Rehabilitation in Chronic Aphasia: Plateau or Potential for Recovery

British Society of Rehabilitation Medicine: Medical Student Essay Prize

Word count: 2,490

Table of Contents

List of Abbreviations

AAT – Aachen Aphasia Test

ANELT-A – Amsterdam-Nijmegen Everyday Language Test – A

BDAE – Boston Diagnostic Aphasia Examination

CAL – Communicative Activity Log

CIAT – Constraint induced aphasia therapy

FCP – Functional Communication Profile

MIT – Melodic intonation therapy

QOL – Quality of life

RCT – Randomised controlled trial

rTMS – Repetitive transcranial magnetic stimulation

tDCS – Transcranial direct current stimulation

TMS – Transcranial magnetic stimulation

WAB-AQ – Western Aphasia Battery – Aphasia Quotient

Introduction

Stroke is typified by the acute onset of neurological deficit as a result of a vascular insult. It is a common, affecting approximately 150 per 100,000 in the United Kingdom each year (Wang et al., 2013). Stroke is associated with a wide range of symptoms including weakness, loss of vision, and aphasia, amongst many others. This essay aims to determine whether there is a recovery plateau in chronic post-stroke aphasia.

Aphasia can be broadly defined as an acquired language impairment occurring as a consequence of a focal brain lesion (Rosenbeck et al., 1989). It is an umbrella term for a spectrum of language disorders, as shown in Table 1. Aphasia is a relatively common clinical feature following stroke; between 21-38% are affected acutely (Berthier, 2005).

Table 1. Clinical Features of Aphasia (Adapted from Feinberg & Farah, 2003)

Aphasia Type	Clinical Features	Neuroanatomical Lesion*
Broca's Aphasia	Non-fluent speech, relatively intact comprehension, agrammatism	Inferior frontal gyrus/ frontal operculum (Brodmann areas 44 and 46)
Wernicke's Aphasia	Fluent speech with normal sentence length and normal use of grammar, impaired comprehension, content may be extremely paraphasic with neologisms and phonemic paraphasias	Superior temporal gyrus back to the end of the sylvian fissure and adjacent areas
Global Aphasia	Significant impairments in all aspects of language, language output and comprehension are both severely limited	Large lesion involving entire perislyvian region involving typical Broca's and Wernicke's lesions
Transcortical Sensory	Language output fluent, paraphasias common, repetition is normal	Lesions of middle and inferior temporal gyri
Transcortical	Non-fluent speech, relatively	Dorsolateral prefrontal cortex

Motor	intact comprehension, often initially mute, repetition normal/ vastly superior to spontaneous speech	(Brodmann areas 44, 46, 6, and 9), or damage to subcortical frontal white matter
Conduction Aphasia	Language output fluent, comprehension intact, speech largely normal, repetition is poor and dominated by phonemic paraphasias	Inferior parietal lobule, classically involving the supramarginal gyrus and the arcuate fasciculus

* The neuroanatomical lesion refers to the typical/ most common site of lesions causing the respective aphasia. However, it is well established that there is a large degree of overlap and a wide variety of lesions may cause each type of aphasia

Aphasia is often worst in the acute setting and subsequently improves (Watila & Balarabe, 2015). It is widely believed that patients have maximal opportunity to recover during the acute phase post-stroke, and little or no capacity to recover in the chronic phase, the so-called recovery plateau. Despite these beliefs, there is emerging evidence to suggest that even patients with chronic post-stroke aphasia have capacity to improve (Allen et al., 2012). Given the significant burden that aphasia imposes, it is imperative that the evidence base surrounding these claims is understood.

This essay will review pertinent literature surrounding the efficacy of interventions in chronic aphasia to determine if the notion of a plateau in post-stroke aphasia is justified.

Methods

Search Strategy

Medline, Embase, and Cochrane central register of controlled trials (CENTRAL) databases were searched from their inception until April 2017. The search strategy in Medline included the following Medical Subject Headings: Stroke, Cerebrovascular

Disorder, Brain Ischemia, Brain Infarction, Cerebral Infarction, Stroke Rehabilitation, Rehabilitation, Neurological Rehabilitation, Speech Therapy, Language Therapy, Aphasia, Language Disorders, Speech Disorders, and free text words: stroke, brain isch$emia, brain infarction, rehabilitation, stroke rehabilitation, speech and language therapy. The search was limited to English language articles and randomised controlled trials (RCTs) to gather robust evidence. One reviewer assessed the search results against eligibility criteria to identify relevant articles. Review articles were screened to identify additional primary literature. This search was adapted to the syntax of abovementioned databases and repeated.

Eligibility Criteria

All primary literature evaluating the efficacy of interventions in chronic aphasia, at least 6 months post-stroke, were considered. Studies were also required to report aphasia severity and/or quality of life as their primary outcome. Studies were excluded if aphasia was not due to stroke.

Data extraction/ synthesis

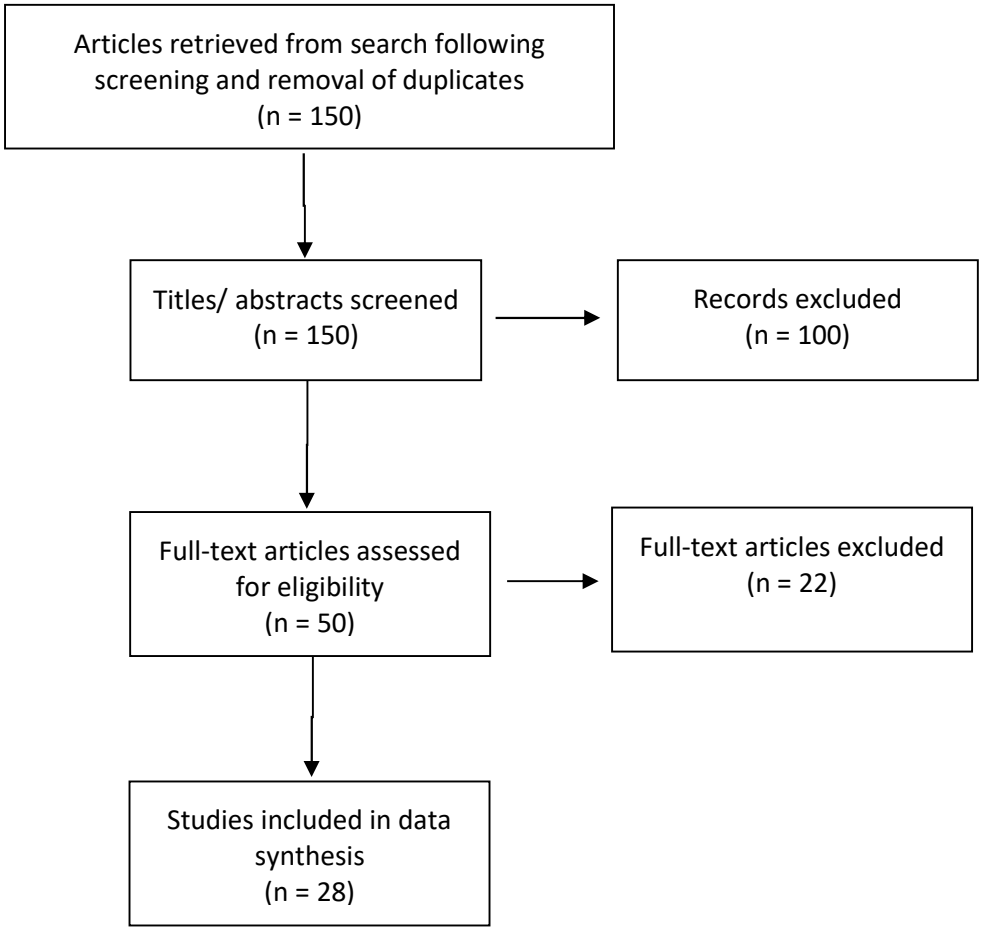
A single reviewer extracted information pertaining to the severity of aphasia and/or quality of life, and the demographics of participants. Due to the heterogeneity of interventions and methodology used it was deemed inappropriate to combine the results of individual studies.

Results

Search Results

Search results are depicted in a flow diagram in Figure 1. Following application of eligibility criteria 32 studies were retrieved. The interventions considered in these studies may be categorised into four broad themes: speech and language therapy, neurostimulation, pharmacological, and miscellaneous interventions. The results of these studies will now be considered, followed by a critical evaluation of how they support or refute the notion of a recovery plateau in chronic aphasia.

Figure 2. Search Results (adapted from PRISMA guidelines)



Neurostimulation

7 of the 28 articles retrieved evaluated neurostimulation techniques in chronic aphasia. The techniques included transcranial magnetic stimulation (TMS) (Barwood et al., 2011; Cotelli et al., 2011), transcranial direct current stimulation (tDCS) (Fiori et al., 2013; Sebastian et al., 2017; Baker et al., 2010; Floel et al., 2011), and epidural cortical stimulation (Cherney et al., 2016). A summary of the results of these studies is shown in Appendix A.

Barwood and colleagues (2011) found an increase in the overall Boston Diagnostic Aphasia Examination (BDAE) score after two months for those who underwent low frequency repetitive TMS (rTMS) of pars triangularis compared to sham stimulation, without accompanying speech and language therapy (SLT). Cotelli and colleagues (2011) found a significant improvement in object naming following high frequency rTMS of the dorsolateral prefrontal cortex combined with 25 minutes of SLT per day.

Four studies (Fiori et al., 2013; Sebastian et al., 2017; Baker et al., 2010; Floel et al., 2011) evaluated the efficacy of tDCS applied to a variety of locations including frontal, temporal, and cerebellar regions. Together they suggested that tDCS combined with SLT could benefit patients' naming and spelling ability. Temporal tDCS was most effective for noun naming and frontal tDCS for verb naming, increasing percentage correct from baseline by 21% and 29%, respectively (Fiori et al., 2013).

Cherney and colleagues (2016) suggested epidural cortical stimulation combined with intensive SLT to improve mean Western aphasia battery – Aphasia quotient (WAB-AQ) score greater than SLT alone. However, it is unclear whether these differences were statistically significant.

Speech and Language Therapy and Related Interventions

9 of the 28 articles retrieved evaluated the efficacy of SLT in chronic aphasia. The results of these studies are summarized below in Appendix B. Breitenstein and colleagues (2017) performed a large, well-powered RCT consisting of 156 participants comparing the efficacy of intensive SLT, consisting of over 10 hours per week for at least 3 weeks, to deferral of intensive SLT. Intensive SLT resulted in significant improvement in language ability at 6 months, measured by the Amsterdam-Nijmegen Everyday Language Test – A (ANELT-A). Notably, improvements were not related to time since last stroke. A smaller scale study evaluating the efficacy of intensive SLT, consisting of 25 hours per week for 12 weeks, found significant improvements in speech, reading, and overall scores using the Functional Communication Profile (FCP).

Constraint induced aphasia therapy (CIAT) is a type of intensive speech therapy that aims to promote aphasia recovery by restricting patients to using spoken language without compensatory mechanisms such as gestures (Pulvermeller et al., 2011). Using different methodologies, three studies (Pulvermeller et al., 2011; Szaflariski et al., 2015; Meinzer et al., 2007) have demonstrated benefit in chronic aphasia. Pulvermeller and colleagues (2011) found 30-35 hours of CIAT over 10 days generated an average 30% improvement

on the Communicative Activity Log (CAL) compared to the equivalent SLT over 4 weeks. Meinzer and colleagues (2007) compared the efficacy of CIAT to CIAT 'plus', which supplemented CIAT with written materials. Overall AAT score significantly improved at the group level and for 86% of individuals in CIAT and CIAT 'plus' groups.

Other SLT interventions trialled in chronic post-stroke aphasia included group communication treatment (Elman & Bernstein-Ellis, 1999), mapping therapy (Rochon et al., 2005), and intensive multimodal therapy (Kendall et al., 2015), which demonstrated mixed results as shown in Appendix B.

Pharmacological

Pharmacological agents were trialled in 7 of the 28 articles considered, and for the vast majority of these studies pharmacological agents were used in conjunction with SLT. Studies by Gupta and colleagues (1995), and Sabe and colleagues (1995) used bromocriptine independently of SLT. A summary of results is provided Appendix C.

Donepezil, in conjunction with SLT, improved scores on the WAB-AQ by an average of 2.9 points compared to placebo ($p = 0.037$) (Berthier et al., 2006). However, no improvement was evident post washout. Notably, the WAB-AQ score also increased for those who underwent SLT with placebo, to a lesser extent. Berthier and colleagues (2009) evaluated the efficacy of memantine as an adjunct to CIAT, compared to placebo. Results suggested that CIAT and memantine could both improve outcomes on the CAL and WAB-AQ in chronic aphasia, with maximal benefit occurring in combination. Whiting

and colleagues (2007) found mixed improvements using dexamphetamine as an adjunct to naming therapy. Other drugs trialled in chronic aphasia with no clear benefit include L-Dopa and bromocriptine (Breitenstein et al., 2005; Gupta et al, 1995; Sabe et al., 1995)

Miscellaneous

Other interventions evaluated in chronic post-stroke aphasia include music therapy and computer based language therapy. Raglio and colleagues (2016) compared the efficacy of SLT alone, to SLT combined with active music therapy based upon musical improvisation together with the therapist. A significant improvement was found in spontaneous speech on the AAT for those that underwent music therapy together with SLT ($p = 0.02$). Van Der Meurlen and colleagues (2016) investigated the efficacy of melodic intonation therapy (MIT), which requires patient to 'sing' phrases used in daily life. A significant task related improvement for the MIT group was found compared to the control group, however this was not maintained at 6 week follow up.

Computer (Palmer et al., 2012, Katz et al., 1997) and electronic devices (Nobis Bosch et al., 2011) have also appeared to benefit patients with chronic aphasia. Palmer and colleagues (2012) found an average increase in naming ability of 19.8% at 5 months for those who underwent computer therapy compared to usual treatment ($p = 0.014$). Results of miscellaneous studies are detailed in Appendix D.

Discussion

The extent to which the results of these studies provide evidence for or against a recovery plateau in chronic aphasia will now be considered, along with the limitations of these studies.

Neurostimulation

The results presented above suggest that recovery is possible in the chronic phase of stroke using neurostimulation independently, or as an adjunct to SLT. These studies included patients up to 21 years post-stroke, yet still suggested potential for recovery. A meta-analysis of tDCS and rTMS suggested tDCS to be more effective in the chronic phase compared to earlier stages (Shah-Basak et al., 2016), and rTMS to be more effective earlier in post-stroke aphasia. These conflicting results may suggest that the potential for recovery in different phases is dependent upon the type of intervention used.

Despite providing some evidence against a recovery plateau in chronic aphasia there were methodological limitations. Firstly, all of the studies considered have modest follow up lengths with none exceeding one year. Secondly, benefits of language were only evidenced using formal neuropsychological testing. Therefore, meaningful long-term improvements, including improvement in quality of life (QOL), should be evidenced before the presence of a recovery plateau in chronic aphasia can be refuted. Furthermore, the total sample size of all studies combined was limited to 53 participants and the methods used, including the location/ duration of stimulation and outcomes measured, were heterogeneous. In addition, the findings of individual studies have not been

replicated, raising the possibility of publication bias. Taking these limitations into consideration, it would be premature to conclude that a recovery plateau does not exist in chronic aphasia. Nonetheless, the results do make some suggestion that patients with chronic aphasia have some potential for recovery.

Speech and Language Therapy

The results from SLT studies have shown benefit for patients with chronic aphasia. Results from Breitenstein and colleagues (2017) will be the focus of discussion as they offer the most convincing evidence to suggest that patients with chronic aphasia post-stroke have the potential for recovery.

Breitennstein and colleagues (2017) conducted a well-powered robust study with a large sample of 156 patients that minimized the risk of bias. They found intensive SLT to improve language outcomes for patients up to 5.7 years post stroke by an average of 2.61 points on the ANELT-A at 6 months follow up. Strengths of this study included an outcome measure pertinent to everyday life, and a diverse demographic of participants due to a wide inclusion criteria. Given the high quality of the study this provides good evidence that patients with chronic post-stroke aphasia have the potential to recover. Despite offering convincing evidence, intensive therapy is usually associated with higher dropout rates (Brady et al., 2012), which may limit the efficacy of intensive SLT in clinical practice. Secondly, the benefit was relatively small at 2.61 points on the ANELT-A and the follow up length was modest at 6 months. Therefore, demonstrating reproducibility in another cohort with long-term follow up should be a priority. Despite

these limitations, this study provides solid evidence against a plateau in chronic post-stroke aphasia by demonstrating potential for recovery in patients up to 5.7 years post-stroke.

Pharmacological

There is mixed evidence surrounding pharmacological adjuncts in chronic aphasia. Whilst many studies suggested improvement, the duration of benefits and effect sizes were often modest. Furthermore, methodological flaws limit the significance of many findings. Firstly, sample sizes were modest with all having less than 50 participants and most less than 30. Secondly, the demographics of participants for many of the studies were not representative of the stroke population as a whole. For example, two studies only included patients with non-fluent aphasia caused by ischemia (Gupta et al., 1995; Sabe et al., 1995). Additionally, a number of studies only included patients less than 70 years of age, younger than the typically elderly stroke population. Finally, bromocriptine and L-Dopa showed no benefit.

In contrast to these findings, there is some evidence to support pharmacological adjuncts in acute rehabilitation (Berthier et al., 2011) In particular piracetam has shown promise and a Cochrane review (Greener et al., 2001) suggested further research to determine its efficacy in acute aphasia rehabilitation after stroke. There is no equivalent evidence base for the use of piracetam in chronic aphasia, possibly suggesting that aphasia recovery plateaus in the chronic phase.

Miscellaneous

Active music therapy (Raglio et al., 2016) and MIT (Van Der Meurlen et al., 2016) both benefited language abilities in chronic aphasia patients. However, the benefits of MIT were confined to trained tasks and not maintained at follow up. Therefore, this does not provide evidence of meaningful recovery in chronic aphasia. There is also evidence for the use of electronic/ computerised reading therapy, with all three studies demonstrating positive effects in chronic aphasia patients.

Limitations

In addition to the limitations of relevant studies, the limitations of this literature review should be considered. Firstly, data extraction and application of the eligibility criteria was performed by a single author and therefore may be subject to bias. Furthermore, the search was limited to RCTs and to English language articles, potentially missing important literature. Finally, only published articles were included without consideration of unpublished material and this could lead to publication bias and skew towards positive results.

Conclusion

Overall, the evidence surrounding the proposed recovery plateau in chronic aphasia is mixed. Most studies are limited by common deficiencies including sample size, relevant outcome measures pertinent to everyday life, long term follow up data, and a lack of reproducible results. These limitations prevent definitive conclusions being drawn about the potential for recovery in chronic aphasia for most interventions. However,

Breitenstein and colleagues (2017) in particular offer convincing evidence against a recovery plateau in chronic aphasia. A robust study design was used and demonstrated potential for meaningful recovery in patients with chronic aphasia at 6 month follow up. Therefore, whilst most interventions require further investigation with regards to their use in chronic aphasia it appears that intensive SLT may be efficacious. These findings conflict with widely held beliefs of a recovery plateau in chronic aphasia and it is imperative that clinical practice begins to reflect these findings. Future studies should aim to reproduce these findings and determine the optimal intensity, dose, and adjuvants that may be used to improve outcomes in chronic post-stroke aphasia.

References

Allen, L., Mehta, S., Andrew McClure, J. and Teasell, R., 2012. Therapeutic interventions for aphasia initiated more than six months post stroke: a review of the evidence. *Topics in stroke rehabilitation*, 19(6), pp.523-535.

Baker, J.M., Rorden, C. and Fridriksson, J., 2010. Using transcranial direct-current stimulation to treat stroke patients with aphasia. *Stroke*, 41(6), pp.1229-1236.

Barwood, C.H.S., Murdoch, B.E., Whelan, B.M., Lloyd, D., Riek, S., O'Sullivan, J.D., Coulthard, A. and Wong, A., 2011. Improved language performance subsequent to low□frequency rTMS in patients with chronic non□fluent aphasia post□stroke. *European Journal of Neurology*, 18(7), pp.935-943.

Berthier, M.L., 2005. Poststroke aphasia. *Drugs & aging*, 22(2), pp.163-182.

Berthier, M.L., Green, C., Higueras, C., Fernandez, I., Hinojosa, J. and Martin, M.C., 2006. A randomized, placebo-controlled study of donepezil in poststroke aphasia. *Neurology*, *67*(9), pp.1687-1689.

Berthier, M.L., Green, C., Lara, J.P., Higueras, C., Barbancho, M.A., Dávila, G. and Pulvermüller, F., 2009. Memantine and constraint□induced aphasia therapy in chronic poststroke aphasia. *Annals of neurology*, *65*(5), pp.577-585.

Berthier, M.L., Pulvermüller, F., Dávila, G., Casares, N.G. and Gutiérrez, A., 2011. Drug therapy of post-stroke aphasia: a review of current evidence. *Neuropsychology review*, *21*(3), pp.302-317.

Brady, M.C., Kelly, H., Godwin, J. and Enderby, P., 2012. Speech and language therapy for aphasia following stroke. *The Cochrane Library*.

Breitenstein, C., Grewe, T., Flöel, A., Ziegler, W., Springer, L., Martus, P., Huber, W., Willmes, K., Ringelstein, E.B., Haeusler, K.G. and Abel, S., 2017. Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. *The Lancet*.

Breitenstein, C., Korsukewitz, C., Baumgärtner, A., Flöel, A., Zwitserlood, P., Dobel, C. and Knecht, S., 2015. L-dopa does not add to the success of high-intensity language training in aphasia. *Restorative neurology and neuroscience*, *33*(2), pp.115-120.

Brindley, P., Copeland, M., Demain, C. and Martyn, P., 1989. A comparison of the speech of ten chronic Broca's aphasics following intensive and non-intensive periods of therapy. *Aphasiology*, *3*(8), pp.695-707.

Cherney, L.R., 2016. Epidural cortical stimulation as adjunctive treatment for nonfluent aphasia: phase 1 clinical trial follow-up findings. *Neurorehabilitation and neural repair*, 30(2), pp.131-142.

Cotelli, M., Fertonani, A., Miozzo, A., Rosini, S., Manenti, R., Padovani, A., Ansaldo, A.I., Cappa, S.F. and Miniussi, C., 2011. Anomia training and brain stimulation in chronic aphasia. *Neuropsychological Rehabilitation,* 21(5), pp.717-741.

Di Carlo, L.M., 1980. Language recovery in aphasia: effect of systematic filmed programmed instruction. *Archives of physical medicine and rehabilitation*, *61*(1), pp.41-44.

Elman, R.J. and Bernstein-Ellis, E., 1999. The efficacy of group communication treatment in adults with chronic aphasia. *Journal of Speech, Language, and Hearing Research*, *42*(2), pp.411-419.

Feinberg, T.E. and Farah, M.J., 2003. *Behavioral neurology and neuropsychology*. McGraw-Hill Professional.

Fiori, V., Cipollari, S., Di Paola, M., Razzano, C., Caltagirone, C. and Marangolo, P., 2013. tDCS stimulation segregates words in the brain: evidence from aphasia. *Frontiers in human neuroscience*, 7.

Flöel, A., Rösser, N., Michka, O., Knecht, S. and Breitenstein, C., 2008. Noninvasive brain stimulation improves language learning. *Journal of Cognitive Neuroscience*, 20(8), pp.1415-1422.

Greener, J., Enderby, P. and Whurr, R., 2001. Pharmacological treatment for aphasia following stroke. *The Cochrane Library*.

Gupta, S.R., Mlcoch, A.G., Scolaro, C. and Moritz, T., 1995. Bromocriptine treatment of nonfluent aphasia. *Neurology*, *45*(12), pp.2170-2173.

Hong, J.M., Shin, D.H., Lim, T.S., Lee, J.S. and Huh, K., 2012. Galantamine administration in chronic post-stroke aphasia. *Journal of Neurology, Neurosurgery & Psychiatry*, *83*(7), pp.675-680.

Kendall, D.L., Oelke, M., Brookshire, C.E. and Nadeau, S.E., 2015. The influence of phonomotor treatment on word retrieval abilities in 26 individuals with chronic aphasia: An open trial. *Journal of Speech, Language, and Hearing Research*, *58*(3), pp.798-812.

Meinzer, M., Elbert, T., Djundja, D., Taub, E. and Rockstroh, B., 2007. Extending the constraint-induced movement therapy (CIMT) approach to cognitive functions: Constraint-induced aphasia therapy (CIAT) of chronic aphasia. *NeuroRehabilitation*, *22*(4), pp.311-318.

Pedersen, P.M., Vinter, K. and Olsen, T.S., 2004. Aphasia after stroke: type, severity and prognosis. *Cerebrovascular Diseases,* 17(1), pp.35-43.

Pulvermüller, F., Neininger, B., Elbert, T., Mohr, B., Rockstroh, B., Koebbel, P. and Taub, E., 2001. Constraint-induced therapy of chronic aphasia after stroke. *Stroke*, *32*(7), pp.1621-1626.

Rochon, E., Laird, L., Bose, A. and Scofield, J., 2005. Mapping therapy for sentence production impairments in nonfluent aphasia. *Neuropsychological Rehabilitation*, *15*(1), pp.1-36.

Rosenbek, J.C., LaPointe, L.L. and Wertz, R.T., 1989. Aphasia: A clinical approach. Pro Ed.

Sabe, L., Salvarezza, F., Cuerva, A.G., Leiguarda, R. and Starkstein, S., 1995. A randomized, double-blind, placebocontrolled study of bromocriptine in nonfluent aphasia. *Neurology*, *45*(12), pp.2272-2274.

Sebastian, R., Saxena, S., Tsapkini, K., Faria, A.V., Long, C., Wright, A., Davis, C., Tippett, D.C., Mourdoukoutas, A.P., Bikson, M. and Celnik, P., 2016. Cerebellar tDCS: A Novel Approach to Augment Language Treatment Post-stroke. *Frontiers in Human Neuroscience*, 10.

Shah-Basak, P.P., Wurzman, R., Purcell, J.B., Gervits, F. and Hamilton, R., 2016. Fields or flows? A comparative metaanalysis of transcranial magnetic and direct current stimulation to treat post-stroke aphasia. *Restorative neurology and neuroscience*, *34*(4), pp.537-558.

Szaflarski, J.P., Ball, A.L., Vannest, J., Dietz, A.R., Allendorfer, J.B., Martin, A.N., Hart, K. and Lindsell, C.J., 2015. Constraint-induced aphasia therapy for treatment of chronic post-stroke aphasia: a randomized, blinded, controlled pilot trial. *Medical science monitor: international medical journal of experimental and clinical research*, *21*, p.2861.

Wang, Y., Rudd, A.G. and Wolfe, C.D., 2013. Age and Ethnic Disparities in Incidence of Stroke Over Time. *Stroke*, 44(12), pp.3298-3304.

Watila, M.M. and Balarabe, S.A., 2015. Factors predicting post-stroke aphasia recovery. *Journal of the Neurological Sciences,* 352(1), pp.12-18.

Whiting, E., Chenery, H.J., Chalk, J. and Copland, D.A., 2007. Dexamphetamine boosts naming treatment effects in chronic aphasia. *Journal of the International Neuropsychological Society*, *13*(06), pp.972-979.

Appendices

Appendix A – Summary of Neurostimulation Results

Reference	Number of participants	Intervention	Mean Age (range)	Timing of Intervention (mean time post stroke years)	Patient selection/ pathology	Primary Outcome Measure	Results
Barwood et al., 2011	12 (6 intervention, 6 sham control)	Low frequency 1 Hz rTMS 20 min per day for 10 days. No speech therapy during trial. Target area - BA 45 right (pars triangularis)	Intervention - 60.8, Control - 67	Intervention - 3.49, Control - 3.46	Left MCA stroke 2-6 years previously. Mild-severe non-fluent/ global aphasia. Selected via two hospital/ university databases in Brisbane	Boston Naming Test, Boston Diagnostic Aphasia Examination	Significant interactions of group (rTMS, sham) x time (baseline, 2 months) were found for BDAE naming actions ($p< 0.01$), BDAE repetition of sentences ($p < 0.05$), Cookie Theft picture description ($p<0.01$), commands $p < 0.01$). Overall BDAE subsets ($p <0.01$), BNT ($p < 0.05$). No significant difference between sham and rTMS baseline but there was at 2 months for BDAE naming ($t = 4.16$, $p < 0.01$, df 10), BDAE overall ($t = 3.7$, $p <0.05$, $df = 10$). Also, performance at 2 months within the stimulation group was significantly higher on BDAE overall ($t = 4.145$, $p < 0.05$, $df = 5$), however PN latency significantly lower at 2 months ($t = 3$, $p <0.05$, $df = 5$). No significant differences in sham group.
Baker et al., 2010	10 (5 intervention, 5 control)	Annodal tDCS and computerised anomia training versus sham tDCS and computerised anomia training	65.5	5.37	Left hemisphere stroke causing nonfluent aphasia or anomia	Naming accuracy	Significant improvement on naming of treated items ($p <0.04$) which persisted at 2 week follow up
Cherney et al., 2016	8 (4 intervention, 4 control)	Epidural cortical stimulation and intensive SLT versus intensive SLT	51 (34-61)	3.4 (1 - 16.2)	12 months post stroke. Locations included frontoparietal, temporal, frontoinsular, parieal, temporal. Non-fluent aphasia	Aphasia quotient of the Western Aphasia Battery	Baseline - post treatment 7.98 versus 4.59 (effect size 0.67), 6 week follow up 7.98 versus 5.54 (effect size 0.48), 12 week follow up 12.3 versus 3.55 (effect size 1.32), long term follow up 10.3 versus 6.48 (effect size 0.54) - all effect size 95 CI's span zero.

					following single left hemisphere ischaemic infarction, confirmed by MRI, WAB of 20/80, premordibly right handed, English language		
Cotelli et al., 2011	3 (participants acted as their own controls)	High frequency rTMS over left dorsolateral prefrontal cortex for 25 mins. Over 2+ weeks.50 mins per day (25 mins rTMS, 25 mins SLT)	52.33 (41-71)	3 (1-4.5)	2 left MCA infarcts, one left capsulo-thalamic haemorrhage. Non-fluent aphasia and naming deficit but could understand single words	Aachener aphasic test, battery for the analysis of aphasic deficits, tests of naming	No changes in AAT and BADA but significant improvements for object naming
Fiori et al., 2013	7	Language training and tDCS (two different areas and sham)	58.4	(0.6 - 4.4)	Single left hemispheres stroke and aphasia, native Italian proficiency, right handed pre morbid	Naming test	Significant improvement in noun naming (temporal 31% p = 0.000, frontal 12% p = 0.04, sham 10% p =0.04) and verb naming (frontal 42% p=0.000, temporal 15% p=0.012, sham 13% p =0.019) No difference between sham and stimulation.
Floel et al., 2011	12	Randomised double blind sham controlled crossover trial of tDCS (annodal versus cathodal) over tempero parietal cortex in conjunction with anomia training	56.3 (39-67)	7.0 (1.2 - 21.7)	Single left sided ischaemic stroke, chronic anomia.	Naming outcome	Significantly improved after training from 0% naming to mean 83% +/- 22% overall. Main effect of stimulation ($F(2,22)=4.23$, $p=0.05$. Post hoc tests revealed better overall improvement in the anodal condition compared to sham stimulation (paired t test, $t=2.54$, $p=0.03$) but not for cathodal.
Sebastian et al., 2017	1	Cerebellar tDCS to augment language treatment	57	5	Left MCA infarct followed by right MCA infarct years later both caused by carotid dissection	Spelling and naming	Overall improvement in spelling with notable increased writing speed. Fewer sessions to reach criterion in tDCS. Significantly greater improvement in spelling after tDCS compared with control and this continued 2 months post-treatment

Appendix B – Summary of SLT and Related Therapies Results

Reference	Number of participants	Intervention	Mean Age	Timing of Intervention (mean time post stroke)	Pathology/ impairment	Primary Outcome Measure	Results
Breitenstein et al., 2017	156 (78 per group)	Intensive speech and language therapy (over 10 hours per week) for at least 3 weeks or deferral of intensive speech and language therapy.	Intervention 53.5, Control - 52.9	Intervention 43.0, Control 27.0	Unilateral haemorrhagic or ischaemic stroke at least 6 months prior with aphasia of any type with some ability to communicate verbally retained	Change in verbal communication effectiveness in everyday life scenarios (Amsterdam-Nijmegen Everyday Language Test A-scale) from baseline to immediately after 3 weeks treatment/ deferral.	Mean difference since baseline in ANELT-A scale score was significantly larger after 3 weeks of intensive therapy (2.61 points, CI 1.49 to 3.72) compared to deferral (-0.03 points, CI -0.94 to 0.88), group difference p = 0.0004. Cohen's d 0.58. Group differences independent of time since last stroke. Control group has similar improvements in verbal communication after 3 weeks of intensive SLT. Treatment effects fairly stable at 6 months.
Di Carlo, 1980	14	Filmed language instruction and SLT versus non-programmed activity	Intervention - 57.6 Control - 55.3	1.6	Left MCA infarct. Unclear	Study specific outcomes measure	No significant difference
Kendall et al., 2015	26 (13 immediate treatment, 13 delayed treatment)	60 hours of intensive multimodal therapy designed to enhance access to and efficiency of phonemes and phonologic sequences	56 (SD 15)	48 months (SD=53)	Single stroke documented by MRI/ CT	Accuracy of confrontation naming of untrained nouns at 3 months. Secondary outcome measures assessed acquisition generalisation maintenance and indicators of QOL.	5.28% absolute increase in confrontation naming accuracy pre versus post treatment at 3 months p=0.02 and ES 0.22.
Pulvermeller et al., 2001	17 (10 intervention, 7 control)	Constraint induced aphasia therapy versus		Intervention - 98.2 (74.2 SD)	Single LMCA stroke causing aphasia	Standard aphasia tests, CAL	Group that received CI showed substantial improvement at 10 day interval (F=17.3, p<0.0008), no

		conventional therapy		control - 24 (20.6 SD)			significant improvement for conventional aphasia treatment. CAL revealed CI performance in everyday life of 30% after treatment (F=25, p>0.001) but no improvement in convectional therapy
Rochon et al., 2005	5 (2 intervention, 3 control)	Mapping therapy versus control	51.0 (31-82)	4.4 (2-9)	4 Left MCA infarction, 1 left AVM.	BDAE, PCB, Sentence production, QPA	Increase in performance across average of all sentence types X2 range 8.9-30 and p<0.01 to P<0.001. Not significant for control patients.
Szaflarski et al., 2015	24 (14 intervention, 10 control)	Constraint induced aphasia therapy versus no intervention	Intervention - 57 (11) Control - 51 (13)	Unclear but all suffered with chronic aphasia from stroke	Left MCA ischaemic infarct	NAT battery	Patients who received CIAT scored higher on the mini CAL 12 weeks follow up (mean 31 versus 23, p =0.019)
Elman & Bernstein-Ellis 1999	24 (12 intervention, 12 control)	Group communication treatment versus deferred group communication treatment	Intervention - 58.3 Control - 60.7	Interventio n - 71.1 Control - 32.5	Single left MCA stroke. Aphasia included Broca's, anomia, transcortical motor, conduction	SPICA, WAB AQ, CADL, CETI, ABS	Significant improvement on WAB-AQ [F(1,19) = 7.43, p < 0.05] and CADL [F(1,19) = 5.50 p < 0.05] for those who were in immediate treatment group compared to deferred. Measured up to 4 months
Brindley et al., 1989	10 (5 intervention 5 control)	Intensive versus non-intensive speech therapy	36	51	Broca's aphasia from varying aetiology including SAH, thrombus, embolus, closed head injury	FCP, LARSP,	Significant improvement for speech (p <0.01), reading (P < 0.01), reading (P < 0.03), and overall (p < 0.01) during the intensive block but long term effects unclear
Meinzer et al., 2007	44	CIAT - 3 hours per day for 10 days of communicative language games versus CIAT plus	56.1	3.2	Mixed	AAT, CAL	Significant improvement on overall AAT score as a group and for 85% of individual patients that was maintained at 6-month follow up. Improvements also found on the CAL. Not related to time since stroke

Appendix C – Summary of Pharmacological Therapy Results

Reference	Number of participants	Intervention	Mean Age	Timing of Intervention (mean time post stroke)	Pathology/ impairment	Primary Outcome Measure	Results
Berthier et al., 2006	26 (13 intervention, 13 control)	Donepezil as adjunct to speech and language therapy	Note - had to be younger than 70. Intervention - 48.0, Control - 48.3	Intervention - 33.9, Control - 38.2	Unilateral stroke lesion from over one year	Aphasia quotient of the Western Aphasia Battery and communicative activity log	Severity of AQ of the WAB improved more in donepezil group than placebo at 16 weeks (donepezil 6.4 +/- 3.8, 95% CI 4.13 to 8.81, placebo 3.5 +/- 2.7 95% CI 1.93 to 5.52, p - 0.037). Large effect size - Cohen's d = 0.87. At post-washout testing donepezil group decreased with respect to endpoint compared to control (-4.6 +/- 8.6 95% CI -2.1 - 11.7, placebo 4.8 +/- 4.5 CI 1.27 to 12.55, p = 0.008). Between group differences not seen at week 20 post-washout Adverse events higher in donepezil group (irritability, insomnia/tiredness, recurrence of post-stroke seizures), in placebo group (headache, abnormal dreams, anorexia
Berthier et al., 2009	28 (27 completed both treatment phases)	Memantine versus placebo first 16 weeks then 16-18 combined with CIAT, then 18-20 memantine/ placebo alone, then washout 20-24	Intervention - 53.7, control - 48.5	Intervention 1.8, control - 6.2	Unilateral cortical/ subcortical stroke caused by single infarction/ haemorrhage	Aphasia Quotient of the Western Aphasia Battery, Communicative Activity Log. Looked at percentage improvers and improved defined as an increase of 5% or more of its range.	Significant improvement in memantine compared to placebo at both end points with large effect size of Cohen's d 1.28 at week 16 ($p < 0.002$) and 1.44 at week 18 ($p < 0.005$) and 1.28 week 20 ($p < 0.005$) and medium effect of 0.65 at week 24 ($p < 0.041$).
Breitenstein et al., 2015	10	L-Dopa with three daily hours of naming exercises and one hour of conversational training	range 34 - 67	6.3 +/- 3.4	12 months + post stroke, mixture of aphasia (Broca 7, Wernicke 1, global 2, 8/10 midbrain dopaminergic lesion	Primary - two sets of 50 object names matched for difficulty, linguistic parameters and complexity of pictures. Secondary outcomes - five ANELT conversation scenarios, Communication Activity Log	No significant difference

Whiting et al., 2007	2	Dexamphetamine In conjunction with naming versus placebo treatment	72 (68 - 76)	4.5 (3-6)	One acute right basal ganglia infarct. Other patient left embolic MCA infarct. Both were fluent but produced errors on BNT	BNT	Analysis was done separately for each patient. No statistically significant differences in naming for patient one in dexamphetamine compared with control. However, for patient 2 there was statistically significant increase in named treated items under dexamphetamine (Z=1.523, p=0.032). However, there was more accurate naming for both placebo and dexamphetamine for untreated items at the end of therapy blocks but no significant difference between improvement
Gupta et al., 1995	43	Bromocriptine versus placebo	62.2	66.8	Cerebral infarction causing nonfluent aphasia at least 1 year ago	WAB, BNT	No significant difference on any outcome
Sabe et al., 1995	7	Bromocriptine versus placebo	54	30	Cerebral infarction causing nonfluent aphasia	BDAE, WAB, BNT	No significant difference on any outcome
Hong et al., 2012	45 (23 intervention, 22 control)	Galantamine versus no treatment	60.4 +/9 11.9	2.2 +/-1.5	Left hemisphere stroke causing aphasia (subcortical and cortical)	WAB AQ, MMSE	Significant increase in the total AQ score in galantamine group (p =0.007) compared to no treatment (p =0.308)

Appendix D – Summary of Miscellaneous Results

Reference	Number of participants	Intervention	Mean Age	Timing of Intervention (mean time post stroke)	Pathology/ impairment	Primary Outcome Measure	Results
Palmer et al., 2012	34 (17 control, 17 intervention)	self managed computer treatment with volunteer support versus usual care	Intervention - 69.5 (37.8 - 82.6) Control - 66.2 (48.2 - 83.7)	Intervention - 6.2, control - 6.6	Stroke and aphasia with word finding difficulties as predominant feature. Ability to repeat spoke word.	Primary outcomes were related to feasibility. Secondary outcome clinical effectiveness and cost effectiveness. Clinical - change in word retrieval ability measured by naming words that had been practiced in treatment at 5 and 8 months	Difference in change in naming ability from baseline to 5 months between groups was 19.8% (CI-4.4-35.2%), p =0.014
Raglio et al., 2016	20 (10 intervention, 10 control)	Active music therapy based on free-improvisation in addition to SLT compared to SLT alone.	Intervention - 61.3 (42 - 89) Control - 70.9 (61 - 89)	Intervention - 3.4 +/- 4.1 Control - 3.8 +/- 3.3	Left sided stroke causing aphasia (fluent, non-fluent, global)	Primary outcome - Speech language using token test for comprehension, Boston Naming Test, AAT Picture Description Subtest and Spontaneous Speech subtest. Secondary outcomes - psychological (Beck Depression Inventory, Big Five Observer	Significant improvement in spontaneous speech AAT subset in patients with MT and SLT but not in SLT alone 14 - 17 increase p = 0.02, Cohen's d = 0.35
Van Der Meurlen et al., 2016	17 (10 MIT, 7 delayed MIT)	Musical intonation therapy versus delayed start musical intonation therapy	Intervention - 58.1 (15.2), control - 63.6 (12.7)	Intervention - 33.1 (19.4) Control - 42.6 (23.7)	Non-fluent aphasia, after unilateral left hemisphere stroke with poor language repetition even for single words.	MIT repetition test, AAT subtests - naming, repetition, auditory comprehension, ANELT, Sabadel story retell task	At end of therapy there was significant improvement in AAT repetition for control group (35.3 - 43.3, p=0.046) but no difference between groups. Significant improvement for MIT group on MIT task trained and untrained (17.2 - 30, P < 0.01) and significantly better for MIT versus control (beta 13.32, p 0.02). Not maintained at follow up assessment.

Katz & Wertz 1997	55	Computer reading treatment versus computer stimulation versus no treatment	Computer reading - 61.6 Computer stimulation - 66.4 No treatment - 62.8	Computer reading - 6.2 Computer stimulation - 5.4 No treatment - 2.4	Aphasia due to single thromboembolic infarct of left hemisphere	PICA, WAB AQ,	PICA improvement at 26 weeks ($p < 0.01$) overall (9.1 change), verbal (7.9 change), pantomime (15.2 change), WAB AQ (4.7 change) for those on computer reading treatment but no change for no treatment
Nobis Bosch et al., 2011	18 (9 B.A Bar linguistic training first, 9 nonlinguistic cognitive training first)	Intensive language training via electronic learning device (B.A Bar)	Intervention - 50 Control - 48	Intervention - 2.1 Control - 2.4	7 Broca's aphasia, 1 global aphasia, 1 transcortical aphasia. Aetiology - infarct. Severity moderate-severe	AAT	Significant improvement in participants' linguistic and communicative abilities using B.A Bar compared to non-linguistic training