the functioning of people with aphasia whereas hope is likely to be more interwoven with the rating of the partner – a natural coping mechanism.

In randomized clinical trials in aphasia, a functional outcome measure like the ANELT is often used. However, the results of the present study suggest that one should verify whether the rating corresponds to the judgement of the proxy. This is vital for the validity of the findings in an intervention study: if the test indicates a significant improvement after intervention, the proxy should recognize this improvement in daily life. Proxy views of the abilities of people with aphasia are important for planning rehabilitation goals and therapy and are crucial for the motivation and active involvement of people with aphasia and their relatives.[11] It is promising that we found moderate agreement between expert and proxy judgement. The ANELT appears to be a fair test with significant ecological validity, particularly in people with milder aphasia. The fact that all participants received therapy in our study might have influenced the level of agreement: expert and proxy ratings were shown to align better in couples of whom the person with aphasia was receiving aphasia treatment.[2, 4]

In conclusion, our findings suggest that the judgments of verbal communicative ability by experts and proxies align reasonably well, but that in cases of more severe aphasia, proxies rate higher than experts. The discrepancy might be due to the abstractness of the test used and experts' lack of knowledge of premorbid functioning, and for the proxies to factors like acceptance and the difficulty to differentiate between verbal and non-verbal communicative acts. This implies that SLTs should provide specific guidance and information to partners of people with severe aphasia. Future research should focus on gaining more insight into relevant mechanisms behind the diverging judgments.

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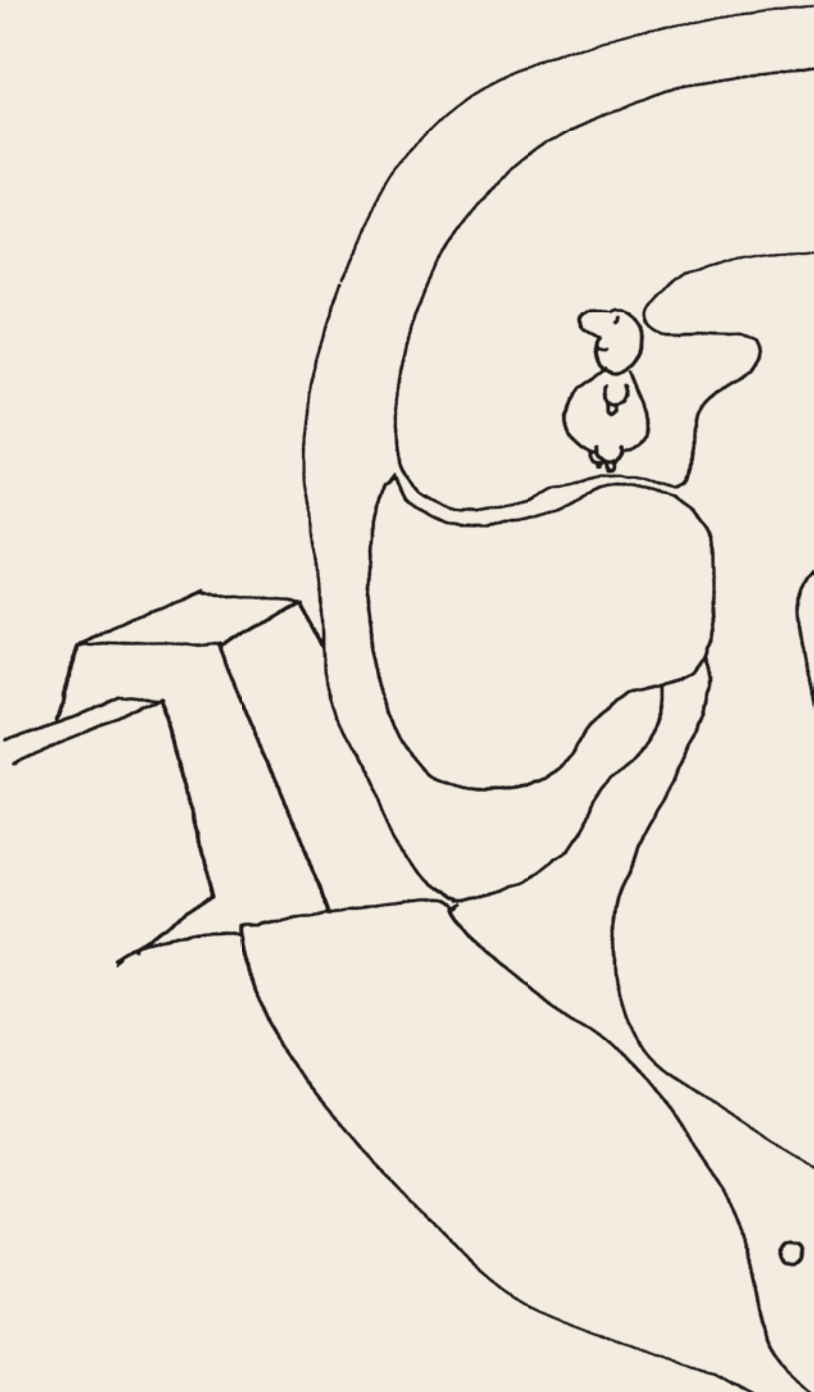
APPENDIX

Examples from the Amsterdam-Nijmegen Everyday Language Test (ANELT)

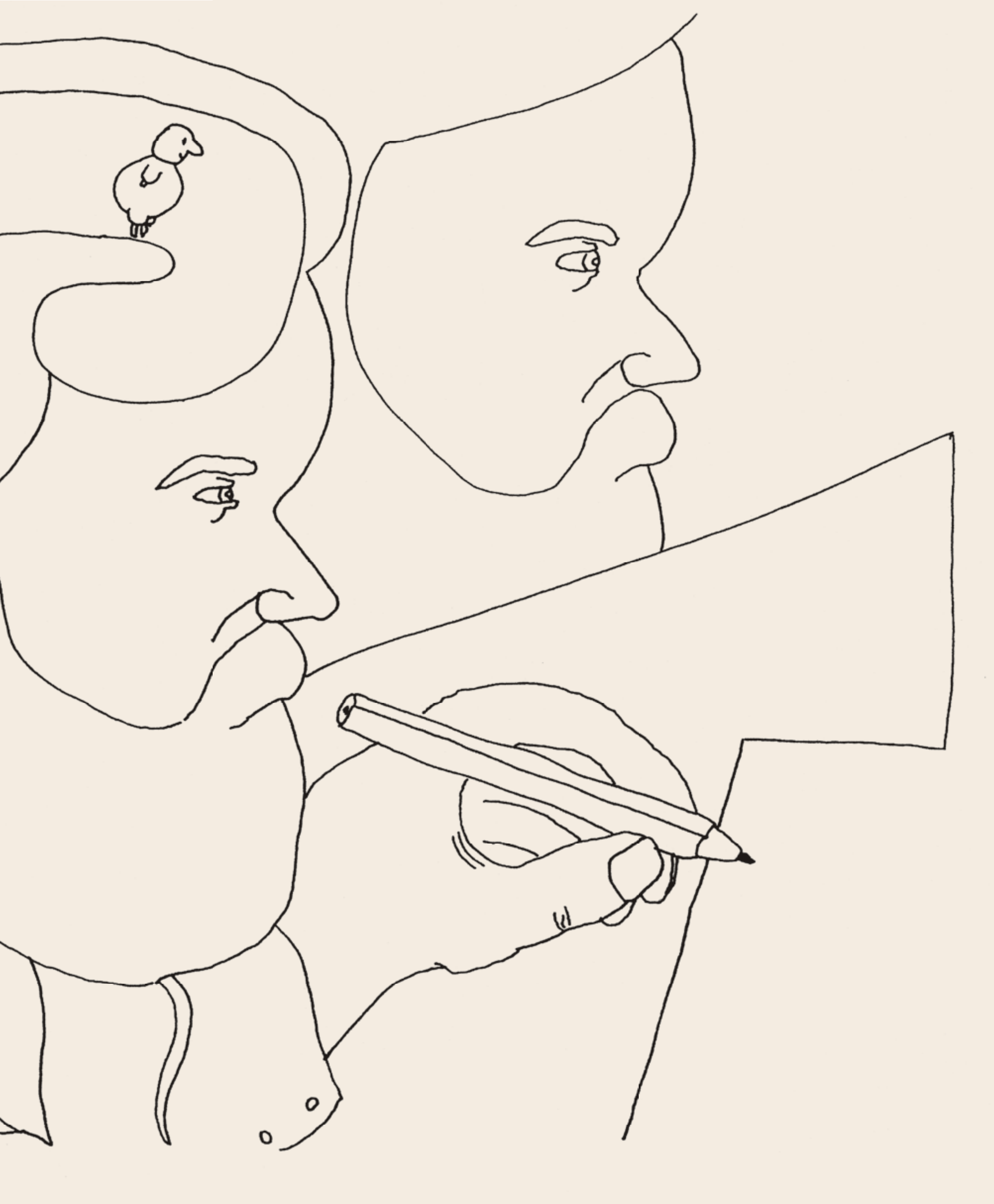
- You have just moved in next door to me. You would like to meet me. You ring my doorbell and say ...
- You are in a store and you want to buy a television. I am the salesperson here. "Can I help you?"

Examples from the Partner Communication Questionnaire (PCQ)

- Your partner worries about the future. Can your partner *tell* you what bothers him/her?
- Can your partner *ask* for directions when he/she is lost?
- Your partner runs into a friendly couple. They ask if they can visit you that evening. That is possible! Can your partner *answer* that it is okay?



General Discussion



In this final chapter of my thesis about aphasia therapy and diagnosis, I summarize the main findings, address several methodological issues and discuss the clinical implications of my findings. Next, I discuss which aspects of aphasia therapy beside type of treatment are essential, and which factors need to be further explored. Finally, I provide suggestions for future research.

Summary

The core of this thesis is RATS-2; the second randomized controlled trial (RCT) in our series of RCTs under the name of Rotterdam Aphasia Therapy Studies. In these studies we aim to evaluate cognitive-linguistic therapy (CLT), a disorder-oriented approach to the improvement of verbal communication, directed to the disturbed linguistic levels. The specific linguistic exercises could promote recovery of specific neural circuits by activating the ones responsible for semantic and phonological processing, especially during natural recovery in the early stages of a stroke.[1–2] A central deficit in all types of aphasia is word finding difficulty. Selecting and pronouncing the right content words in speech requires intact semantic and phonological processing. In RATS-1 we compared the effect of semantic (BOX[3]) with phonological therapy (FIKS[4]) and found selective improvement on a semantic test after semantic therapy and selective improvement on phonological tests after phonological therapy. Both treatments yielded an equal improvement on a functional test for verbal communication.[5] In RATS-2 we compared CLT consisting of BOX and FIKS with communicative therapy, a different, more functional approach to the improvement of verbal communication. Results indicated that CLT and communicative therapy equally improved verbal communication when provided in the first six months after stroke, with the most improvement in the first three months. However, results on nearly all semantic and phonological tests were in favor of CLT and for the category and letter fluency tasks the group differences were statistically significant in favor of CLT.

Semantic disorders are also common in other diseases of the brain, for example Alzheimer's disease. We explored the semantic system in people with Alzheimer dementia (AD) and found that picture naming and the underlying verbal and visual semantic processing do not degrade to the same extent. For the group, naming was within the normal range and better than verbal and visual semantic processing. Three patients showed relatively intact naming with disturbed semantic processing (i.e. automatic naming), three others showed intact verbal semantic processing with impaired naming and visual semantics. Naming appears insufficient as a single task to measure language disorders in AD.

The phenomenon that often more than one measure is needed is, in a way, the object of our study on the level of agreement between expert and proxy rating of verbal communicative ability of aphasic stroke patients. The judgment of the patient's partner provides indispensable insights and is important in the care for people with aphasia. We showed that, although proxies (who filled out the Partner Communication Questionnaire[6]) are slightly more positive than experts (who used the Amsterdam-Nijmegen Everyday Language Test[7]), there is moderate agreement between both ratings, especially in milder cases.

Severe cases were the focus of our study in which the spontaneous and therapy-induced recovery of aphasia in the most severely affected patients was compared with moderate and mild cases. It appeared that these patients' verbal communication improves significantly during the first six months after stroke and that they seem to benefit more from CLT than from communicative therapy, suggesting that aphasia therapy should not be postponed in severely aphasic patients and that therapy with an emphasis on nonverbal and augmentative techniques might not necessarily be the most suited therapy.

Methodological considerations

In designing and conducting RCTs one encounters many challenges. The key point is that one has to compromise and make choices.

A difficult hurdle to take was the control group. It is generally considered unethical, by those who commonly provide the treatment, to withhold aphasia therapy in patients with acute aphasia after a stroke. Consequently, it is problematic to disentangle the potential effect of treatment from spontaneous recovery, which especially takes place in the first months after stroke onset. It is feasible and ethical, however, to compare different strategies of cognitive rehabilitation or schedules of treatment, which could provide crucial efficacy data[8], like in RATS-1, in which semantic and phonological therapy were compared. In RATS-2, we maximally contrasted the interventions by choosing communicative therapy for the control group. An advantage of this comparison approach is that the groups are matched regarding therapist contact, or amount of stimulation.

We preferred a functional primary outcome measure since the ultimate goal of every treatment method is to improve functioning in daily living. Also, we think results are stronger if they show improvement on the end stage of the target ability (everyday communication) as opposed to untrained, artificial material or even trained items. In the Netherlands, the only functional test for verbal communicative ability is the ANELT.[7] It was not feasible to administer every test ourselves so we also depended on the administration by others. The ANELT is not always easy to administer and the scoring requires some training as well. We made large efforts to instruct and train all SLTs in correctly administering the ANELT. Furthermore, efforts were made to maximize the number of blinded assessments, meaning that someone other than the treating SLT administered the test. However, 100% blinding is not always possible because in the spontaneous speech interview and other interactions with the patients and proxies, sometimes cues are given about the content of the treatment the patient receives. But most importantly, the judgment of all ANELT samples was carried out by two expert, independent SLTs, blinded for time of assessment post stroke and content of therapy. A last issue concerning the ANELT is the fact that it measures only verbal communication; nonverbal communicative behavior is not considered. This could disadvantage more severely aphasic persons who may rely more on nonverbal communication. However, especially this patient group seemed to have profited significantly from verbal treatment as measured with this verbal test (Chapter 4).

Regardless of the rehabilitation research question, development of protocol interventions is necessarily influenced by existing standards of care.[9] Both CLT and communicative therapy are used in aphasia rehabilitation, with generally a preference for CLT in the more acute stages. In order to test our hypothesis that particularly CLT is effective in the first three months after stroke onset – the acute period in which most neural recovery takes place – we had to compare its efficacy with that of a control therapy (communicative therapy) in the first three months and with the efficacy in the post-acute stage – from three to six months. As for treatment intensity, we attempted to take into account that an intervention needs to be reasonable to implement in daily clinical practice and on the other hand that the amount and intensity needs to be sufficient for the intervention to be effective. This led to a minimum of two hours per week and a preference for five hours per week.

An advantage of RATS-2 is that the target intervention was well defined. This is in accordance with the position of various authors that RCTs should focus on specific, well defined interventions.[10–11] However, a point of concern in large trials like RATS-2 might be to what extent the treatment is custom-made to the individual patient. The treatment protocol prescribed the use of BOX and FIKS only in the CLT group. There are probably cases in RATS-2 in which the SLT would have chosen different methods, materials or approaches would the patient not have participated in the trial. Obviously, the choice of the subparts from BOX and FIKS, the specific exercises or combination thereof and manner of application was always determined by the patient's aphasic profile and personal preferences. All patients had a semantic and/or phonological disorder and could profit from exercises that target word finding problems, which are central for all aphasic patients.

One aspect of doing research is that one cannot answer all questions in a single study, regardless of its size and quality, and that knowledge is a matter of progression through small steps forward. In that way, the consequences of having to choose one primary outcome measure became clear when the results on some secondary outcome measures (semantic and phonological fluency) appeared to be interesting, as were the results in a post-hoc subgroup (severe aphasia). Although post-hoc and subgroup results can seem excitingly promising, these analyses do not provide as high a level of evidence as the test of the primary hypothesis. They should be considered hypothesis generating and as such may provide directions for further research.

Clinical implications

Internationally, there has been much debate about the choice between, and timing of, disorder-oriented and communicative (or functional) therapy. In the Netherlands, the general view is that both therapy approaches, complemented by the social approach, make up the extensive process of aphasia rehabilitation and that, depending on the stage, one approach can be more important than the others. Also, a widespread assumption is that in general, the best way is to start with CLT in order to regain as much linguistic skills as possible, and then to proceed to a more communicative approach, focusing on an optimal use of residual communicative skills and on compensation for lost skills.[1–2, 12] In RATS-2, we found an equal improvement on the primary outcome measure and were not able to confirm this assumption.

Strikingly, when the results of RATS-2 were obtained, there was a publication on an identical RCT on rehabilitation of traumatic brain injury with similar results.[13] This study also compared a disorder-oriented with a functional approach. The 'cognitive-didactic approach' aimed to develop cognitive self-awareness, target specific cognitive processes and enhance underlying cognitive abilities, assuming generalization to functional deficits. The 'functional experiential approach' comprised motor and other forms of implicit learning, group settings and learning-by-doing functional daily activities, emphasizing environmental support to help compensate. Both interventions seemed to have had effect, although natural recovery influences were entangled because the authors considered untreated controls unethical. On the broad functional 1-year primary outcomes, no difference was found between both treatments. However, after cognitive-didactic therapy, patients scored significantly better on a measure of cognitive function. Furthermore, treatment-specific effects were found in subgroup analyses. It was concluded that there are two viable interventions for use in this patient population and that targeting specific populations and goals may maximize treatment effectiveness.

Our conclusion that therapy for severely aphasic stroke patients does not need to be postponed implies that neurologists should be as eager as with milder aphasic patients in consulting an SLT. And contrary to what many SLTs think, an effective approach for these patients might well be CLT, not necessarily communicative therapy with a focus on nonverbal communication and augmentative communication aids.

I would suggest that researchers continue examining, in well-designed multiple-case studies, which factors influence the effectiveness of aphasia therapy for specific patient groups, and besides, to apply therapy methods that match the specific patient – e.g. taking into account the severity of the aphasia – and the goals that are set for the treatment. Results can direct what should be evaluated in RCTs.

Brain damage can affect one or more cognitive functions, or domains: attention, concentration, memory, language, visual perception and constructional abilities, apraxia, and executive functioning. It is not always easy to demarcate the domains and some clinicians even propose that attention and executive function for example might represent a single domain.[14] Another issue is the relation between memory and language: what are the connections between the two and is there a serial or parallel way of accessing, can language be viewed as being a linguistic component of memory, or is language the operating system for memory like Windows is for the computer.

Likewise, an important question remains – assuming that the domains are demarcated – if cognitive rehabilitation has its effects specifically on the cognitive function targeted by the treatment, or if the treatment generalizes to other cognitive domains. From visuospatial training for example, moderately sized and significant treatment effects were found on attentional and language measures. Unfortunately, not enough language studies used outcome measures from other cognitive domains to determine the level of treatment specificity for aphasia therapy.[15]

Similarly, the influence of disorders in other cognitive functions on language processing and treatment effects in aphasia are relatively unknown. A study that shed light on this issue explored the predictive potential for treatment outcome of the Multi-Axial Aphasia System (MAAS), containing the following information: (1) aphasia and communication, (2) somatic condition, (3) neurological disorders, (4) neuropsychological disorders and (5) psychosocial and socio-economic situation and stressors. Neuropsychological information was found to be most predictive of the outcome of CLT.[16]

A large multicenter study, the Sequential Prognostic Evaluation of Aphasia after stroKe (SPEAK), followed 147 patients with respect to linguistic recovery and recovery of the other cognitive domains during the first year after stroke onset. The results, which will be published soon, will provide more insight into the influence of co-existing cognitive disorders on language.

In summary, it is clear that the cognitive domains are closely interrelated. As for the planning and efficacy of aphasia therapy, it is recommended to pay careful attention to neuropsychological factors.

A diagnostic test is restricted in its scope; it is only capable of measuring what it is designed for. A test used as an outcome measure in a study also has its limitations. These statements were illustrated in the following findings in this thesis.

Naming is a widely used diagnostic task. But some people with Alzheimer dementia appeared to be capable of naming well, whereas their underlying semantic processing was disturbed, and some others had disturbed naming but intact verbal semantics. Therefore, a naming task is insufficient to base conclusions about the language abilities of a person with AD on. One should include tasks that measure verbal and nonverbal semantic processing.

In people with aphasia after a stroke, CLT and communicative therapy proved to be equally effective as measured with the ANELT, whereas a significant difference was found in favor of CLT on the semantic and letter fluency tasks. Both fluency tasks are explicitly related to the aim of CLT, that is to improve semantic and phonological processing, which has a positive influence on word finding. The fluency tasks are productive tasks that require self generation of words, a stage in the pursuit of adequate verbal communication in general, which can be measured by the ANELT. Since almost all outcomes showed at least some amount of profit of CLT over communicative therapy, CLT seems to have specific potential.

It can be concluded that we should be very critical as to what measure to use for what purpose and be aware of the conclusions we draw based on a certain test.

Although my thesis brought about some useful clinical suggestions, there is still much that needs to be explored. Before mentioning targets for future research, I will give an overview of key aspects of aphasia therapy that were not yet or not fully addressed in this thesis.

Key aspects of aphasia therapy

Timing

The latest Cochrane Database of Systematic Reviews[11] does not mention timing of aphasia therapy. However, it has been the subject of many studies. A recent meta-analysis advised to start therapy as early as possible.[15] An evidence-based review concluded that aphasia therapy is efficacious when provided intensely for the first three months.[17] A classic meta-analysis concluded that when treatment is begun in the acute stage, the average effect for treated recovery is nearly twice that for untreated recovery and when treatment is delayed until the chronic stage (over one year after stroke onset), the average effect size for treated patients is smaller, but still exceeds that of untreated patients.[18] The AHA/ASA-Endorsed Practice Guidelines[19] stressed that early assessment and intervention are critical to optimize rehabilitation and that aphasia treatment can result in maximizing gains during the period of spontaneous recovery. Some authors stated that the brain appears to be primed to recover early after stroke and that different therapeutic approaches may be required at different stages to gain most from rehabilitation.[20] A theory that is still to be proven is that treatment aimed at restoration of function (cognitive restoration without cognitive reorganization) is appropriate in early acute stages when natural spontaneous recovery occurs.[1–2]

However, studies in RATS showed that intensive intervention early after injury may adversely affect recovery. It is suggested that because early overuse of a weak limb can result in greater deficits, and complete disuse can slow recovery, acute rehabilitation should be less intensive and then, over time, become more "aggressive". It remains to be established what period should be considered "acute" in humans. In a meta-analysis[18], the acute phase covered a rather broad 3-months period. Studies examining recovery in aphasia show that most spontaneous recovery actually occurs within the first two months. For example, a pilot study[21] found that the scores on the Token Test[22], the ScreeLing[23] – a screening test suitable for the acute stage measuring disorders on the semantic, phonological and syntactic level – and the ScreeLing scores on the semantic and syntactic level each seemed to reach a plateau at seven weeks after stroke onset. Research efforts are needed to identify at what exact stage rehabilitation (A) is most effective, (B) is not effective, and (C) might actually be harmful.[24]

To summarize, there are strong indications but far from conclusive proof that aphasia therapy should be started as early as possible.

Intensity and duration

Already in 1974, it was stated that the studies that found no effect investigated treatment given in 'homeopathic' (i.e. low intense) doses.[25] It may be that permanent effects (as opposed to short-term effects) of treatment are only found after a critical amount of treatment has been given.[26]

Aphasia therapy administered high-frequently is assumed to strengthen neuronal circuits more efficiently than the same amount of therapy administered low-frequently. The more frequently that a neuronal circuit is activated in a synchronous manner, the more its connections will be strengthened ("cells that fire together, wire together"). It is the same as with learning any new skill: the more often one trains, the faster results are obtained. High-frequency therapy might also minimize intervening – and possibly interfering – neuronal activation that might occur when language is used in an inappropriate context, which could lead to weakening of recently strengthened neuronal links.[27]

The latest Cochrane Database of Systematic Reviews observed a consistency in the direction of results which favored intensive over conventional aphasia therapy, though significantly more people withdrew from intensive than from conventional therapy.[11] An often cited review article concluded that studies that demonstrated a positive effect of aphasia therapy provided 8 hours per week for 11 weeks, whereas studies that found no significant impact of aphasia therapy on recovery provided only 1.9 hours per week for 23 weeks.[28] A classic meta-analysis proved that the treatment effect of studies providing two to three and five hours or more is twice as great as that of studies providing up to 1.5 hours per week. In the acute and post-acute stages, treatment is best provided on a 2-plus hour-per-week schedule. The high-intensity outcome is more than twice as great as the no-treatment outcome. In contrast, the acute-stage outcome for low-intensity treatment is only slightly greater than the no-treatment value.[18] A recent evidence-based review concluded that aphasia therapy is efficacious when provided intensely; less intensive therapy given over a longer period of time does not provide a statistically significant benefit, although clinical benefits can be achieved.[29] In a review on evidence-based cognitive rehabilitation, high intensity is considered essential for the efficacy of therapy; they formulated as a Practice Guideline that therapy intensity should continue to be considered as a factor in the rehabilitation of language skills after left hemisphere stroke.[30]

Several authors concluded that the conventional outpatient treatment schedule, two to three times per week, is challenged by the data on treatment intensity. Additional studies aimed at examining the effects of treatment intensity are certainly warranted, along with an evaluation of the effects of language activities designed to complement treatment sessions, like homework.[24]

To summarize, in most reviews and guidelines it is stated that aphasia therapy should be delivered intensively – exceeding the 30 minutes twice a week often provided by SLTs.

Other rehabilitation methods

Some current trends in rehabilitation research are to evaluate the effects of drug therapy as an adjunct to aphasia therapy, with stimulants, cholinesterase inhibitors, dopamine agonists, and other medications that influence availability of particular neurotransmitters. Randomized, placebo-controlled trials are scarce in this area, but several are under way. There is no evidence that medications are useful in the absence of language therapy.[31]

Noninvasive brain stimulation is also being investigated as a method of enhancing aphasia recovery. Two forms are reported: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Some small case series show some benefit of noninvasive transcranial stimulation. Controlled studies that assess the utility of these techniques in large patient populations are needed.[27]

In conclusion

A high intensity and early start of aphasia therapy are generally advocated, but their value has not been decisively demonstrated. Furthermore, it is unknown whether a specific type of treatment best fits a certain stage since there is a lack of RCTs on the efficacy of early specific therapy methods. Possibly, the interaction with timing is stronger for CLT than for communicative therapy. Similarly, until now researchers have shown little interest in the interaction between type of treatment and intensity. High treatment intensity might not be as important for communicative therapy as for CLT. Also, probably not all patients need an equal amount and frequency of therapy of a specific type.

Because of the possible overlap between the two treatments and the low treatment intensity in RATS-2, the question whether CLT is particularly efficacious in the acute stage remains open. We found indications of an advantage of CLT over communicative therapy (significantly higher scores on the fluency tasks and somewhat higher on all other tasks and outcomes). Therefore, we adhere to the aim of the Rotterdam Aphasia Therapy Studies: to evaluate CLT, that is, semantic and phonological therapy.

Future directions

On the basis of this thesis, I can suggest several focuses for future research.

We should continue conducting RCTs to examine in detail which factors influence the effectiveness of aphasia therapy. Important factors to address are patient characteristics such as severity of the aphasia and aphasia profile, and treatment characteristics such as the optimum approach, the length of time since the stroke (timing), the intensity and duration of therapy.

Furthermore, there is a continued need to investigate the aspects of intensive language treatment that contribute to therapy effectiveness, such as timing, dosage and type of treatment. We need to discover the most effective combinations of type, timing and intensity of treatment, in order to provide tailored therapy rather than standard packages.

Standardized outcome measures should be used to evaluate the effectiveness of aphasia therapy on functional communication, expressive and receptive language skills and severity of aphasia, as well as on quality of life of the person with aphasia. Moreover, researchers should fully publish the findings from trials. The recommendations of the CONSORT statement[32] should be followed and a full description of the relevant statistical summary data (means and standard deviations of final scores) should be provided thus allowing inclusion of the data in systematic reviews.

Our next RCT, RATS-3, is designed to compare the effect of short and intensive CLT provided very early post stroke, with deferred therapy. A control group with deferred aphasia therapy is possible because the target intervention takes place within the first six weeks – the period in which normally aphasia therapy is still being organized. Outcome measures will again be the ANELT and semantic and phonological tests. Excitingly, RATS-3 is combined with a sideline study that evaluates functional magnetic resonance imaging (fMRI): Functional Imaging in Aphasia Treatment (FIAT). The aim of FIAT is to evaluate the neurophysiologic correlate of the effect of CLT on verbal communication. Both acute (RATS-3) patients and patients with chronic aphasia will be scanned while they perform semantic and phonological tasks, before and after four weeks of intensive CLT or rest, and at three months. FIAT could enable us to depict the neural restitutional and reorganizational processes as a consequence of CLT.

As for our pilot study on people with AD, a neuropathological substrate of our functional findings should be sought in order to link behavioral and biological manifestations of AD.

Other areas of future research should include transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Controlled studies that assess the utility of these techniques in large patient populations, probably always as an adjunct to aphasia therapy, are needed. The same holds for pharmacological treatment of aphasia.

In conclusion

It proved feasible to conduct a multicenter RCT on aphasia therapy in the Netherlands and Belgium and enroll enough patients in a reasonable amount of time, including severely aphasic stroke patients. This would not have been possible without the excellent cooperation with the SLTs in many hospitals, rehabilitation centers, nursing homes and private practices in the two countries.

The challenge for aphasia researchers and clinicians will be to design, develop, conduct and support larger trials. Besides, collaboration between investigators in vascular and cognitive neurology, neuroradiology, neuroscientists, geriatricians, SLTs, linguists and neuropsychologists will be important to optimize prevention, assessment and treatment of people who suffer from aphasia due to a stroke or dementia.

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Summary

The **General Introduction** outlines that a stroke is the most frequent cause of aphasia, resulting in probably 10,000 new aphasia patients each year. The consequences of aphasia, irrespective of the severity, are far-reaching. Language is needed in almost all human activities; therefore a language disorder impedes social participation. A central deficit in all types of aphasia is word finding difficulty. Selecting and pronouncing the right words in speech requires intact semantic (word meaning) and phonological (word sounds) processing.

Chapter 1 describes that an approach in aphasia rehabilitation that applies disorder-oriented exercises on the semantic and phonological level is cognitive-linguistic therapy (CLT). Suitable treatments are BOX (a lexical semantic program) and FIKS (a phonological program). Another route to improvement of verbal communication is a more functional one: communicative therapy. Applications of both approaches have been evaluated in studies on different levels: from single-case studies to randomized controlled trials (RCTs). In clinical research, RCTs are considered the gold standard and are reviewed in the Cochrane Database of Systematic Reviews. The most recent update for aphasia therapy concluded that there is some indication of the effectiveness of aphasia therapy. On lower levels of evidence, many treatments have proven their value for the rehabilitation of aphasic stroke patients.

In **Chapter 2** the relation between word finding and semantic processing in people with Alzheimer dementia (AD) is explored. The Semantic Association Test was administered in 19 AD patients and 19 matched healthy controls. First they were asked to name 30 pictures. Then they had to make a semantic association between a written word and one of four encircling words (verbal semantic processing). Finally, they had to perform the same task in a version that uses pictures (visual semantic processing). Naming and the underlying verbal and visual semantic processing appeared not to degrade to the same extent in the AD patients. Three patients showed intact verbal semantic processing with impaired naming and visual semantics. Three others showed much better naming than semantic processing, so called automatic naming. These results contradict the notion that a global conceptual degradation forms the background of linguistic problems, and naming appears insufficient as a single task to measure language disorders in AD.

Chapter 3 reports on the Rotterdam Aphasia Therapy Study–2, an RCT in which 85 patients were included. CLT was hypothesized to be more effective than communicative therapy in the first months after stroke onset: the specific exercises are assumed to address specific neural networks, involved in semantics and phonology, which could facilitate neural recovery processes. Results indicated that CLT and communicative therapy, provided in the first six months after stroke, brought about a comparable amount of improvement in verbal communication. However, results on all but one semantic and

phonological tests were in favor of CLT, and for the semantic and letter fluency task the profit of CLT over communicative therapy was statistically significant. The intensity of the treatment might have been too low to find potential treatment effects over spontaneous recovery, and the two treatments possibly had too much overlap. Therefore, the question whether CLT is effective particularly in the acute stage remains open.

In **Chapter 4** the focus was on the spontaneous and therapy-induced recovery of aphasia in the most severely affected patients. In the group of RATS-2 participants, three equally large groups were formed, based on baseline Amsterdam-Nijmegen Everyday Language Test (ANELT) scores. The verbal communication of the severely aphasic patients appeared to improve substantially during the first 6 months after stroke onset and they seemed to have benefited more from CLT than from communicative therapy. These results challenge the theory that people with extensive neural damage are unlikely to benefit from restorative treatment and that communicative therapy is preferable for these patients. We suggested that aphasia therapy should not be postponed in severely aphasic patients.

The final study in this thesis, described in **Chapter 5**, focused on the score the partner or relative of the patient, so called proxy, gave for the verbal communicative ability of the patient on the Partner Communication Questionnaire, compared with the score the speech-language therapist gave the patient on the ANELT. We explored the level and nature (direction) of disagreement between both judgments, and what factors influenced this disagreement: the severity of the aphasia, the quality of life of the patient, his/her age and level of independence, and whether the proxy is a spouse or other significant other. Proxies appeared to be slightly more positive than experts. Still, moderate agreement between both ratings was found . Aphasia severity proved to be the best predictor of the level of agreement: the milder the aphasia, the less the proxies overestimated the verbal communicative ability of their aphasic relative.

In the **General Discussion**, the main findings of the studies described in this thesis are summarized. Also, several methodological issues are discussed that occurred in designing and conducting our RCT. The clinical implications – the next section of this chapter – of the RCT are that communicative therapy might be as effective as CLT in the first half year of a stroke, but that future studies should aim to determine the influence of factors like treatment intensity and the match with specific patient groups on the effectiveness of aphasia therapy. For the most severe patients it appeared that starting early is feasible and advisable, and CLT is potentially more effective than generally assumed. Important to always bear in mind is that brain damage mostly affects more than one cognitive domain; in this paragraph some issues related to the cognitive functions other than language, and interactions between them are briefly discussed. A final clinical implication discussed is that the choice of a certain test as outcome measure in clinical studies is decisive. In addition, timing and intensity of aphasia therapy are reviewed. I conclude with presenting the plan for our next RCT, in which we will measure the effect of very early and intensive CLT compared with deferred or standard treatment, and the exciting imaging study in which we aim to show the neurophysiologic correlate of the effect of CLT.

Samenvatting

In de **Introductie** wordt geschetst dat een beroerte de meest frequente oorzaak van afasie is en dat er jaarlijks naar schatting 10.000 nieuwe afasiepatiënten bijkomen als gevolg van een beroerte. Afasie heeft, onafhankelijk van de ernst ervan, verstrekkende gevolgen. Taal zit verweven in vrijwel alle menselijke activiteiten; een taalstoornis belemmert dus sociale participatie. Een centrale stoornis in alle vormen van afasie is woordvindproblemen. Het selecteren en uitspreken van de juiste woorden bij het spreken vereist intacte semantische (woordbetekenis) en fonologische (woordklanken) verwerking.

In **Hoofdstuk 1** wordt beschreven dat cognitief-linguïstische therapie (CLT) een benadering in de afasierevalidatie is die stoornisgerichte oefeningen toepast op semantisch en fonologisch niveau. Geschikte therapieën zijn BOX (een lexicaal-semantisch programma) en FIKS (een fonologisch programma). Een andere route naar verbetering van de verbale communicatie is een meer functionele: communicatieve therapie. Toepassingen van beide benaderingen zijn geëvalueerd in studies op verschillende niveaus: van gevalsbeschrijvingen tot gerandomiseerde gecontroleerde trials (RCT's). In klinisch onderzoek worden RCT's beschouwd als de gouden standaard en ze worden gereviewd in de Cochrane Database of Systematic Reviews. De meest recente update van afasietherapie concludeerde dat er aanwijzingen zijn voor de effectiviteit van afasietherapie. Op lagere niveaus van evidentie zijn al vele behandelmethodes waardevol gebleken in de revalidatie van patiënten met een afasie na een beroerte.

In **Hoofdstuk 2** wordt het verband tussen woordvinding en semantische verwerking bij mensen met Alzheimer dementie (AD) onderzocht. De Semantische Associatie Test is afgenomen bij 19 AD patiënten en 19 gezonde controles. Zij moesten eerst 30 plaatjes benoemen. Vervolgens werden zij gevraagd een geschreven woord semantisch te associeren met één van de vier woorden eromheen (verbale semantische verwerking). Ten slotte voerden zij dezelfde taak uit maar dan gebruikmakend van plaatjes (visuele semantische verwerking). Er bleek geen gelijke achteruitgang in benoemen en de onderliggende verbale en visuele semantische verwerking bij de AD patiënten. Drie patiënten hadden intacte verbale semantische verwerking terwijl benoemen en visuele semantiek gestoord waren. Drie anderen toonden veel beter benoemen dan semantische verwerking, zogenaamd automatisch benoemen. Deze resultaten zijn in tegenspraak met het idee dat een globale conceptuele achteruitgang de oorzaak is van taalproblemen. Bovendien blijkt enkel een benoemtaak niet toereikend om taalstoornissen in AD te onderzoeken.

Hoofdstuk 3 gaat over de Rotterdamse Afasie Therapie Studie–2, een RCT waarin 85 patiënten onderzocht zijn. Onze hypothese was dat CLT effectiever is dan communicatieve therapie in de eerste maanden na de beroerte. Specifieke oefeningen die specifieke neurale netwerken activeren – netwerken die betrokken zijn bij semantische en fonologische verwerking – zouden het natuurlijke neurale herstelproces kunnen faciliteren. Na CLT en communicatieve therapie bleek een vergelijkbare vooruitgang in verbale communicatie te zijn opgetreden. Maar de resultaten op vrijwel alle semantische en fonologische tests waren ten gunste van CLT en op de semantische en fonologische fluency taak was het verschil ten gunste van CLT zelfs statistisch significant. Mogelijk is de intensiteit van de therapie te laag geweest om een potentieel therapie-effect te kunnen aantonen bovenop het spontane herstel en er zou teveel overlap geweest kunnen zijn tussen de twee behandelingen. Daarom blijft het een (onderzoeks)vraag of CLT vooral in de acute fase effectief is.

In **Hoofdstuk 4** staat het herstel van afasie bij de mensen met een ernstige afasie centraal. De groep van RATS-2 deelnemers werd in drie gelijke groepen verdeeld op basis van de baseline scores op de Amsterdam-Nijmegen Test voor Alledaagse Taalvaardigheden (ANTAT). In de ernstigste groep bleek de verbale communicatie aanzienlijk te verbeteren in de eerste zes maanden na de beroerte. Bovendien leek CLT effectiever te zijn geweest dan communicatieve therapie. Deze resultaten zijn in tegenspraak met de theorie dat mensen met uitgebreide neurale schade waarschijnlijk geen baat hebben bij stoornisgerichte therapie en dat communicatieve therapie te prefereren is bij deze patiënten. Wij suggereren dat afasietherapie niet uitgesteld moet worden in het geval van een ernstige afasie.

Het laatste onderzoek in dit proefschrift, beschreven in **Hoofdstuk 5**, gaat over de score die de partner of andere naaste van de patiënt, de zogenaamde proxy, gaf voor de verbale communicatie van de patiënt op de Partner Communicatie Vragenlijst, vergeleken met de score die de logopedist gaf op de ANTAT. Wij onderzochten de mate en aard (richting) van de discrepantie tussen de beide beoordelingen en welke factoren deze discrepantie veroorzaakten: de kwaliteit van leven van de patiënt, zijn/haar leeftijd, mate van zelfredzaamheid en of de proxy de partner of een andere naaste van de patiënt is. Proxy's bleken iets positiever te zijn in hun beoordeling dan logopedisten. Toch was er sprake van een matig-sterke overeenkomst tussen beide beoordelingen. De ernst van de afasie bleek de beste voorspeller te zijn van de mate van overeenkomst: hoe lichter de afasie, hoe minder de proxy's de verbale communicatie van hun afatische partner overschatten.

In de **Discussie** worden de belangrijkste bevindingen van de studies in dit proefschrift samengevat. Tevens wordt een aantal methodologische kwesties besproken die speelden bij het opzetten en uitvoeren van onze RCT. De klinische implicaties – de volgende paragraaf in dit hoofdstuk – van de RCT zijn dat communicatieve therapie even effectief zou kunnen zijn als CLT in het eerste half jaar na een beroerte, maar dat toekomstig onderzoek zou moeten uitwijzen wat de invloed is van factoren als behandelintensiteit en de aansluiting bij specifieke patiëntgroepen op de effectiviteit van afasietherapie. Het bleek dat het mogelijk en wenselijk is om snel met de behandeling te starten bij patiënten met een ernstige afasie en dat CLT mogelijk effectiever is dan algemeen wordt aangenomen. Het is belangrijk om te beseffen dat bij hersenschade vrijwel altijd meer dan één cognitief domein is aangedaan; in deze alinea bespreek ik enkele zaken omtrent andere cognitieve functies dan taal en interacties tussen functies. Een laatste klinische implicatie is dat de keuze voor een bepaalde test als uitkomstmaat in een klinische studie en als diagnostisch instrument zeer bepalend is. Verder wordt een review gegeven van timing en intensiteit van afasietherapie. Ten slotte presenteer ik het plan voor onze volgende RCT, waarin we het effect van zeer vroege en intensieve CLT zullen vergelijken met uitgestelde of standaard behandeling, en de spannende functionele MRI studie waarmee we het neurofysiologisch correlaat van het effect van CLT zichtbaar willen maken.

List of abbreviations

AAT	*Aachen Aphasia Test*
AD	*Alzheimer dementia*
ANELT	*Amsterdam-Nijmegen Everyday Language Test*
CIAT	*constraint-induced aphasia therapy*
CLT	*cognitive-linguistic therapy*
EQ-5D	*European quality of life-5 dimensions*
MAAS	*Multi-Axial Aphasia System*
MMSE	*Mini-Mental State Examination*
PACE	*Promoting Aphasic's Communicative Effectiveness*
PALPA	*Psycholinguistic Assessment of Language Processing in Aphasia*
PCQ	*Partner Communication Questionnaire*
RATS	*Rotterdam Aphasia Therapy Study*
RCT	*randomized controlled trial*
SAT	*Semantic Association Test*
SLT	*speech-language therapist*

Appendix

ANTAT

Amsterdam-Nijmegen Test voor Alledaagse Taalvaardigheden
L. Blomert, Ch. Koster en M-L. Kean

Testinstructie

Aan het begin van de testsessie wordt de patiënt letterlijk de volgende instructie gegeven: *Ik leg u dadelijk een aantal situaties voor. Het zijn alledaagse gebeurtenissen die iedereen wel eens meegemaakt heeft of zou kunnen meemaken. Ik wil weten wat u in zo'n situatie zou zeggen. We zullen dit eerst proberen aan de hand van twee voorbeelden.*

Oefenitems

A U zit bij een nieuwe kapper en u bent aan de beurt. Ik ben de kapper. Wat zegt u tegen mij?

B U staat met uw boodschappen bij de kassa van een supermarkt. Als het meisje alle boodschappen heeft aangeslagen en u moet betalen merkt u dat u uw portemonnaie kwijt bent. Wat zegt u?

ANTAT I

1 U bent nu in de stomerij. U komt dit (overhemd) ophalen en krijgt het zo terug. Wat zegt u?

2 De kinderen op straat voetballen vlak voor uw voordeur. U heeft dat al vaker verboden. U gaat naar buiten om de jongens toe te spreken. Wat zegt u?

3 We zijn in een winkel en u wilt een televisie kopen. Ik ben de verkoper/verkoopster daar. "Kan ik u van dienst zijn mevrouw/mijnheer?"

4 U gaat met deze schoen naar de schoenmaker. Er is veel aan de hand met de schoen, maar om een of andere reden wilt u slechts één ding laten repareren. U mag kiezen wat. Wat zegt u?

5 U heeft een afspraak met de dokter maar er is iets tussen gekomen. U belt op en wat zegt u?

6 U bent bij de slager en dit (handschoen) ligt op de grond. Wat zegt u?

7 U ziet uw buurman lopen. U wilt hem vragen om een keertje op bezoek te komen. Wat zegt u?

8 De hond van uw buurman blaft de hele dag. U heeft er echt genoeg van. U wilt het er met hem over hebben. Wat zegt u?

9 U bent net bij mij in de straat komen wonen en u wilt met mij kennismaken. U belt bij mij aan en zegt?

10 U bent in een groentezaak en u wilt een fruitmand laten bezorgen bij een kennis. Ik ben de groenteman. Wat zegt u tegen mij?

Dankwoord

You cannot spend a lifetime just going along for the ride. Sooner or later, you will have to help pull the wagon.
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geschreven. Wie weet wat de toekomst nog brengt! *Barbara van der Vlugt*, de spannendste RATS-2 belevenis komt op jouw conto: helemaal naar Antwerpen gereisd en door de deur van een patiënt de echtgenote door de telefoon horen zeggen tegen mij dat ze niet thuis zijn! Bedankt voor al je testings. *Marleen Kuipers*, bedankt voor de fijne samenwerking en je hulp tijdens de slotbijeenkomst! *Arlette Thiellier*, wat een data heb jij voor me in orde gemaakt en gecontroleerd. Hoe lastig kan het zijn om een patiënt telefonisch te bereiken om zijn handigheid vast te stellen. *Tineke Ernest*, *Annemarie Hordijk*, *Marloes van Korven* en *Andrea Sweerts*, bedankt voor het vervaardigen van makkelijker BOX en FIKS oefeningen. *Lieke Kros*, als ik jou niet had gehad dan was de EuroQol-moed me in de schoenen gezakt. Enorm bedankt voor al je werk voor het PCV-artikel! Daar staat je naam toch maar mooi in mijn "list of publications". *Charlotte Landers* en *Mariela van Hasselt*, bedankt voor de stagewerkzaamheden. *Lonneke Kuiper*, wat een tweedejaars Logopedie allemaal niet kan! Jouw toekomst in de logopedie en de wetenschap lacht je toe.

Sandra Wielaert, Dineke Blom, Jane van Gelder-Houthuizen
Beste keien van 'onafhankelijke ANTAT beoordelaars', ik denk dat jullie verbaal-auditieve verwerkingssysteem permanent veranderd is na het beluisteren en scoren van de in totaal 220 samples (de herbeoordelingen nog niet eens meegerekend!). We kunnen het ons niet voorstellen na de ervaring van dit hele proces maar de objectieve statistiek concludeerde toch echt dat er op 0 en 3 èn 6 maanden "excellent agreement" was!

Afasieteam
Beste Jiska, Yvonne, Ineke, Sandra en Mieke, hartelijk dank voor de perfecte afname en uitwerking van vele RATS-2 testen.

Mijn buren
Lieve Marjolein&Michael, Melanie&Ronnie en Esther, dankzij jullie heb ik ook op de dagen dat ik thuis was met Dominique nog heel wat uurtjes zwoegen kunnen meepakken! Bedankt voor het opvangen.

Mijn (schoon)familie
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Jeroen, grote broer, ik had me geen betere tweede paranimf kunnen wensen (en nee, je hoeft geen vinnen te laten groeien). Wat een weelde om een groot deel van de organisatie met het volste vertrouwen aan jou over te laten, en wat ben ik trots dat je het maken van mijn proefschrift hebt geregeld. Laten we genieten van deze dag!

Allerliefste *paps* met lieve *Rosalie*, dankzij jou ben ik waar ik nu ben. Nooit opzichtig maar altijd voelbaar heb je me geadviseerd en gesteund in mijn opleiding, carrière en privéleven. Bij elke stap en in elke fase heb je me op afstand bijgestaan. Nu de promotiehectiek achter de rug is, kom ik lekker weer eens genieten in jullie tuin en huis.

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Tot slot, lieve lieve *Arnoud* en *Dootje*, wat voor fratsen ik ook uithaal en wat we ook beleven, wij komen overal met z'n drieën doorheen. BEDANKT voor alle liefde, lol en levensgeluk.

About the author

Marjolein Hagelstein was born in Zwijndrecht on May 3rd 1977 and moved to Dordrecht where she grew up until the age of 6. She then lived in Oud-Beijerland with her parents, two brothers and dog. After graduating in 1994 from secondary school at the Regionale Scholengemeenschap Oud-Beijerland (HAVO) she started both the Speech-language therapy education at the Hogeschool Rotterdam and the Gymnastics instructor training in Rotterdam. She obtained her Gymnastics instructor license in 1996 and became a speech-language therapist in 1998. She then moved in with Arnoud in Rotterdam and started studying Psychology at Leiden University, chose the mayor Cognitive Psychology and specialization Neuropsychology. During this study she gave several workshops Speaking in public to first aid instructors and worked as a speech-language therapist in a hospital, nursery home and private practice consecutively and later as project worker at Leiden University, section Psychology, department of Safety. She obtained her Master degree (cum laude) in 2002. Between 1996 and 2006 she was active as gymnastics instructor and committee member of several gymnastics clubs. From 2003 to 2005 she worked as a speech-language therapist in Logopediepraktijk Rotterdam-Schiebroek and was then asked by Dr. Visch-Brink to become the coordinator of RATS-2. In July 2005 she and Arnoud moved into their own house in Oud-Beijerland and Marjolein started the job at the department of Neurology, Erasmus MC (under the supervision of Prof. dr. P.J. Koudstaal), resulting in this thesis. In 2007 daughter Dominique was born.

List of publications

E.G. Visch-Brink, **M. Hagelstein**, H.A.M. MIddelkoop, T.J.M. van der Cammen.
Naming and semantic processing in Alzheimer dementia: A coherent picture? (Abstract)
Brain and Language 2004;91:11-12.

M. Hagelstein.
RATS-2: De effectiviteit van cognitief-linguïstische therapie in de acute fase van afasie: een gerandomiseerde gecontroleerde trial.
Afasiologie 2006;4:62-64.

M. de Jong-Hagelstein.
De effectiviteit van vroeg ingezette cognitief-linguïstische therapie en communicatieve therapie voor afasie na een beroerte: een gerandomiseerde gecontroleerde trial (RATS-2).
Stem-, Spraak- en Taalpathologie (accepted).

M. de Jong-Hagelstein, H.A.M. Middelkoop, T.J.M. van der Cammen, E.G. Visch-Brink.
Naming and semantic association in Alzheimer dementia: A coherent picture?
Submitted.

M. de Jong-Hagelstein, W.M.E. van de Sandt-Koenderman, N.D. Prins, D.W.J. Dippel, P.J. Koudstaal, E.G. Visch-Brink.
The efficacy of early cognitive-linguistic treatment and communicative treatment in aphasia after stroke: a randomized controlled trial (RATS-2).
Journal of Neurology, Neurosurgery and Psychiatry 2011;82:399-404.

M. de Jong-Hagelstein, L. Kros, H.F. Lingsma, D.W.J. Dippel, P.J. Koudstaal, E.G. Visch-Brink.
Expert versus proxy rating of verbal communicative ability of aphasic stroke patients.
Journal of the International Neuropsychological Society (major revision).

M. de Jong-Hagelstein, W.M.E. van de Sandt-Koenderman, H.F. Lingsma, D.W.J. Dippel, P.J. Koudstaal, E.G. Visch-Brink.
Recovery of severe aphasia after stroke.
Submitted.

PhD portfolio

Name PhD student: Marjolein de Jong-Hagelstein
Erasmus MC Department: Neurology
Research School: COEUR
PhD period: 2005 - 2011
Promotors: P.J. Koudstaal, D.W.J. Dippel
Supervisor: E.G. Visch-Brink

1 PhD training

	Year	Workload (ECTS)
General academic skills		
• Access training	2005	0.2
• Biomedical English Writing and Communication	2008 - 2009	4.0
• PhD Day 5x	2006 - 2011	2.0
• Workshop EndNote & Literature search	2010	0.2
• COEUR PhD Day	2010	0.4
• PCDI Postdoc Retreat (Heeze)	2011	0.9
Research skills		
• Clinical cardiovascular epidemiology	2006	1.5
• Workshop top quality clinical trials	2006	0.1
• Mini course methodology and grant proposals	2006	0.2
• Autumn symposium RCTs	2006	0.2
• Introduction to clinical research	2007	0.9
• Vascular clinical epidemiology	2008	1.5
In-depth courses		
• Clinical forum aphasia therapy (Rijndam rehabilitation center)	2006	0.1
• Aphasia clinics: primary progressive aphasia (Erasmus MC)	2011	0.1
Presentations		
• Results meeting RATS-2 (Rotterdam)	2008	1.0
• Lab meeting C.K. Thompson (Chicago)	2008	0.2
• ASHA (Chicago)	2008	0.3
• CBO Guideline stroke (Utrecht)	2008	0.2
• Symposium Hogeschool&Alumnivereniging (Eindhoven)	2008	0.8
• Science of Aphasia (Greece, Turkey)	2008, 2009	0.6
• Master Neurologopedie publicity meeting (Rotterdam)	2009	0.4
• Neurovascular group (Erasmus MC)	2009	0.3
• British Aphasiology Society (Sheffield)	2009	0.3

	Year	Workload (ECTS)
• Workshop conference Vereniging Revalidatieartsen (Ermelo)	2009	0.3
• Refereren Neurology (Erasmus MC)	2010	0.3
• COEUR PhD Day	2010	0.1
• Lab meeting Prof. Lambon Ralph (Erasmus MC)	2011	0.1
(Inter)national conferences		
• Academy of Aphasia (Amsterdam)	2005	0.9
• NVLF day (Ede)	2005	0.6
• Junior aphasia researchers day (Groningen)	2006	0.9
• Clinical Aphasiology Conference (Gent)	2006	1.8
• Aphasia conference GAB (Hamburg)	2006	0.9
• Werkverband Amsterdamse Psycholinguïsten conference	2008	0.6
• ASHA (Chicago)	2008	0.9
• Science of Aphasia (Greece, Turkey)	2008 - 2009	2.4
• British Aphasiology Society (Sheffield)	2009	0.9
Seminars, workshops and lectures		
• Neurologische Taal- en Spraakstoornissen 7 lectures	2005 - 2009	0.7
• COEUR Research seminar	2006	0.4
• Cognitive neuroimaging and psycholinguistics (Neuroscience)	2006	0.1
• Lab meeting C.K. Thompson (Chicago)	2008	0.1
• CBO Guideline stroke (Utrecht)	2008	0.3
• Alzheimer and Vascular cognitive impairment (Epidemiology)	2009	0.1
• Neurovascular group	2009	0.1
• Lab meeting (Prof. Lambon Ralph) (Erasmus MC)	2011	0.1
2 Teaching activities		
Lecturing		
• Practicals Neuropsychology (BA) Leiden University	2006 – 2010	2.5
• Neurologische Taal- en Spraakstoornissen (Erasmus MC)	2007	0.1
• Retraining neurology nurses (Rotterdam)	2009, 2010	0.6
Supervising Master's theses		
• Universiteit Nijmegen, Leiden, Logopedie Eindhoven	2006, 2009 2x	0.6
Supervising internships		
• 9 students (3 BA, 6 MA)	2006 - 2011	1.9
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