Chapter 5

General discussion

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

MAIN FINDINGS

The following three questions were addressed in this thesis:

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

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

Efficacy of early intensive CLT

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

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

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

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

Factors associated with efficacy of treatment

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

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

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

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

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

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

Early diagnosis of aphasia

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

Predicting aphasia outcome after stroke

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

Language recovery after intra-arterial treatment for ischemic stroke

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

METHODOLOGICAL LIMITATIONS

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

Ethical considerations

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

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

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

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

Feasibility of intensive treatment

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

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

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

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

Intervention

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

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

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

Outcome measures

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

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

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

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

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

Randomized controlled trials in aphasia research

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

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

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

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

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

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

CLINICAL IMPLICATIONS

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

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

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

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

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

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

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

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

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

FUTURE RESEARCH

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

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSION

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

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

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

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