Cyprus University of Technology

ASPIRE

Principles of neuroplasticity in assessment and therapy of aphasic language

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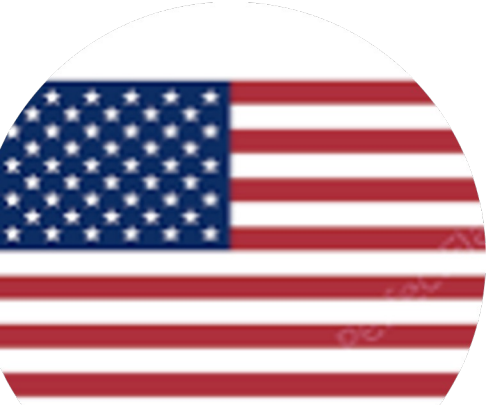

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Today's talk

1. Explore principles of neuroplasticity for post-stroke aphasia rehabilitation

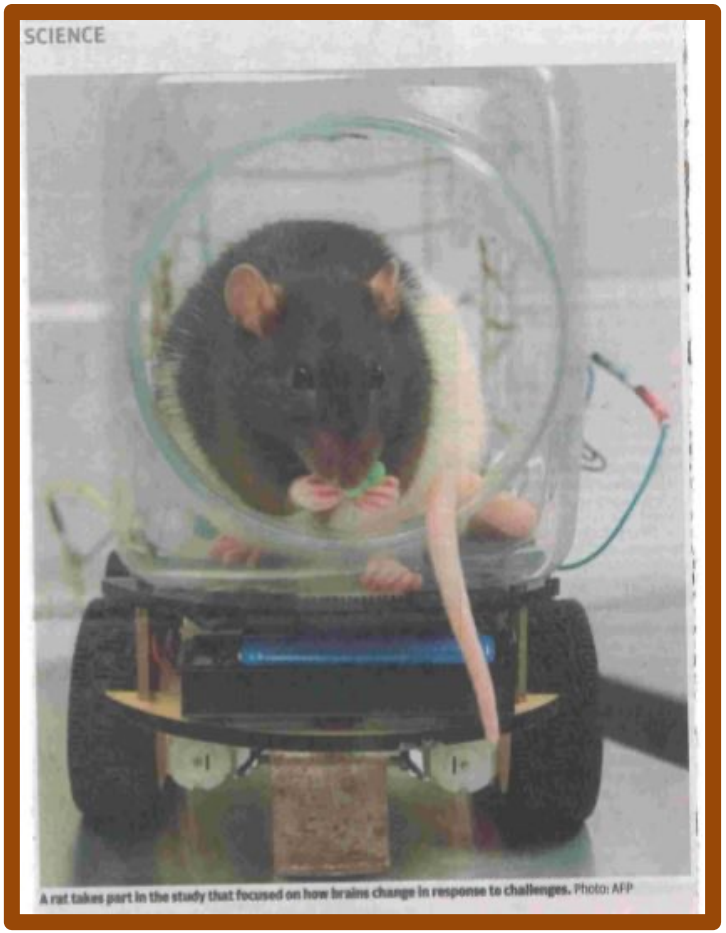
2. Describe the ASPIRE project (Assessment of of post-stroke aphasia for rehabilitation research)

- ✓ significance
- ✓ implementation
- ✓ dissemination

Rodents taught to drive tiny cars relaxed by learning new skills

A robot car kit was modified by adding a clear plastic food container to form a driver compartment with an aluminium plate on the bottom.

A copper wire was threaded horizontally across the car to form 3 bars: left, centre & right



When the rat placed itself on the aluminium floor & touched the wire with its paws, it completed an electrical circuit & the car moved in the direction selected.

The rats (17) were taught **to drive forward as well as steer in more complex navigational patterns**

The rats' faeces were collected after their trials to test for the **stress hormone corticosterone** as well as **dehydroepiandrosterone** which counters stress

All rats that underwent training had **higher levels of dehydroepiandrosterone** indicating a more relaxed state, which could be linked to **the satisfaction of gaining mastery over a new skill.**

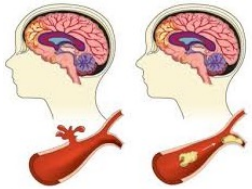
Rats that drove themselves showed higher levels of dehydroepiandrosterone as compared to those who were merely passengers when a human controlled the vehicle, meaning they were **less stressed**- something that would be familiar to back-seat drivers.

Rats kept in **stimuli-rich environments** performed better than their lab rat counterparts

Crawford LE, Knouse LE, Kent M, Vavra D, Harding O, LeServe D, Fox N, Hu X, Li P, Glory C, Lambert KG, Enriched Environment Exposure Accelerates Rodent Driving Skills, *Behavioural Brain Research* (2019), doi: https://doi.org/10.1016/j.bbr.2019.112309

Stroke

- A **stroke** occurs when a blood vessel that carries oxygen and nutrients to the brain is either **blocked** by a clot or **bursts** (or ruptures)



- Weakness/loss of feeling on one side of the body
- Visual impairment
- Speech difficulties
- Confusion
- Loss of coordination
- Severe headache

In 2017, **1.5 million** people were diagnosed with stroke, **9 million** were living with stroke and **0.4 million died** because of stroke in 32 European countries. *European Stroke Journal* DOI:10.1177/2396987319883160

Aphasia

An **acquired language** disorder

- injury to the brain – most typically **stroke** in the left hemisphere

More than 1/3 of post stroke patients become aphasic

- 1/3: improvement within the first 4 weeks
- 1/2: improvement within the first **6 months**

(Heiss & Thiel, 2016)

- Auditory comprehension
- Expression
- Reading
- Writing

Mild → **Severe**

non-fluent: **reduced speech output**

fluent: **speech output is not reduced, but speech is incoherent**

Aphasia awareness in Greece

Population	10,722 million
N	800
Mean age	48.6 (range 15-95 years)
Heard of aphasia	46%
Basic knowledge of aphasia	10.6%
Media	64
Work	15
Rel/friend	6

Results have implications for targeting awareness raising and campaigning

Code, Papathanasiou et al.2016. International patterns of the public awareness of aphasia Int J Lang Commun Disord 51(3):276-84. doi: 10.1111/1460-6984.12204

Aphasia for the stroke survivor…

- Is associated with **reduced social activities, higher levels of depression**, and **lower return to work** when compared with stroke survivors without aphasia.
- If untreated or disregarded, aphasia **isolates** the stroke survivor from their spouse, family, friends and community.
- This has a significant effect on the person's and the family's emotional and financial **wellbeing** and general **quality of life**.
- It also places **an enormous socio-economic cost and strain on public health** and rehabilitation services.

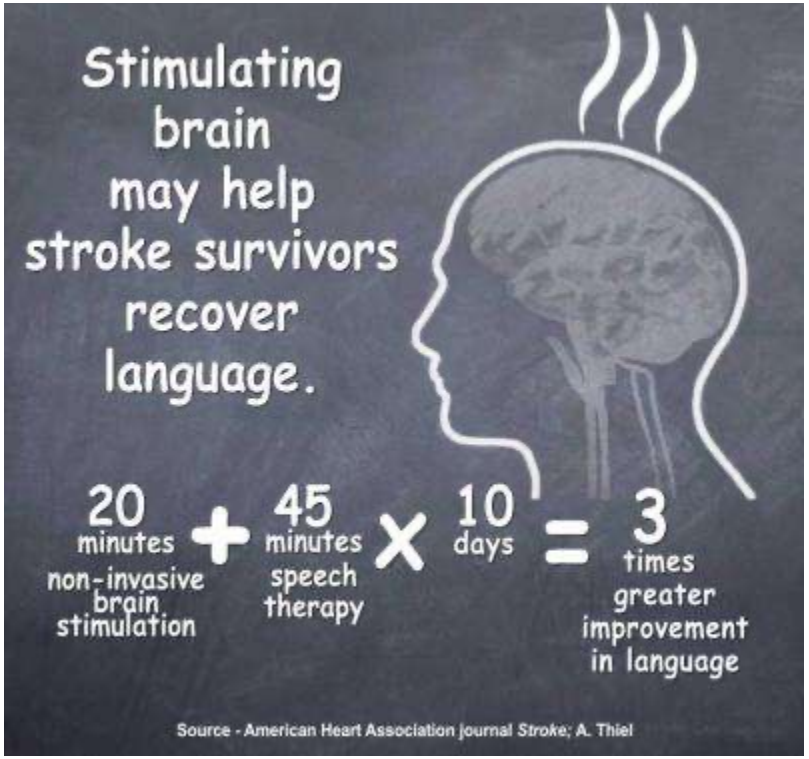
Northcott, S., Marshall, J., & Hilari, K. (2016). What factors predict who will have a strong social network following a stroke?. *Journal of Speech, Language, and Hearing Research*, *59*(4), 772-783..

Northcott, S., Moss, B., Harrison, K., & Hilari, K. (2016). A systematic review of the impact of stroke on social support and social networks: associated factors and patterns of change. Clinical rehabilitation, 30(8), 811-831.

Aphasia for the speech-language therapist

- Earlier and more accurate rehabilitation tools may save costs in the long term, particularly when institutionalisation of patients with aphasia can be reduced.

- Thus it is critical **to improve efficacy and cost-effectiveness of existing practice, and develop evidence-based best practice recommendations for diagnosis and treatment of aphasia** in this large, under-researched population.

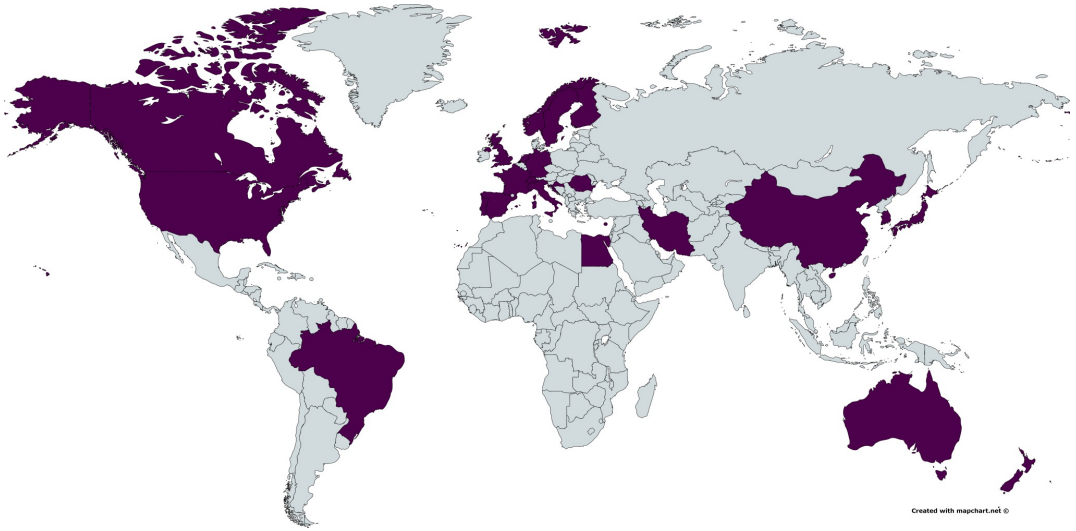


Brady M, Kelly H, Godwin J, Enderby P (2012). Speech and language therapy for aphasia following stroke. Cochrane Database of Systematic Reviews Art. No.: CD000425.

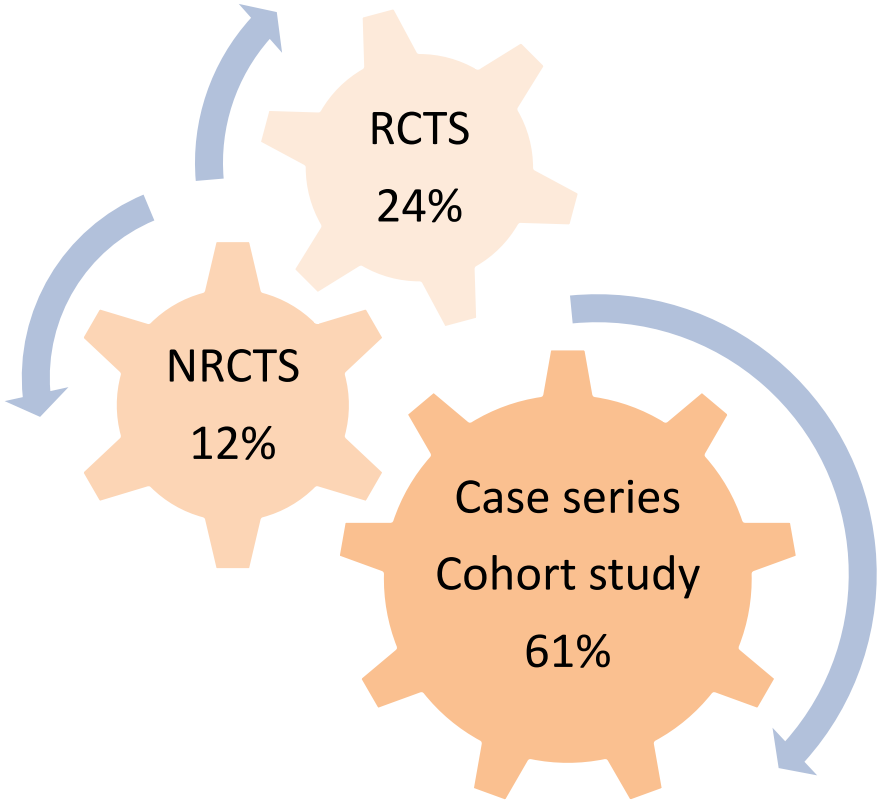
World-wide **research** on **aphasia recovery after stroke**.

RELEASE
REhabilitation and recovery of peopLE with Aphasia after StrokE

Language recovery in people with **aphasia**



RELEASE data



Approximately half the datasets included an SLT intervention (91/174) (52.3%); 2746/5928 (46.3%)) while the remainder were non-interventional in nature.

People with aphasia (PWA) in the RELEASE datasets

63 YEARS

61.3% WERE MALE

95% RIGHT HANDED

82% **ISCHEMIC STROKE**

95% LEFT HEMISPHERE INFARCT

MEDIAN OF 12 (IQR 10 TO 16) EDUCATIONAL YEARS.

3/4 OF PARTICIPANTS WERE FROM A **WHITE ETHNIC BACKGROUND**

23.5% LIVED ALONE,

65% LIVED IN A HOME ENVIRONMENT

9.7% LIVED IN FORMAL CARE

RELEASE results on assessment

overall language ability was captured using **21 different measures**

auditory comprehension using *35 measures*

naming using *33 measures*

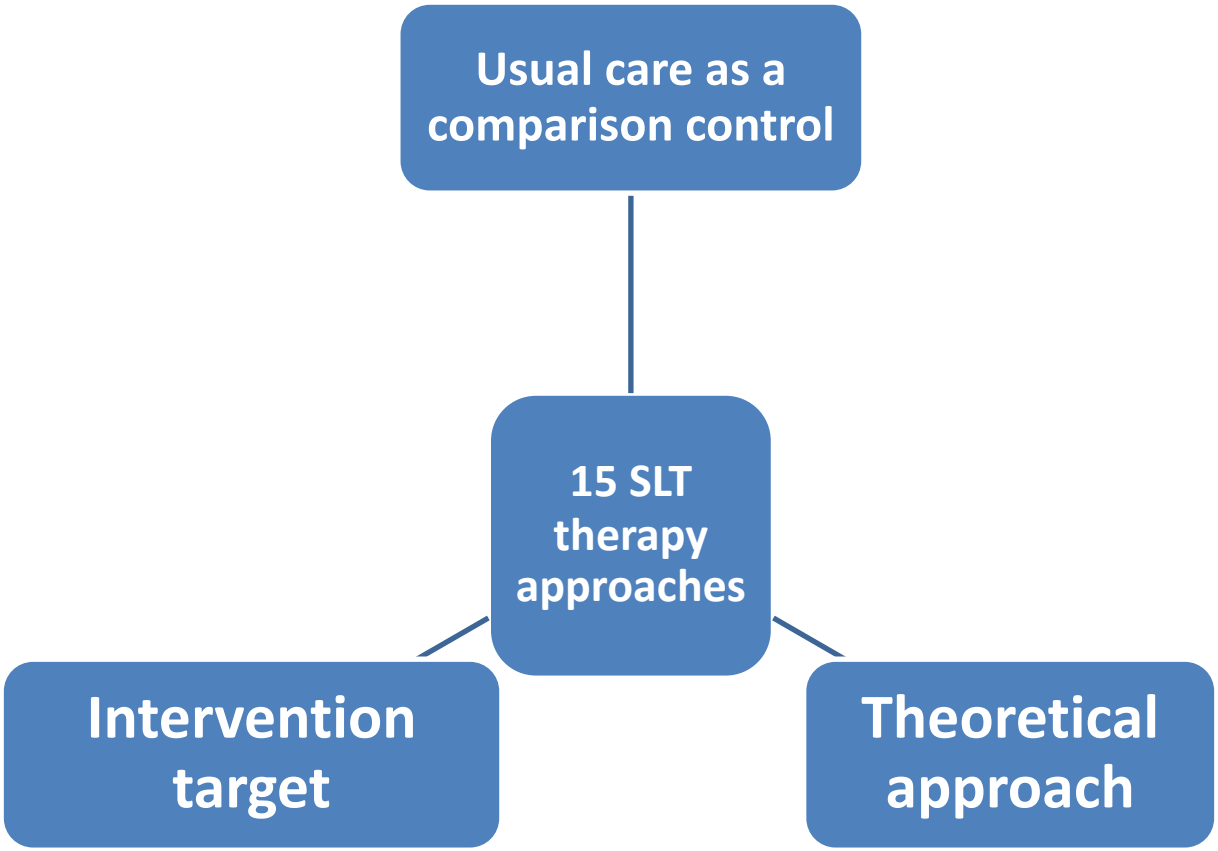
reading using *21 measures*

writing using *18 measures*

functional communication using *16 outcome measures*

A standardisation of assessment procedures is urgently required with the long-term aim of establishing national clinical registries for post-stroke aphasia outcome and rehabilitation around the world.

RELEASE results on intervention



Inadequate reporting of therapy interventions, procedures and materials

RELEASE findings

- Collaborative efforts created a large, international IPD aphasia after stroke database which will **inform our understanding of language recovery and the components of effective therapeutic interventions**.

- **Heterogeneity** continues to be evident in the reporting of demographic and clinical data in aphasia studies.

- Take home message: Urgent need for **further research to establish the best treatment approach or type of therapy,** in relation to three key treatment components:

✓ frequency (how often),

✓ duration (how long for)

✓ dosage (how much).

Assessing and treating PWA as related to brain recovery

Neuroplasticity

- **Reorganization in the neural representation of language functions occurs spontaneously** (i.e., without any directed interventions) soon after the onset of aphasia after stroke.
- The **neuroplastic changes** that subserve this functional reorganization occur **not only within the damaged left hemisphere but also in the uninjured right hemisphere.**
- It is generally agreed upon that **the recruitment of areas surrounding the damaged left hemisphere is associated with some degree of aphasia recovery**.
- However, because the evidence regarding the recruitment of **right hemispheric language homologues** is mixed, their overall role in recovery remains controversial.

Warburton E, Price CJ, Swinburn K, Wise RJS (1999) Mechanisms of recovery from aphasia: evidence from positron emission tomography studies. J Neurol Neurosurg Psychiatry 66(2):155–161. Karbe H, Thiel A, Weber-Luxenburger G, Herholz K, Kessler J, Heiss WD (1998) Brain plasticity in poststroke aphasia: what is the contribution of the right hemisphere? Brain Lang 64(2):215– 230. Cornelissen K,Laine M, Tarkiainen A, Jarvensivu T, Martin N, Salmelin R (2003) Adult brain plasticity elicited by anomia treatment. J Cogn Neurosci 15(3):444–461. Thulborn KR, Carpenter PA, Just MA (1999) Plasticity of language-related brain function during recovery from stroke. Stroke 30(4):749–754 .Tillema JM, Byars AW, Jacola LM, Schapiro MB, Schmithorst VJ, Szaflarski JP, Holland SK (2008) Cortical reorganization of language functioning following perinatal left MCA stroke. Brain Lang 105(2):99–111. Szaflarski JP, Allendorfer JB, Banks C, Vannest J, Holland SK (2013) Recovered vs. not-recovered from post-stroke aphasia: the contributions from the dominant and non-dominant hemispheres. Restor Neurol Neurosci 31(4):347–360. Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF, Heiss WD (2005) Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia – a combined repetitive transcranial magnetic stimulation and positron emission tomography study. Stroke 36(8):1759–1763. Thiel A, Habedank B, Herholz K, Kessler J, Winhuisen L, Haupt WF, Heiss WD (2006) From the left to the right: how the brain compensates progressive loss of language function. Brain Lang 98(1):57–65. Postman-Caucheteux WA, Birn RM, Pursley RH, Butman JA, Solomon JM, Picchioni D, McArdle J, Braun AR (2010) Single-trial fMRI shows contralesional activity linked to overt naming errors in chronic aphasic patients. J Cogn Neurosci 22(6):1299–1318.

Reduced connectivity in both language & domain general networks in aphasia

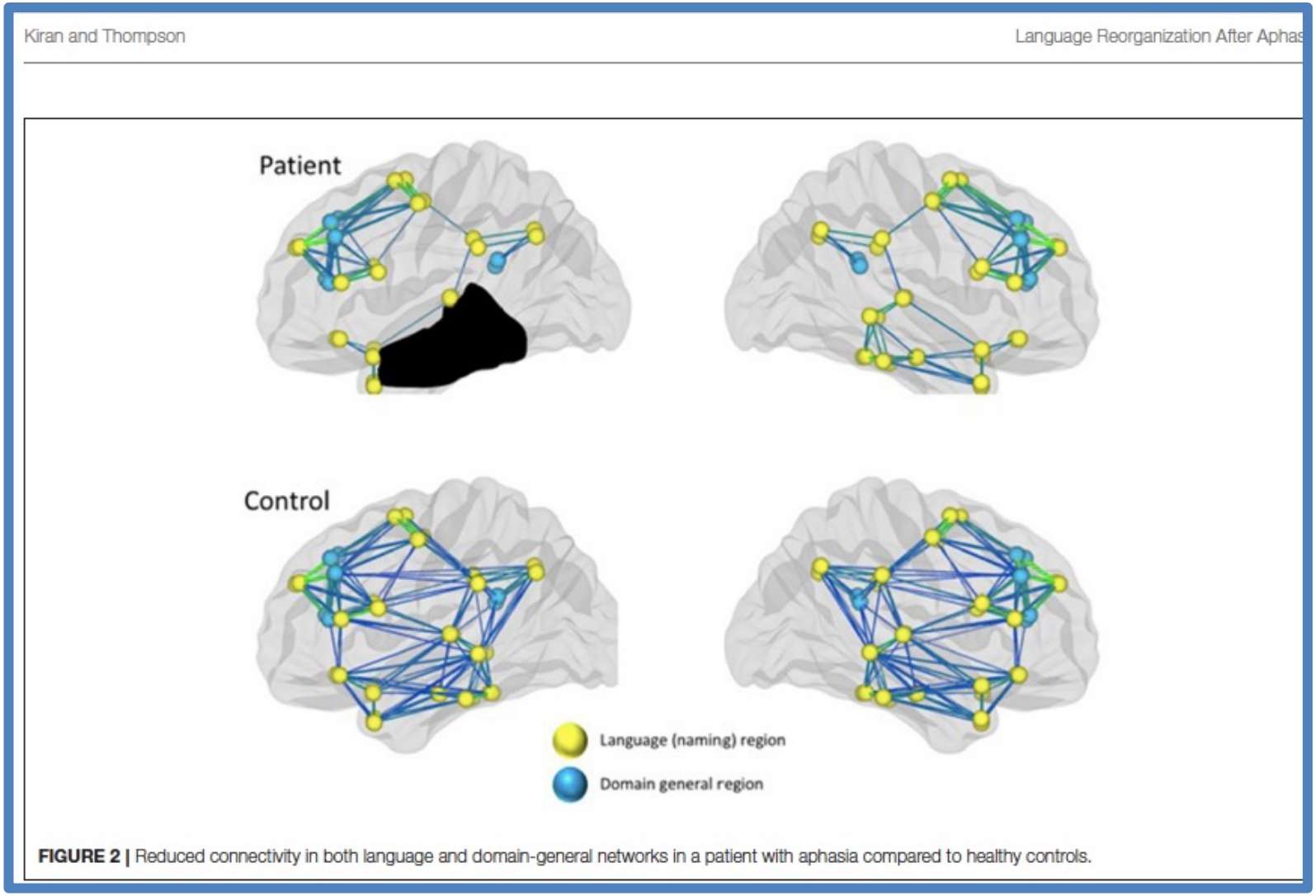


FIGURE 2 | Reduced connectivity in both language and domain-general networks in a patient with aphasia compared to healthy controls.

What we know about language recovery & the brain

- 3 epochs of brain recovery: **acute**, **subacute** & **chronic**
- Recovery is a *non-linear* process with *differences in recovery processes* and *patterns* associated with the *age of the stroke*
- Greatest changes in the neural architecture for language occur in the *early stages of recovery*

Acute recovery: beginning immediately after stroke & lasting several hours

- **Disruption of neurophysiological and metabolic processes** both proximal and distal to the infarct results in detrimental but dynamic changes in the brain.
- **Edema** may result in a shift of midline structures, affecting several bilateral cortical, and subcortical regions with associated multiple behavioral deficits.
- **Excitotoxicity**, the **abnormal release of neurotransmitters** such as glutamate in the synapse results in high levels of calcium ions in neurons, which results in cell death.
- Ultimately, since healthy neurons are deprived of input from destroyed neurons via interruptions in intra- or inter-hemispheric pathways, this cascading process results in **additional cell death and transneuronal degeneration**.
- Changes in blood flow (perfusion) also result in **hypoperfusion in both cerebral hemispheres** and particularly in the penumbral (perilesional) region within the first 24h following stroke onset.

Kiran, S & Thompson, C. K. (2019). *Frontiers in Neurology*

Subacute recovery

- The brain undergoes several changes enabling **spontaneous recovery** and **repair**.
- In this phase, **edema is resolved** and several abnormal processes return to more normal state.
- The injured tissue recovers from detrimental events, several **brain-repair-related events occur.**
- **Synaptogenesis** results in new connections that may either involve unmasking of previously latent pathways or formation of new pathways.
- Additionally, if the cell body remains functional, **axons and dendrites may regenerate leading to axonal and collateral sprouting**, which **expand existing synaptic connections and consequent neurogenesis in cortical tissue adjacent, and remote to the infarcted tissue**.
- These processes reach peak levels during this period, resulting in a shift from initial increases in excitation of contralesional tissue due to decreases in inhibition from the lesioned hemisphere, to **upregulation of functionally viable brain tissue**.

Kiran, S & Thompson, C. K. (2019). *Frontiers in Neurology*

Chronic recovery: may span months to years after stroke

- Although physiological changes occurring during the repair phase have generally subsided as **the brain reaches a stable state**, **mechanisms that facilitate plasticity** (i.e., synaptic sprouting) remain at play and are adaptable to environmental experience.
- Notably, it is now known that brain changes occur throughout the life span, particularly associated with **experience**.
- For many stroke survivors with aphasia, **treatment improves language abilities and associated neural processing of language several years post-stroke.**
- However, not all patients show the same degree of recovery over time.
- Among other reasons that influence recovery, **the neural sequela of stroke persists into this phase of recovery and interacts with experience.**

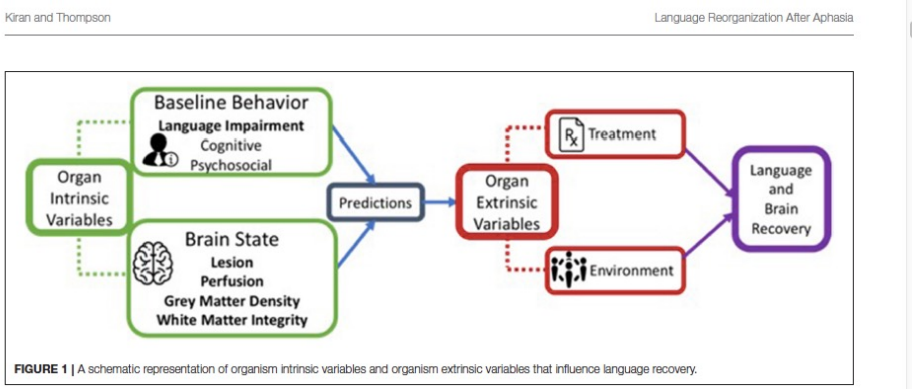
Kiran, S & Thompson, C. K. (2019). *Frontiers in Neurology*

Factors that influence neuroplasticity in stroke-induced aphasia

- Neuroplastic changes among people with aphasia are highly influenced by **individual patients' clinical characteristics.**

- Evidence suggests that these characteristics include but are not limited to the **size and location of stroke**, the resulting **type of language deficits**, the **time since stroke onset**, **genetic variation** and other **molecular biological factors**.

- **Non-patient related factors** (therapy method, intensity, living environment).



A key issue in understanding aphasia recovery and its treatment is the enormous degree of **inter-subject variability**.

Promoting Neuroplasticity of Language Networks

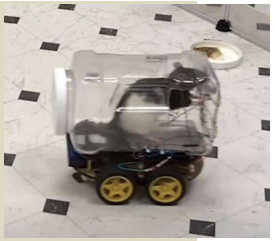
Cortical rewiring

	Principle for Treatment of Aphasia Based on research in aphasia	Suggestions from animal models (Kleim & Jones, 2008)
1	**Use, improve,** or lose it	Principle 1. Use it, lose it Principle 2. Use it, improve it
2	**Specificity** rebuilds targeted networks	Principle 3. Specificity
3	**Salience** is essential	Principle 7. Salience matters
4	**Repetition** and **intensity** strengthen neural pathways	Principle 4. Repetition matters Principle 5. Intensity matters
5	Promote **generalization**; avoid interference	Principle 9. Transference Principle 10. Interference
6	**Complexity** promotes learning and generalization	NA

From: Kiran & Thompson, 2019


Use it, Improve it

What do we know about SLT for PWA?



- Speech and language therapy (SLT) interventions for people with aphasia are **complex**.
- **Interventions vary by delivery model** (face-to-face, tele-rehabilitation), dynamic (group, 1-to-1), and provider.
- Therapists tailor the functional relevance and intervention difficulty to the **individual's needs**.
- Traditional **speech and language therapy** (SLT) methods robustly remain the **gold standard for aphasia rehabilitation** (Breitenstein et al., 2017).
- **Intensive and targeted SLT intervention improves language abilities** for all aphasia types irrespective of time post-onset and aphasia severity (Saxena & Hillis, 2017).

Where do PWA go after SLT ends?

Cypriot and Greek therapists face serious limitations in moving their clients on after therapy has ended

Aphasia Support Groups in Cyprus "The Aphasia Communication Team- TACT"

This group aims to provide opportunities for **support**, **learning**, and **communication**
…to promote **living well with aphasia**

Commentaries

Discharge experiences of speech-language pathologists working in Cyprus and Greece

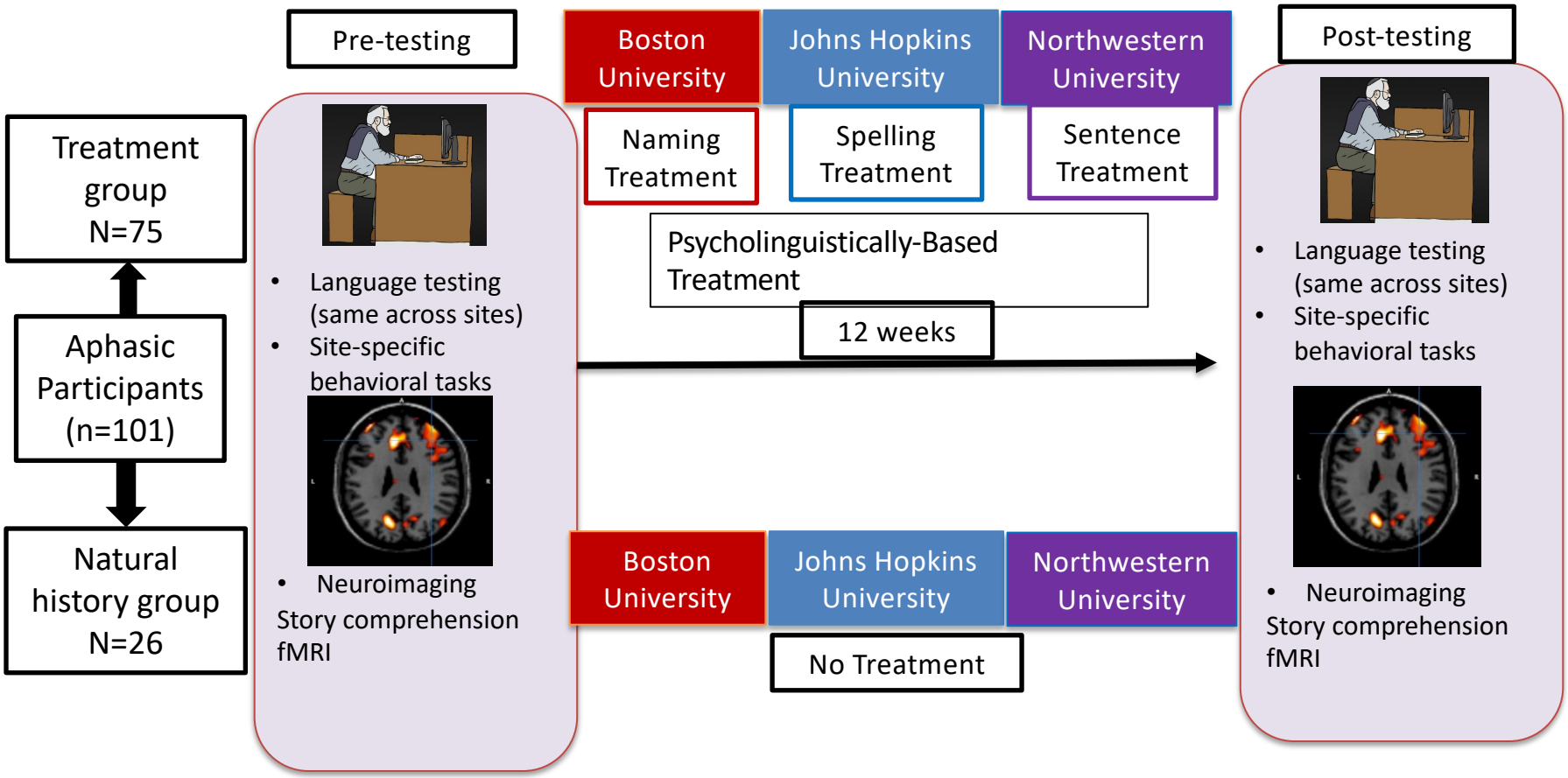
Maria Kambanaros

Pages 296-300 | Published online: 01 Jul 2010

Download citation https://doi.org/10.3109/17549507.2010.485331

Specificity Rebuilds Targeted Networks

Multi-site Study: Experimental Design



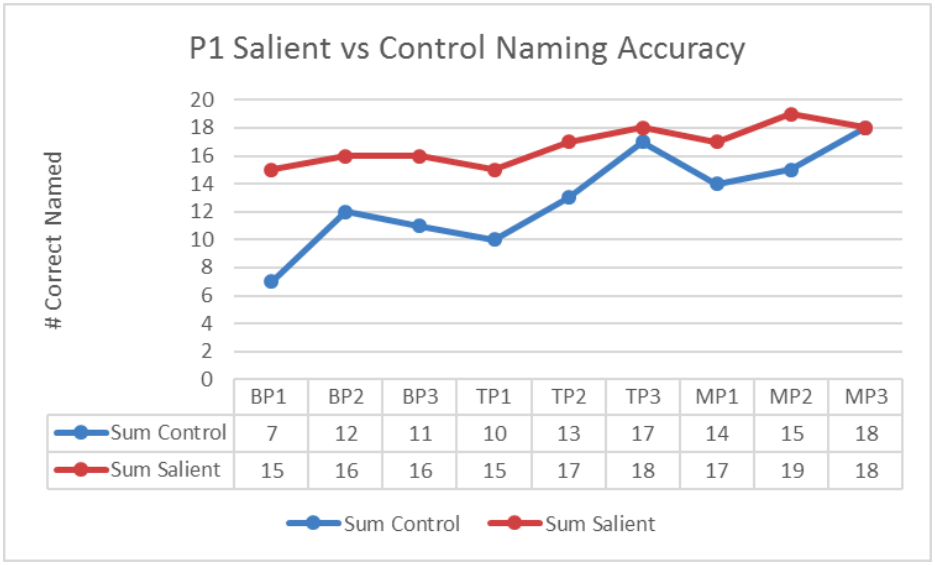
Salience is essential

The **phenomenon that the brain pays attention to what it finds important**

More salience

What is salient to you? This question is important for those who treat stroke survivors to keep in mind. In most cases, things that are really important to you, are the same things that are really important to PWA.

- **Salience** has received less attention from researchers than other principles
- Neuroscientists have identified a **salience network** (Menon,2015; 2017) in the brain that identifies biologically and cognitively relevant events that shape behavior (Besissner et al., 2017).
- **Language therapies that incorporate salience rely on personally important and motivating stimuli**
- Preliminary studies that incorporate salience during picture word matching and script-training therapies are promising (McKelvey et. al., 2010; Cherney et al., 2015)



Molesh, Kathy Kay, "The Impact of Salient Naming Targets During Aphasia Therapy" (2019). *UM Graduate Student Research Conference (GradCon)*. 11. https://scholarworks.umt.edu/gsrc/2019/posters/11

The salience network has distinct patterns of intrinsic cortical and subcortical connectivity from the lateral frontoparietal central executivenetwork in the anterior thalamus (antTHAL), dorsal caudate nucleus (dCN), dorsomedial thalamus (dmTHAL), hypothalamus (HT), periaqueductal gray(PAG), putamen (Put), sublenticular extended amygdala (SLEA), substantia nigra/ventral tegmental area (SN/VTA), and temporal pole (TP).

If its not important to you, it won't be important to your brain (Michael Merzenich)

PLOS ONE

RESEARCH ARTICLE

What do people with aphasia want to be able to say? A content analysis of words identified as personally relevant by people with aphasia

Rebecca Palmer[1,2]*, Helen Hughes[2], Tim Chater[1]

1 School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom, 2 Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

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- **100 participants** representing 20 areas of the United Kingdom (aged between 23 to 85 years).
- **Word finding difficulties ranged from mild to severe**.
- The sample of **9999 words selected for practice** included 3095 different words in 27 topics.
- The majority of words selected (79.4%) were from the topics **`food and drink' (30.6%), `nature and gardening'(10.3%), `entertainment' (9.4%)**, **`places' (7.3%), `people' (6.7%), `house' (6.5%), `clothes'(5.2%)** and **`travel' (3.5%).**
- The 100 words types chosen with the greatest frequency were identified. These account for 27 percent of the 9999 words chosen by the participants

Repetition and intensity strengthen neural pathways

CILT

- The background of **CILT** is well documented having derived from constraint-induced movement therapy that has a rich literature on neuroplasticity and motor skill learning.

- The treatment principles of CILT include **constraining the response format, treating in an intensive schedule and shaping verbal responses.**

- This involves the **'forced-use' of language** through manipulation of the communication context to ensure that communication can only occur via spoken language production and comprehension, and not via any other modality (e.g., gestures).

- In a review of CILT studies (18 studies, n=202 patients) conducted over the last ten years (Mozeiko et al. 2016/*Aphasiology*) it was found that **individuals with acute and those with chronic aphasia showed improvement on treatment task**

Efficacy of intensive aphasia therapy in patients with chronic stroke: an RCT

Table 1 Intensive regimens

	Group I	Group II
Intervention type	ILAT	ILAT
Daily practice	4 hours	2 hours
Weekly practice	12 hours	6 hours
Therapy frequency	3 weekly sessions	3 weekly sessions
Duration of each trial phase	6 consecutive working days	6 consecutive working days
Total amount of practice	48 hours	24 hours
Total treatment duration	4 weeks	4 weeks

Thirty patients with chronic post-stroke aphasia were randomly assigned to one of two treatment groups: patients receiving ILAT with 4 hours (Group I) or with 2 hours of daily practice (Group II).
ILAT: Intensive Language-Action Therapy.

Duration > Intensity

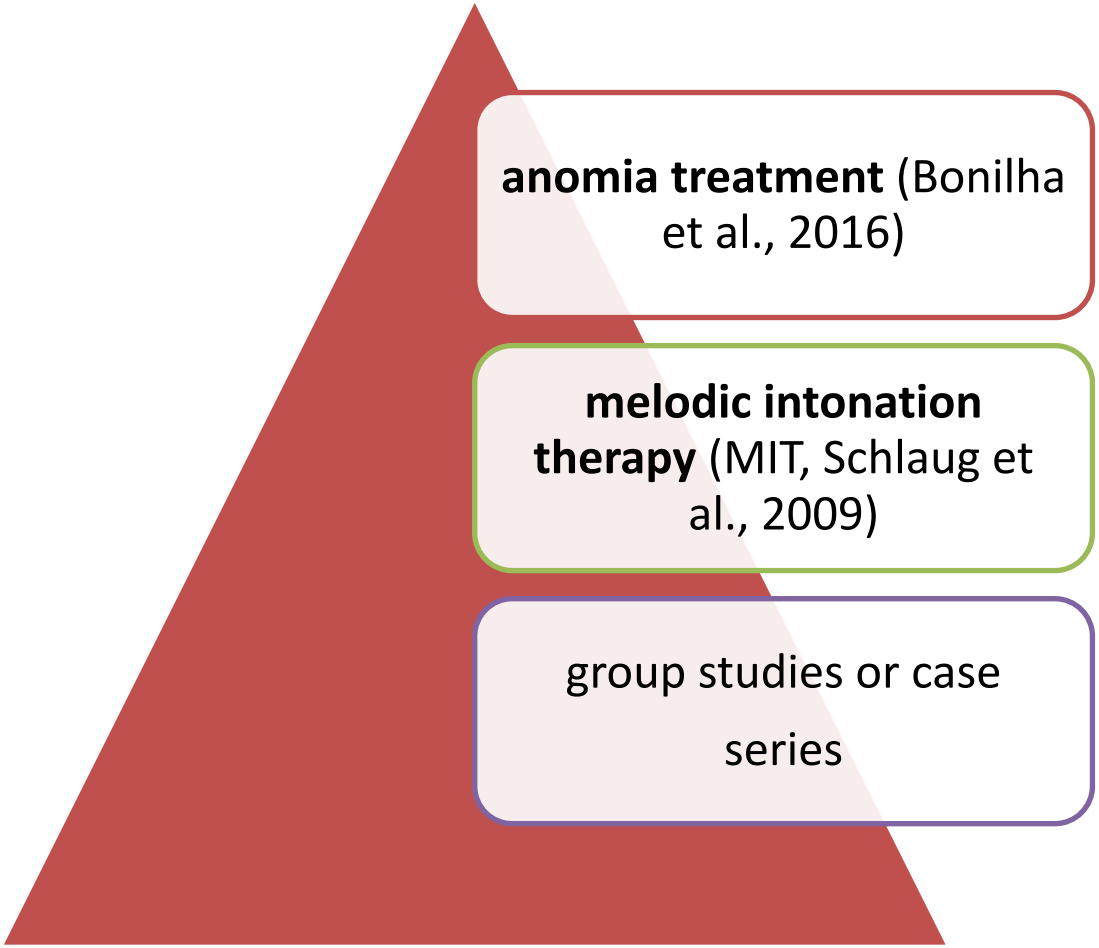
Stahl B, Mohr B, Büscher V, et al.
J Neurol Neurosurg Psychiatry 2018;**89**:586–592.

No added value from
more than 2 hours of daily speech-language therapy within 1 month.

whereas
a 2-week extension in treatment duration contributed substantially to recovery from chronic poststroke aphasia.

In light of previous concerns about the feasibility of highly-intensive SLT, a lower-than-expected dosage of 2 hours per day is sufficient and therefore easier to achieve within the constraints of clinical practice

To date, very few studies on neuroplastic changes following intensive, successful SLT have been published



What about PWA in the chronic stage?

- In *The Lancet*, Caterina Breitenstein and colleagues report an RCT in 19 rehabilitation centres in Germany investigating intensive speech and language therapy in patients with **chronic aphasia**
- The intervention group received **10 h or more of therapy per week for at least 3 weeks** (n=78) and a control group (n=78) in which treatment was deferred for 3 weeks.
- Therapy consisted of combined **one-to-one speech and language therapy**, **group therapy provided by an SLT** and prescribed (but self-managed) **computer-based or paper-and-pencil linguistic exercises.**
- The primary endpoint was **change from baseline in effectiveness of verbal communication in everyday life scenarios.**
- The **10% improvement in this primary outcome among patients in the intervention group** (mean difference 2·61 points [SD 4·94]; 95% CI 1·49 to 3·72) compared with the control group.
- This study also adds weight to the argument made in recent systematic reviews that **substantial and clinically important improvements can be made in the chronic phase of stroke recovery.**

The study had broad inclusion criteria, allowing participation of people of diverse ages, stroke type, time after onset of aphasia, aphasia severity, and aphasia syndrome. Additionally, participants with global and severe aphasia were included; such people are often excluded from efficacy studies but must be included in effectiveness studies in usual care contexts. The study included a 6 month follow-up (for which only one person in each group was lost), no differences between control and treatment groups were observed at baseline, and both effect sizes and

Conclusion

Intensive aphasia treatment in chronic PSA leads to **reorganization of the functional and structural language network in both hemispheres.**

The involvement of each hemisphere in neuroplasticity is probably independent from the neuroimaging method used, but may be strongly influenced by the therapy method, its intensity, duration, and the language materials and tasks.

Promote generalization

Are we fishing for generalisation?

- **Generalisation is of central interest to clinicians and researchers in aphasia therapy** as it is firmly embedded in the discussion of both **demonstrating and maximising therapy effectiveness**.

- We want to know that **therapy is 'making a difference**' to the individual **with the benefits of our intervention extending, or generalising, beyond the focus of our therapy targets**.

- Within spoken production, **the generalisation of our treatment effects to everyday conversation is often viewed as the standard for determining whether our interventions have been successfu**l (e.g. Carragher, Conroy, Sage, & Wilkinson, 2012; Lind, Kristoffersen, Moen, & Simonsen, 2009), irrespective of our understanding as to whether this is predicted.

- **The temptation is, therefore, to 'fish' for any evidence of change in communication to demonstrate generalisation of therapy.**

Webster J, Whitworth A, Morris J. (2015). Is it time to stop 'fishing'? A review of generalisation following aphasia intervention. *Aphasiology 29(11), 1-25* DOI:10.1080/02687038.2015.1027169


Complexity
promotes learning
& generalization

The Complexity Account of Treatment Efficacy (CATE)

Thompson et al., 2003

- Training complex linguistic structures results in generalization to less complex structures within the same linguistic domain
- Top-down training

- Teaching English as second language (Eckman, 1988)
- Phonological development (Gierut, 1998, 1999, 2007)
- Lexical semantic (naming) deficits (Kiran & Thompson, 2003; Kiran et al., 2008)
- Phonological dyslexia (Riley & Thompson, 2018)
- Sentence comprehension/production (Thompson et al., 2003, 2010a, 2010b)

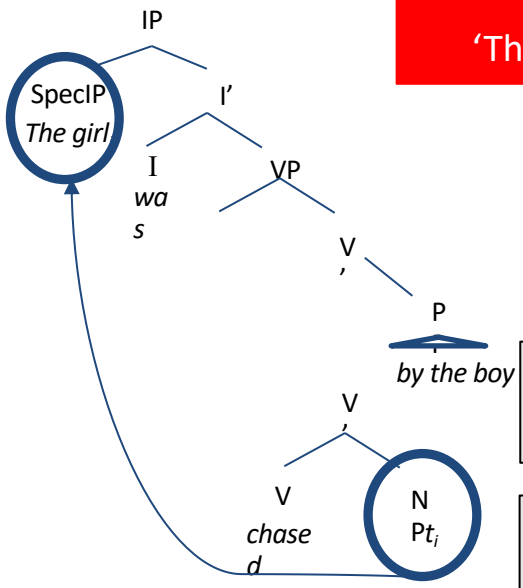
SENTENCE PROCESSING TREATMENT

NP-movement structures

Trained Structure

Full passive sentences with adjunct clause

'The girl was chased by the boy at the fairgrounds'



Tested for Generalization

Truncated passives

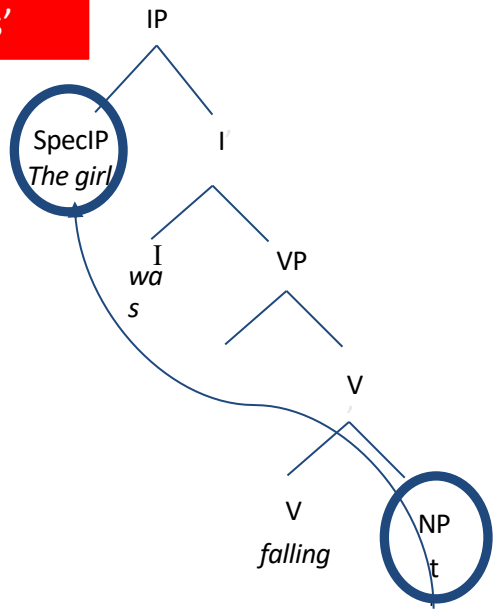
'The boy was chased at the station'

Actives with unaccusative verbs

'The boy fell at the factory'

Object Cleft Structures

'It was the boy fell who fell at the factory'



Barbieri, Mack, Chiappetta, Europa, & Thompson (2019). *Cortex*

Stroke in Cyprus

- **Stroke** is **the most frequent cause of disability** in Cyprus (CYPRUS WHO, 2015).
- Current figures reveal that on average **1200-1400 people each year suffer a stroke in Cyprus** (Ministry of Health report, 2016).
- The actual number of people living with post-stroke aphasia and other disabilities in Cyprus is **unknown** but years-of-healthy-life lost due to disability (YLD) is 20-30 years (CYPRUS WHO, 2015).

CYPRUS STROKE ASSOCIATION

CYPRUS STROKE ASSOCIATION

Cost of stroke treatment

- **230 euros per day to cover rehabilitation treatments** (one treatment session of SLT, occupational therapy (OT) and neuropsychology each; and two physiotherapy sessions daily) and medical care.
- The average stay is **88 days for patients with an ischaemic stroke** and **111 days for patients with haemorrhagic stroke**.
- This puts the **cost of stroke rehabilitation between 20,000 to 25,000 euros per stroke survivor**.
- Given the increasingly constrained national health budgets, there is currently a window of opportunity to develop **novel cost-effective treatments** to address this problem and aid service providers in their management of these growing numbers.

In 2010, the annual cost of stroke in Europe was €64.1bn (Gustavsson et al., 2011), with approximately 70% attributed to hospital services incurred during inpatient stay and care.

Background

- Given the profound impact of language impairment after stroke (aphasia), **neuroplasticity research is gathering considerable attention as means for eventually improving aphasia treatments and how they are delivered.**

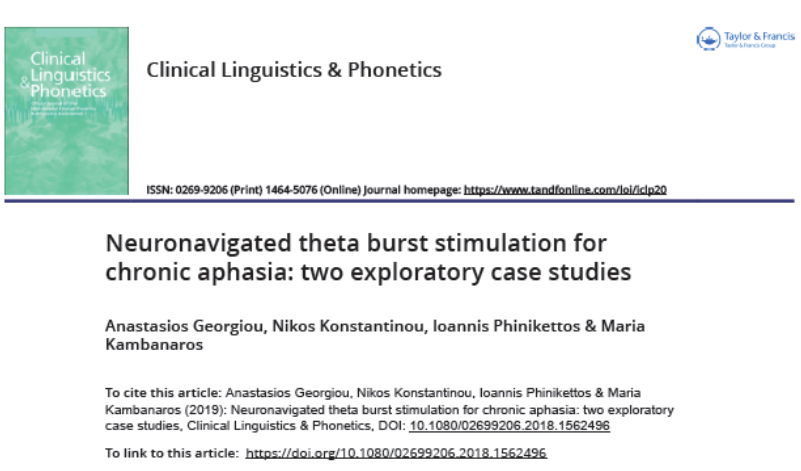
- **Functional and structural neuroimaging** studies indicate that aphasia treatments can **recruit both residual and new neural mechanisms to improve language function** and that neuroimaging modalities may **hold promise in predicting treatment outcome**.

- In relatively small clinical trials, both **non-invasive brain stimulation and behavioural manipulations targeting activation or suppression of specific cortices can improve aphasia treatment outcomes**.

Treatments that induce neuroplasticity

Noninvasive brain stimulation (NIBS)

Research in Cyprus so far



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Neuronavigated theta burst stimulation for chronic aphasia: two exploratory case studies

Anastasios Georgiou, Nikos Konstantinou, Ioannis Phinikettos & Maria Kambanaros

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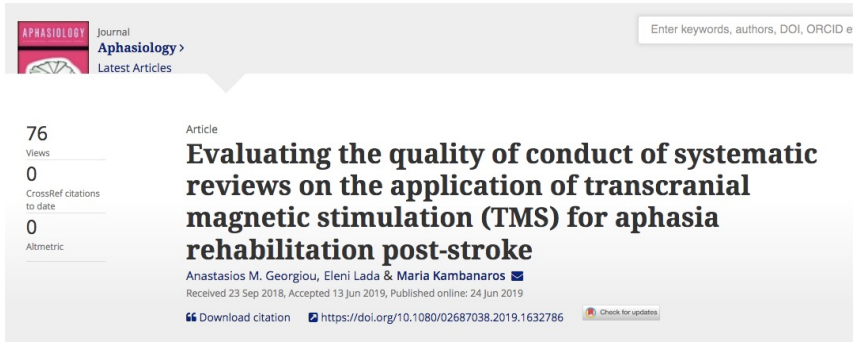
To link to this article: https://doi.org/10.1080/02699206.2018.1562496



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Evaluating the quality of conduct of systematic reviews on the application of transcranial magnetic stimulation (TMS) for aphasia rehabilitation post-stroke

Anastasios M. Georgiou, Eleni Lada & Maria Kambanaros

Received 23 Sep 2018, Accepted 13 Jun 2019, Published online: 24 Jun 2019

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Evidence so far...

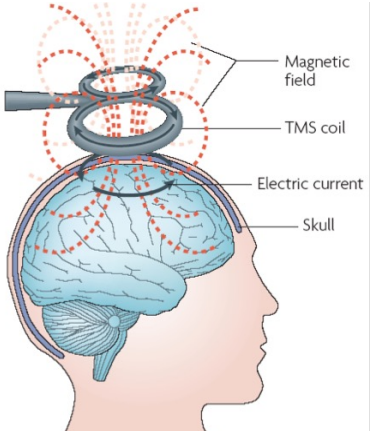
- Over the last few years, **positive effects of low frequency (1-Hz) rTMS over the right triangular part of the inferior frontal gyrus (IFG) was shown to improve language function in individuals with aphasia in the sub-acute and chronic stage after first-time stroke.**

- Several drawbacks: (i) **small numbers** of patients were treated in each case (between 8 to 20 patients treated with real TMS); (ii) the amelioration in **overall aphasia severity** is reported in only a handful of studies; (iii) **outcome measures varied widely** across studies making the results difficult to compare; (iv) **different rTMS protocols** were applied (inhibitory vs excitatory rTMS) and not all patients showed significant post-rTMS improvements; and (v) **few studies included an ecological language measure**, making it unclear whether the improved performance carried over in improving patients' everyday communication abilities and consequently quality of life.

Weiduschat N., Thiel A., Rubi-Fessen I., Hartmann A., Kessler J., Merl P., et al. (2011). Effects of repetitive transcranial magnetic stimulation in aphasic stroke a randomized controlled pilot study. Stroke 42, 409–415 10.1161/STROKEAHA.110.597864; Rubi-Fessen, I., Hartmann, A., Huber, W., Fimm, B., Rommel, T., Thiel, A., et al. (2015). Add-on effects of repetitive transcranial magnetic stimulation on subacute aphasia therapy: enhanced improvement of functional communication and basic linguistic skills: a randomized controlled study. Arch. Phys. Med. Rehabil. 96, 1935–1944.
Kakuda, W., Abo, M., Kobayashi, K., Momosaki, R., Yokoi, A., Fukuda, A., ... & Kameda, Y. (2011). Anti-spastic effect of low-frequency rTMS applied with occupational therapy in post-stroke patients with upper limb hemiparesis. Brain injury, 25(5), 496-502.; Abo M., Kakuda W., Watanabe M., Morooka A., Kawakami K., Senoo A. (2012). Effectiveness of low-frequency rTMS and intensive speech therapy in poststroke patients with aphasia: a pilot study based on evaluation by fMRI in relation to type of aphasia. Eur. Neurol. 68, 199–208.

The TMS procedure

- During a TMS procedure, a magnetic field generator, or "coil", is placed near the head of the person receiving the treatment.
- The coil is connected to a pulse generator, or **stimulator**, that delivers electric current to the coil.
- The coil produces small electric currents in the region of the brain just under the coil via electromagnetic induction
- Treatment can involve delivering **repetitive magnetic pulses**, so it's called **repetitive TMS** or **rTMS**.



Models of neuroplasticity using rTMS

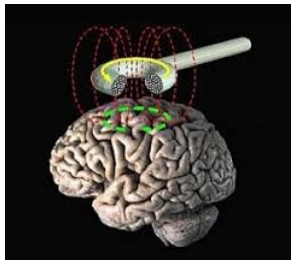
Hamilton and colleagues (2011) outline 2 theoretical models of recovery-inducing neuroplastic changes that are highly relevant to the therapeutic applications of rTMS.

1. **Recruitment of residual and perilesional language areas in the damaged left hemisphere.**

2. **Compensatory recruitment of homotopic language areas in the right hemisphere.**

Hamilton RH,Chrysikou EG,Coslett B(2011) Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. Brain Lang 118(1–2):40–50.; Ohyama M, Senda M, Kitamura S, Ishii K, Mishina M, Terashi A (1996) Role of the nondominant hemisphere and undamaged area during word repetition in poststroke aphasics – a PET activa- tion study. Stroke 27(5):897–903 ; Musso M, Weiller C, Kiebel S, Muller SP, Bulau P, Rijntjes M (1999) Training-induced brain plasticity in aphasia. Brain 122:1781–1790.

TMS with SLT treatment

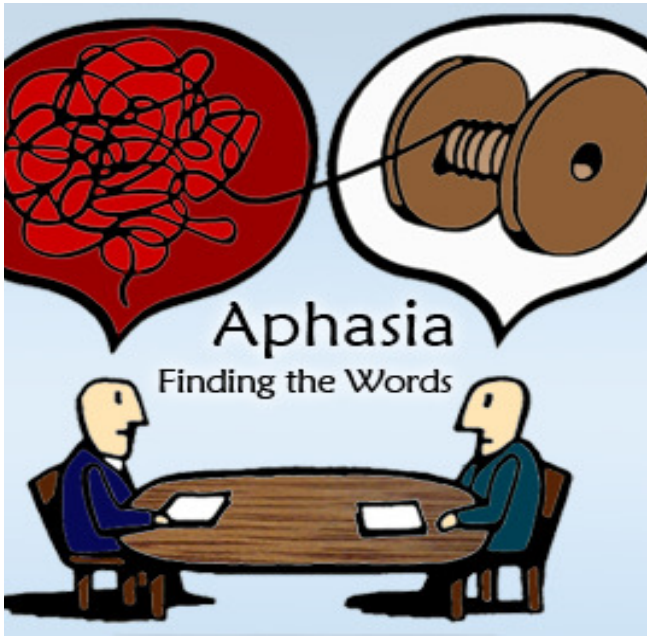


- Naming (e.g. Hu et al., 2018; Rubi-Fessen et al., 2015)
- Repetition (e.g. Barwood et al., 2013; Seniow et al., 2013)
- Comprehension (e.g. Hu et al., 2018)
- Naming reaction time (e.g. Waldowski et al., 2012)
- Spontaneous speech (e.g. Hu et al., 2018)
- Aphasia profile (Rubi-Fessen et al., 2015; Heiss et al., 2013)

➢ **significant inconsistencies between studies regarding type & intensity of SLT and TMS**

- 30-minute SLT, post-TMS, focusing on **naming** (Hu et al., 2018)
- 45-minute SLT, post-TMS, focusing on **word retrieval** (Rubi-Fessen et al., 2015)
- 60-minute SLT, post-TMS, twice a week focusing on **expressive skills** (Wang et al., 2014)

The ASPIRE project



- The research project **As**sessment of **P**ost-stroke Aphas**i**a for **Re**habilitation **Re**search (**ASPIRE**) involves interdisciplinary research on the effects of TMS into applications for clinical practice with stroke survivors.
- The project aims to obtain evidence through **a pilot randomised control trial** on the effectiveness of different treatment protocols using TMS on language recovery after first-time stroke.
- It is the goal of the study to explore the feasibility of **integrating TMS as an adjunctive therapy into typical standard rehabilitation care** for communication deficits/ aphasia therapy.

"The Project EXCELLENCE/1216/0517 is co-financed by the European Regional Development Fund and the Republic of Cyprus through the Research and Innovation Foundation"

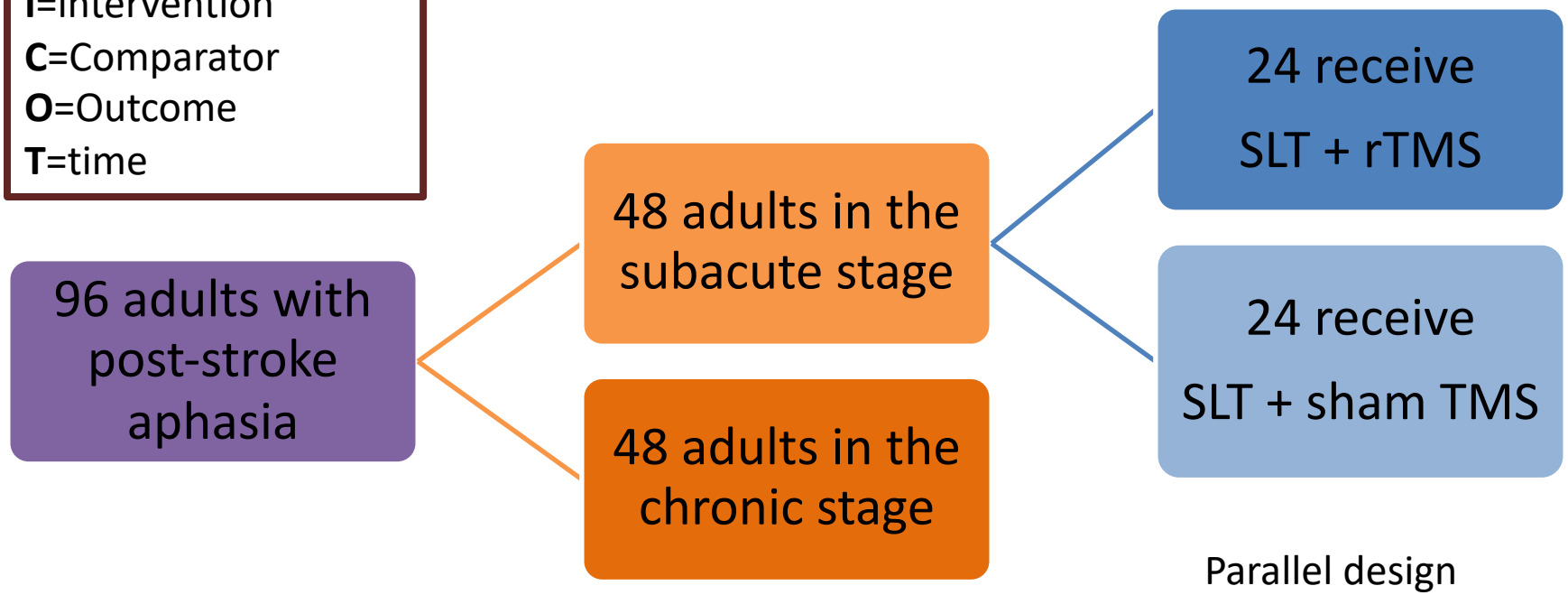
ASPIRE Partners

Role	Name	Stakeholder
HO	Cyprus University of Technology	Public University
Foreign Partner	University of Trento/Centre for Mind/Brain Sciences	University Research Centre
PA1	Melathron Agoniston tis EOKA	Medium Enterprise
PA2	Gialletto Ltd.	Small Enterprise
PA3	University of Nicosia	Research Centre
PA4	Ministry of Health	Policy maker
PA5	Scico	Third Party
PA6	Cyprus Stroke Association	Third Party

Small-scale RCT

PICOT format
P=population
I=intervention
C=Comparator
O=Outcome
T=time

Intervention A & B

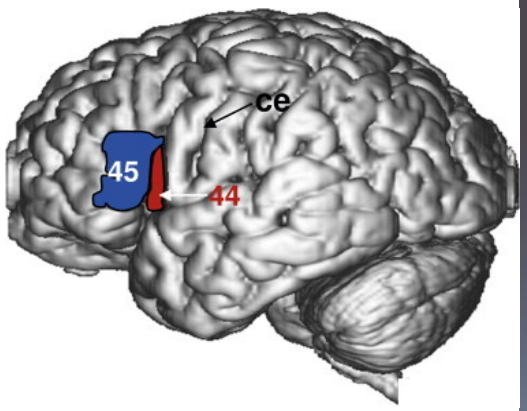


ASPIRE will employ a **double-blind design where researchers and patients will be blinded to treatment assignment**. Each treatment protocol will be carried out every day over a two-week period (excluding the weekends).

Parallel design Superiority trial: that **intervention A is superior to intervention B**

rTMS treatment protocols

- Half of the participants will receive 20 minutes of 1-Hz rTMS over the right triangular part of the inferior frontal gyrus (center of Brodmann area 45)



- The other half of the participants (sham group) will receive the same stimulation over the vertex.

- Both groups will be given an intensity of 90% of the individual resting motor threshold.

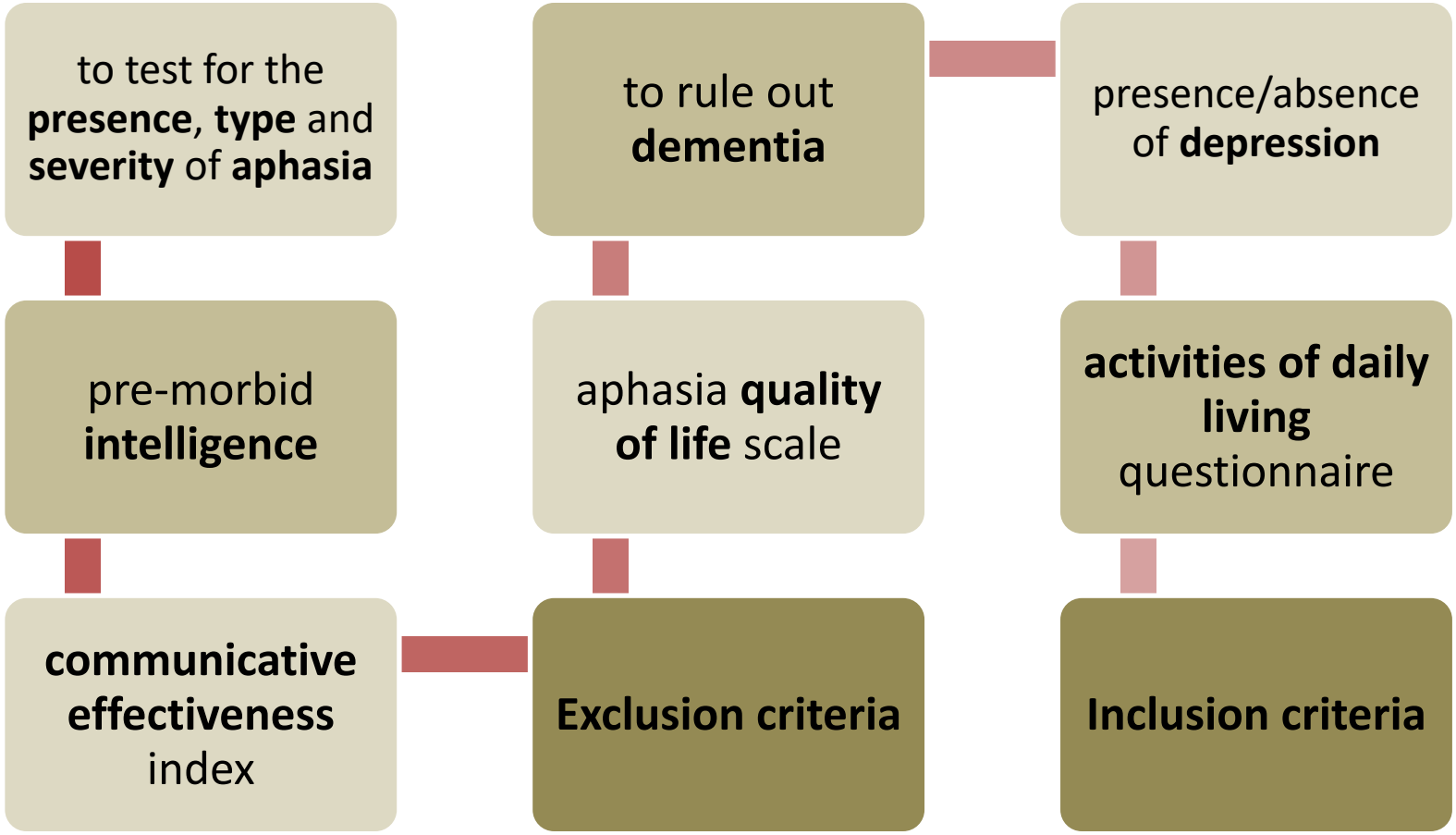
The sham coil can stimulate the peripheral nerves of the scalp, it looks, sounds and feels exactly the same as an active coil, both to the patient and the operator, but importantly it does not deliver active stimulation of brain cells.

The resting motor threshold was defined as the minimum stimulator output that elicited a visible contraction on the first dorsal interosseus muscle of the unaffected hand in more than 5 of 10 stimulation trials.

Intensive speech & language therapy (SLT)

- This involves naming treatment at the word and sentence levels using **intensive language action therapy** (ILAT: Difrancesco et al., 2012).
- The activity central to the therapy is essentially, the well-known “Go Fish” game in which one participant asks another for a card that matches one of those he has been dealt. If the person has the requested card, it is surrendered; if not, the requestor must “go fish” or draw from the deck. The activity continues until one player is holding no remaining unmatched cards.
- Card sets will be created to include photographs of concrete (imageable) high (e.g., driving) and low frequency (e.g., peeling (a banana/orange) occurrence pictureable verbs.
- Every two participants allocated to this group will make up the dyad and each dyad will receive 30 hours of ILAT over 2 weeks.

Background measures



Participant criteria: inclusion

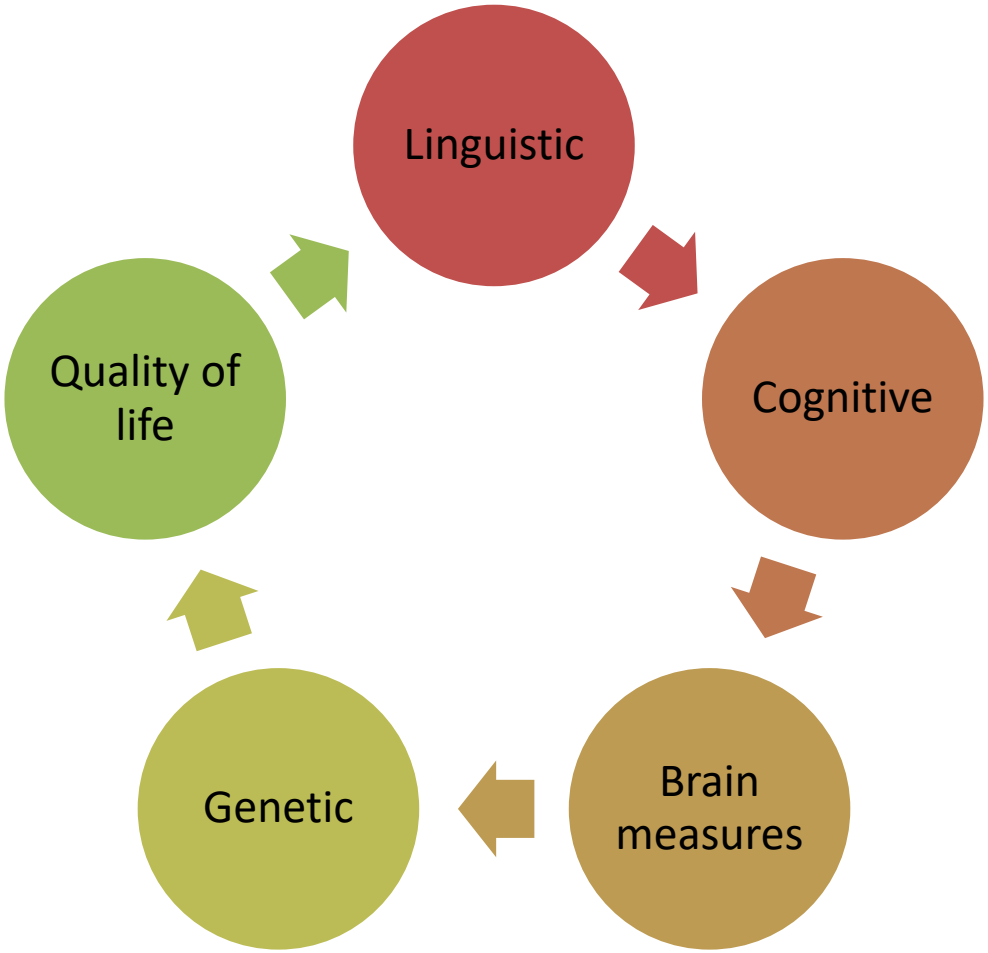
- no more than one stroke located in the left hemisphere (on MRI or CT scan)
- sub-acute (between 1-3 months post-stroke) or chronic (> 6 months post-stroke)
- pre-morbid right-handed
- native speakers of (Cypriot) Greek
- presence of aphasia (excluding global aphasia)
- no severe apraxia of speech or dysarthria affecting intelligibility
- moderate naming deficit (as evidenced by confrontation & responsive naming subtests of BDAE)
- no intellectual disability
- reduced ADL & quality of life
- participant confirmation that language deficits have a negative impact on return to a meaningful life
- adequate hearing, vision and manual dexterity for test purposes

Participant criteria: exclusion

- symptomatic prior CVAs
- moderate-severe depression
- neurodegenerative or psychiatric disease
- epilepsy or electroencephalography-documented epileptic charges
- insulin-dependent diabetes mellitus
- renal or liver failure
- metal parts in the body
- life-threatening diseases
- auditory or visual deficits that impair testing
- history of substance abuse
- medication that alters brain excitability
- non-native speaker of Greek

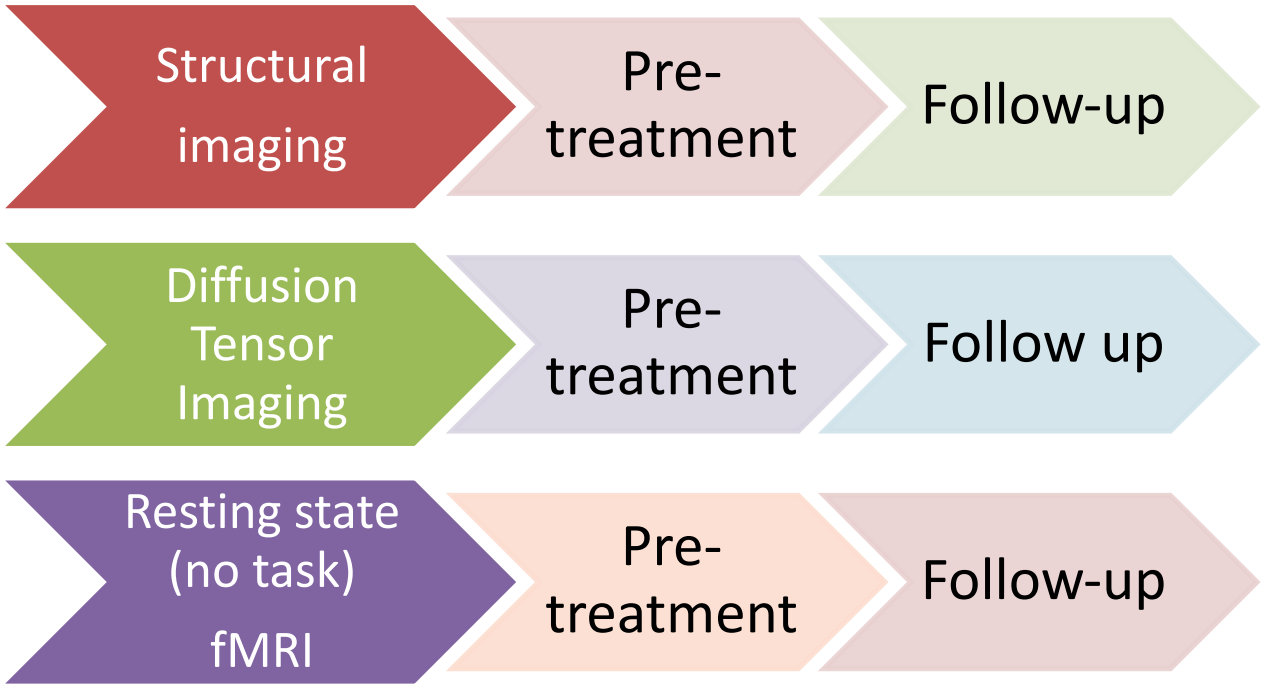
Baseline measures

Patients will be assessed using comprehensive neurocognitive and linguistic batteries, molecular measures (genetic and biomarkers), and neuroimaging measures (brain volumetric, anatomical and functional connectivity measures).



These measures will be repeated before treatment, immediately after treatment, and at three months post-treatment.

Brain measures



Can identify practice-induced neuroplastic changes in both **grey & white matter,** particularly in longitudinal studies

Predicting treatment outcomes based on the **integrity of white matter networks**

Measure changes in **functional connections** between brain regions

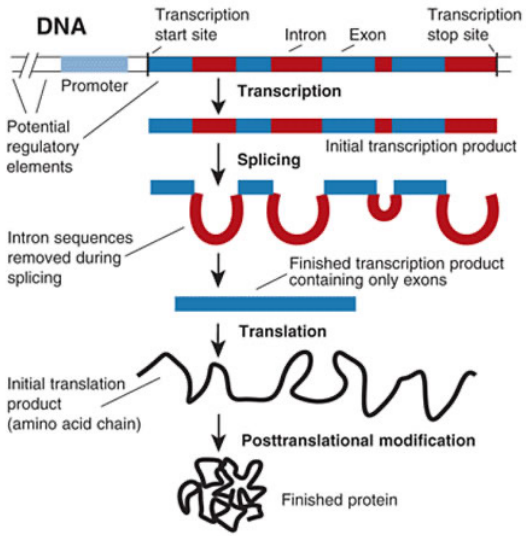
Genetic testing

- Blood samples will be taken from each participant and used for assessing specific biomarkers (miRNAs)

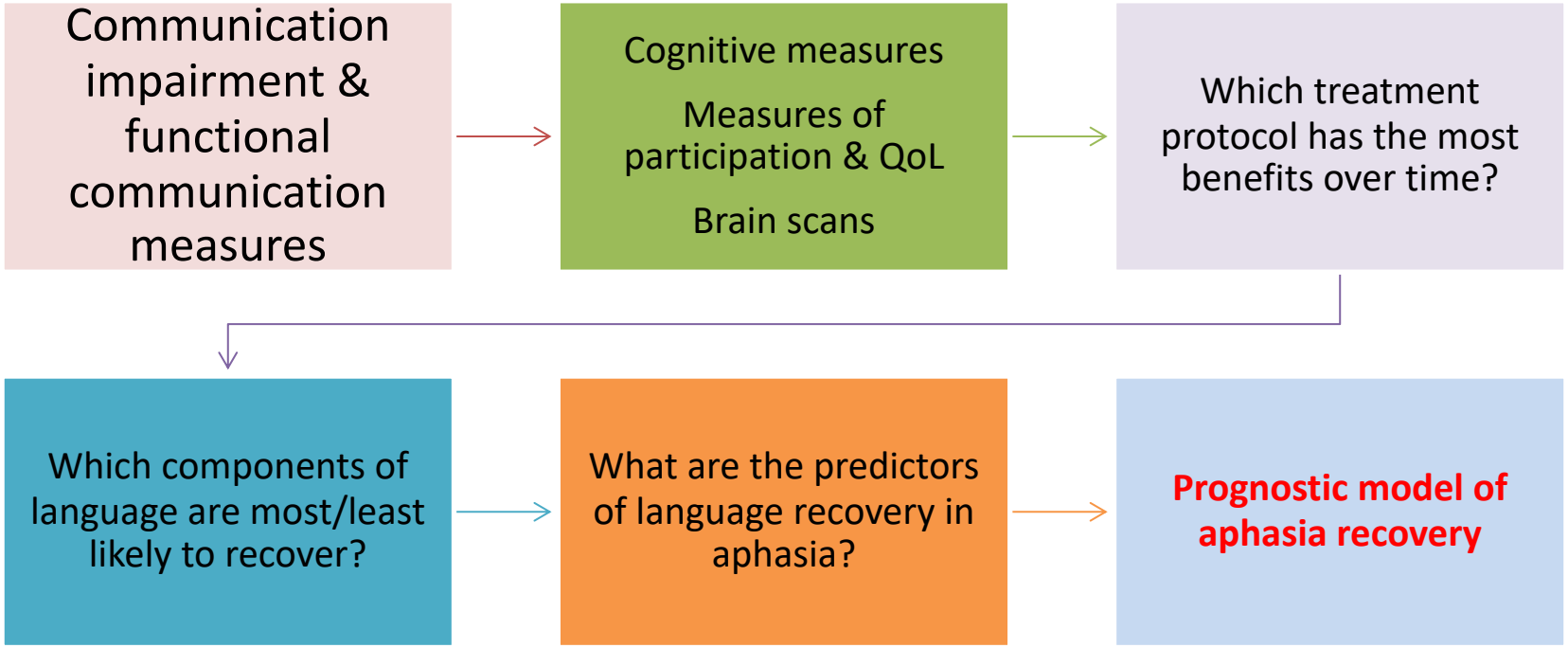
SNP selection

- The genotype for each participant will be determined for particular **polymorphisms** (SNPs) for which there is previous strong evidence of being **implicated in neuronal survival and neuroplasticity** as well as with **poor outcome of recovery after stroke**.

Gene	SNP	Physiological effect
BDNF	rs6265 (val66met)	Neuronal survival, plasticity and neurogenesis
ApoE 4	ε4	Impairment of neural repair processes
COMT	rs4680	Effects on learning and plasticity



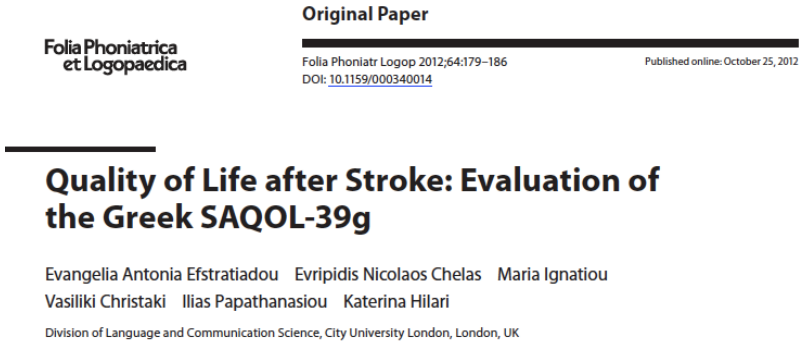
Aphasia rehabilitation outcomes



Quality of life measures

- An additional problem with traditional applications of rTMS in Aphasia is the use of experimental language tasks as dependent measures for assessing the performance of people with aphasia.

- The problem with this approach is that it fails to capture any possible effects of rTMS treatment in **improvements in everyday language**, and thus fails to assess the possible effects of rTMS treatment on the **quality of life** for people with aphasia (e.g. improved communication, increased job productivity, etc.).



Original Paper

Folia Phoniatrica et Logopaedica

Folia Phoniatr Logop 2012;64:179–186
DOI: 10.1159/000340014
Published online: October 25, 2012

Quality of Life after Stroke: Evaluation of the Greek SAQOL-39g

Evangelia Antonia Efstratiadou Evripidis Nicolaos Chelas Maria Ignatiou
Vasiliki Christaki Ilias Papathanasiou Katerina Hilari

Division of Language and Communication Science, City University London, London, UK

ASPIRE employs ecologically valid measures that assess not only the effects of rTMS in experimental linguistic and cognitive tasks but also in everyday life tasks.

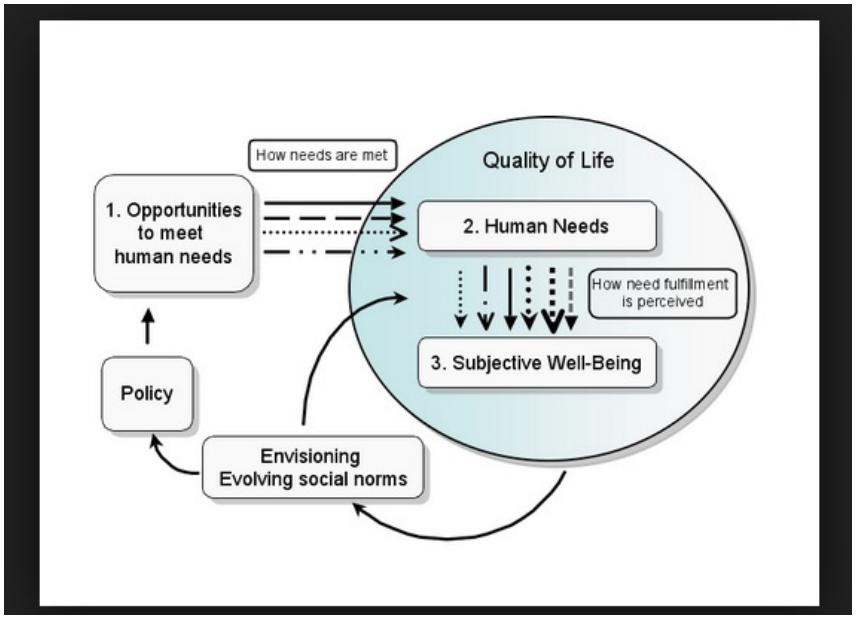
Dissemination

- The resulting information will be provided in a report to the **policy-maker**, and new knowledge will be exchanged with the **rehabilitation industry**, **research institutions** and **third sector groups**.

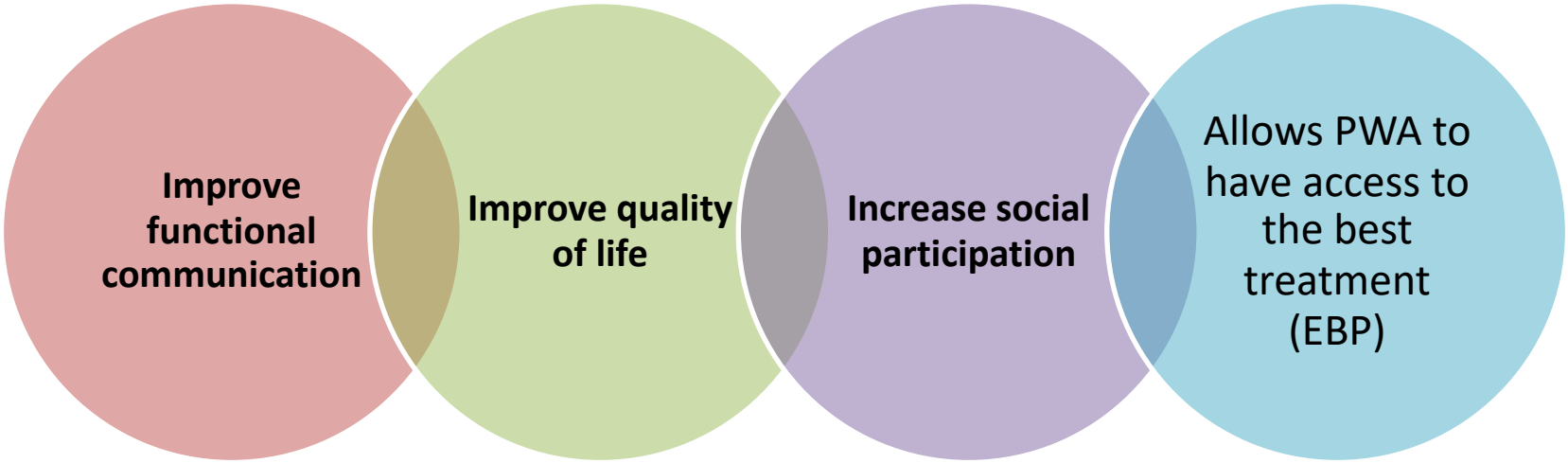
- These findings will be **disseminated** through peer-reviewed papers, relevant conference presentations, international project collaborations (e.g., I-PRAISE and RELEASE) and the Cyprus Association of Registered Speech-Language Pathologists.

Our aspirations…to take an **international leadership role in aphasia stroke care** by producing findings on:

- the **treatment-type(s)** (traditional vs. TMS vs. both) that enhance recovery of language after stroke
- the **characteristics** shared by people who made a good (or not so good) recovery from aphasia are;
- the **common elements to therapy** that facilitated recovery (e.g., timing after stroke)
- whether people with **particular aphasia characteristics** do better with specific therapies



Why is aphasia rehabilitation research important for PWA?



Thankyou

The Team