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Can software change your hardware?

The relationship between brain structure and app-based therapies in patients with chronic post-stroke aphasia

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National Hospital for Neurology & Neurosurgery

Plan

- Two practice-based digital neuro-interventions brain structure by therapy interactions
  i. Listen-In: patients with auditory perceptual impairments
  ii. iReadMore: patients with central alexia
- Behaviour: do they work?
- Behaviour: what drives therapeutic effects?
- Structure: can it predict response to therapy?
- Structure: can it be altered by therapy?

Upping the dose in practice-based therapy: e-Therapies

Why do we need e-Therapies?

- Average stroke in-patient stay in UK is 14 days
- Average amount of SALT in that time is 5 hours
- Average amount of community SALT is 8 sessions
- Bhogal meta-analysis

  Positive SALT studies = 98hrs

  Negative SALT studies = 43hrs

Experimental pipeline for all interventions

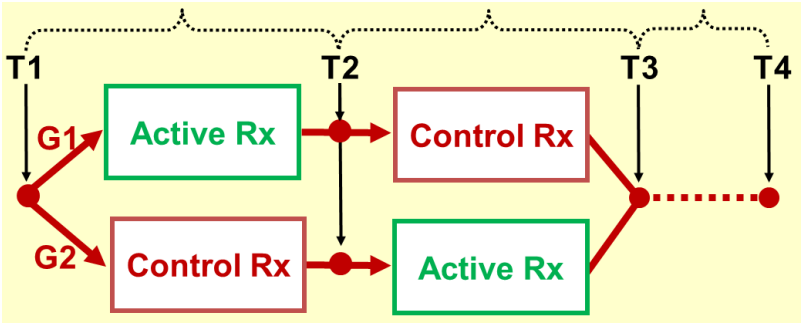
Neurotherapeutics Group
Institute of Cognitive Neuroscience

connect
Patient Co-creation

Development Phase

SOFT/U DIGITAL GAMIFICATION
Gaming Experts

Phase II trial



Phase III/IV web-release trial

"X patients like you practiced for Y hours and improved their function by Z"

baseline assessment

Database: pre-existing patients matched on baseline assessment and demographics

UCL

Dr Sonia Brownsett

LISTEN-IN

Victoria Fleming

Speech comprehension therapy program for people with post-stroke aphasia

Therapy Task:

Word/phrase/sentence → picture matching

1. Patient hears a word, phrase or sentence

2. They choose the matching picture, and get visual feedback (ticks/crosses)

3. They get 'rewarded' with coins for every answer

- **2 coins if correct on first response**
- **1 coin any other response**

> They can listen again if they want

> Target items include nouns, verbs, prepositions, adjectives, pronouns and tense

Therapy ‘challenge’

- 3298 unique challenges
- 894 unique lexical items

- >4000 photos
- >4000 audio recordings, male+ female

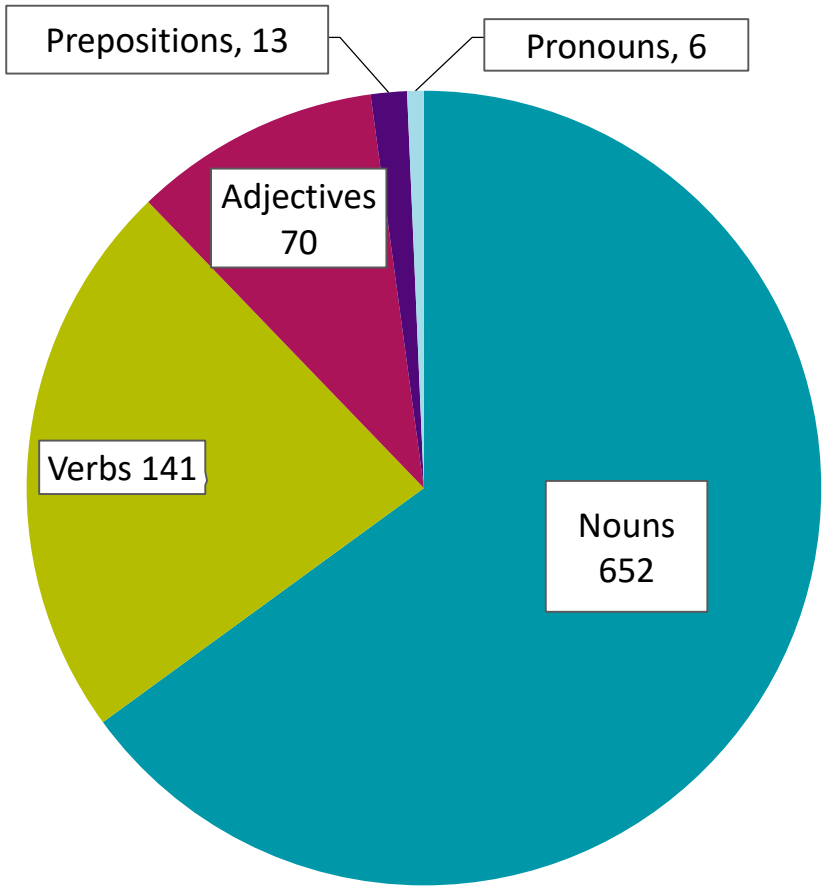
E.g.

X1 Lexical item: eye

X4 Challenges (across grammatical foms):

- Eye (single word)
- A blue eye (adjective phrase)
- The eye blinks (intransitive sentence)
- The girl closes her eye (transitive sentence)

Breakdown of lexical items



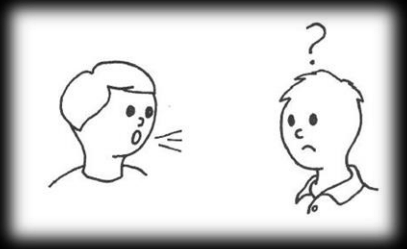
Listen-In therapy

36 patients with post-stroke aphasia

UCL

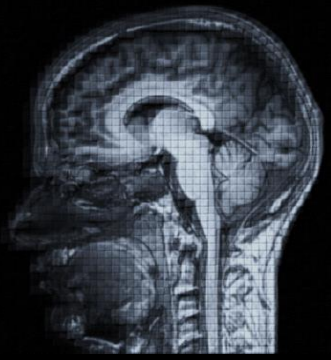
Hypotheses

1. Can high dose digital therapy improve speech comprehension skills in persons with aphasia?



2. Which stimuli are driving these effects?

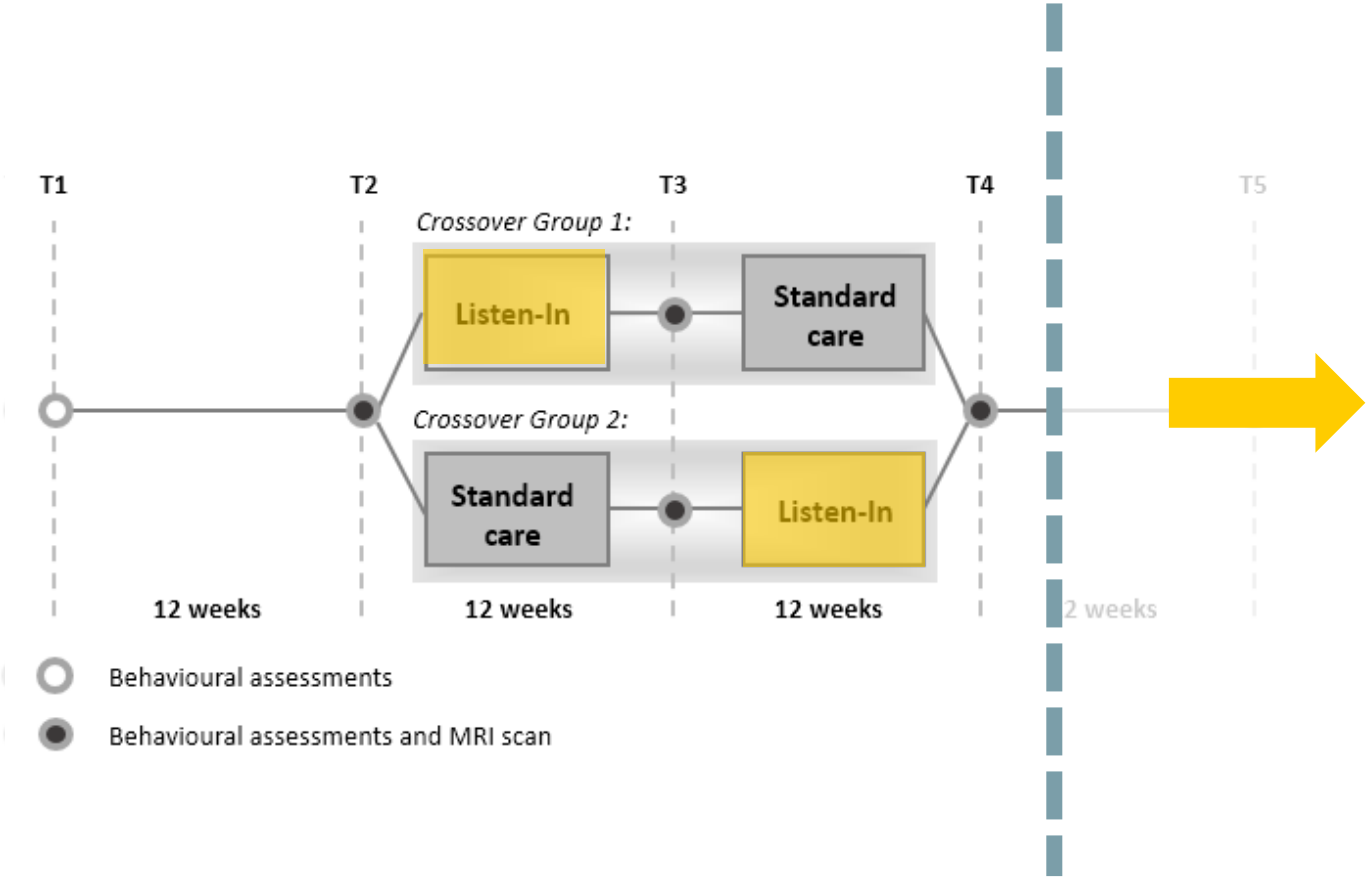
3. Does pre-therapy brain structure predict response to therapy?



4. What therapy induced structural changes are associated with response to speech comprehension therapy?

Aims and Research Question

Test the **clinical efficacy of Listen-In** in a small scale, **randomised cross over trial**, with 36 **persons with aphasia** (N=36)

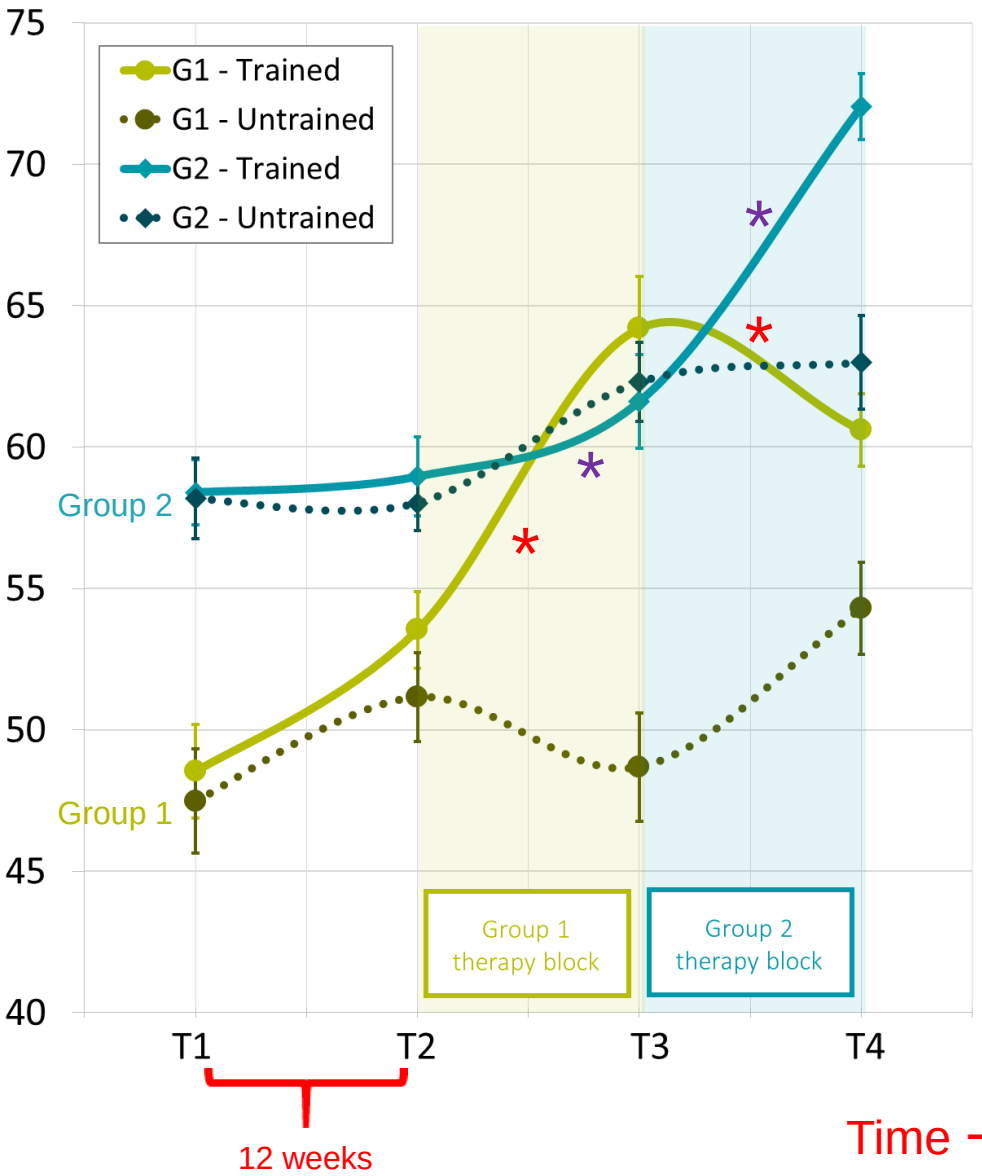


Mean =

85.27 hours
(SD 32)

Auditory Comprehension Test (ACT):

Item specificity with generalization across grammatical forms



Therapy v. standard care change: $t(34)=4.09$, $p<.001$

2 treatment block x 2 item condition ANOVA

Block * item condition $p<.001$

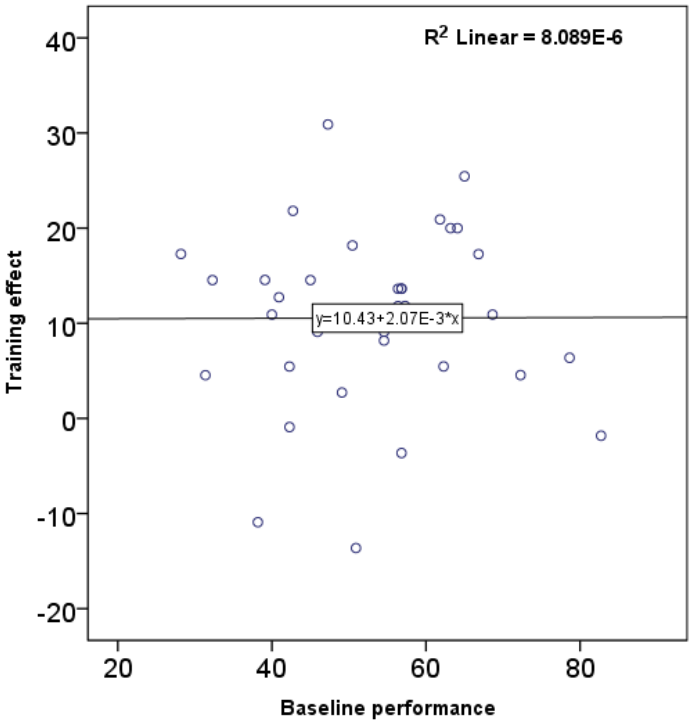
<u>Effect size</u>

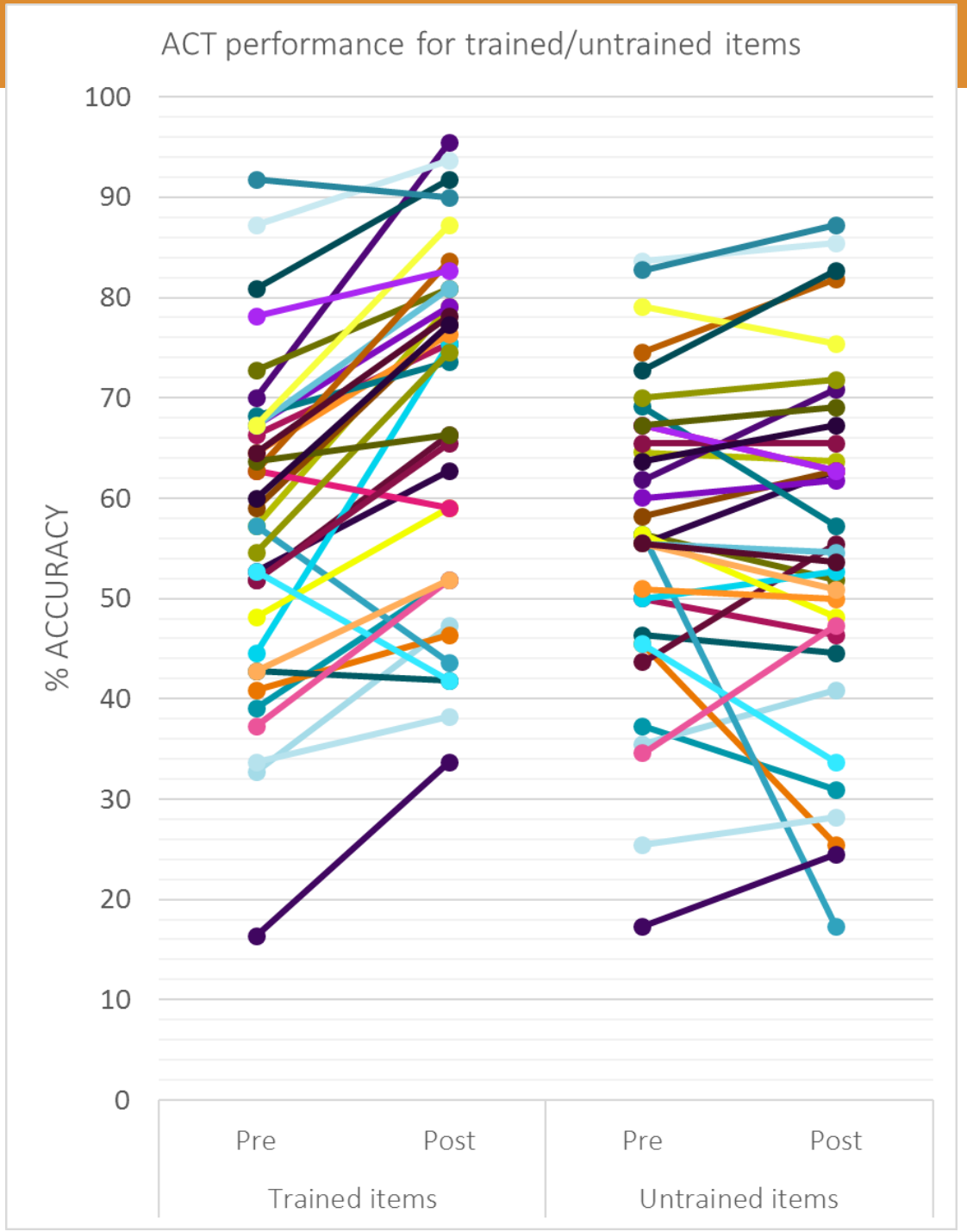
Unstandardised: 11%

Standardised: large Cohen's $d=1.12$

Individual response to therapy:

Training effect *
baseline performance (ACT)





36 patients with post-stroke aphasia

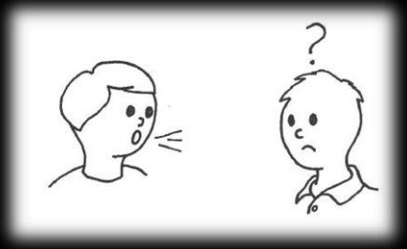
Hypotheses

1. Can high dose digital therapy improve speech comprehension skills in persons with aphasia?

2. **Which stimuli are driving these effects?**

3. Does pre-therapy brain structure predict response to therapy?

4. What therapy induced structural changes are associated with response to speech comprehension therapy?



What is driving therapy effects?

Therapy challenges: 'identical' vs. 'different' exposure count

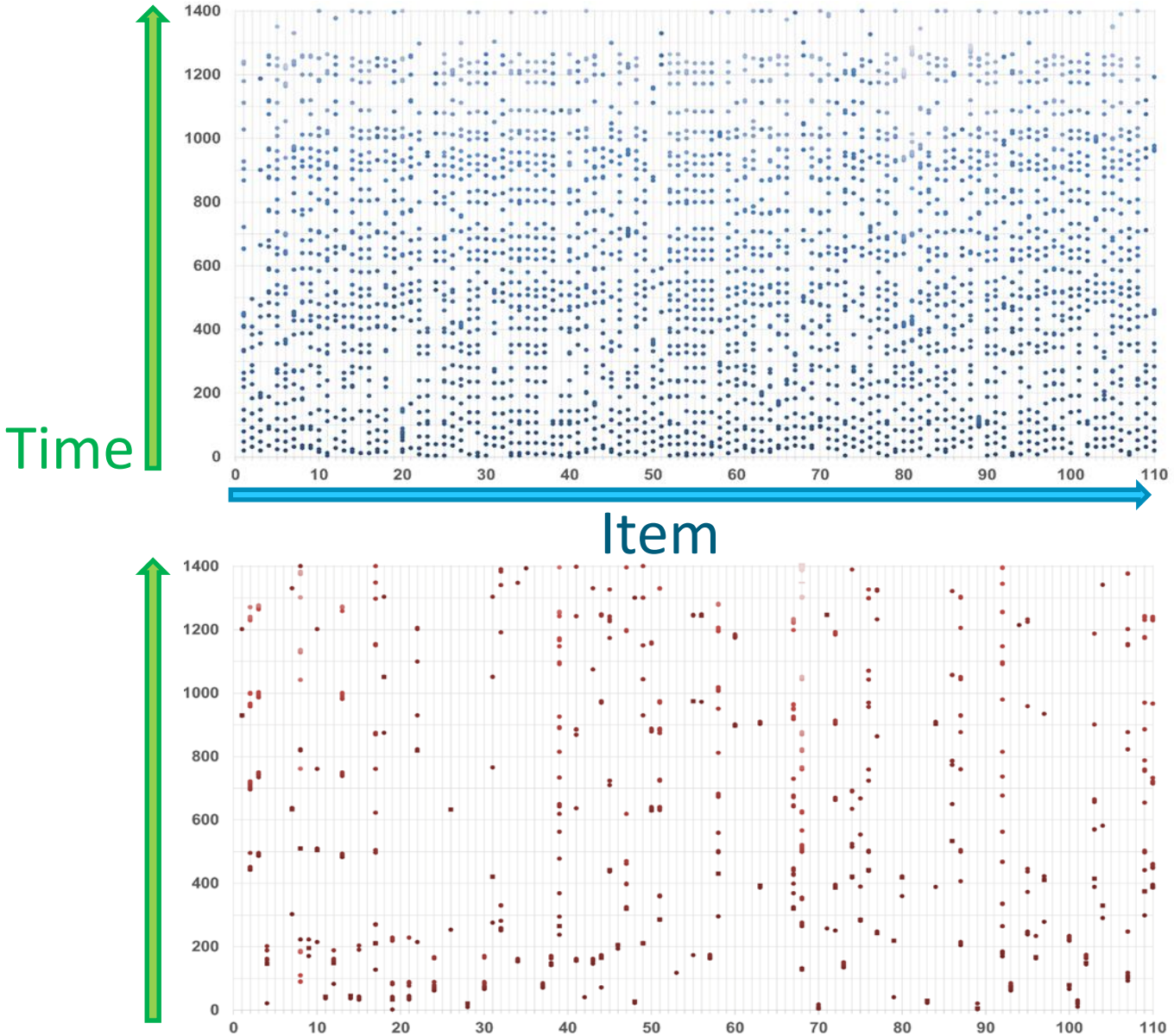
- Eye 4
- A blue eye 2
- The eye blinks [exemplar challenge in ACT] 18
- The girl closes her eye 6

Which challenge type drives therapy gains?

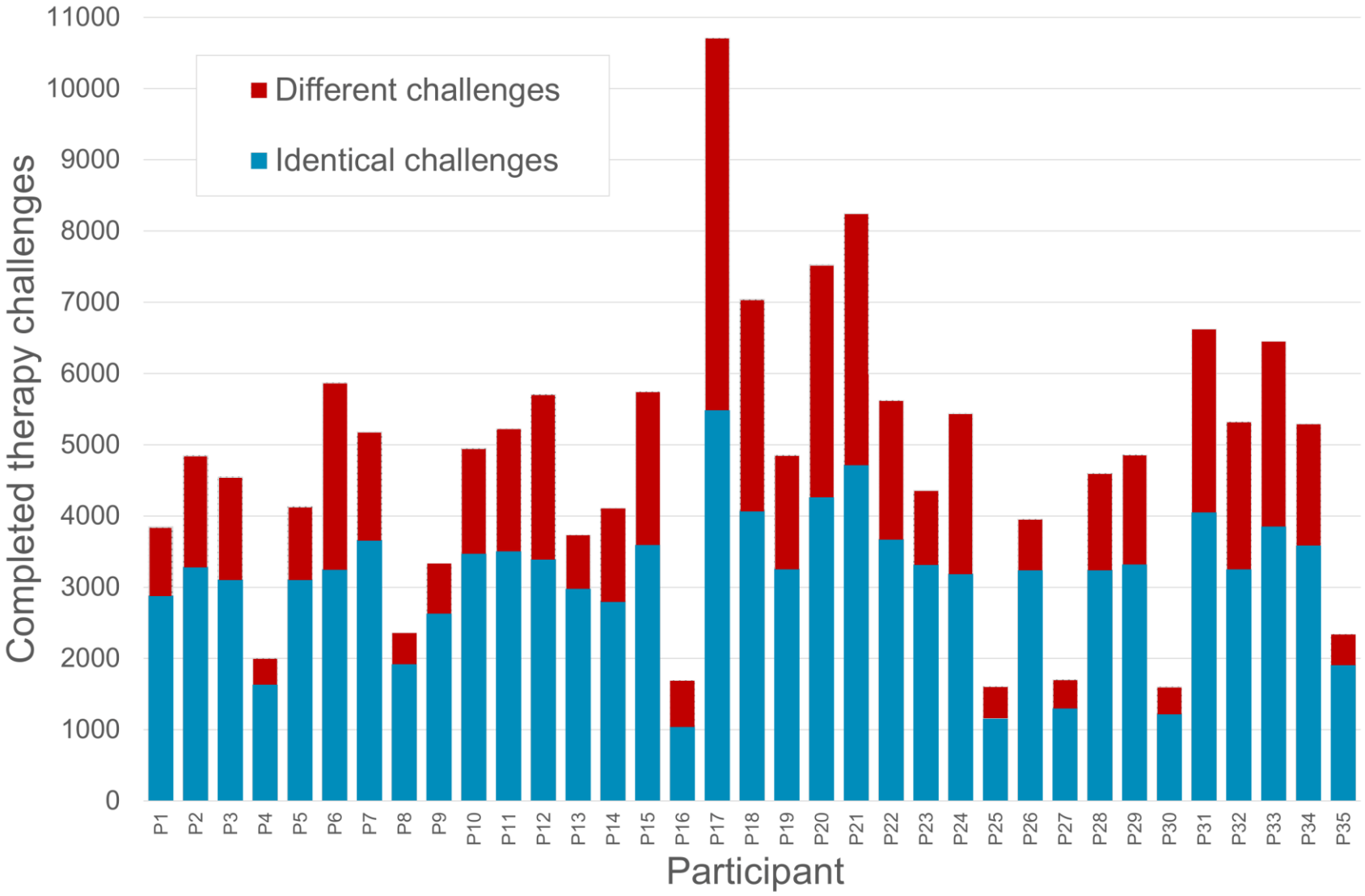
Identical = exemplar exposure 18

Different = all exposures – identical 12

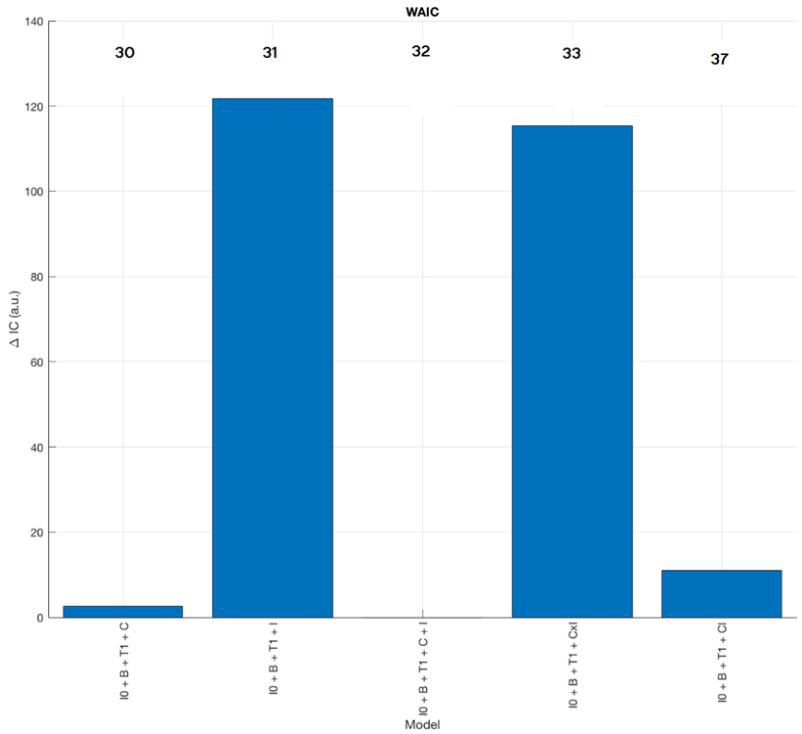
What is driving therapy effects?



What is driving therapy effects?



What is driving therapy effects?: 49 models



- Hierarchical Bayesian parameter estimation for logistic regression
- Widely Applicable Information Criterion (WAIC): 0-2: weak; 2-6: positive; 6-10: strong; >10: very strong
- Winning model = 32 = I+D > I by 2.5 units = +ve effect
- Treatment effects are still item specific
- These therapies may best achieve clinical effectiveness by training words across different spoken contexts

36 patients with post-stroke aphasia

Hypotheses

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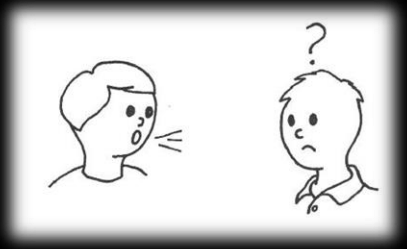
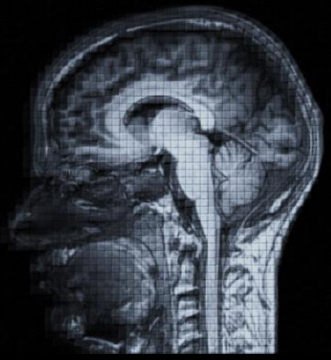


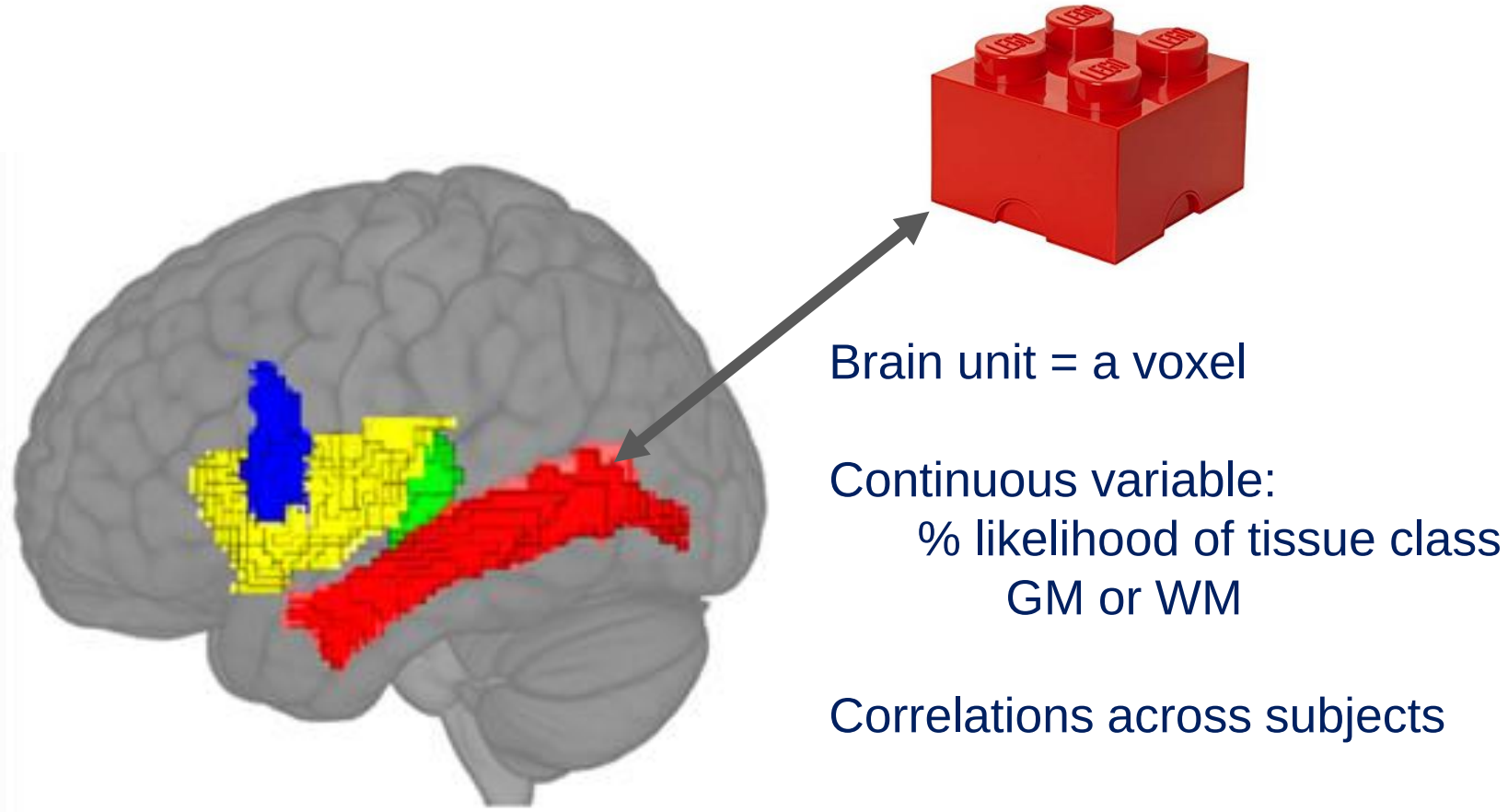
2. Which stimuli are driving these effects?

3. **Does pre-therapy brain structure predict response to therapy?**



4. What therapy induced structural changes are associated with response to speech comprehension therapy?

Voxel Based Morphometry: method



Brain unit = a voxel

Continuous variable:
% likelihood of tissue class
GM or WM

Correlations across subjects

Multiple regression, mass univariate

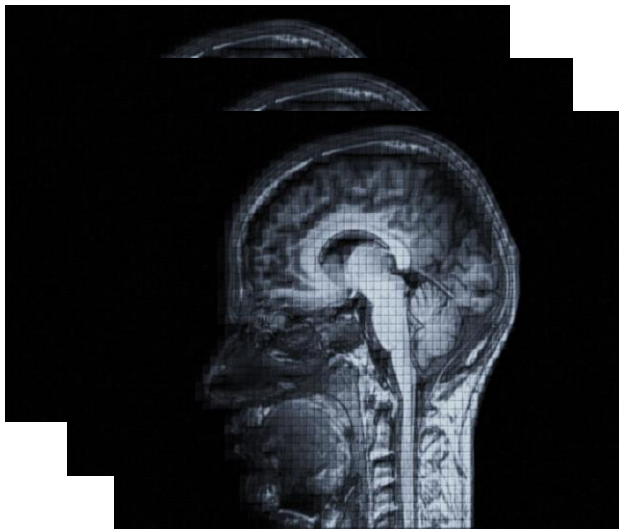
Does pre-therapy brain structure predict response to therapy?

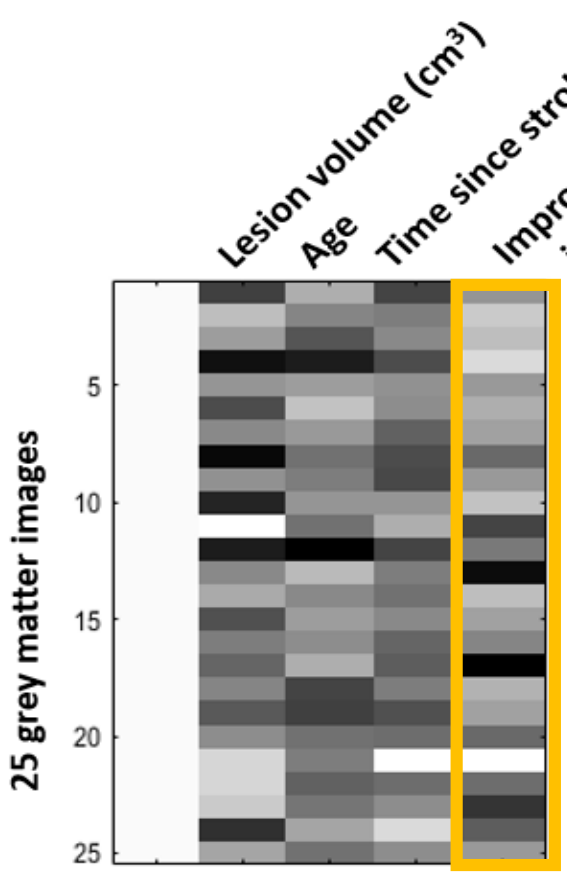
Multiple linear regression in SPM

N=25

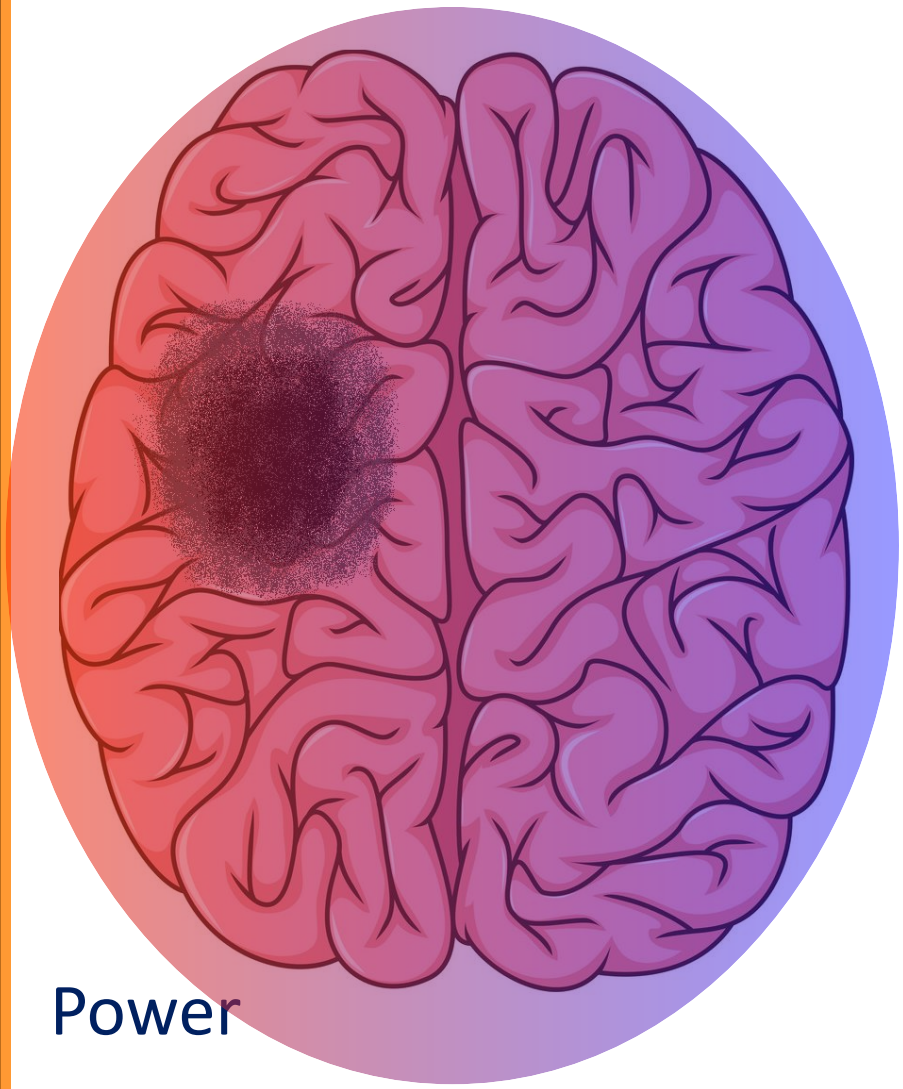
T1 Structural MRI scans

Baseline pre-therapy scans (from T2)





Voxel Based Morphometry: method



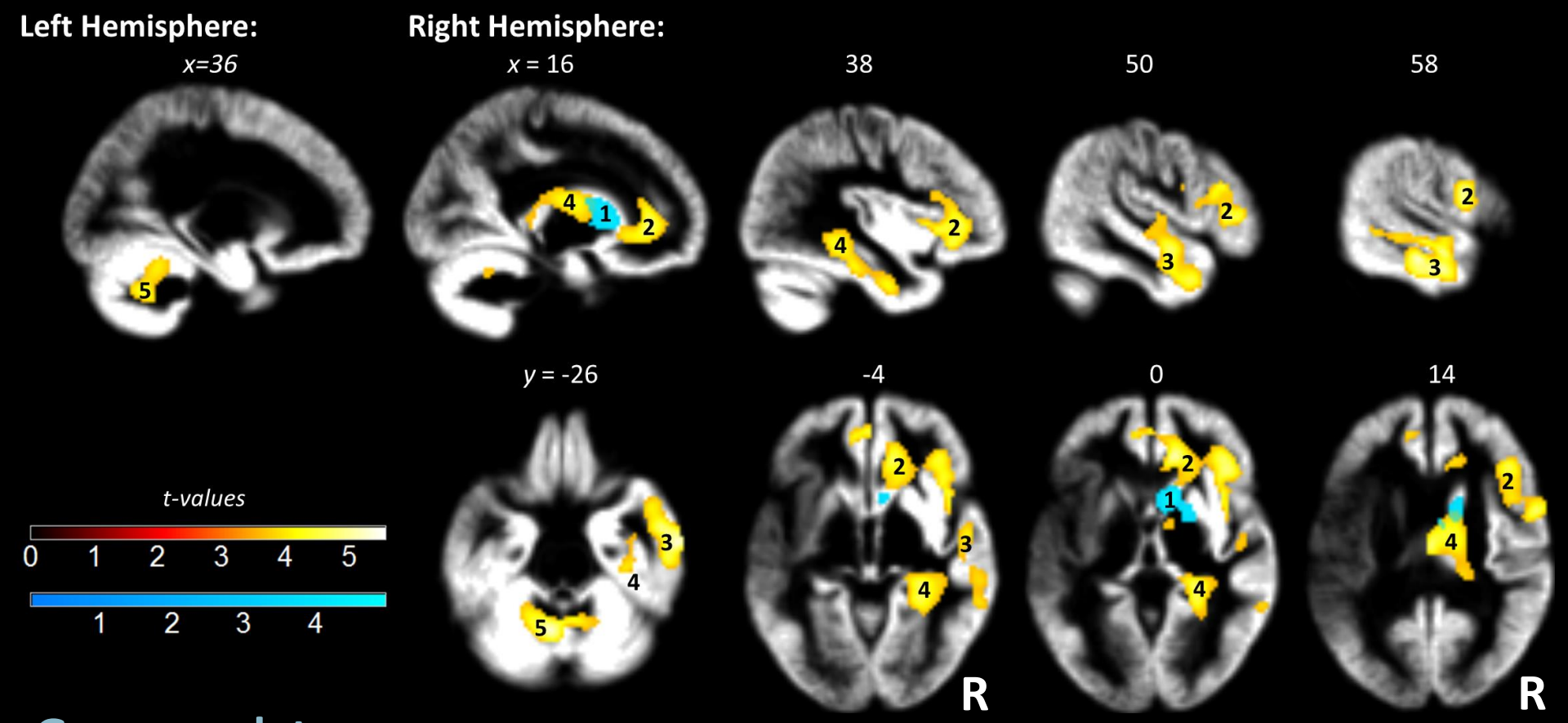
Power

More variability in left hemisphere structure than right due to stroke damage.

Positive correlations between perilesional structure and % improvement suggest that regions affected by stroke are also responsible for recovery.

Positive correlations distant from lesion suggests other mechanisms.

Does pre-therapy brain structure predict response to therapy?



Grey: caudate

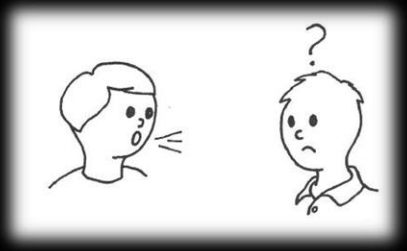
White: deep to inferior frontal cortex and lateral temporal lobe

Right hemisphere residual structure predicts response to therapy

36 patients with post-stroke aphasia

Hypotheses

1. Can high dose digital therapy improve speech comprehension skills in persons with aphasia?



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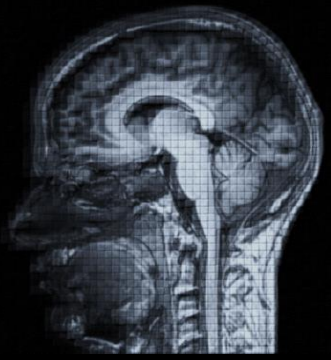
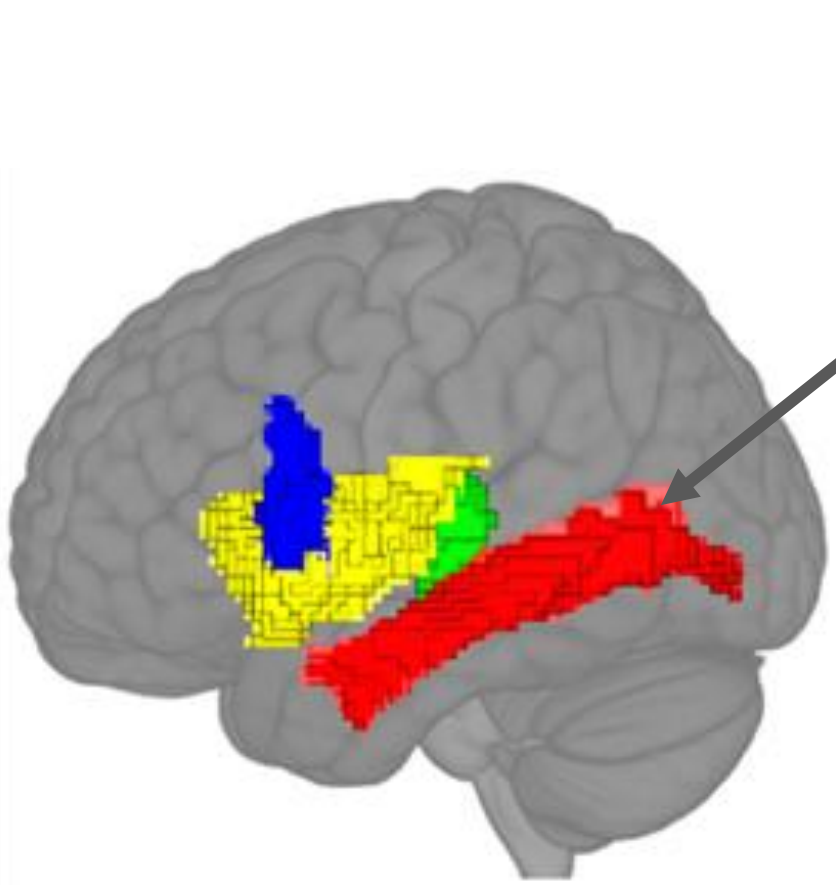


4. **What therapy induced structural changes are associated with response to speech comprehension therapy?**

Longitudinal Voxel Based Morphometry



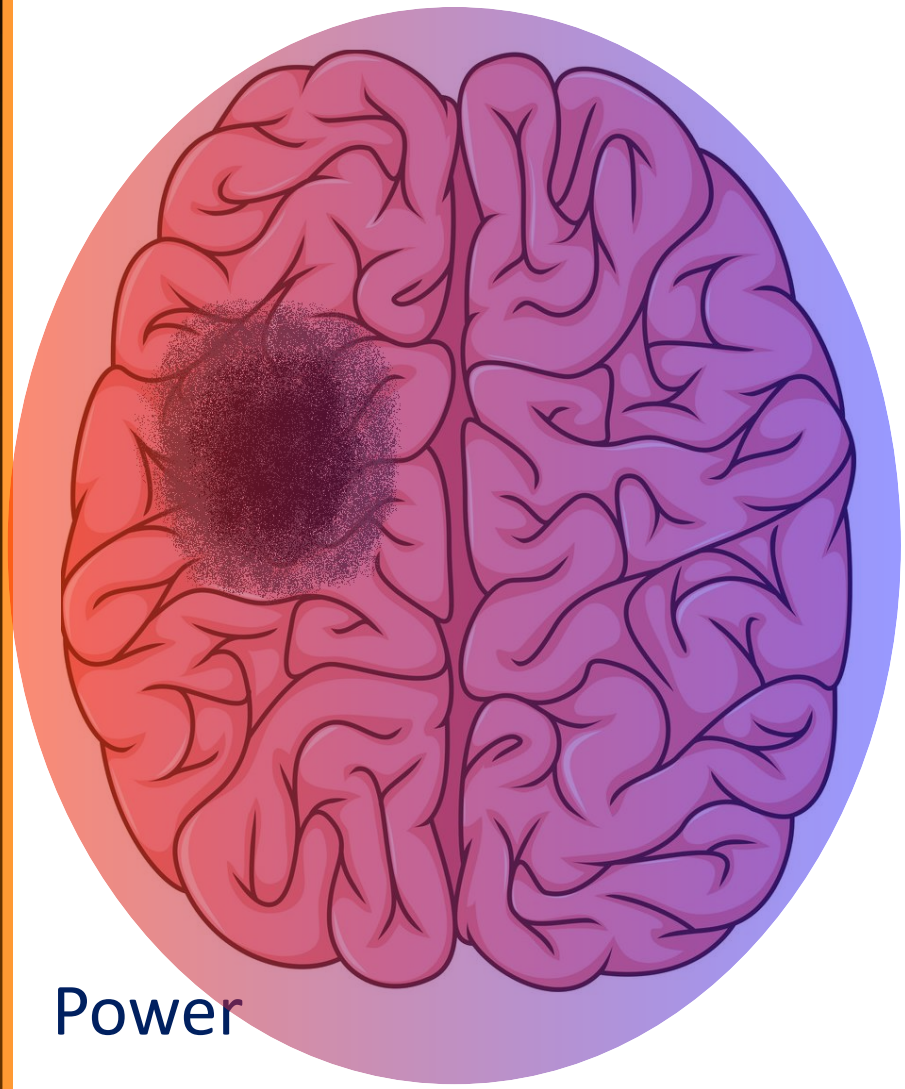
Brain unit = a voxel

Continuous variable
(% likelihood of GM or WM)

Correlation within subjects:
Do changes in WM or GM volume correlate with % improvement?

Simple regression

Voxel Based Morphometry: method



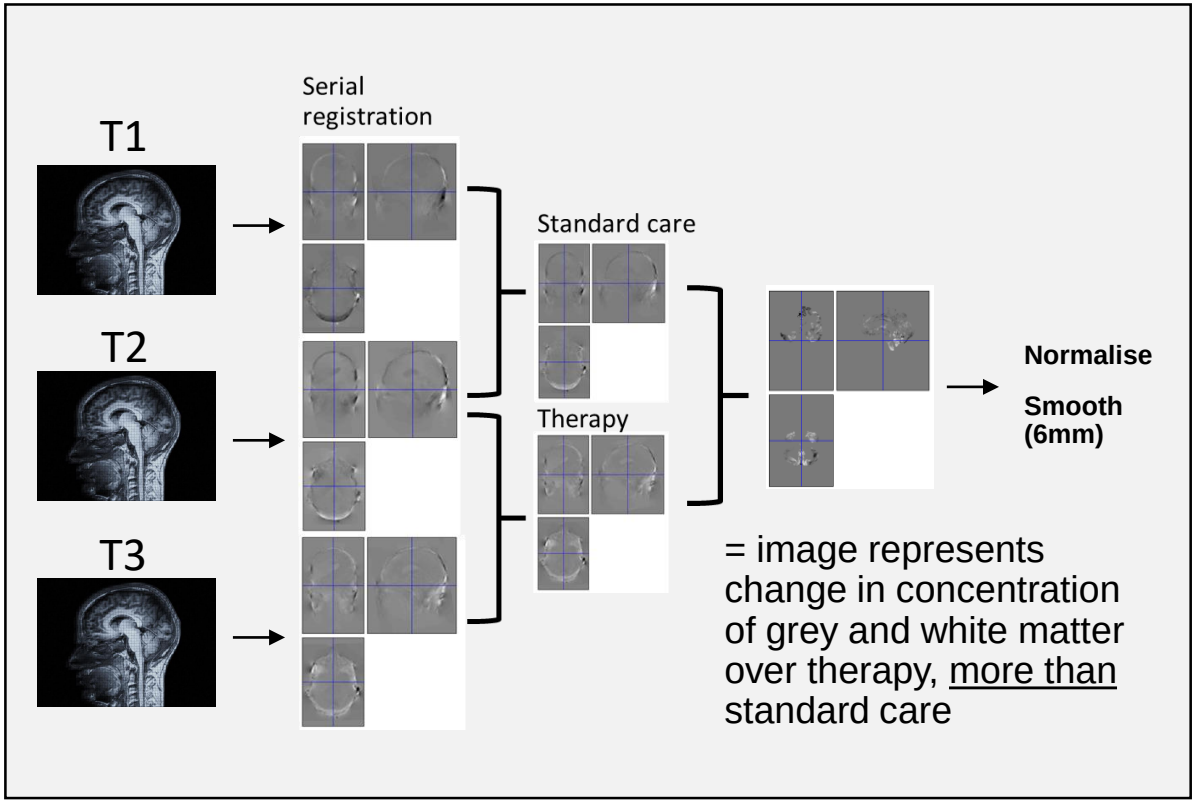
Power

More variability in left hemisphere structure than right due to stroke damage.

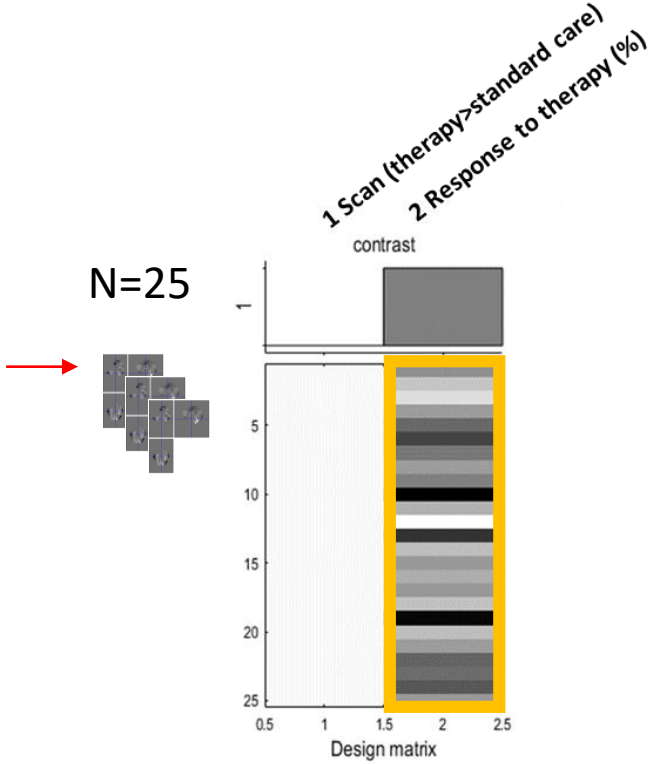
Positive correlations suggest that these areas change, specifically, in response to therapy

NB: time and test-retest controlled

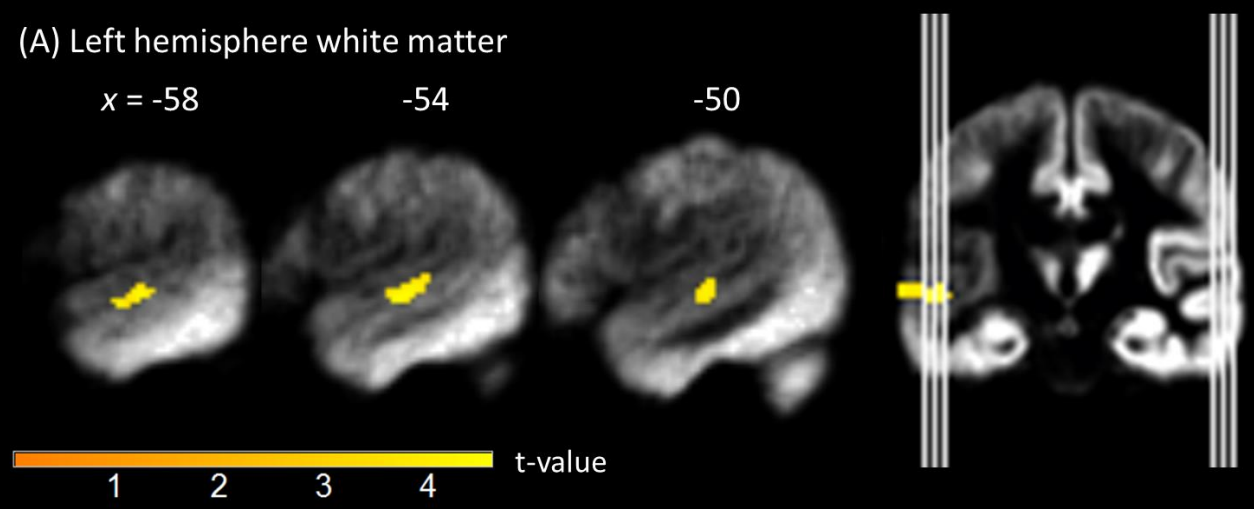
Longitudinal voxel based morphometry

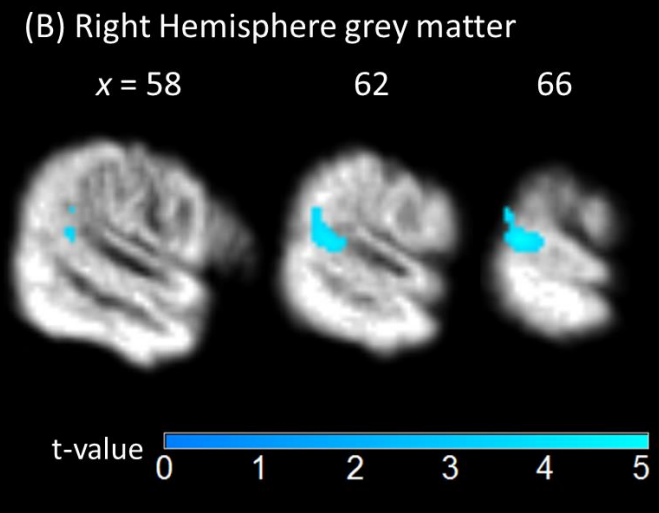


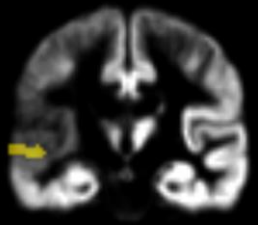
Simple linear regression model



Does therapy induce changes in brain structure?





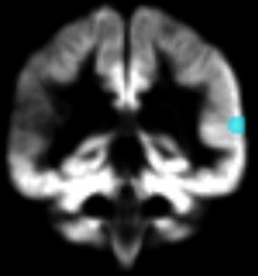


Increase in white matter concentration

→Superior temporal gyrus

Increase in grey matter concentration

Right hemisphere homologue to Wernicke's area



Therapy induces structural changes in both temporal lobes

Listen-In: Summary

- Large therapy effects, but these are item specific, many hours of practice required
- Effects are driven by stimuli using multiple spoken contexts
- Pre-therapy brain structure predicts response to therapy (right hemisphere F-T WM)
- Therapy induces structural changes in bilateral temporal lobes

iReadMore trial

Dr Zoe Woodhead

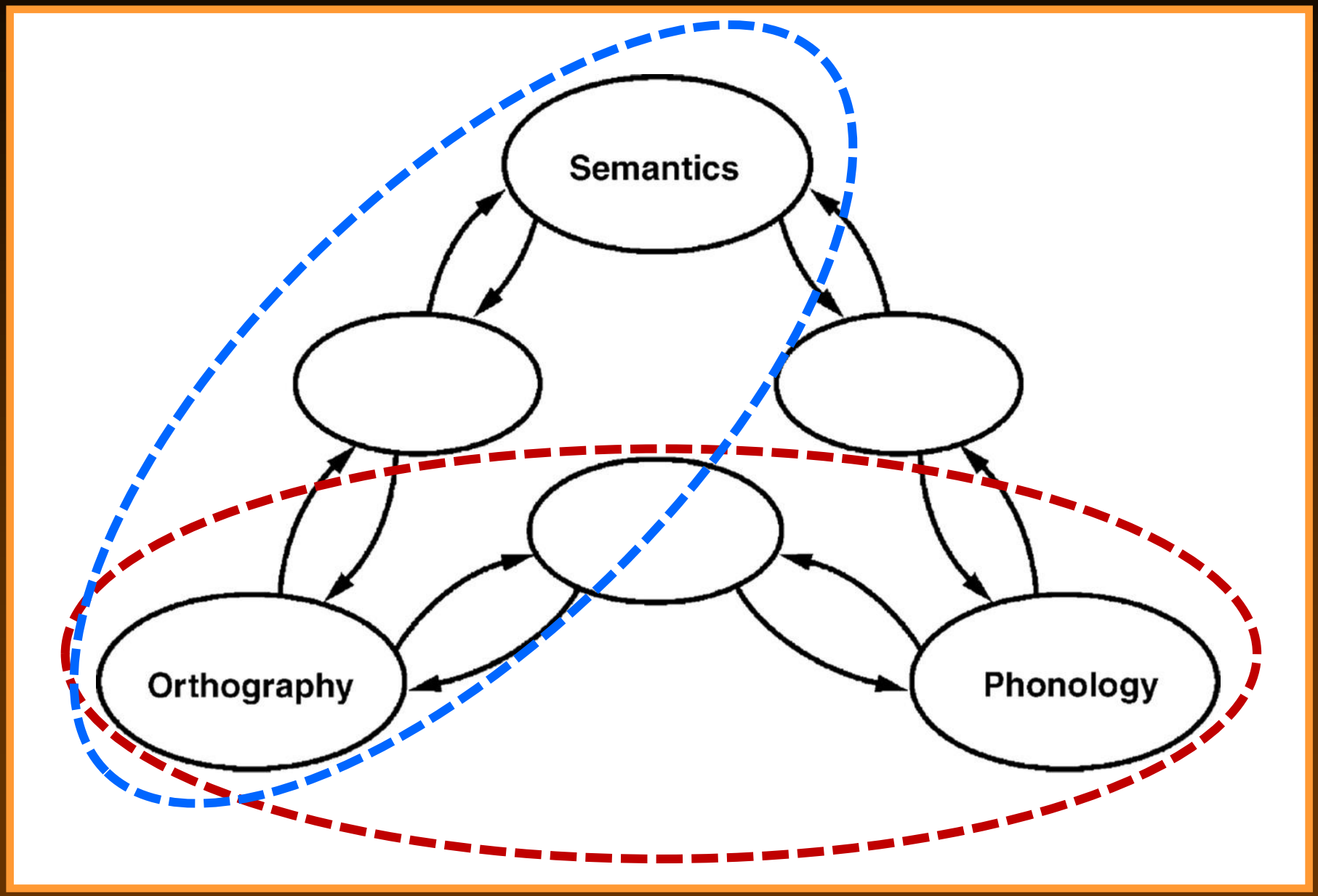
Dr Sheila Kerry

iReadMore

Word-reading therapy

Word-reading therapy for stroke survivors with acquired reading problems

Central Alexia Rx: based on triangle model of reading



iReadMore

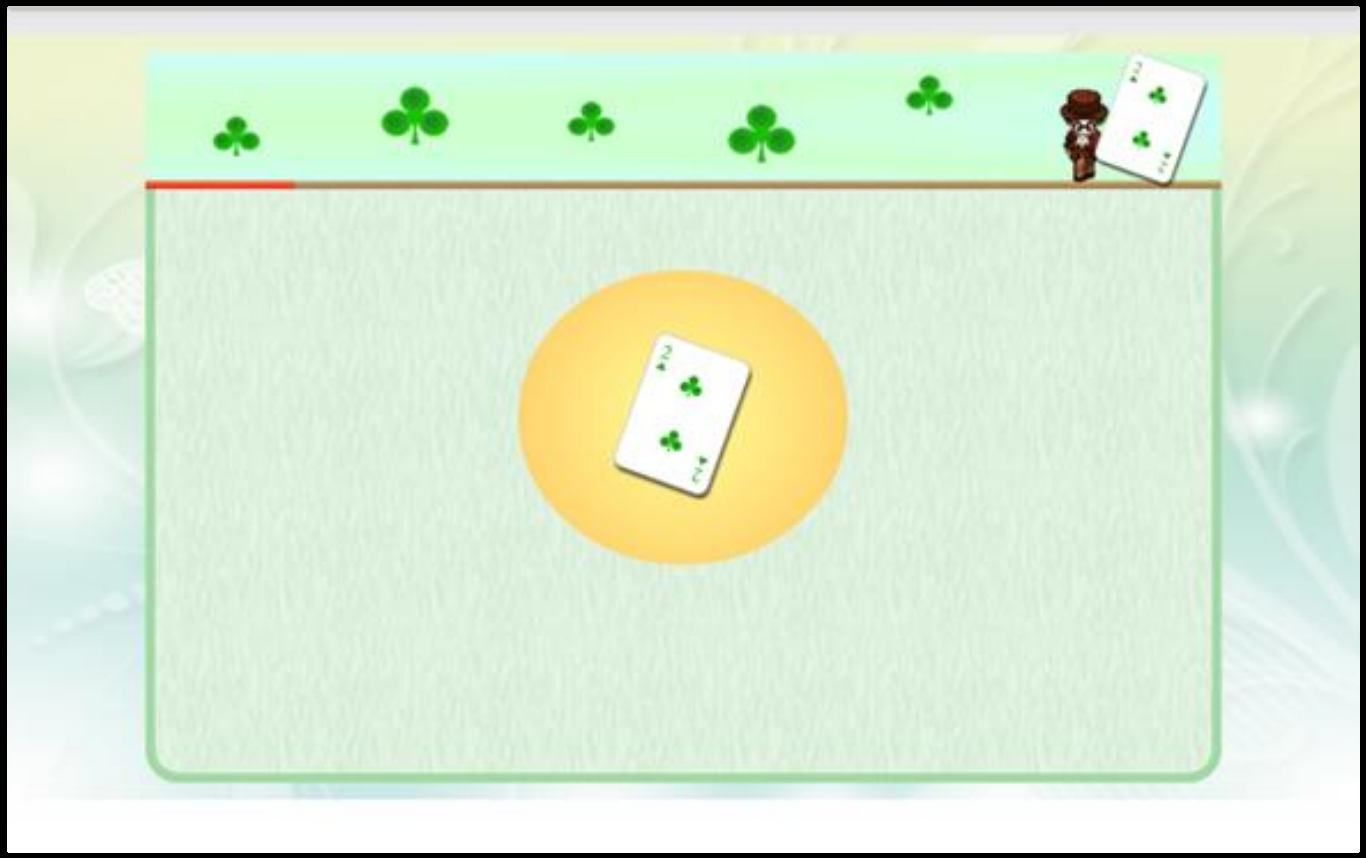
Key Design Features

- Aims to improve patients' word reading accuracy
  - Repetitive Word-Picture-Sound pairings to rebuild associations
- Suitable for patients with different types / severities of central alexia
  - Adaptive difficulty
- Suitable for unassisted use via the internet
  - Intuitive design, with gamification to encourage prolonged use

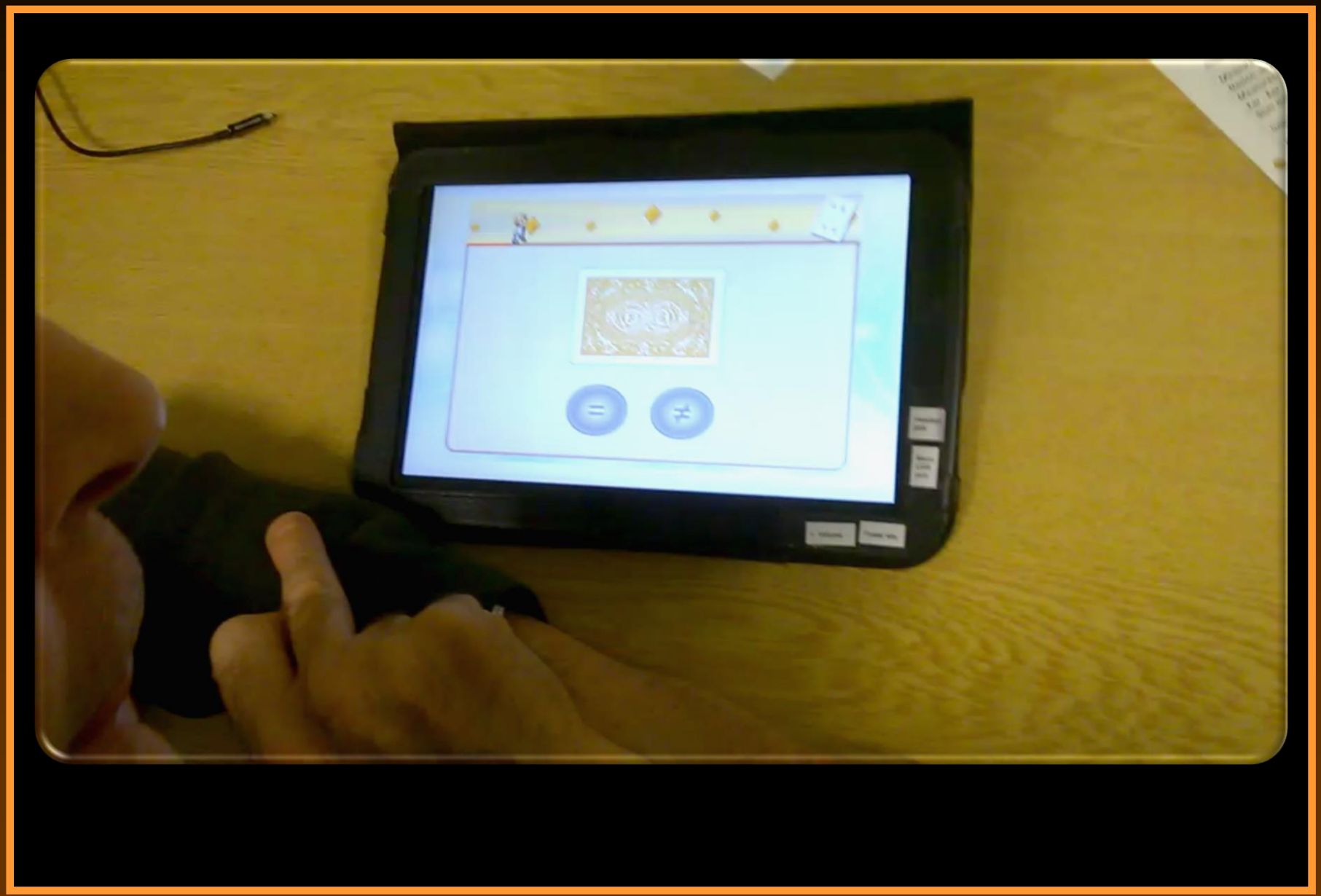
Hypotheses

- Does iRM improve single word reading?
- If so, what factors predict variability in response across subjects

iReadMore



Reinforce written and heard word representations



iReadMore: patients

<u>21 patients with CA</u>

Recruited from PLORAS

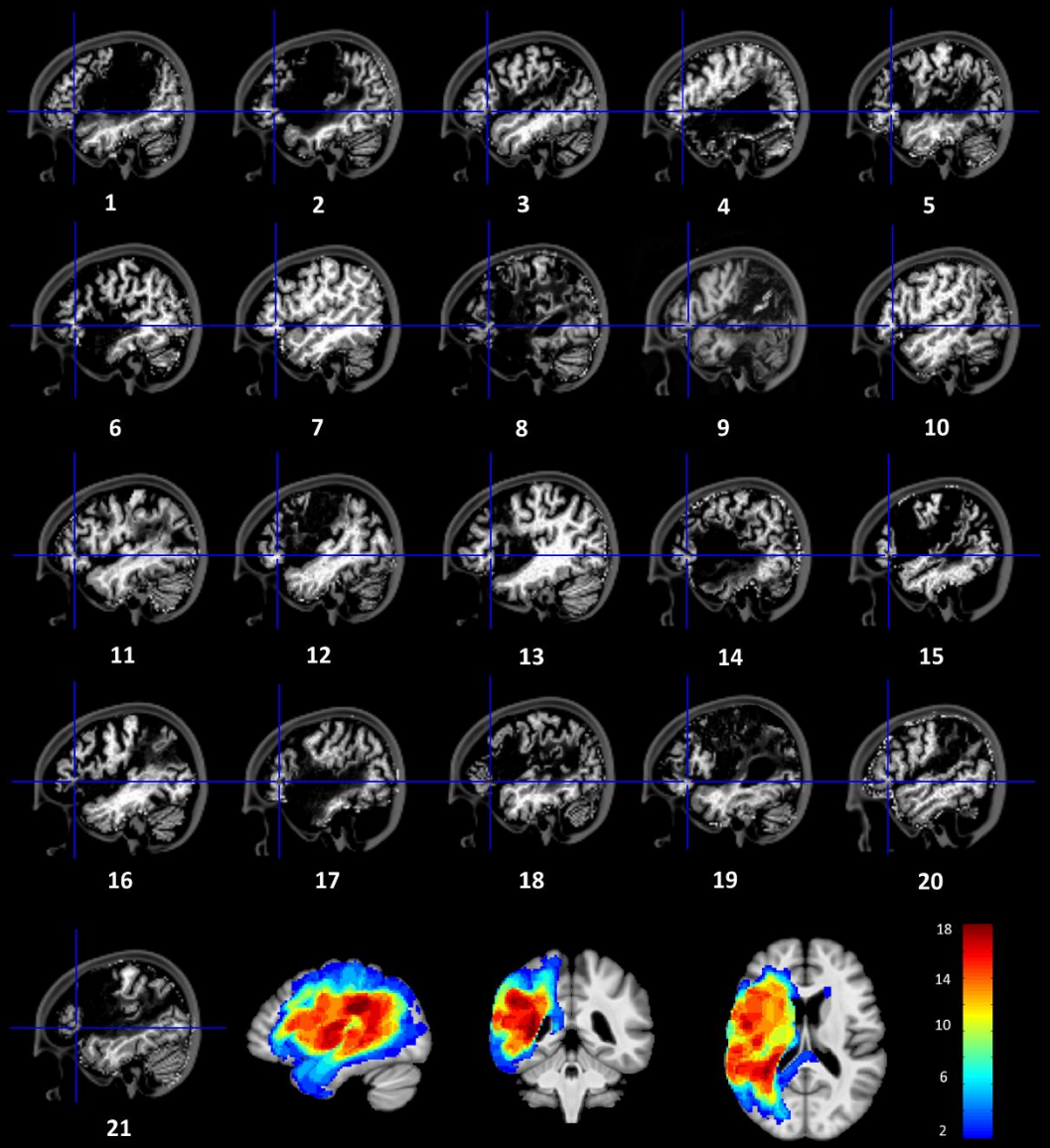
Impaired speech output (aphasic)

Impaired word reading (alexic)

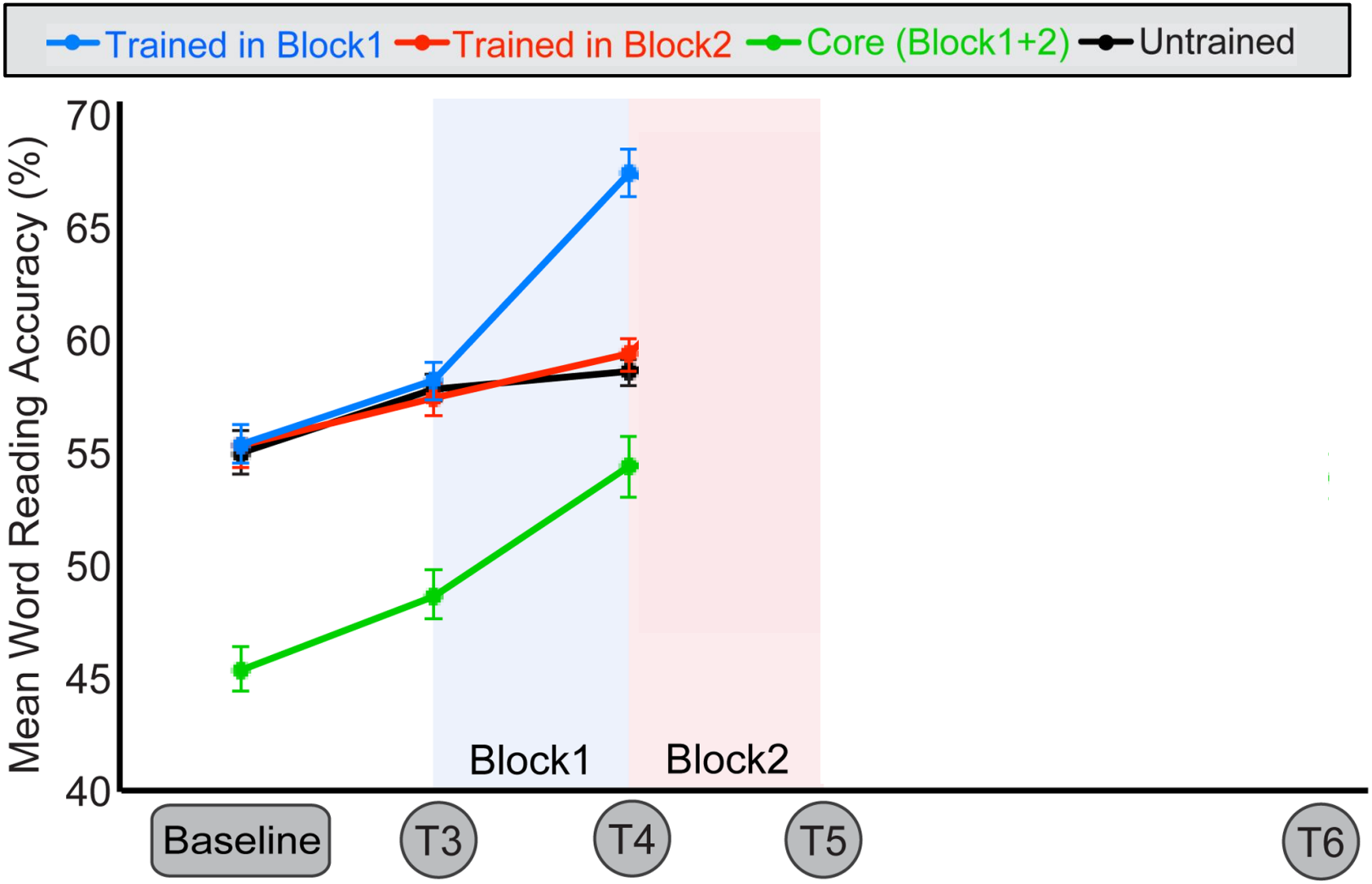
>1 year post stroke (chronic)

Sparing of left IFG

- **Change in word reading accuracy**



Results: Word Reading Accuracy (n=21)

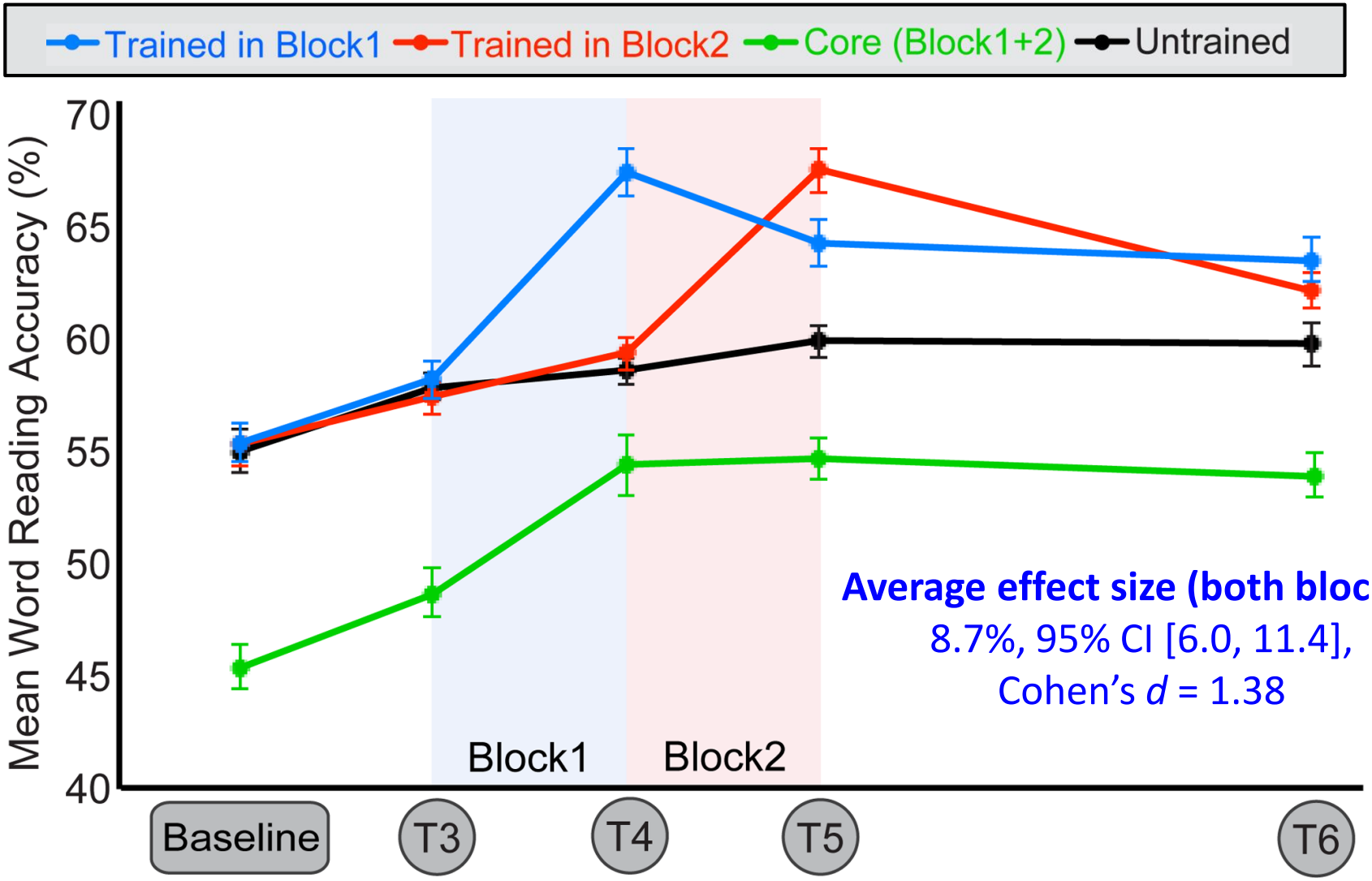


Significant Block 1 Training Effect, T3 to T4

Specific to Trained Words

Woodhead et al Brain 2018

Results: Word Reading Accuracy (n=21)



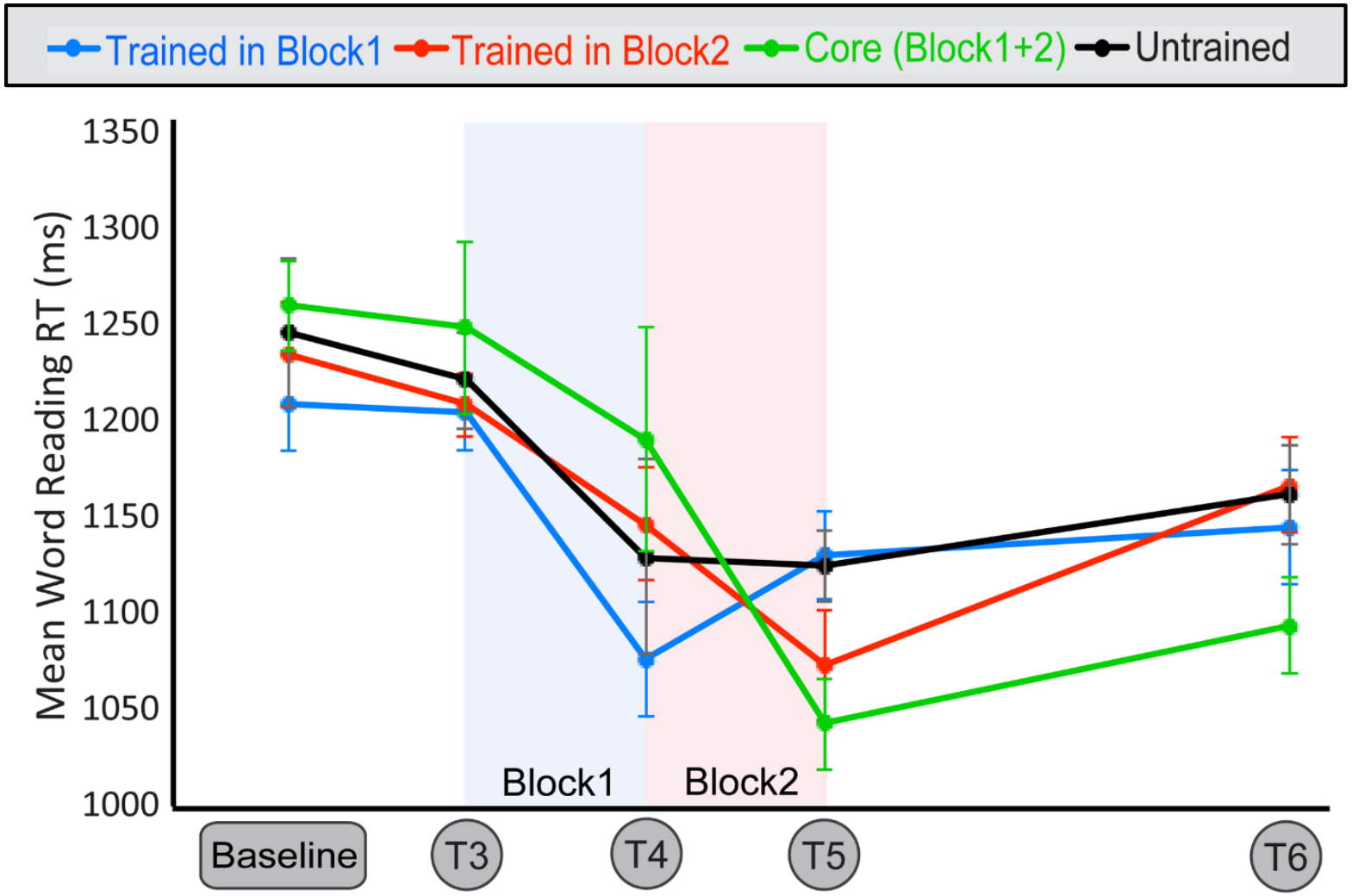
Average effect size (both blocks):
8.7%, 95% CI [6.0, 11.4],
Cohen's *d* = 1.38

Significant maintenance at 3-month follow-up (T6)

Accuracy remained above T3 levels

Woodhead et al Brain 2018

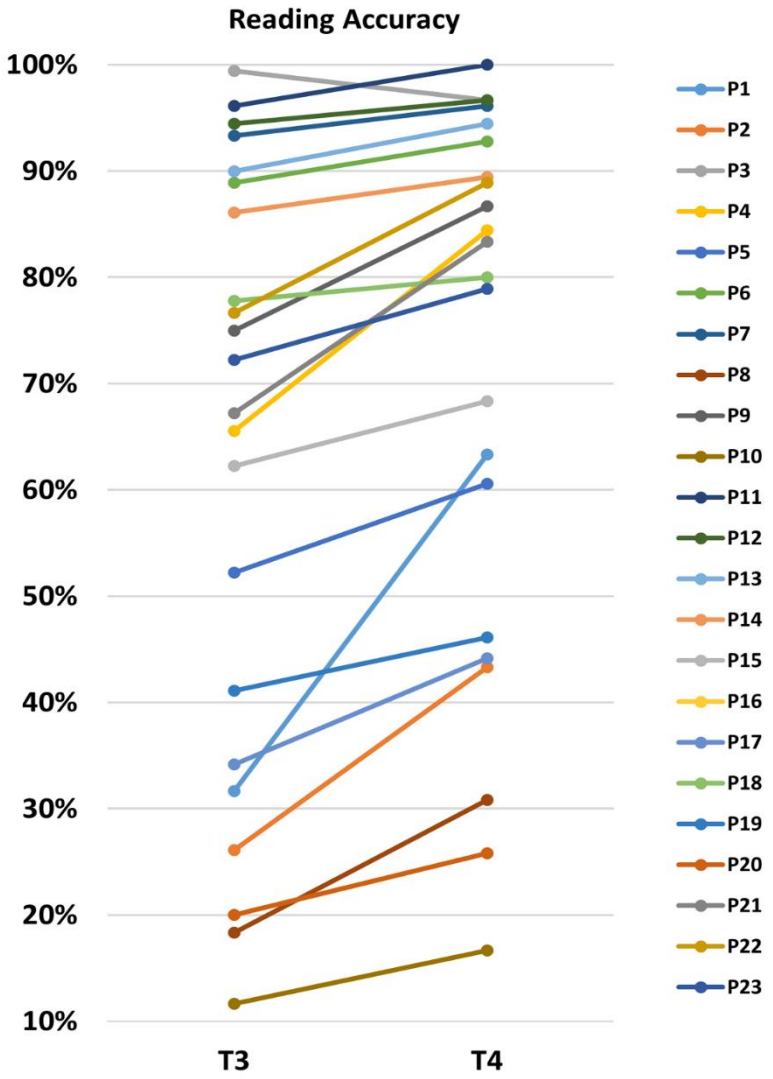
Results: Word Reading RT (n=20)



Significant training effect, strongest for trained words

(average 100ms, Cohen's *d* = 0.98)

What factors predict response to therapy?



Variety in two key behavioural measures:

1. Initial severity
2. % improvement

Explanatory variables:

1. Demographics

2.a Reading performance (baseline severity)

2.b Executive functions

3. Brain structure

Automatic linear modelling: method

Dr Oscar Aguilar

Dr Tom Hope

Analysis 1: explanatory (in-sample) analysis

We did this by fitting linear models using each set of variables, both separately and in combination, using the Automatic Linear Modelling (ALM) a form of multiple linear regression facility distributed with the SPSS software package.

Two measures of model goodness:

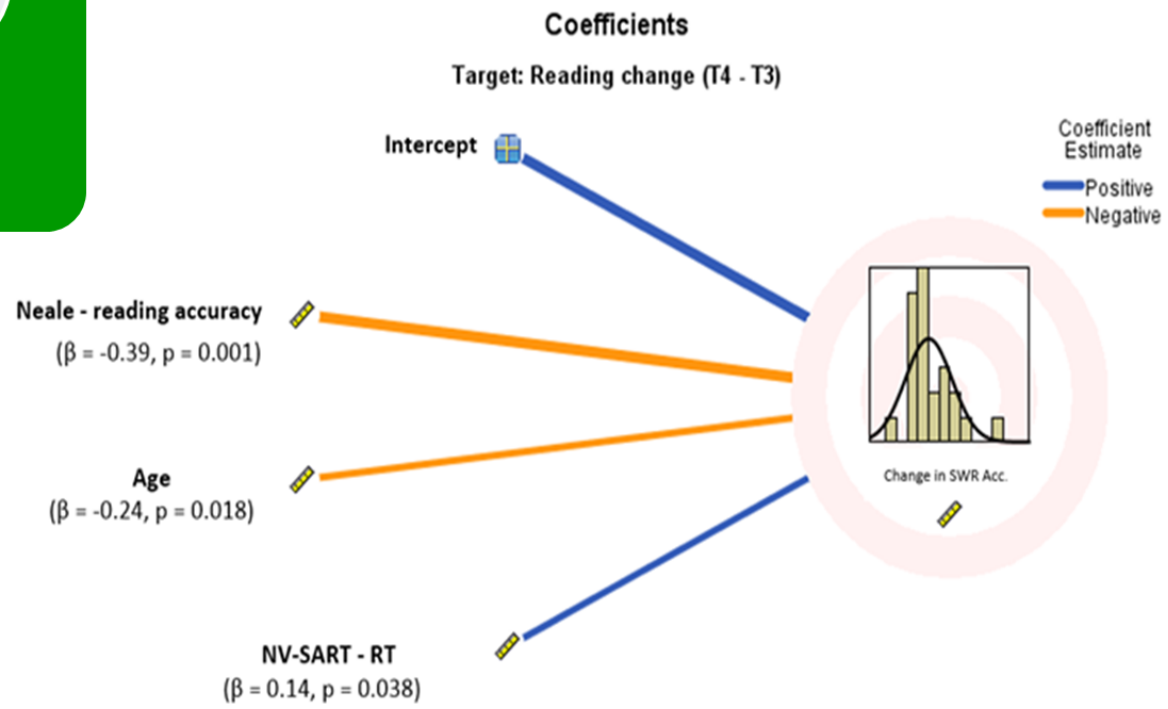
R^2	As model improves ↑
AIC	As model improves ↓

Aguilar et al JNNP 2018

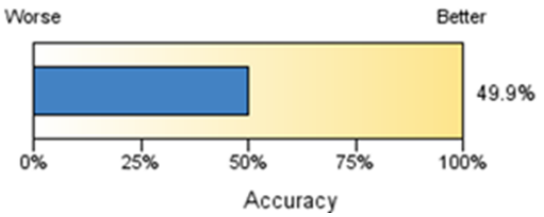
What factors predict response to therapy?

Demographics
Behaviour

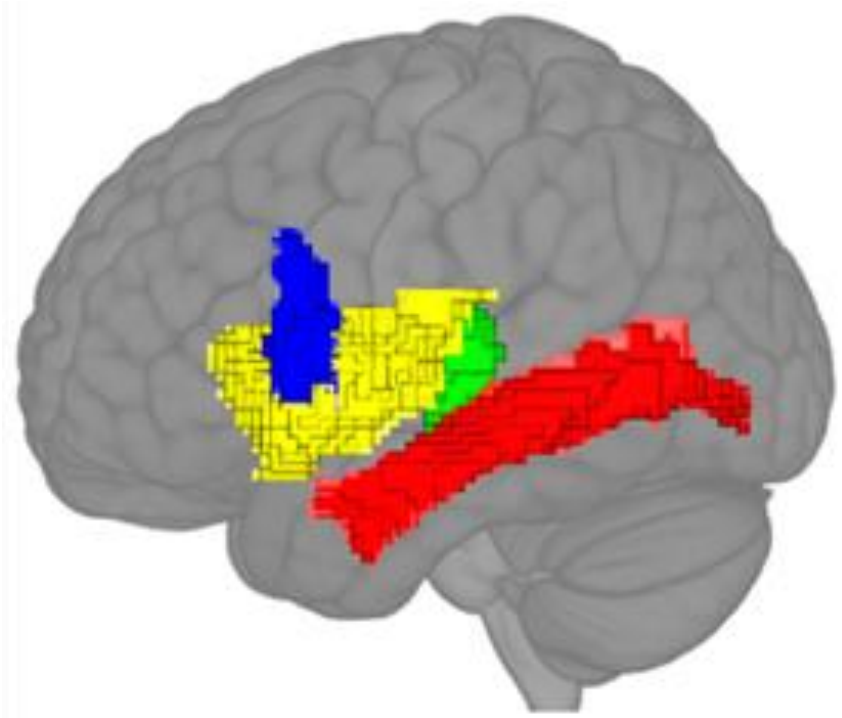
41 variables



Adjusted R^2 = 0.50
AIC= 81.75



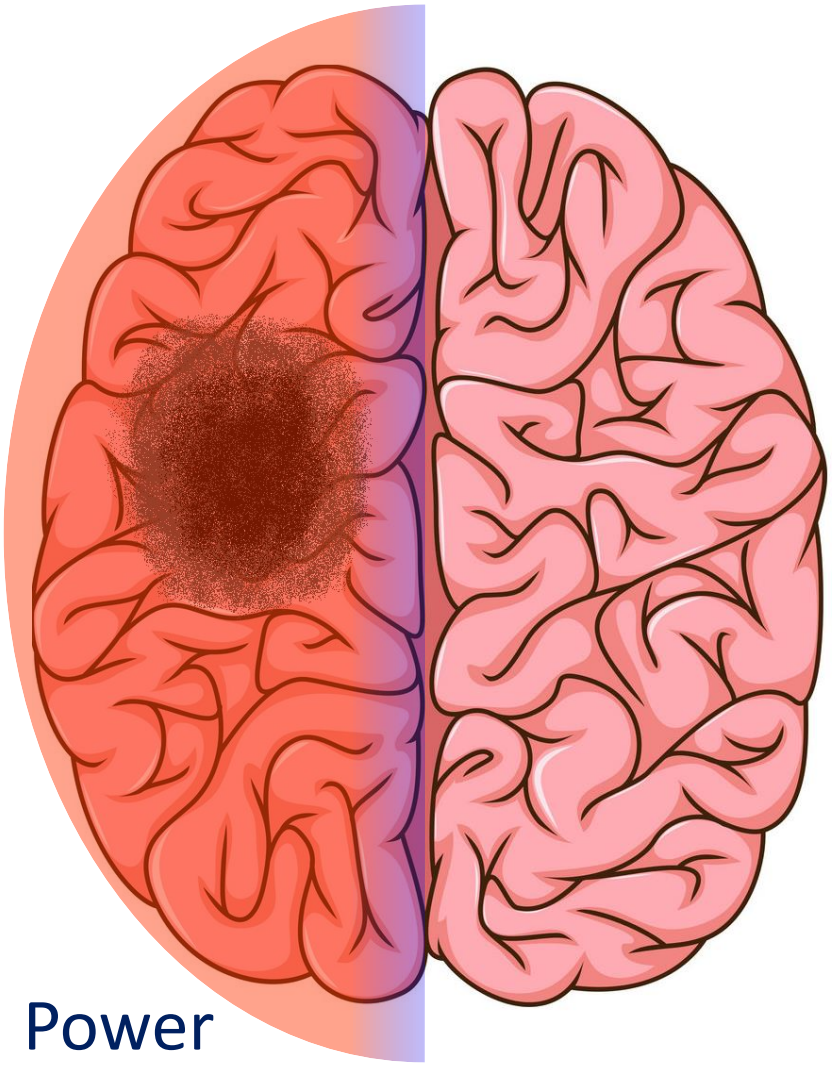
Adding in brain structure: method



Lesion = a region on a template
% of damage to that region
Continuous variable

Correlations across subjects
Multivariate analysis

Automatic linear modelling: method

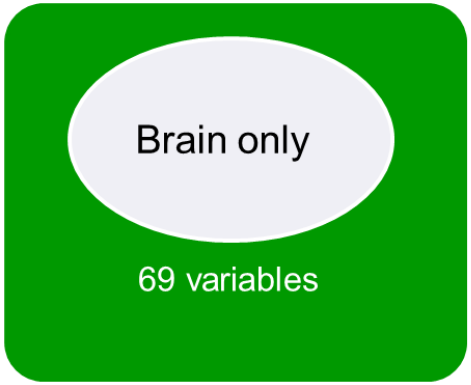


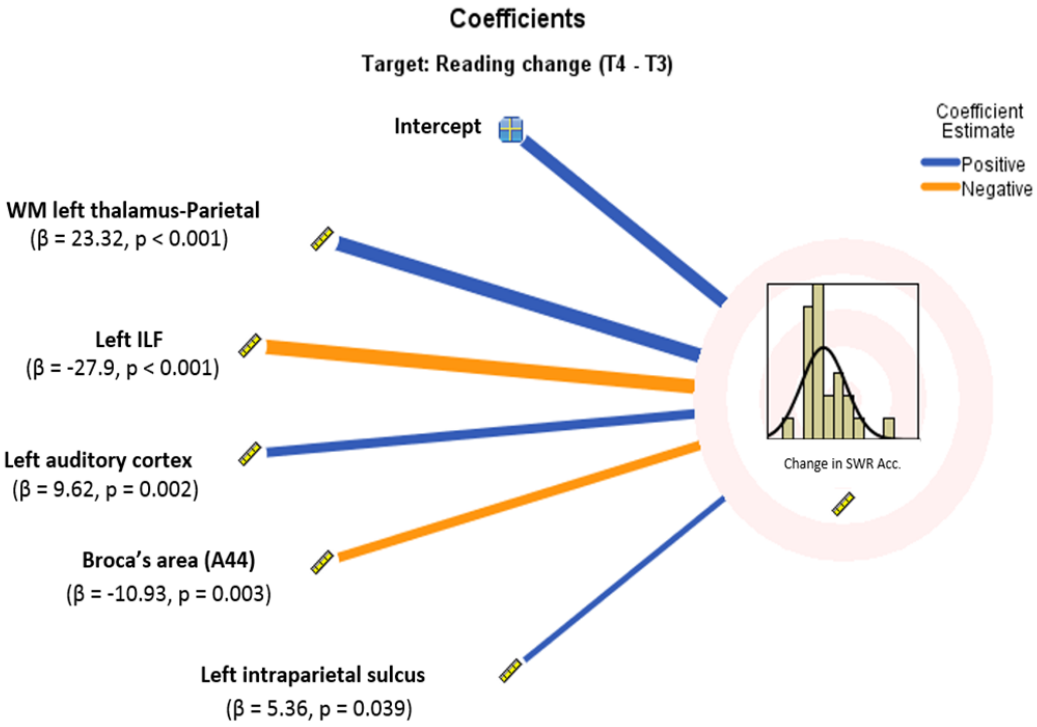
Power

Binary lesion images are created for each subject from a variety of GM and WM SPM toolboxes.

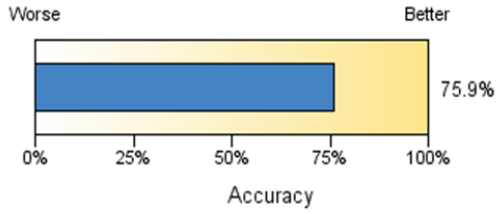
Only those regions where at least 10 patients had lesion loads of at least 10% were included. From a total of 398 regions covering the whole brain, 69 regions in the left hemisphere that met the criteria were included in the analyses.

What factors predict response to therapy?





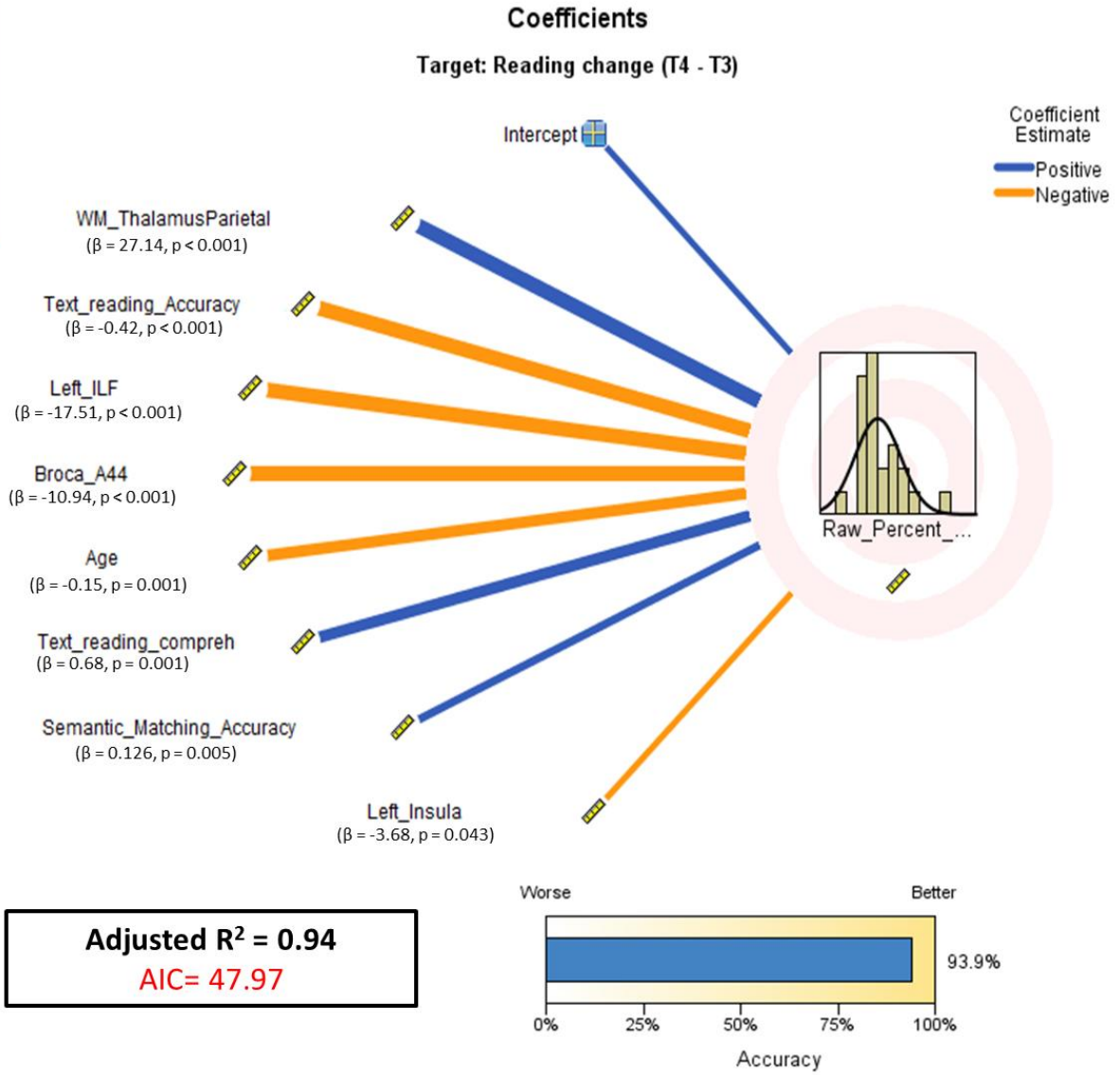
Adjusted R^2 = 0.76
AIC= 69.35



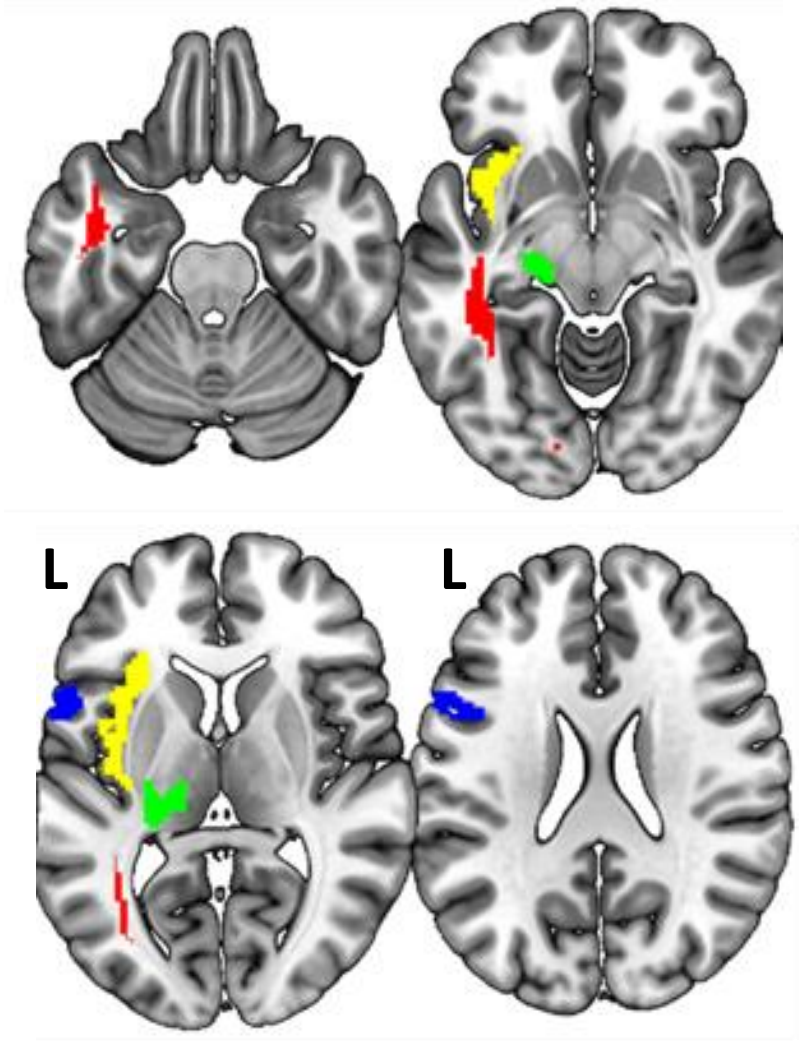
What factors predict response to therapy?

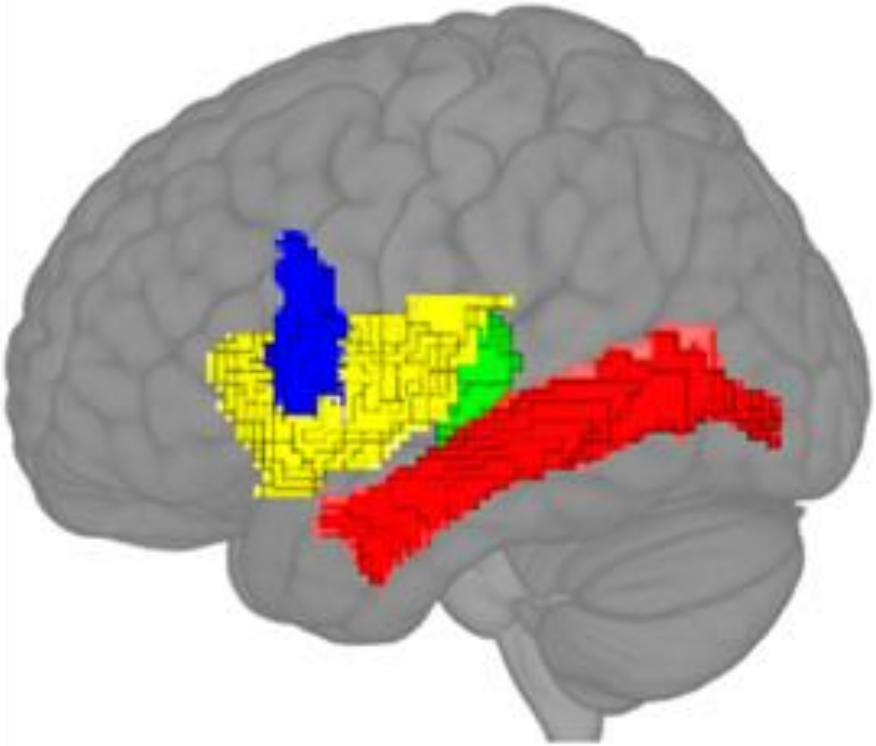
Behaviour & brain

110 variables



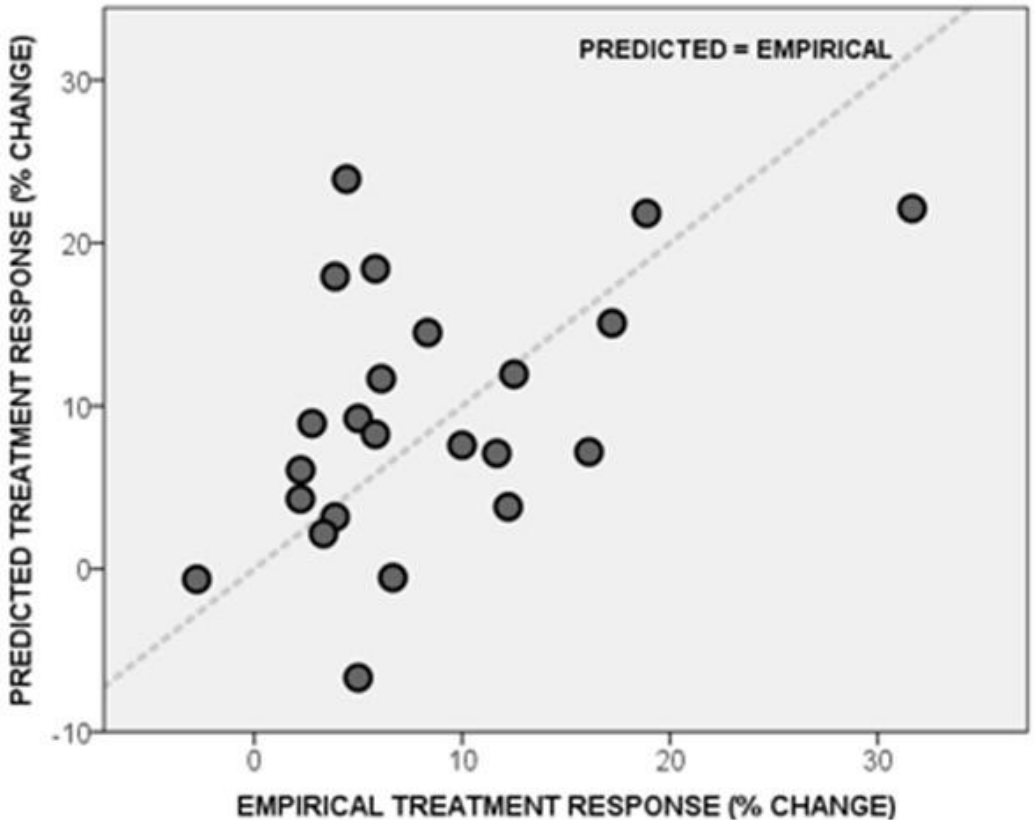
Four significant regions: interaction





Aguilar et al JNNP 2018

Analysis 2: predictive (out-of-sample) analysis



Predicted treatment responses from the cross-validation analysis, using the combined demographic, behavioural and lesion location data, were significantly correlated with the patients' empirical treatment responses ($r = 0.48$, 95% CI 0.08, to 0.75, $p = 0.02$).

iReadMore: Summary

- iReadMore improves word reading accuracy
- Effects are item specific (accuracy and speed)
- Main outcome measure (raw % improvement) was dependent on residual brain structure
- Brain structure explained more of the variance in this measure than demographics or behaviour
- Behavioural variables can take a long time to collect, brain structure is quicker…

Conclusions

Practice-based e-therapies work in aphasic patients

- Item specific: i) big effect sizes, ii) can train lots of items, iii) AI algorithms → optimise item pathways, iv) users to choose items

Explaining responses to therapy

- Brain structure demonstrably dictates responses to practice-based therapies (Listen-In & iReadMore)
  - L-I: VBM identified RH regions
  - iRM: ALM identified combinations of LH regions

  Disparity is probably due to the different techniques used

  Language is a network not a regional property so contributions from both hemispheres most likely

Therapy-induced responses

- For auditory perception of language, this plays out in both hemispheres
- These structural findings are likely to be therapy specific

2 New Aphasia Therapy Apps Out Now!

iReadMore

Word-reading therapy

Click Here or search for 'iReadMore App' to find out more

GET IT ON Google Play

Download on the App Store

Evidence-based therapies proven effective for people with aphasia
(Woodhead et al., 2018; Fleming et al., 2021)

Co-designed by people with aphasia

Both come with a 7-day free trial

Get in touch at:
ireadmore@ucl.ac.uk
listen-in@ucl.ac.uk

Listen-In

Speech Comprehension Therapy

Click Here or search for 'Listen-In App' to find out more

GET IT ON Google Play

References

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