Chapter 4

Treatment of aphasia

Chapter 4.1

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

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ABSTRACT

Background

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

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

Methods

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

INTRODUCTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EXPERT COMMENTARY

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

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

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

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

FIVE-YEAR VIEW AND PRINCIPLES FOR FUTURE RESEARCH

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

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

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

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

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

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

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

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

CONCLUSION

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

Key issues

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

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