PERSPECTIVES

Recent advances in the treatment of post-stroke aphasia

Aphasia is an impairment of language use following brain damage. There is no consensual definition of aphasia beyond this general description (Code and Petheram, 2011). In a more restricted definition, however, aphasia is an impairment of linguistic processing at the phonological, morphological, lexical semantic or syntactic level which is usually caused by lesions of the left cerebral hemisphere. This impairment can affect language reception and expression depending on the various aphasic syndromes (McNeil and Pratt, 2001). Aphasia results in restrictions in those activities of daily living which rely on communication. In terms of the International Classification of Functioning, Disability and Health (WHO, 2001), limitations in functional communication pose significant challenges to social participation (Davidson et al., 2008) and reduce the patients' quality of life (Kauhanen et al., 1999; Shadden, 2005). Recent data on the incidence of aphasia following stroke range between 0.02 and 0.06 % with a prevalence between 0.1 and 0.4 % in the developed world (Code and Petheram, 2011). Spontaneous behavioral recovery usually occurs to some degree in the weeks to months after stroke and depends on many factors such as the infarct size and location and the severity of initial stroke deficits (Cramer, 2008). Traditionally, proposed mechanisms of the neurological intrinsic recovery are the resolution of edema surrounding the infarcted area (Katzman et al., 1977; Lo, 1986) and reperfusion of incompletely damaged, but highly vulnerable perilesional tissue (see Donnan et al., 2013). These local mechanisms are supposed to support early recovery (in days to weeks after stroke) and do not depend on behavioral experience but have been targeted by pharmacological treatments: of more than a thousand drugs tested in animal models, 114 have been studied in clinical trials (Pérez de la Ossa and Davalos, 2007) and to date none of these potentially neuroprotective agents was found to be effective in humans. Only rapid reperfusion with recombinant tissue plasminogen activator (rTPA) does improve functional outcome after ischemic stroke, but its use is limited by a short therapeutic window (4.5 hours following stroke), the risk of hemorrhage and potential ischemia/reperfusion injury (Lakhan et al., 2009). In contrast, neuronal network reorganization, which also occurs spontaneously, has been related to later recovery and can be influenced by environmental and behavioral factors (Cramer, 2008; Nudo, 2011, 2013). On the molecular level, regulation of gene expression in the unaffected peri-infarct tissue seems to favour the synthesis of growth promoting and to suppress the synthesis of growth inhibiting proteins thus creating a permissive environment for axonal/dendritic sprouting and may thus offer a window of opportunity for behavioural interventions to be effective (Carmichael, 2006).

Even after standard treatments provided by the health care systems, the majority of people with aphasia have a chronic communication disability. Speech and language therapy (SLT) is the current standard of care for aphasia treatment but supplemental therapeutic strategies are emerging. The aim of this short review is to give an overview of current advances in research on behavioural, pharmacological and electrophysiological treatments for post-stroke aphasia.

SLT

Research on SLT efficacy in post-stroke aphasia has accelerated dramatically in the last decade. Until 1999, only 12 trials fulfilled the rigorous Cochrane criteria for inclusion into a systematic Cochrane review (Greener et al., 1999). This initial review was updated in 2011 based on 39 randomized controlled trials (RCT) involving 2,518 randomized patients (Brady et al., 2012) and came to the conclusion that the analyzed studies gave some evidence of the effectiveness of SLT for the improvement of functional communication, receptive and expressive language after stroke. Notably, they found a significant effect in the meta-analysis of nineteen randomized comparisons (1,414 participants) of SLT versus no SLT on patients' functional communication (standardised mean difference 0.30, 95% *CI* 0.08 to 0.52, $P = 0.008$). The molecular mode of action of SLT is still largely unknown.

Traditionally, SLT consists of *impairment-based therapies*, which aim at improving functional communication in targeting the underlying linguistic deficits. For example, an SLT targeting semantic deficits will use semantic decision tasks at the word, sentence or text level to improve linguistic semantic processing whereas in the case of phonological deficits, SLT will train phonological input and output processing (Doesborgh et al., 2004). A few impairment-based therapies are designed to be used as a holistic treatment program to improve language in daily communication. Examples are the melodic intonation therapy (Sparks et al., 1974; AAN, 1994) which uses a specific singing-speech technique that presumably engages language capable areas in the right hemisphere (but see Zumbansen et al., 2014, for a critical review) and the constraint induced language therapy (Pulvermüller et al., 2001) that extends principles of constraint-induced movement therapies to language rehabilitation by setting intensive stimulation training of the impaired linguistic functions while supressing compensatory behaviors such as gestures. To date, however, there is no conclusive evidence that one SLT approach is better than another on functional communication outcomes (Brady et al., 2012).

In clinical practice, SLT clinicians commonly use combinations of different therapeutic approaches on an attempt to tailor the language treatment to each patient's clinical profile (Rose et al., 2014). In order to document therapeutic efficacy, Beeson and Robey (2006) recommend using outcome measures based on untrained test material and assessment of connected natural speech or similar evaluation tools for functional communication. Although these latter measures have rarely been reported in efficacy studies, as already mentioned, impairment-based therapies have shown some effectiveness on functional communication in patients with aphasia after stroke (Brady et al., 2012) and the most recent RCTs have reinforced the level of evidence of these approaches (Godecke et al., 2012; Sickert et al., 2014; van der Meulen et al., 2014).

However, despite the efficacy of these therapies the majority of stroke survivors do not recover completely from their language impairment, necessitating a quest for alternative therapeutic approaches in SLT practice to help patients regaining a better quality of life with aphasia (Rose et al., 2014). So-called *functional-based* approaches do not aim at improving language *per se* but focus instead on the larger level of functional communication. Functional communication refers to the ability to communicate in real world settings (Brady et al., 2012) and includes both linguistic and extra-linguistic means (Worrall and Frattali, 2000; Holland and Hinckley, 2004). Those treatments target non-linguistic communicative skills which can be optimized to improve daily communication activities relevant to the patient (*e.g.*, mimic and gestures). It also involves training of the patient's relatives to make them better communication partners. Because functional-based approaches are relatively new in comparison to their impairment-based counterparts, the available evidence of their efficacy is weaker to date and more well-designed studies are needed to document the efficacy of these interesting new therapeutic strategies.

In sum, there is good evidence that SLT benefits patients' functional communication, receptive and expressive language compared to no SLT and it is likely that results are better with intensive rather than low-frequency treatment. There is no evidence that any of the discussed therapies is superior to the others (Brady et al., 2012). Aphasia treatment is usually provided at the intensity of one to five hours per week on average. Recent studies seem to suggest that treatment of such intensity is likely insufficient and it is estimated that almost twice this intensity is required to achieve significant

treatment effects beyond spontaneous recovery (Code and Petheram, 2011). However increasing treatment intensity often is not feasible due to economic limitations in most public health systems but also due to the lack of various other resources, such as time and space (Rose et al., 2014). Thus, research on non-behavioral supplementary treatments is needed, which may potentiate the effectiveness of SLT, particularly in acute and subacute stages where the SLT is currently provided with highest intensity (Katz et al., 2000; Verna et al., 2009). Such possible adjuvant strategies may comprise pharmacological approaches as well as non-invasive brain stimulation (NIBS).

Adjuvant pharmacotherapy for enhancement of SLT effects

As for any other post-stroke deficits, adequate acute stroke management according to current guidelines (Jauch et al., 2013) to minimize primary (*e.g.*, by reperfusion therapies) and secondary brain damage (*e.g.*, through treatment of edema, neuroprotection, *etc.*) is also fundamental for aphasia recovery. In this review, we only focus on pharmacological therapies which have specifically been investigated in conjunction with SLT and may have the potential to enhance SLT efficacy. A number of drugs have been studied for possible SLT enhancing effects (Berthier et al., 2011; Salter et al., 2013; Cahana-Amitay et al., 2014). Here, we briefly present those substances which have been tested in RCTs for their presumed neuromodulatory effect on various neurotransmitters systems.

Piracetam, a cyclic derivative of γ-aminobutiric acid (GABA), has been considered as promising in conjunction with intensive SLT in the acute and sub-acute phases (Greener et al., 2001; Liepert, 2008; Berthier et al., 2011). In one study, 2,400 mg taken twice daily had a positive effect on several expressive and receptive language subtests as well as spontaneous speech (Kessler et al., 2000). The specific mechanisms of action of Piracetam are not well understood. Kessler and colleagues (2000) found increases in cerebral blood flow in key language areas which were positively correlated with language recovery. Other mechanisms might involve modulation of cholinergic, glutamatergic and possibly GABAergic neurotransmitter systems.

Donepezil and other cholinergic agents (*e.g.*, Galantamine, Bifelemane and Physostigmine) have shown some positive therapeutic effects in post-stroke aphasia (Berthier et al., 2011; Berthier, 2014). Notably, 10 mg of Donepezil per day in combination with only two hours of SLT per week improved picture naming (Cohen's d = 0.92, large effect size) and the severity of aphasia (Cohen's d = 0.87, large effect size) in a RCT with 26 participants (Berthier et al., 2006). By inhibiting acetylcholinesterase, Donepezil is thought to facilitate neurotransmission in cerebral cholinergic connections to language brain areas (Kasa et al., 2000). These pathways play an important role for practice-related plasticity based on long-term potentiation enhancing attention, learning and memory (Sarter et al., 2005).

Memantine (10 mg twice daily) was tested in one RCT only and seemed to be associated with long-lasting effects on outcome measures of language function and functional communication. In this study, pharmacotherapy was combined with intensive SLT administrated as group therapy to patients with chronic aphasia (Berthier et al., 2009). As NMDA receptor agonist, Memantine is supposed to act on glutamatergic transmissions and enhance the activity of preserved neural networks. Further studies are needed to support these promising results.

Several cathecholaminergic drugs have been investigated in conjunction with SLT with inconclusive results. To date, two dopaminergic agents (Bromocriptine and Levodopa) have been tested in two RCTs each (Gill and Leff, 2014). Bromocriptine showed no treatment effect (Sabe et al., 1995; Ashtary et al., 2006) but no SLT treatment was provided during these studies. In contrast, Seniów et al. (2009) found L-dopa to be effective when paired with intensive SLT over three weeks during the sub-acute phase, particularly in patients with frontal lesions. However, Leemann et al. (2011) found no effect of Levodopa over placebo with intensive SLT over two weeks.

The effect of amphetamines was subject to one RCT with aphasic patients in the sub-acute phase post-stroke. 10 STL sessions over five weeks preceded by intakes of 10 mg of Dextroamphetamine improved language recovery (Walker-Batson et al., 2001). However, for now, the use of amphetamines for improving recovery after stroke is not recommended in clinical practice (Martinsson et al., 2007).

In summary, following the criteria for the evidence based review in stroke rehabilitation (Salter et al., 2013), the level of evidence supporting the general use of these drugs to improve aphasia recovery is moderate. Strongest evidence to date exists for the efficacy of Piracetam in combination with SLT and strongest evidence for inefficacy exists for Bromocriptine. For now, none of the drug is recommended for routine use in aphasia rehabilitation and further research are warranted both to support clinical pharmacological treatment for post-stroke aphasia and to better understand the mechanisms by which the different drugs act on language and communication recovery.

Noninvasive brain stimulation (NIBS) as adjuvant therapy for SLT

NIBS can modulate the excitability and activity of targeted cortical regions. With increasing knowledge and improved understanding of the roles of the dominant (usually left) and nondominant (usually right) hemisphere language networks in brain reorganization after stroke, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have emerged as new electrophysiological approaches to aphasia rehabilitation (Table 1). Aphasia recovery can be supported by reactivation of perilesional cortical areas (intrahemispheric compensation) or by transfer of language functions into the nondominant, nonaffected hemisphere (interhemispheric compensation) (Heiss and Thiel, 2006).

Table 1 Comparison of two NIBS techniques: rTMS and tDCS

	rTMS	tDCS
Stimulation principle	Electromagnetic pulses at a sufficient intensity applied over the scalp induce a current in the underlying cortical neurons	Week currents between a pair of saline-soaked surface sponge electrodes are transmitted through the cortex (one electrode over the target area and the other as a reference on another part of the body)
Target precision	Focal (using a figure-of-eight coil)	Non-focal (large electrodes)
Type of currents induced	Large (~5 kA) but brief (in μs) currents	Weak (1–2 mA) but long (minutes) currents
Inhibitory mode	Low frequency rTMS (≤ 1 Hz)	Cathode over the target area
Excitatory mode	High frequency rTMS (> 1 Hz)	Anode over the target area

rTMS: Repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation.

Interhemispheric compensation is thought to occur by unmasking of possibly language related areas in the right hemisphere (RH) through reduction of transcallosal inhibition by a lesion in the left hemisphere (LH) (Winhuisen et al., 2005). There is an on-going debate on whether this released activity in those RH networks is beneficial for recovery of language function (Anglade et al., 2014). In post-stroke aphasia, regions of the RH that are homologue to the language areas in the damaged left hemisphere (LH) can support some language recovery, however, the best rehabilitation results have so far been observed with intrahemispheric rather than interhemispheric compensation (Heiss et al., 1999; Rosen et al., 2000). Therefore, the majority of NIBS studies have tried to facilitate recruitment of perilesonal cortex in the damaged hemisphere (Torres et al., 2013). Excitatory NIBS (high-frequency rTMS > 1 Hz; intermittent theta burst stimulation; anodal tDCS) has been used to augment cortical excitability of the left hemispheric language network, whereas inhibitory NIBS (low-frequency rTMS ≤ 1Hz; cathodal tDCS)

aims at reducing RH over-activations (Heiss and Thiel, 2012). Both approaches are based on the idea that re-establishing left hemisphere language network activity results in better rehabilitation results (Crosson et al., 2007).

To date, RCTs using *inhibitory rTMS* have shown some evidence of effectiveness on language and functional communication outcomes in chronic post-stroke aphasia even without SLT (Barwood et al., 2011; Medina et al., 2012). However, patients in the acute stages undergoing SLT seem to benefit more from this type of brain stimulation (Kindler et al., 2012). In fact, several recent RCTs involving right-handed patients with sub-acute aphasia support the enhancing effect of inhibitory rTMS on language recovery when combined with SLT (Weiduschat et al., 2011; Kindler et al., 2012; Heiss et al., 2013; Seniów et al., 2013; Thiel et al., 2013). Because not all patients seem to benefit equally from this treatment (Waldowski et al., 2012; Heiss et al., 2013; Seniów et al., 2013), there is a need to refine the criteria identifying those patients which are likely to best respond to this kind of therapy. For example, Seniów and colleagues (2013) report better efficacy in participants with severe aphasia and Heiss and colleagues (2013) showed that left handers might not respond to the treatment in the same way as right handers. Recently, language improvements have been related to SLT in combination with *inhibitory and excitatory rTMS* in patients with subacute non-fluent aphasia (Khedr et al., 2014). Some positive results on anomia (as measured by picture naming and semantic fluency tasks) have also been reported in case series with *excitatory rTMS* (Cotelli et al., 2011; Szaflarski et al., 2011), but no RCT testing this stimulation mode has been published to date.

In comparison to rTMS, available evidence for tDCS in aphasia rehabilitation is scarce. In 2013, a Cochrane review included four randomized controlled cross-over trials with a total of 33 patients with chronic aphasia (Monti et al., 2008; Flöel et al., 2011; Kang et al., 2011; Marangolo et al., 2011) and one RCT with 21 patients with subacute aphasia (You et al., 2011). This was the first systematic review of this stimulation modality and it was concluded that at present there is insufficient evidence to support the view that tDCS enhances SLT outcomes, contrary to the conclusion of many published trials (Elsner et al., 2013). However, the authors found some indication of positive effects with cathodal tDCS (*i.e.*, inhibitory NIBS) over the non-lesioned hemisphere based on three studies (Flöel et al., 2011; Kang et al., 2011; You et al., 2011) and advocated further randomized controlled trials with a parallel group design and sample-size estimation.

Beyond improved clinical trial design future RCTs on NIBS efficacy also need to investigate alternate stimulation sites for tDCS (Baker et al., 2010; Fiori et al., 2013; Marangolo et al., 2014) and for rTMS (Heiss et al., 2013), possibly neuroimaging guided and should control for lesion location and premorbid hemispheric speech dominance.

Conclusion

SLT is the best treatment to improve language and functional communication in post-stroke aphasia. However, even well studied impairment-based approaches show limited effects on language recovery. Pharmacological (in particular Piracetam) and NIBS strategies (mainly inhibitory rTMS over the contralesional hemisphere) offer promising new ways to optimize SLT effects and clearly merit further research.

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Funding: *Canadian Institutes for Health Research.*

Conflicts of interest: *None declared.*

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Accepted: *2014-04-15*

doi:*10.4103/1673-5374.131570 http://www.nrronline.org/*

Zumbansen A, Thiel A. Recent advances in the treatment of post-stroke aphasia. Neural Regen Res. 2014;9(7):703-706.

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