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The first decade of research on constrained-induced treatment approaches for aphasia rehabilitation

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Abstract

Approaches for treating post-stroke language impairments (aphasia) based upon Constraint-Induced (CI) principles were first introduced in 2001. CI principles as previously applied to upper extremity and locomotor retraining in stroke survivors were derived from basic neuroscience. They comprise forced-use of the affected modality, a gradual rebuilding of targeted functions using a highly intensive treatment protocol, administered in a behaviorally-relevant context.

CI-based approaches have stimulated considerable neurorehabilitation research interest in the past decade. The original CI aphasia treatment protocol was tailored to improve functional communication in chronic aphasia (i.e., 6–12 months after stroke) and more recently, it has been adapted to treat language impairments in acute stroke survivors as well. Moreover, CI therapy applied to aphasia has been used as a model to assess language network plasticity in response to treatment using functional imaging techniques.

In the following paper, we review the first 10 years of behavioral and functional brain imaging research on CI-based approaches for aphasia rehabilitation.

Keywords

language impairment; stroke; neurorehabilitation; forced-use

Post-stroke aphasia is a devastating language disorder that affects language production and comprehension. Constraint-Induced (CI) based approaches for treating stroke induced aphasia were first introduced approximately 10 years ago. CI principles known also as `use dependent learning" principles were derived from basic neuroscience investigations[1] and subsequently applied in human trials investigating treatment of post-stroke motor impairments including retraining of locomotion in hemiplegia,[2] in partial spinal cord injury,[3] and bimanual usage in hemiplegia.[4]

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In 2001, the concept of applying CI-based principles to treat chronic language impairments was introduced, and CI-based approaches have generated considerable interest since that time. The original protocol was tailored to improve functional communication in chronic aphasia (i.e., 6–12 months after stroke) and has subsequently been modified and extended by other work-groups to acute stroke and other diagnoses.[5] It has also been used as a model to assess functional brain reorganization in response to treatment using functional imaging techniques.

In the following paper, we aim to provide the reader with a short history of CI-based concepts and a comprehensive review and evaluation of the first 10 years of behavioral and functional brain imaging research on CI-based approaches for aphasia rehabilitation.

History and development of CI-based treatment: What we learned from treatment of motor impairments after stroke

The basic principles of constraint-induced (CI) based approaches were derived from animal studies[1] in which monkeys with surgically-induced unilateral somatosensory deafferentation would not use the affected extremity spontaneously. Instead, compensatory use of the unaffected extremity occurred. However, it was demonstrated that even years after the deafferentation the monkeys could be trained to make use of the affected limb by restraining the unaffected extremity. In combination with a gradual re-training of motor functions, impairment could be reversed and spontaneous use re-established.

Findings from these early studies led to the development of CI-movement therapy (CIMT) to treat patients with chronic stroke and motor impairments.[1] CIMT is centered on four overarching principles: the non-use hypothesis, massed practice, shaping, and behaviourally relevant treatment settings. In the case of motor rehabilitation, it has been suggested that non-use of an affected (paretic) extremity develops during the first months post-stroke when physiological damage results in depression of function and failure to effectively use the affected extremity ***(non-use hypothesis)***. This `non-use' can be overcome by creating situations that induce patients to re-use a paretic limb. In CIMT, this is achieved by constraining the use of the non-affected extremity by a sling or splint over an extended period of time and training of the affected limb is initiated (`induced') over a period of two or more consecutive weeks for several hours a day ***(massed practice principle)***. Use of massed practice is based on findings from basic animal and human neuroscience research: Here, it has been shown that intensive and high-frequent training results in strengthened neural connections between task relevant brain regions which is thought to be the neural basis of learning and recovery from brain injury.[6, 7] Moreover, depending on treatment success, the difficulty of the required motor actions is gradually enhanced ***(shaping principle)*** and the training is realized in a ***behaviourally relevant setting***, in which patients are trained in activities relevant to their everyday life (e.g. using a spoon, opening doors) in order to enhance transfer.

More than twenty years of research in this area, including several large-scale clinical trials have accumulated a substantial body of evidence that CIMT can improve upper and lower extremity impairments in chronic stroke survivors.[1, 8] Moreover, it has been demonstrated that these effective treatments induce functionally relevant reorganization of brain networks supporting motor functions.[9]

Adaptation of CI approaches to treat aphasia

Despite different terminologies use by different work-groups (e.g., Constraint-Induced Language or Aphasia Therapy, CILT/CIAT,[10, 11] Intensive Language-Action Therapy, ILAN),[7] CI-based approaches to treat aphasia are based on the findings and principles upon which CIMT was founded. Pulvermüller and colleagues[12] were the first to suggest that withdrawal from communication, change of communication strategies and use of compensatory strategies adopted by many patients with post-stroke aphasia could be viewed as a form of learned-non-use in patients with aphasia. Thus, the original CI-based language treatment protocol encouraged patients with aphasia to focus specifically on communication channels they tend to avoid (i.e., verbal communication). As in CIMT, shaping and a highly intensive training environment (usually three hours/day over 10 consecutive days) were established to enhance language re-learning and promote neuroplastic reorganization.[7]

To ensure behavioural relevance of the training is optimized, the therapeutic setting is based on pragmatic and communicative aphasia therapy.[13] Even though implemented with slight variations between work-groups,[10–12, 14] the basic setting comprises a therapeutic language game in a group setting[15]. During therapy sessions up to three patients and the therapist perform an interactive card game. At the beginning of the game pairs of cards depicting object drawings, written words or drawings/photographs of more complex everyday life scenarios are distributed among the players in a way that none of the players has two identical cards. Barriers are used between the players to prevent them from seeing each other's cards, which are typically placed on the surface in front of them.

During the card game, players take turns selecting a card from their own set and asking another player if they have a match. If the other player has the match, he or she will hand it over. The exchange between players (i.e., request, response, reply) is expected to be explicit and in most cases involves spoken words or sentences. Some studies strictly enforced the use of spoken verbal expressions (e.g., by asking the patients to sit on their hands if necessary),[10] whereas other studies allowed gesturing[16–18] in an effort to exploit the potential of gestures to facilitate language processing.[19, 20] Usually, a second therapist is present to help patients with problems that may arise during the game (e.g. by prompting with the first letter in case of word finding difficulties) and to provide positive reinforcement. Shaping of language functions is accomplished by introducing increasingly complex materials across training sessions. Performance requirements are enhanced depending on patient's improvements, and different levels of performance are reinforced by the therapist. Every patient is constantly encouraged by the therapist to activate his upper level of language skills. All the studies reviewed in this manuscript had been approved by the respective local institutional review boards.

Clinical Evaluation in Chronic Aphasia (see Table 1 for a summary)

In 2001, Pulvermüller et al.[12] provided first evidence for the effectiveness of CI-based approaches to improve language functions in chronic aphasia. Ten patients with moderate to severe chronic aphasia (>12 months post-stroke) were treated using CI-principles and compared to seven patients treated with standard aphasia therapy. Patients were randomized either to the CI group that received 30 hours of therapy over ten days (i.e., 3 hours/day) or to the control group that received the same amount of therapy across 3–5 weeks. Both groups underwent comprehensive standardized language testing (Aachen Aphasia Test Battery, AAT)[21] prior to and after the intervention period and a questionnaire about the amount of communication and comprehension in day-to-day communication (Communicative Activity Log, CAL)[7]. The CAL was developed based on a similar instrument used in CIMT studies (Motor Activity Log) and comprises two scales that aim to measure the amount and quality of everyday communication by means of self-ratings (patients) or ratings of therapists not involved in the training. Overall language improvements were significant for the CIAT treatment group only (average weighted score of the AAT subscales Token Test, naming, comprehension and repetition), with the group receiving standard treatment (extended over a longer period of time) only demonstrating improvement on one subtest of the AAT. Additionally, only the patients that received CIAT increased their amount of day-to-day communication as assessed by the CAL. Notably, this effect was found even though time since stroke was shorter in the control group that received standard treatment (Ø 98.2 vs. 24.0 months).

In a subsequent study, Meinzer et al.[11] replicated these immediate treatment gains in a heterogeneous sample of 27 chronic aphasia patients (time since stroke: range: 13–116 months). Most patients were classified as either having Broca's aphasia (N=11) or Wernicke's aphasia (N=7). The primary outcome measure was the AAT and single-case analyses revealed significant improvements in about 85% of the patients (i.e., significant improvement was found in at least on one subtest or subscale of the AAT). The patients were re-examined six months after treatment termination and both individual and group results demonstrated retention of treatment gains compared to baseline assessment. The amount of day-to-day communication and comprehension, as measured by the CAL, was enhanced after therapy and the patients' relatives rated communicative effectiveness as improved (Communicative Effectiveness Index, CETI).[22] About 50% of the patients received an additional training in day-to-day communication (CIATplus) in the form of additional exercises completed in the afternoon on each day of training. Exercises were individually arranged to include daily communication practice with a family member and aimed at gradually re-establishing real life communication. While there were no differences between the CIAT and CIATplus groups immediately after training, only the CIATplus group showed further improvement in the rated quality of day-to-day communication (CETI), and only in these patients was the amount of communication and comprehension still above baseline at the follow-up assessment.

Although these studies demonstrated significant improvement of language functions after CI-based treatment, the impact of treatment intensity vs. therapy type was not specifically addressed.[12] Thus, the question remained whether other types of treatment would also benefit from a more intensive treatment schedule, as suggested by a recent meta-analysis.[23] Moreover, functional communication was only assessed by questionnaires in both studies. To address the first question, Barthel et al.[24] compared the previously described group of patients treated with the CI-approach[11] with a group of 12 chronic patients treated with a so called `model-oriented aphasia therapy (MOAT)'. Patients of both groups were comparable with regard to clinical and sociodemographic variables. MOAT comprised a number of different approaches (e.g., strategy approach, model-based therapy, communicative approach, for details see[24]) individually tailored to the patients language impairment. Intensity of the treatment was matched to that of the CI-group. Treatment gains as assessed with the standardized AAT were comparable between the CI and MOAT groups immediately after treatment and six months after the training, suggesting intensity is one of the main factors affecting treatment-induced recovery in chronic aphasia.

Similarly, in an attempt to determine whether forced use (i.e., strictly limiting the response modality to spoken language) is a critical component for treatment success, Maher et al.[10] compared patients treated with the CI-approach (N=4) and patients treated with a modified PACE protocol (N=5; Promoting Aphasic Communicative Effectiveness).[13] In both groups treatment was administered to dyads of patients, a similar type of card game was used, and treatment intensity was matched. However, in the PACE group alternative means of information transfer were allowed (e.g., writing, gesturing, and pointing). While both groups improved on standardized language tests (e.g., Boston Naming Test, Western Aphasia Battery) and subjective ratings of narrative discourse, these gains were more pronounced in the CI group, suggesting a beneficial effect of forced use of spoken language. However, these results are to be interpreted with caution as the sample size was small, a potential benefit on non-verbal measures of communication in the PACE group was not assessed, and patients treated with PACE had more severe apraxia of speech.

In another study, Barthel et al.[25] assessed the impact of intensive speech and language therapy (CI-based and MOAT) on connected speech measures. Speech samples were obtained from 12 patients (spontaneous speech scales of the AAT; standard picture descriptions) across two baseline trials prior to treatment and immediately after treatment. Speech samples were analyzed using the Aachen Language Analysis,[26] a computerized tool to determine basic language parameters like syntactic completeness and complexity, mean phrase length, percentage of words, etc. A total of 17 parameters were evaluated and performance during the two pre-treatment assessments was found to be highly stable. At post-treatment, significant improvements were found for the percentage of complete phrases, complex and complete sentences across the entire patient group, with no group differences. Thus, results demonstrate that intensive training regimens like MOAT or CI-based approaches have the potential to improve functional communication on the sentence level as well.

In sum, the first clinical studies on the effectiveness of CI-based approaches suggests beneficial effects on language functions in chronic aphasia, a stage where further improvements are hard to achieve.[27] Improvements have been demonstrated in standardized language tests and subjective and objective measures of functional communication. Moreover, treatment gains were maintained after up to six months in some of the studies that included a follow-up period. Interestingly, two of the above studies assessed the number of (ambulatory) treatment hours between the end of intervention and the follow-up.[11, 24] These accumulated to ~30 hours on average across the six months period, which is comparable to the number of hours the patients received during the two-week treatment period. While stability may have been assured by the non-intensive ambulatory treatment, no further gains were noted during this period, providing further evidence for the necessity of a more intensive treatment schedule in chronic aphasia.[23]

Unfortunately, apart from an intensive training schedule (massed practice principle) there is very limited evidence regarding the effective elements of CI-based approaches and how they contribute to the treatment outcome. On the other hand, standard therapy or different forms of communicative therapy seem to benefit as well from more intense schedules.[10, 24] With regard to constraining of non-verbal communication channels, there is preliminary evidence for a beneficial effect on verbal communication.[10] However, these finding needs to be replicated in larger patient samples, in particular, as evidence from CIMT suggests that restraint of the unaffected extremity plays a relatively minor part for most patients. Instead, inducing activity in the unaffected arm and shaping of functional capabilities seem to more important.[28] This clearly needs to be investigated in future large-scale clinical trials in aphasia as well as the contribution of other CI-elements (e.g., shaping or training in a behaviourally relevant setting). The latter has not been studied so far.

Another variable of interest is the optimal treatment duration. Thus far, no systematic studies have been conducted with regard to this issue. While studies on CIMT have not found substantially enhanced treatment effects with more than three hours of daily treatment, it is unknown if less than three hours of daily training would be sufficient to achieve similar effects. Moreover, more information is needed regarding the type of patients who are best suited for such an intensive treatment regimen. Meinzer et al.[16] reported that patients with more severe aphasia benefited the most from the two-week intensive CI training, in particular with regard to measures of expressive language functions (i.e., repetition and naming subtests of the AAT). They speculated that in more severe aphasia there might be more withdrawal from communication and that intensive stimulation might be maximally beneficial in boosting language skills in these patients. However, other non-language specific explanations, like improved attentional capacities or memory functions in response to the training, need to be scrutinized. For example, it has been demonstrated that simple training of memory and attentional functions can also improve aphasia symptoms.[29]

Alternative strategies to enhance treatment intensity

Based on the previous studies and evidence from a recent meta-analysis[23] there is an emerging consensus for the need to enhance treatment intensity in chronic aphasia. However, given the limited financial resources of the health care system and the limited number of therapists available to provide such services, alternative ways to enhance treatment intensity need to be explored. Previous attempts to increase the availability of treatment hours have relied on computerized treatment. While such strategies have proven to be effective to train specific language functions (e.g., reading) in chronic aphasia[30, 31] they still require the presence of a therapist, as most programs cannot adapt to the patients needs and progress. An alternative approach could be to rely on non-therapist based training as an adjunct to professional intervention to increase the availability of language stimulation. In previous studies, it has been shown that therapy provided by trained and supervised laypersons may improve language functions in aphasia.[32]

CI-based treatment approaches with their highly structured setting and training materials administered in a communicative context may be particularly well-suited to be administered by trained laypersons. This has recently been explored in a controlled trial.[18] Here, 20 patients with mild to severe chronic fluent and non-fluent aphasia were randomly assigned to two treatment groups. One group was treated by experienced therapists and the other received the same treatment administered by trained, supervised laypersons (for pragmatic reasons the patients' relatives were chosen). Treatment groups were comparable with regard to clinical characteristics. Laypersons received a short introduction into CI-principles and acted as therapists under supervision of an experienced therapist for the first two days of training. For the remaining eight days, relatives led the training. Prior to and after each training day, relatives met with the therapists to report problems encountered during that day and receive advice on how to resolve them.

Standardized language assessments showed that both groups equally improved, with no significant differences on any of the subtests of the AAT. Even though the sample size was relatively small, there was no evaluation of the trainers' performance and measures of functional communication were not assessed, the overall positive results of this study suggest that CI-based approaches to treat aphasia may be a viable way to enhance language stimulation through supervised laypersons.

Adaptations of CI-based treatment approaches

In recent years, CI-based approaches have been adapted to target specific language functions[14, 33, 34] and to accommodate treatment in acute stages of recovery.[35] So far, however, very few patients have been treated and these studies have provided only preliminary evidence for a broader application of CI-based approaches in language rehabilitation.

For example, Goral and Kempler[34] modified the original CI protocol to treat verb production deficits in an individual with chronic nonfluent aphasia (60 years old, 12 years post-stroke). The patient's communication attempts were characterized by single word utterances (mostly nouns) and the goal was to increase verb use in the context of sentences and narrative production. During treatment, 57 preselected verbs relevant to the patient were trained and the complexity of the required language tasks, that all involved use of a verb, was gradually increased. Following two blocks of treatment consisting of five hours of treatment per day for four weeks (separated by a block of no treatment for four weeks), the patient demonstrated increased verb generation in narrative production. In addition, 20 naïve listeners, blind to the treatment phase, rated the patient's narrative production as improved after treatment. Similarly, Faroqi-Shah and Virion[33] adapted the CI protocol to treat individuals with chronic patients with severe agrammatic aphasia. Two individuals were treated with the original treatment protocol and two were treated with a modified protocol that employed morphosyntactic shaping. Patients receiving the modified protocol were provided a temporal adverb (i.e., yesterday) to prompt use of appropriate verb tense morphology. They were also asked to make judgments on the grammaticality of the other player's requests. Following 24 hours of treatment over 10 days, the two participants who received the modified protocol improved in their performance on a formal test of verb inflection; however, improvement in morphosyntactic production was not evident in narrative language production. Szaflarski and colleagues[14] also modified the original protocol to create an individualized approach for three chronic, nonfluent aphasic patients based on their linguistic strengths and weaknesses. Targets focused on semantic, syntactic or phonological language production. Following five days of individualized treatment (three to four hours per day), two patients demonstrated improvement in auditory comprehension. While no improvement in formal expressive language tests was observed, linguistic analysis of a story retell task revealed improvement in narrative discourse production. Thus, this individualized CI approach yielded positive treatment outcomes and provided further evidence for the need to employ functional language outcome measures in future studies.

Most recently, the effectiveness of CI treatment in acute stages of aphasia recovery was investigated.[35] Three patients with nonfluent aphasia, who were one to two months post-stroke, were treated for up to three hours per day for 10 days using a modified approach that accommodated the demands of an acute care environment. For example, due to scheduling difficulties and increased patient fatigue, some sessions were administered at the bedside or in smaller time blocks, and two patients received individual rather than group treatment. This study provided first evidence for the feasibility to treat patients in the acute stage of aphasia with such an adapted CI-based approach. However, as no control group was included, it remained unclear whether improved language production after treatment can be attributed to the treatment or other factors, e.g., spontaneous language recovery that typically occurs early after stroke.

In summary, the adaptations described here have extended the research supporting CI therapy. However, they also highlight the need for continued systematic investigation of this approach. Issues that warrant further investigation include not only modification of the structural and temporal aspects of the treatment but also selection of appropriate outcome measures to assess treatment gains. In particular, future studies should include measures that assess the outcome for the specifically trained functions and include measures of generalization (untrained items), and assess language functions that are not specifically trained and the impact on everyday communication.

Adjunct pharmacological treatment

Another promising way to enhance the effectiveness of CI treatment is the pairing of pharmacological agents with therapy. It has been demonstrated that a number of different drugs can modulate neurotransmitter systems in the brain and may have direct effects on specific language functions or may indirectly affect treatment outcome by improving arousal, attentional or working memory functions important for language processing. In particular, drugs affecting glutaminergic, monoaminergic and cholinergic transmitters may have beneficial effects on language and other cognitive functions in stroke survivors,[36, 37] however, very few studies used these drugs as an adjuvant to language therapy and most of these studies found no beneficial effects, in particular, in chronic aphasia (for a recent review see[7]).

Only one study has assessed the impact of a combined drug treatment and CI-based aphasia therapy. In a randomized, double-blind, placebo-controlled study Berthier and colleagues[38] assessed the impact of an N-methyl-D-aspartate (NMDA) receptor antagonist (memantine) on language functions in chronic aphasia. In a parallel group approach 28 patients were randomized to two treatment arms, 14 patients received memantine and 14 received a placebo. Patients were matched with regard to clinical and demographic characteristics and according to the authors `representative of typical samples of patients with chronic aphasia'. Language functions were assessed at six time points using the Western Aphasia Battery-Aphasia Quotient, as a global measure of aphasia severity and the CAL: prior to intervention (baseline) and at the intervals of 16, 18, 20, 24 and 48 weeks. Drug/placebo was administered between baseline and week 16 without additional language therapy, it was then administered along with CI-based therapy from weeks 16–18, and again during a follow-up period from weeks18–20. Weeks 20–24 comprised a washout period, followed by an open-label phase where all patients received the active drug.

Language functions improved more in the memantine group than in the placebo group at all time points. In particular, while language therapy improved aphasia severity in both groups, gains were more pronounced in the memantine group and these differences were maintained during the follow-up and washout period. During the open-label phase, further gains were noted. Even though the exact mechanisms of the drug's effect are unknown, memantine appears to be a promising agent to further enhance the effectiveness of intensive CI-language therapy.

Functional imaging findings

Few studies have assessed changes in neural activity in chronic patients with aphasia before and after intervention. Due to the short-term character and significant changes in language functions that have been demonstrated even in the chronic stage of aphasia following CI-based treatment approaches, researchers have begun to use it as a model to explore mechanisms of treatment induced plastic reorganization in a stage after stroke where spontaneous neurophysiologic changes are unlikely to occur (i.e., one year after stroke). Several studies have used single- or multiple case designs to study neuroplastic reorganization after CI-based language interventions.[17, 39–41] However, even though specific changes in functional activity after treatment were observed, the inherent methodological limitations of single- or multiple case designs do not allow us to draw more general conclusions about the nature and meaning of these changes.[42] In contrast, group studies do allow for generalisation of results, at least to patients with similar lesion patterns or symptom profiles.

A number of group studies in the context of CI-based treatment approaches have been accomplished using different imaging modalities (see Table 2 for an overview and additional demographic information about the respective patient samples). The first group study on functional activity changes was published in 2004 and included 28 patients with mostly mild to moderate non-fluent aphasia (18 where treated using the CI-approach, 12 were treated with MOAT).[43] As there were no differences between the groups with regard to behavioural improvements as assessed with the AAT, the imaging data for both groups was pooled and analyzed together. Functional activity was assessed prior to and after a 2-week intervention period during a 5-minute resting state MEG scan. Data analysis focused on the spatial distribution and intensity of focal slow wave activity in the delta frequency range (1–

5 Hz). Excessive slow wave activity is a marker for dysfunctional information processing and usually found in perilesional areas in stroke survivors. The study confirmed maximum slow wave activity in perilesional areas in 26 patients and the degree of change in slow wave activity after treatment was significantly (r=.60) correlated with more pronounced improvements on a standardized language test, highlighting the importance of these areas for treatment-induced recovery.

To further elucidate the functional significance of perilesional activity changes the same group conducted a follow-up study[44] that assessed MEG slow wave activity prior to treatment to determine areas of dysfunctional information processing in eleven patients with chronic aphasia. Subsequently, this information was used to define individual regions-of-interest (ROIs) to determine functional activity changes during a language and fMRI (overt naming). Using this methodology the authors found increased fMRI activity in perilesional ROIs after therapy to be correlated with treatment gains for specifically trained.

Two larger group studies used electrophysiological methods to assess changes in functional activity before and after CI-based interventions:[45, 46] Pulvermüller and colleagues[46] assessed event-related potentials in nine chronic patients with aphasia during a lexical decision task using EEG (visually presented words and pseudowords). Early word-evoked potentials (250–300 msec after stimulus onset) became significantly stronger after treatment, while the electrocortical response to pseudowords remained unchanged after treatment. Moreover, increased word-related activation in several language related areas (e.g., left posterior temporal and right frontal cortices) was significantly correlated with improved language functions as assessed by the Token Test, a measure of overall aphasia severity. Thus, activity changes in both hemispheres can be associated with a beneficial treatment outcome.

A more recent study comprised 23 patients with moderate to severe chronic aphasia.[45] The patients were assessed at three time points (prior to and after CI therapy, three months after treatment termination) using a word recognition task during MEG. The task was chosen over more direct measures of language production to avoid artifacts associated with spoken language tasks during MEG and because it has been shown to elicit activity in anterior and posterior language areas. Approximately 50% (N=11) of the patients significantly improved after treatment, but treatment gains were only maintained in eight patients during the follow-up assessment. Interestingly, only these patients showed a lasting up-regulation of activity in left (temporal) brain regions at both post assessments. Thus, the study supports previous functional imaging studies during spontaneous recovery[47] or intervention paradigms[44] showing that increased left hemisphere activity might be related to more pronounced and stable improvements. It also supports previous studies demonstrating that activity patterns can change over time and specific patterns of task-related activity may be associated with different types of short- and long-term treatment outcome.[48, 49]

Finally, in the largest published fMRI study, Richter and colleagues[50] investigated brain activity patterns in 16 chronic nonfluent aphasia patients (N=14 Broca's aphasia or anomia; two patients with global aphasia) prior to and after CI-based language therapy. The authors specifically addressed the predictive value of activity in the right hemisphere for treatment success and correlated brain activity changes with improved performance. During fMRI, two covert language-related tasks (reading and word-stem completion) were used. More pronounced functional activity during the pre-treatment scan within the right inferior frontal gyrus and the insula and a region that comprised the right precentral gyrus and middle temporal gyrus predicted treatment-induced improvement. Moreover, decreased activity in several areas of the right hemisphere (IFG/insula, precentral gyrus, middle temporal gyrus) during the post scanning session was associated with more pronounced language improvement after treatment. No correlation was found between changed activity in the left hemisphere and behavioural outcome. The authors interpreted their findings as evidence for a greater potential for improvement when the brain has spontaneously adopted a suboptimal reorganization strategy after stroke (i.e., more pronounced right hemisphere activity).

In sum, the results of the first functional imaging studies in this domain confirm previous findings from longitudinal studies of language recovery across the first year post-stroke or cross-sectional studies in chronic aphasia:[42, 51] (a) at least for language production tasks more pronounced right-hemisphere activity seems to be associated with relatively less favourable recovery that is frequently associated with larger lesions in the language dominant left hemisphere, (b) up-regulation of left-sided perilesional areas or down-regulation of right hemisphere (attention or working memory) areas seems to be associated with improved performance after therapy. However, there are several conflicting results in the above-cited studies. For example while Breier et al.[45] and Meinzer et al.[44] showed that increased perilesional activity is correlated with more pronounced improvement of language functions, Richter et al.[50] could not confirm these findings. Rather, a down-regulation of functional activity in the right hemisphere was associated with improved performance. These differences between studies can most likely be explained by different patients samples (e.g., with regard to aphasia severity, lesion location and extent; see Crosson et al.[52] for a discussion), and the use of different functional imaging techniques and activation paradigms.

In summary, neuroimaging in aphasia treatment research (like CI-based approaches) has the potential to provide insight into the neuroplastic capacities of the adult human brain and the mechanism of language recovery after brain damage. In the future, the combination of functional and structural imaging techniques (like diffusion tensor imaging, DTI)[53] may further increase our understanding of the underlying mechanisms of spontaneous and treatment-induced recovery in the context of CI-based approaches and other effective therapy regimen in the chronic stage of aphasia. This in turn may prompt changes to existing approaches and/or the development of new treatment paradigms that may contribute to the efficacy of rehabilitation efforts.

Summary and Conclusions

Although CI-based approaches for treating post-stroke aphasia were only introduced 10 years ago, a relatively large number of studies have assessed its impact on language functions and indicators of neuroplastic reorganization in response to treatment. Overall, beneficial effects on language functions using standardized tests, connected speech measures and functional communication have been reported in most studies that assessed patients with chronic aphasia. However, the relative contribution of different aspects of the treatment protocol (i.e., constraint, forced use, intensity, duration, and communicative environment) need to be investigated in future studies. Moreover, to date, the small number of published studies (compared to studies on CIMT), relatively small sample sizes and the lack of control groups in some of the studies limit the generalizability of the results.

Modifications to the protocol, such as administration by trained and supervised non-therapists, pharmacological adjuvants to treatment, training of specific language functions, and use in acute stages of recovery have yielded positive preliminary outcomes. While these adaptations demonstrate the potential of this approach to be modified and enhanced to meet the specific needs of individual patients, the sample sizes in these studies were small and the results need to be replicated in larger studies. Finally, future studies should also investigate if CI-based approaches foster real life functional communication and generalization more than other approaches by including valid and reliable measures of functional communication. These future studies will have implications for rehabilitation, which is currently suffering from a health care system that is limited in financial and human resources.

The above-mentioned adaptations of the CI-protocol may also have implications for functional imaging in aphasia treatment research. Due to the short-term character of CI-based approaches the protocol is attractive for researchers interested the neural concomitants of treatment-induced language network plasticity. Thus, modifications of the CI-protocol may allow assessment of neuroplasticity in a more specific way, which may further increase our understanding of the underlying mechanisms of treatment-induced recovery in the context of CI-based approaches (or other effective therapy regimen in the chronic stage of aphasia). This, in turn, may prompt changes to existing approaches and/or the development of new treatment paradigms that may, in the future, increase the efficacy of rehabilitation efforts.

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Table 1

Clinical studies

Study	Aims	Patient characteristics & treatment	Treatment duration/intensity & outcome measures	Main results	Conclusions
Pulvermüller et al., 2001	Comparison of intensive CI-based aphasia therapy with non-intensive “standard" aphasia therapy”	Chronic aphasia; CIAT (N=10), standard treatment (N=7)	CI-group: 3 hrs/ day, 10 consecutive work-days Control group: standard aphasia therapy, 30 hrs/ over ~ 4 weeks AAT, CAL	AAT: CI-group improved on 3/4 subtests; control group 1/4 subtests CAL: Only CI-group improved	Language functions can be improved in chronic stage by highly intensive language training within short period of time The same number of treatment hours spread out over a longer period of time is less effective
Meinzer et al., 2005	Comparison of CIAT and CIATplus; assess stability of treatment gains at 6 months post treatment	Chronic aphasia; CIAT (N=12), CIATplus (N=15)	CIAT and CIATplus: 3 hrs/ day, 10 consecutive work-days AAT, CAL, CETI	AAT: Overall language improvement in both groups; gains maintained at 6 months CAL: Increased amount of communication in both groups; improved comprehension increased only in CIATplus CETI: Improvement in functional communication in both groups; gains maintained at 6 months in CIATplus	Language functions can be improved in chronic stage by highly intensive language training within short period of time Some treatment gains are maintained at 6 months post treatment Inclusion of family and friends may be useful in training
Maher et al., 2006	Comparison of CILT and standard treatment at equal intensities; assess stability of treatment gains at 1 month post treatment	Chronic aphasia; CILT (N=4), standard treatment (N=5)	3 hrs/day, 4 days/ week for 2 weeks WAB, BNT, ANT, QPA	WAB, BNT, ANT: Overall improvement in both groups; some gains maintained at 1 month in CILT group only QPA: Some improvement in story retell in both groups: some gains maintained at 1 month in both groups	Language functions can be improved in chronic stage by highly intensive language training within short period of time CILT group showed more consistent improvement and maintenance of gains on all outcome measures
Meinzer et al., 2007	Comparison of CIAT administered by therapists and trained laypersons	Chronic aphasia; Therapist group (N=10), layperson group (N=10)	Therapist and layperson groups: 3 hrs/day, 10 consecutive work-days AAT	AAT: Similar overall language improvement in both groups	Language functions can be improved in chronic stage by highly intensive language training within short period of time Treatment administered by trained laypersons is as effective as treatment by therapists
Barthel et al., 2008	Comparison of CIAT and MOAT to determine aspects that contribute to treatment success	Chronic aphasia; CIAT (N=27 from Meinzer et al. 2005), MOAT (N=12)	CIAT and MOAT groups: 3 hrs/day, 10 consecutive work-days AAT, CAL, CETI, picture naming task	AAT: Overall language improvement; gains maintained at 6 months CAL: Increased communication, improved comprehension, improved written production, improved perception of communication; gains maintained at 6 month follow up CETI: Improvement in functional communication; gains maintained at 6 months Picture naming: Generalization to untreated items	Language functions can be improved in chronic stage by highly intensive language training within short period of time using MOAT Treatment gains maintained at 6 months post treatment Consideration of functional deficits, written language production, and everyday communication may be important in rehabilitation of aphasia

Study	Aims	Patient characteristics & treatment	Treatment duration/intensity & outcome measures	Main results	Conclusions
Szaflarski et al., 2008	Investigation of modified CIAT approach to address individual semantic, syntactic, and phonologic deficits	Chronic aphasia; N=3	3–4 hrs/day for 5 consecutive days BDAE-3, story retell, mini-CAL	BDAE-3: Improvement in verbal skills and comprehension in 2 patients Story retell: Increase in total number of words and utterances in 2 patients Mini-CAL: No improvement	Language functions can be improved in chronic stage by highly intensive language training within short period of time Modification of CIAT to treat individual deficits in language production may be successful in some cases
Berthier et al., 2009	Comparison of effects of CIAT plus memantine or placebo	Chronic aphasia; N=28	16 weeks drug or placebo; CIAT treatment for 3 hrs/day, 10 consecutive work-days; 2 weeks wash out; 24 weeks open label WAB, CAL	WAB: Improvement in overall language for both groups; significantly greater improvement in memantine group during drug therapy and washout period CAL: Improvement in communication in both groups; significantly better in memantine group	Language functions can be improved in chronic stage by highly intensive language training within short period of time Use of memantine can improve language function in isolation and in conjunction with CIAT Maintenance of treatment gains enhanced with Memantine+CIAT
Faroqi-Shah et al., 2009	Comparison of CILT-O (original) and CILT-G (grammatical)	Chronic, agrammatic aphasia; CILT-O (N=2), CILT-G (N=2)	24 hours over 10 consecutive work-days WAB, BNT, OANB- verb portion), Verb Inflection Test, Cinderella story, informal conversation	WAB, BNT, OANB-verb portion: Improvement on at least one measure of 5 calculated measures by all participants; gains maintained on 4 measures at 3 months Verb Inflection Test: Significant improvement in CILT-G group only; gains maintained at 3 months Cinderella story and informal conversation: Improvement on 4 discourse measures in all participants; gains maintained on 2 discourse measures at 3 months	Language functions can be improved in chronic stage by highly intensive language training within short period of time Grammatical constraints do not significantly impact functional language outcomes Severity and specific aphasic deficits (i.e., agrammatism) may be helpful determining CILT treatment candidacy
Goral & Kempler, 2009	Investigate modified CILT to address verb production sentences and narratives	Chronic, nonfluent aphasia; N=1	ABAB design;1.25 hours/day, 4 days/ week for 4 weeks, no treatment 4 weeks (repeat) BDAE, CLQT, personal narratives, Conversation Perception Questionnaire	BDAE: Improvement only on Auditory Comprehension subtests CLQT: No change Personal narratives: Increase in verb production, noun-verb ration, repertoire of verbs Conversation Perception Questionnaire: Significant difference in social communication abilities, perceived as more a more competent communication partner	Language functions can be improved in chronic stage by highly intensive language training within short period of time Modification of CILT to increase verb production was successful
Kirmess & Maher, 2010	Investigate modified CIAT to treat acute stroke aphasia	Acute aphasia (1–2 months post stroke); N=3	3 hours/day, 10 consecutive work-days NGA, TROG-2, VOST, PALPA, Cookie Theft, CILT baseline measures	Overall improvement in language unction on all 5 language measures Improvement on 6 speech production subtests Improvement on receptive language subtests at the sentence level in 2 patients and at	Language functions can be improved in early stages of recovery by highly intensive language training within short period of time Modification of CILT to adapt to acute care environments is reasonable

Study	Aims	Patient characteristics & treatment	Treatment duration/intensity & outcome measures	Main results	Conclusions
				the word level in 1 patient	

AAT= Aachen Aphasia Test, CAL= Communication Activity Log, CETI= Communicative Effectiveness Index,WAB= Western Aphasia Battery, BNT= Boston Naming Test, ANT= Action Naming Test, QPA= Quantitative Production Analysis, MOAT= Modified-oriented Aphasia Therapy, BDAE= Boston Diagnostic Aphasia Examination, OANB= Object and Action Naming Battery, CLQT= Cognitive Linguistic Quick Test, NGA= Norwegian Basic Aphasia Assessment, TROG-2= Test for Reception of Grammar 2, VOST= Verb and Sentence Test, PALPA= Psycholinguistic Assessments of Language Processing in Aphasia

Table 2

Overview of functional imaging group studies (N>5 patients)

Study	Aims	Patient characteristics	Imaging techniques & paradigms	Main results	Conclusions
Meinzer et al., 2004	Localization of excessive slow wave activity in the delta frequency range and impact of changed activity after treatment	28 chronic patients treated with CI-based aphasia therapy or model-oriented therapy Time since stroke: 13–156 months	MEG, resting state Correlation of activity change with improvement (standardized language test, AAT Token Test and profile score) after therapy	Excessive slow wave activity was found mainly in perilesional areas Change in slow wave activity after treatment is correlated with the degree of improvement	Highlights the importance of perilesional brain areas in language rehabilitation Up- or down regulation of slow wave activity was associated with improvement, pointing to two different mechanisms of brain plasticity
Pulvermüller et al., 2005	Processing of language stimuli before and after intervention	9 patients with chronic aphasia Time since stroke: 16–233 months	EEG, word and pseudoword evoked electrocortical responses	Early word-evoked response changed after treatment, no change for pseudowords Correlation of treatment gains and brain activity changes in both hemispheres	Highlights the importance of right and left hemisphere for treatment success
Meinzer et al., 2008	Pre-post assessment of functional activity changes in individually determined ROIs based on areas of excessive slow wave activity	11 patients with chronic aphasia and anomia Time since stroke: 19–66 months	fMRI, overt picture naming task Correlation of activity changes with naming improvement	Positive correlation between increased activity in pre-defined slow wave ROIs and naming improvement No correlations in left and right hemisphere control ROIs	Study emphasizes importance of perilesional areas for language rehabilitation in the chronic stage of aphasia
Richter et al., 2008	Impact of right-hemisphere activity on “aphasia recovery potential” Pre-post assessments of activity changes in right hemisphere ROIs in response to treatment	16 patients with chronic aphasia Time since stroke: All >1 year	fMRI, reading and wordstem completion tasks Correlation of activity prior to treatment and activity changes after treatment with composite language score	More pronounced activity in right hemisphere ROIs prior to treatment predicted treatment outcome Decreased activity in right hemisphere ROIs after treatment was associated with improvement	Downregulation of “dysfunctional” right hemisphere activity may be associated with treatment-induced improvement
Breier et al., 2009	To assess specific brain activity changes associated with short- and long-term training success	23 patients with chronic aphasia Time since stroke: all >1 year	MEG, word recognition task Three assessment points (prior to and after treatment; 3-months follow-up) Patients were divided in three groups: (1) treatment responders who maintained gains (2) responders who lost gains at follow-up assessment (3) non-responders	Only group that maintained initial treatment gains showed consistent up-regulation of activity in left hemisphere at both assessments	Highlights the importance of perilesional areas in the left-hemisphere Groups with different treatment outcome show specific changes in brain activity Emphasizes the need for follow-up assessments as activity patterns show dynamic changes depending on treatment success

fMRI=functional magnetic resonance imaging; EEG=electroencephalography; MEG=magnetoencephalography; ROI=region-of-interest