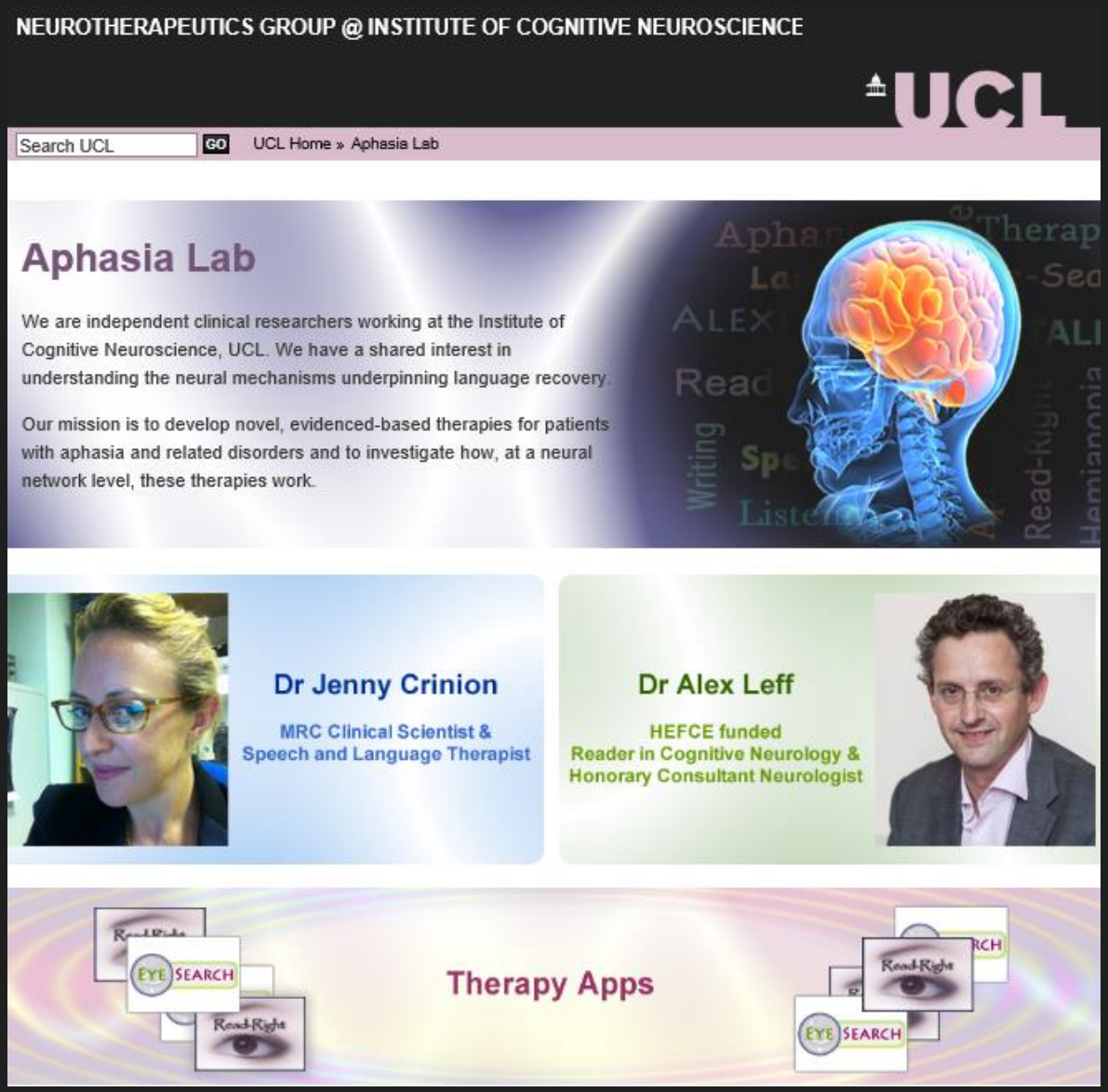
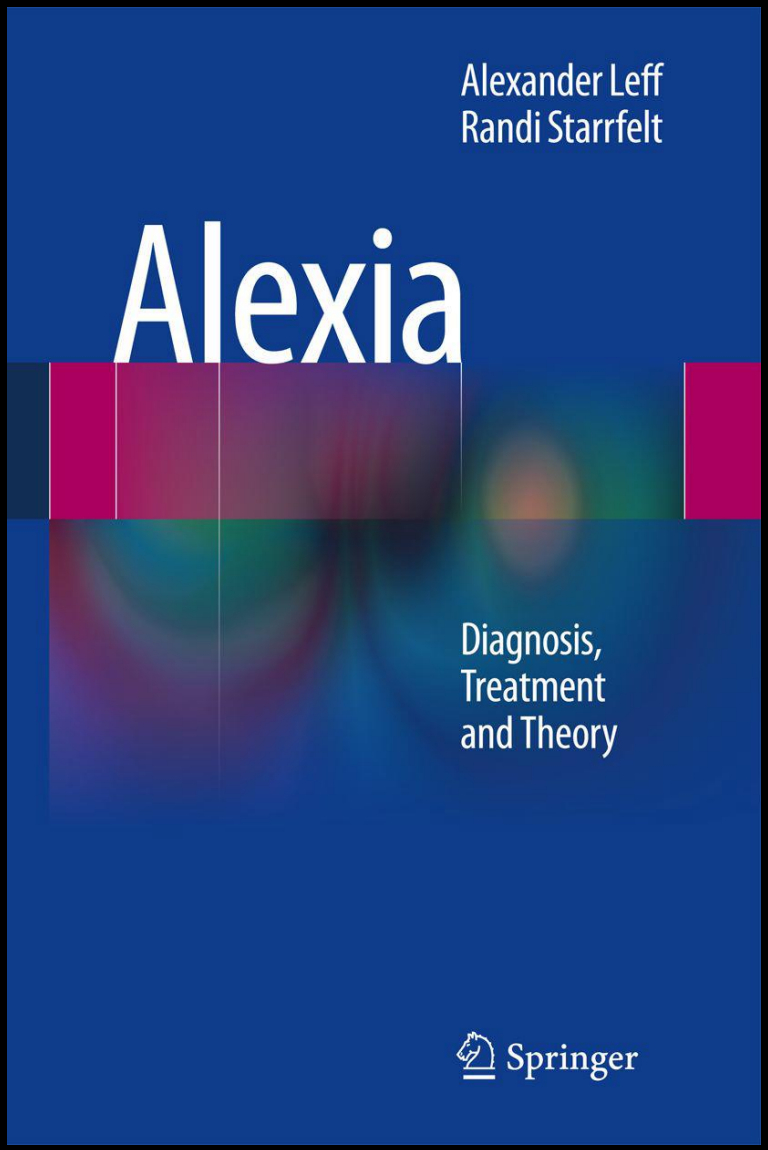
Acquired Alexia and its Treatment

Dr Alex Leff
Reader in cognitive neurology & consultant neurologist
Institute of Neurology &
Institute of Cognitive Neuroscience
National Hospital for Neurology & Neurosurgery

Aphasia Lab @ UCL



Read all about it!



Overview

Three important brain processes involved in reading text:

1. visuo-spatial attention & eye movements

   (getting your eyes to the right visual target)

2. word-form recognition

   (decoding the visual object as a written word)

3. Central language processing

   (ascribing meaning to the written word)

Overview

I will discuss the major forms of acquired alexia:

1) Hemianopic alexia
2) Neglect dyslexia
3) Pure alexia
4) Central alexia

Overview

In each case I will cover:

1) the characteristics of the syndrome
2) neuroanatomical correlates
3) behavioural therapies; and, where known
4) how these behavioural therapies interact with the residual reading network

Which parts of the brain ‘look’ and which ‘see’?

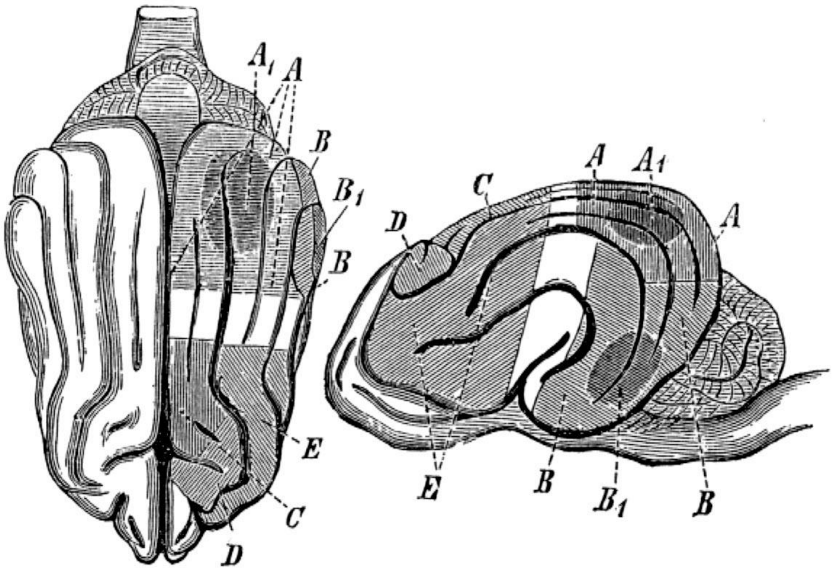


Fig. 4. Dorsal and lateral view of dog's brain. Letters explained in text.

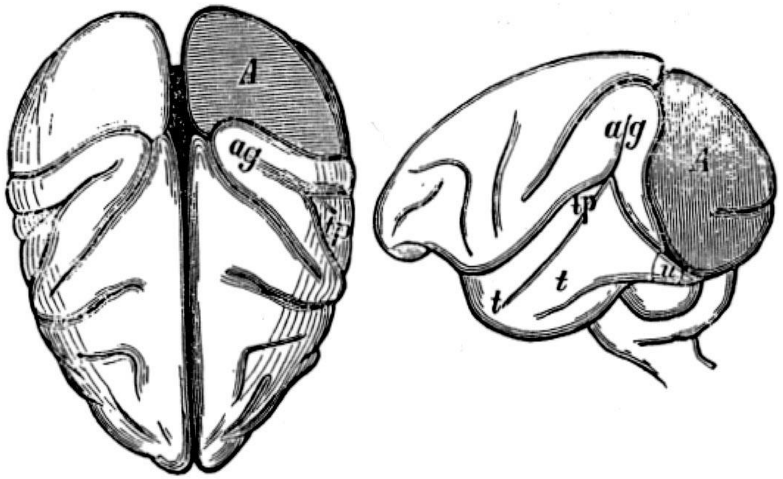


Fig. 5. Dorsal and lateral view of the macaque's brain. Letters explained in the text.

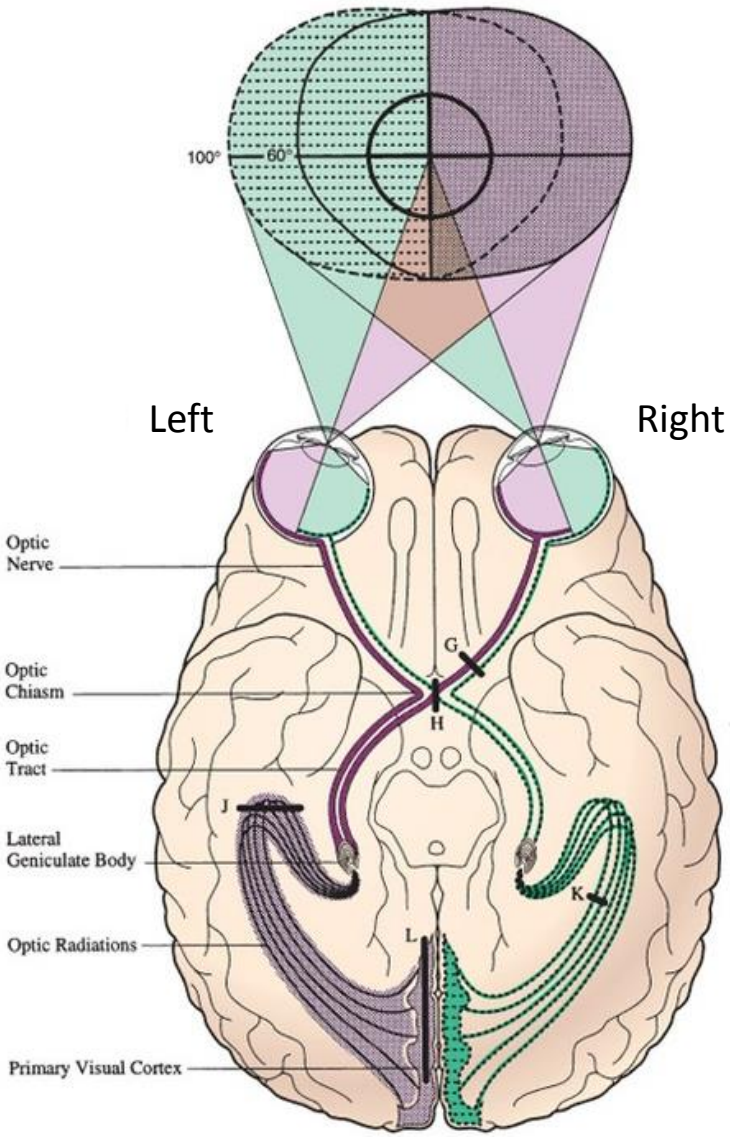
Hermann Munk (1881)
Uber die Verrichtungen des Grosshirns
(On the organization of the cerebrum)

Peer review 19th Century style

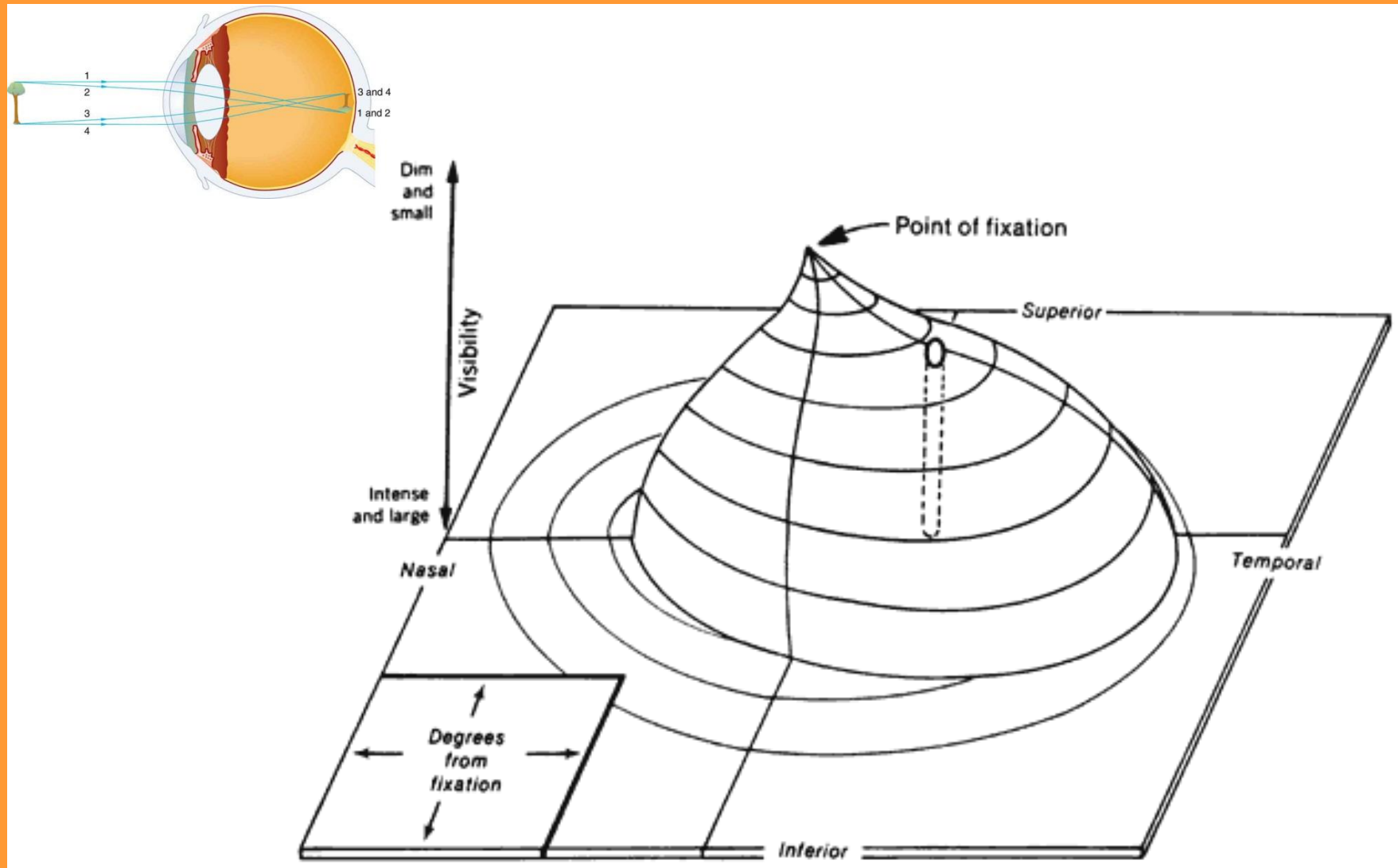
In my first communication on the physiology of the cortex which I made in March of last year I did not say anything about Ferrier's work on the monkey because there was nothing good to say about it. . . All [his] statements are worthless and gratuitous constructions since the operated animals were examined by Mr. Ferrier in quite an insufficient manner. . . Mr. Ferrier had made not one correct guess, all his statements have turned out to be wrong.

(H. Munk 1881).

Anatomy: overview

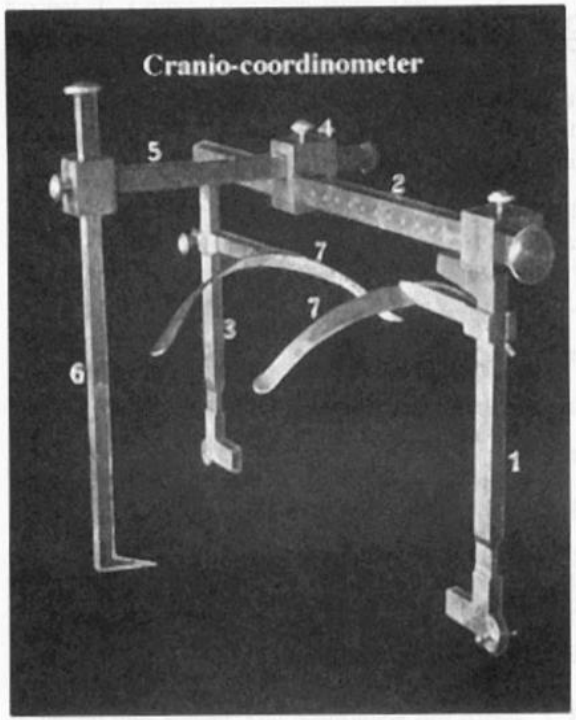


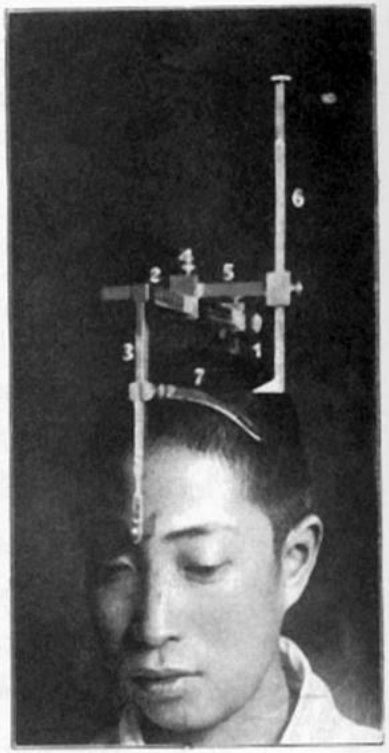
Hill of vision: acuity drops off rapidly from fixation



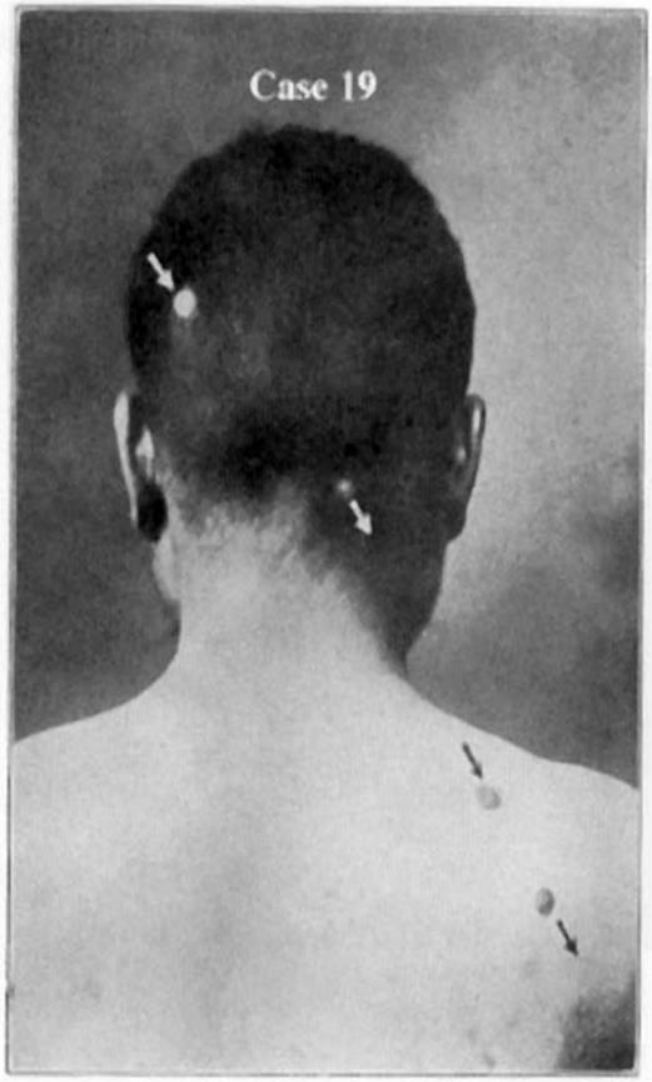
Mapping the world onto visual cortex

Tatsuji Inouye in military uniform





Mapping the world onto visual cortex



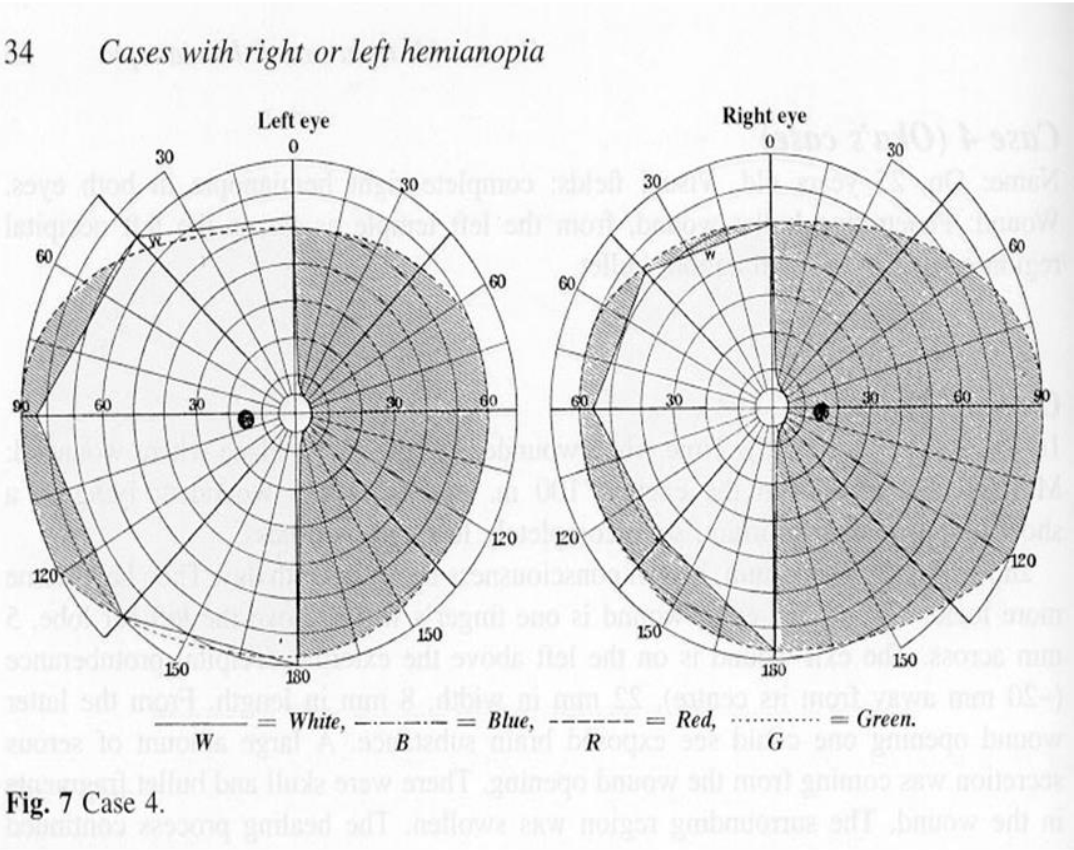
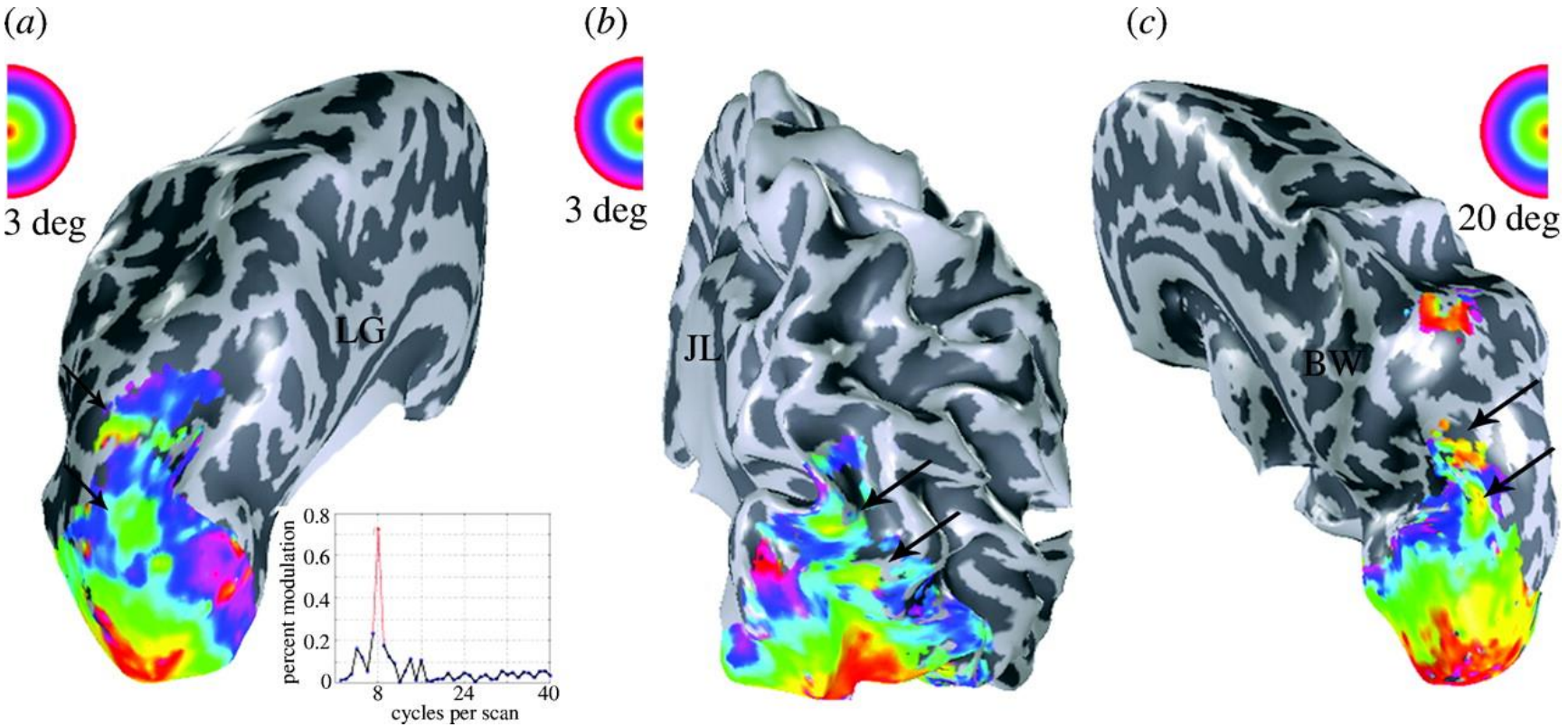
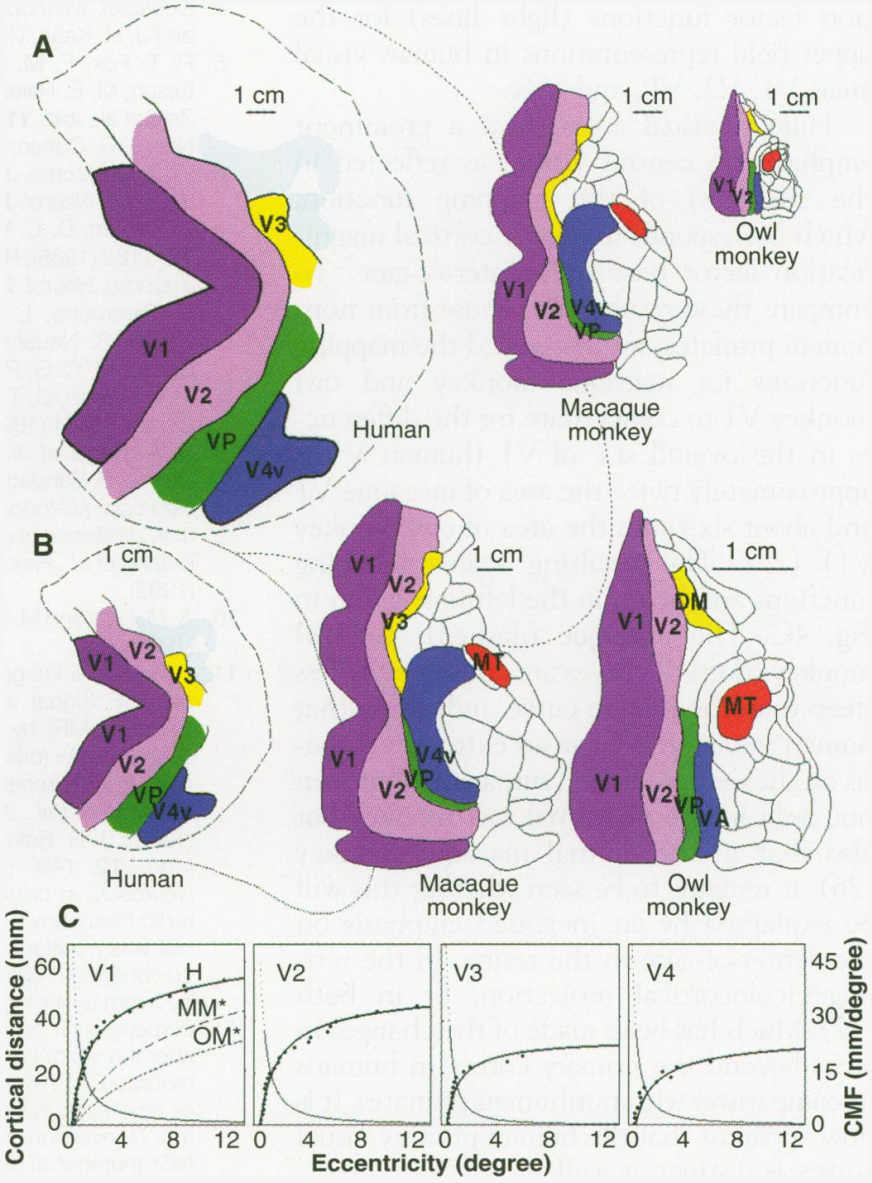


Fig. 7 Case 4.

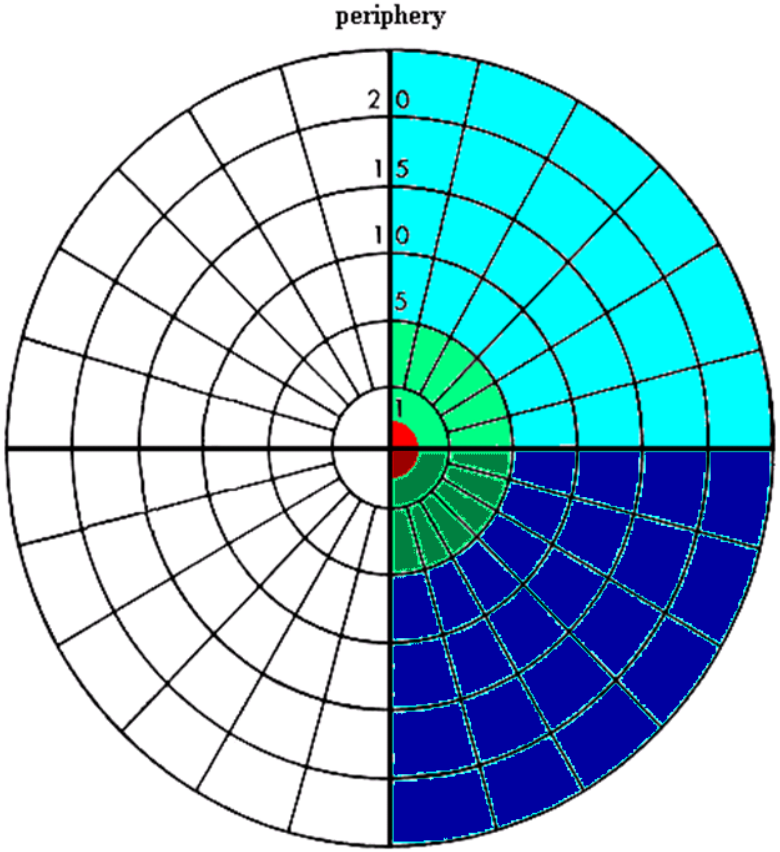
Late 20th Century: fMRI localizers

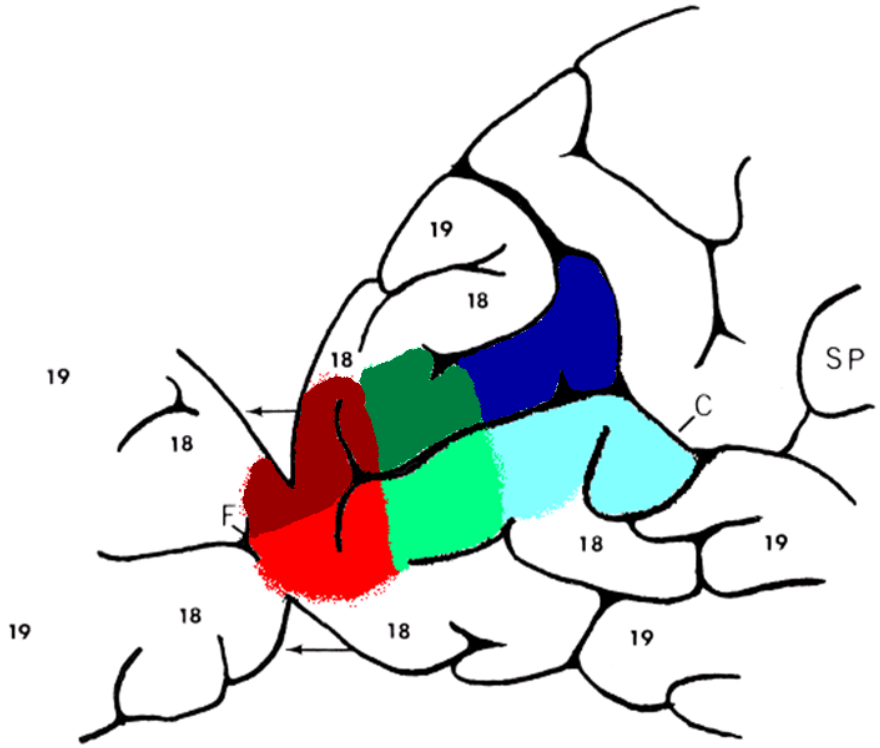


Human visual areas have an extreme emphasis on the centre-of-gaze

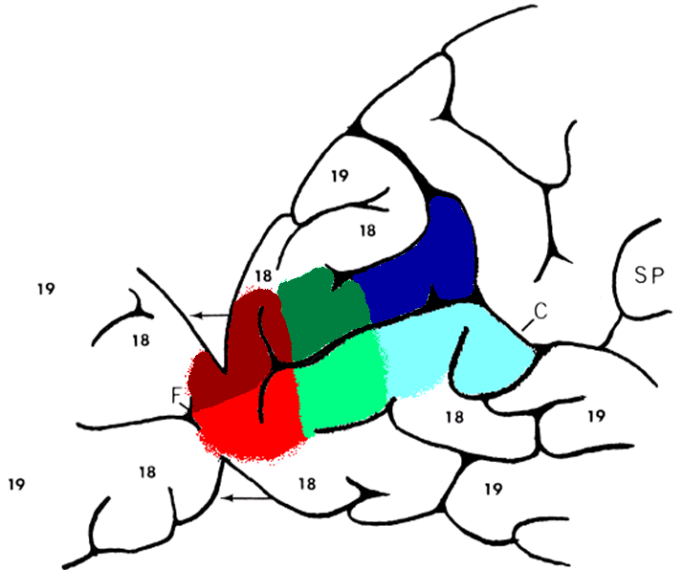


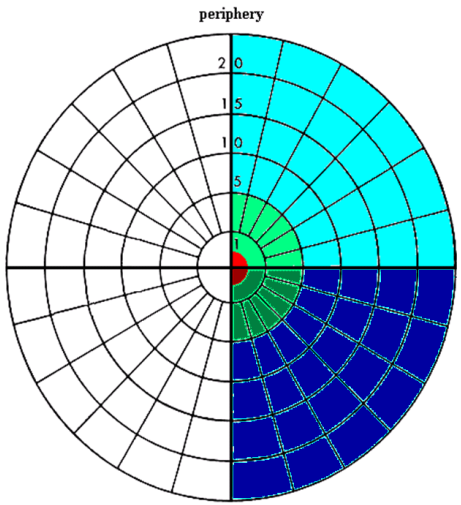
Cortical magnification factor



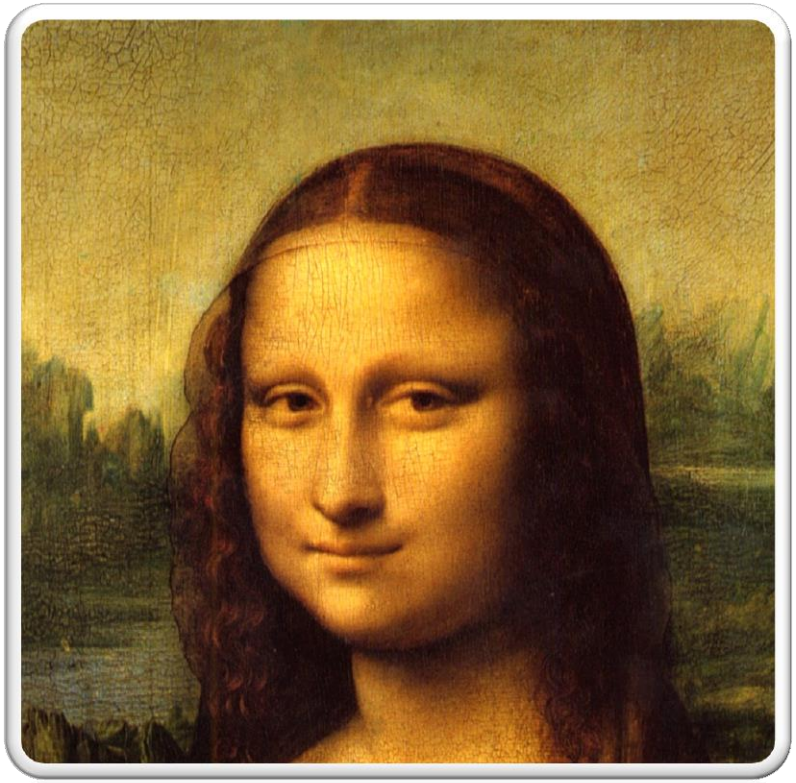


33% of your visual cortex for 0.1% of your visual field

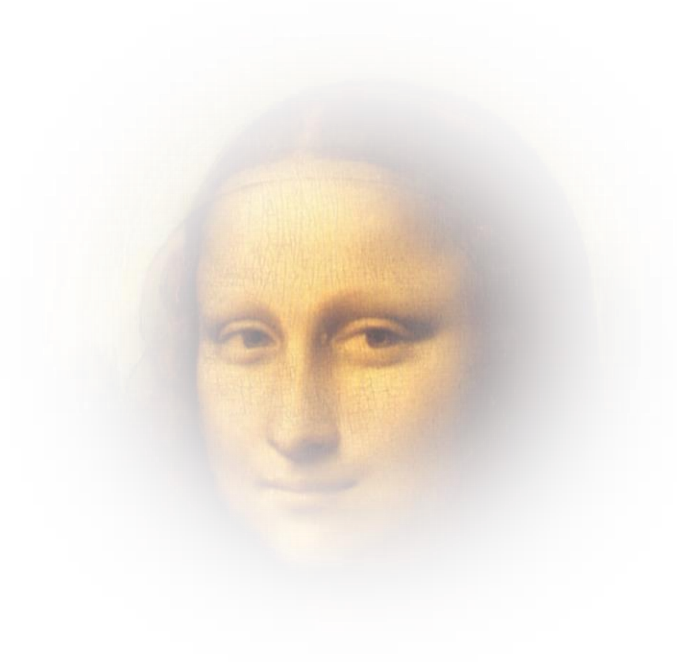




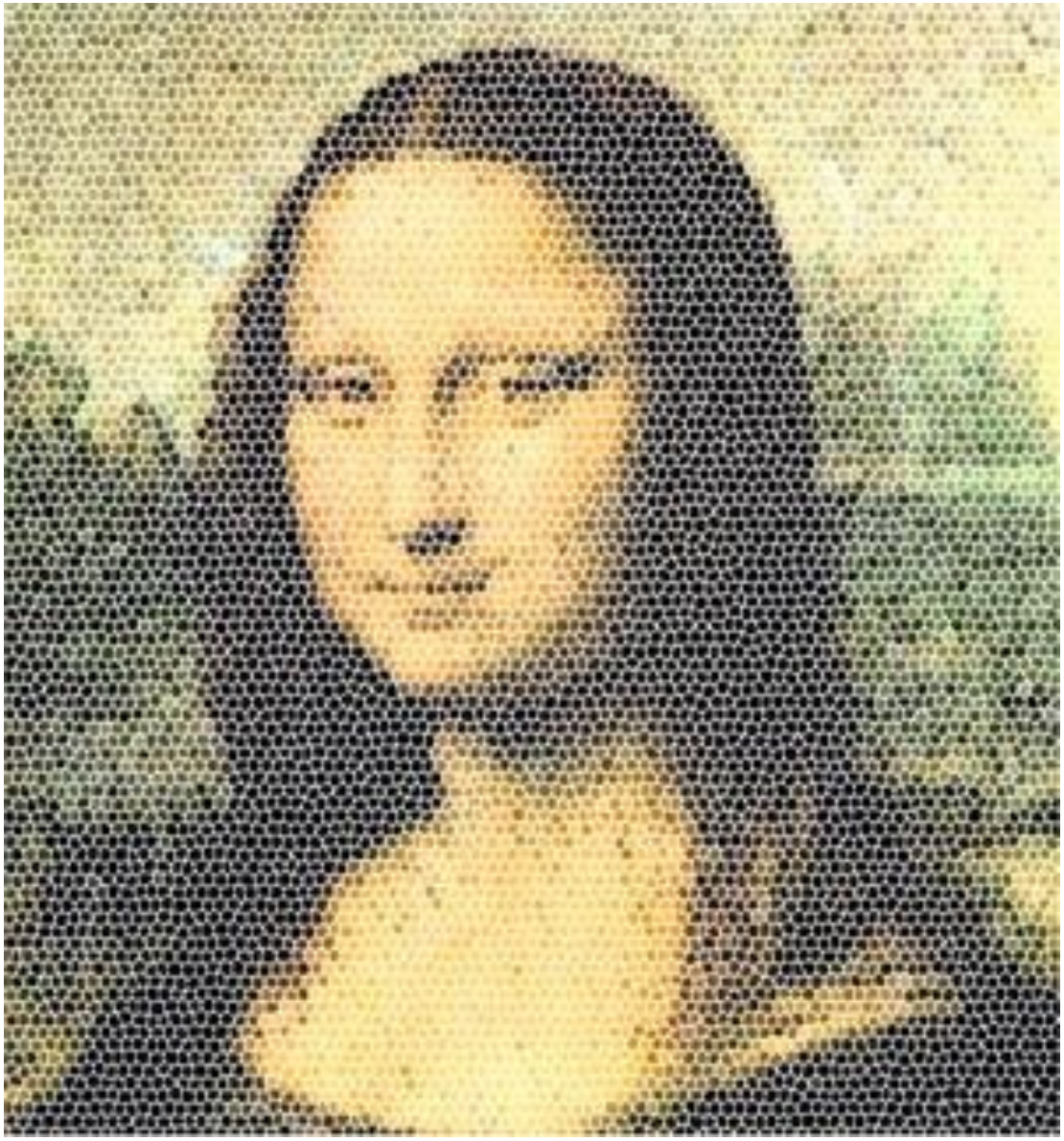
Only central vision provides detail



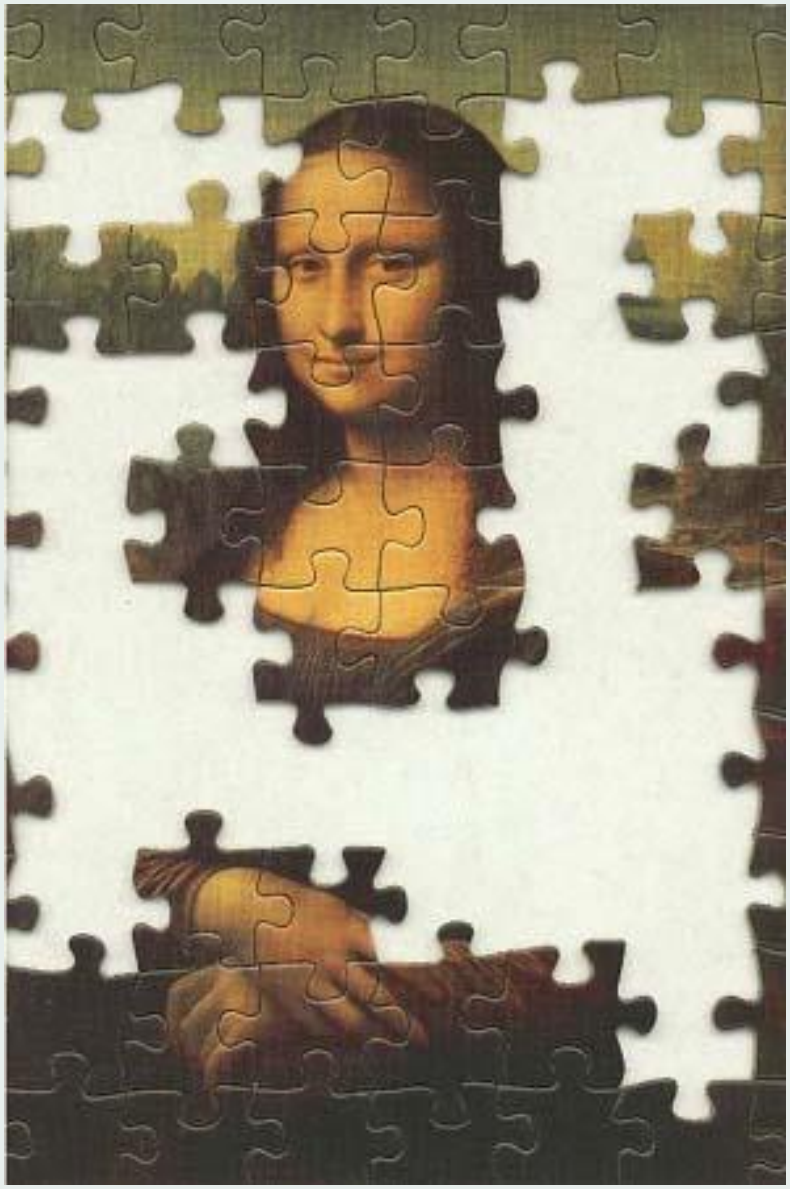
Only central vision provides detail



What a camera ‘sees’

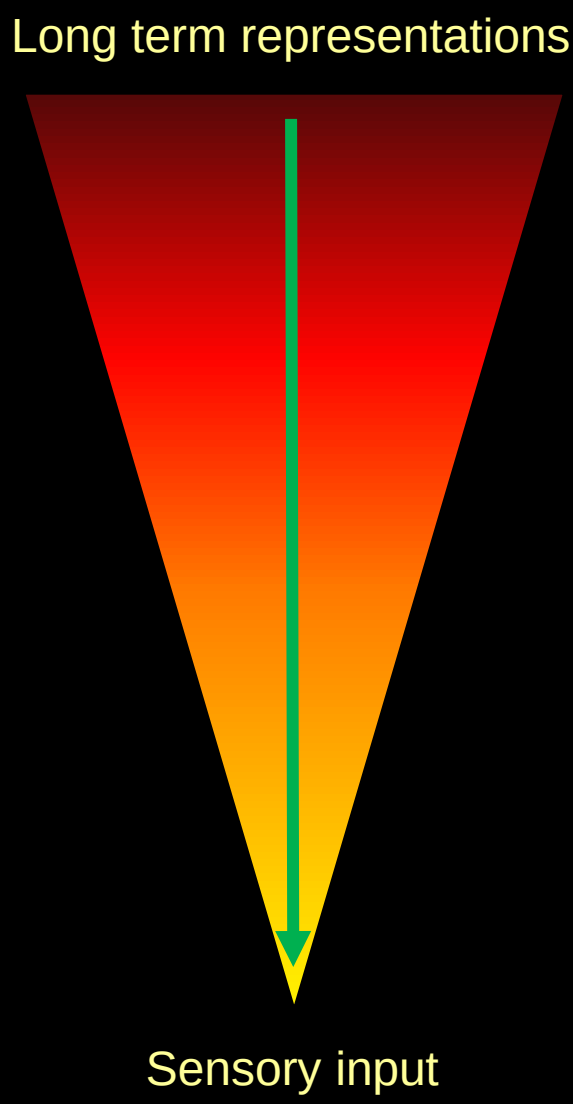


What you see is assembled over time



Visual hierarchy

Visual hierarchy

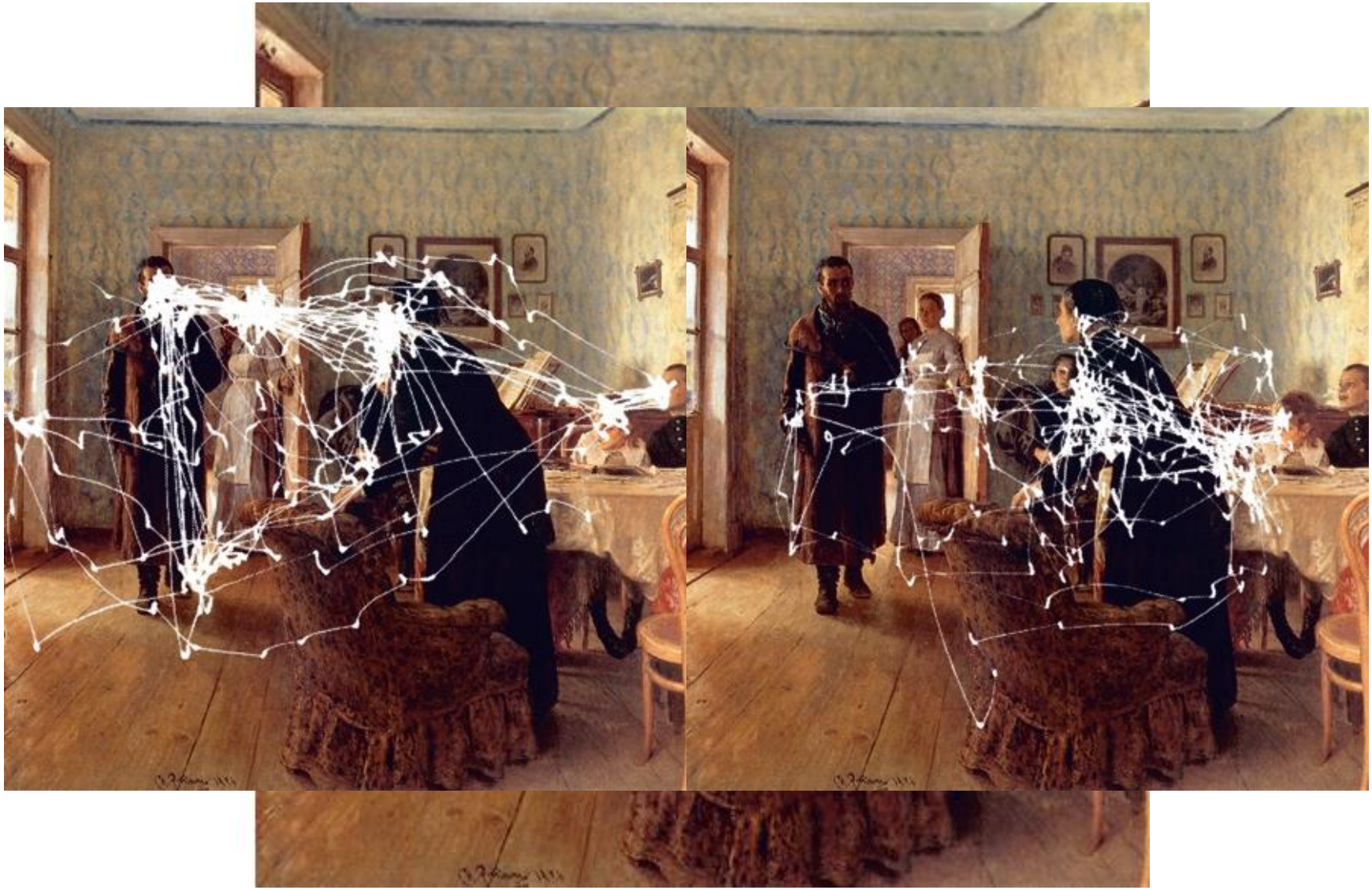


Representations become more abstract (multimodal > unimodal)
Mumford 1992 *Biol Cybern*

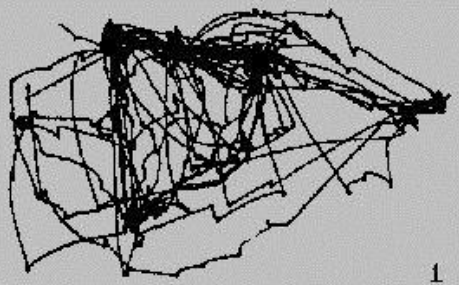
Top down:
Brain signals that convey knowledge derived from prior experience rather than sensory stimulation
EK Miller 2000 *Nat Rev Neuroscience*

Top down:
A fool sees not the same tree that a wise man sees
William Blake 1790 *The marriage of heaven and hell*

Eye movements: Yarbus 1967

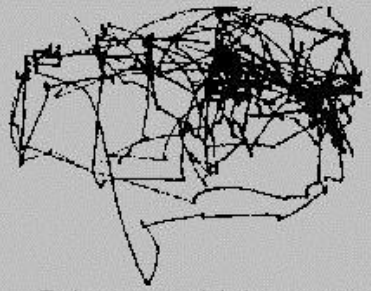


Eye movements depend on the task in hand



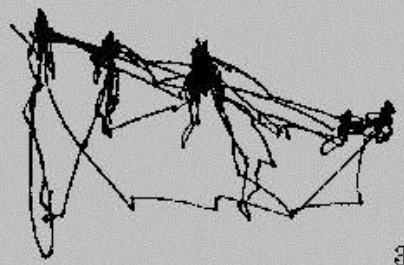
1

Free examination.



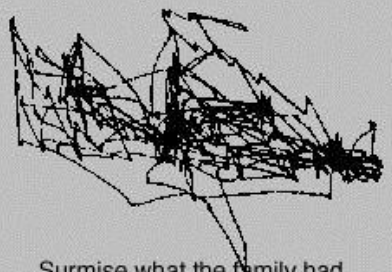
2

Estimate material circumstances of the family



3

Give the ages of the people.



4

Surmise what the family had been doing before the arrival of the unexpected visitor.

5

Remember the clothes worn by the people.

6

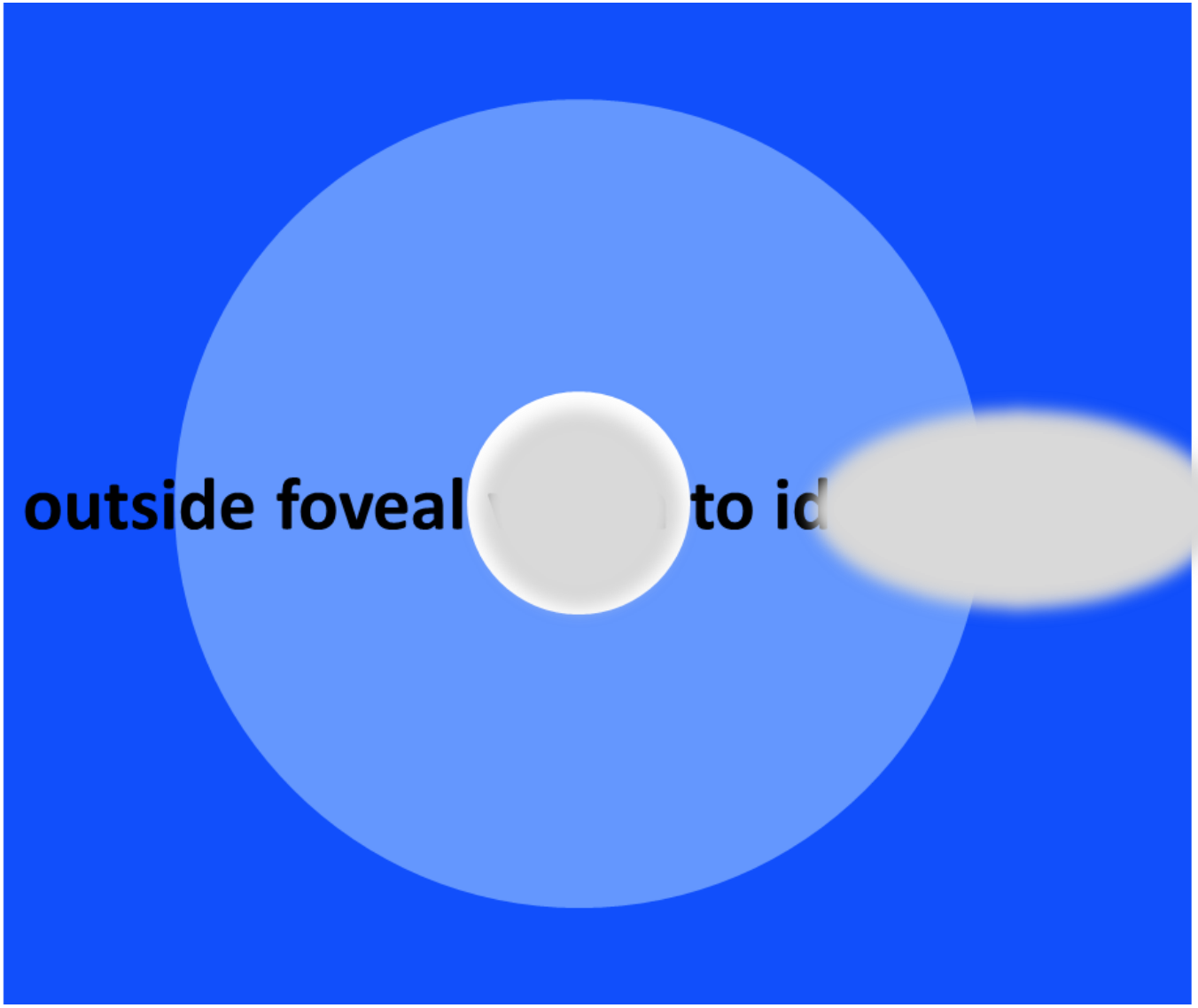
Remember positions of people and objects in the room.

7

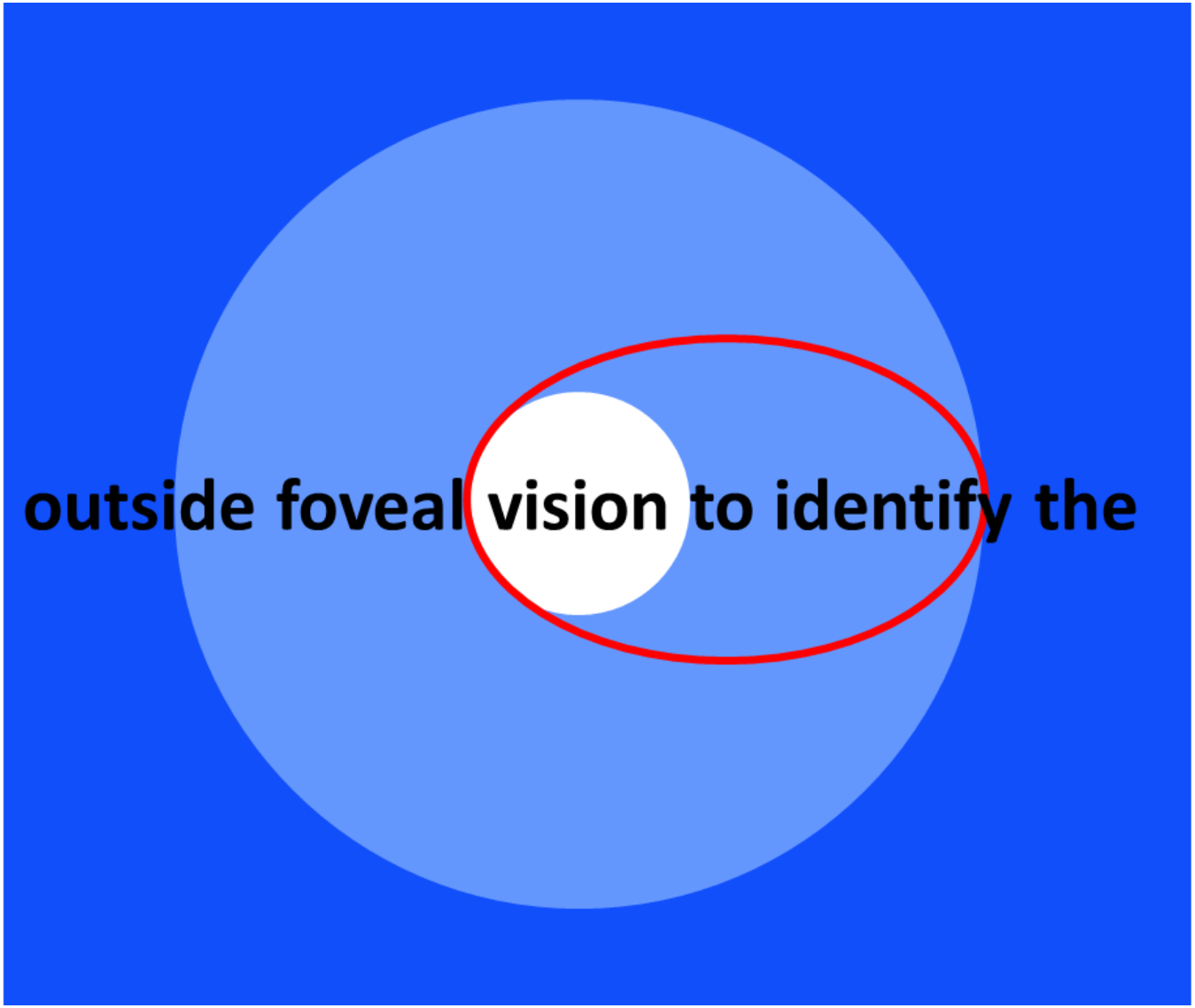
Estimate how long the visitor had been away from the family.

3 min. recordings of the same subject

How do you read text?



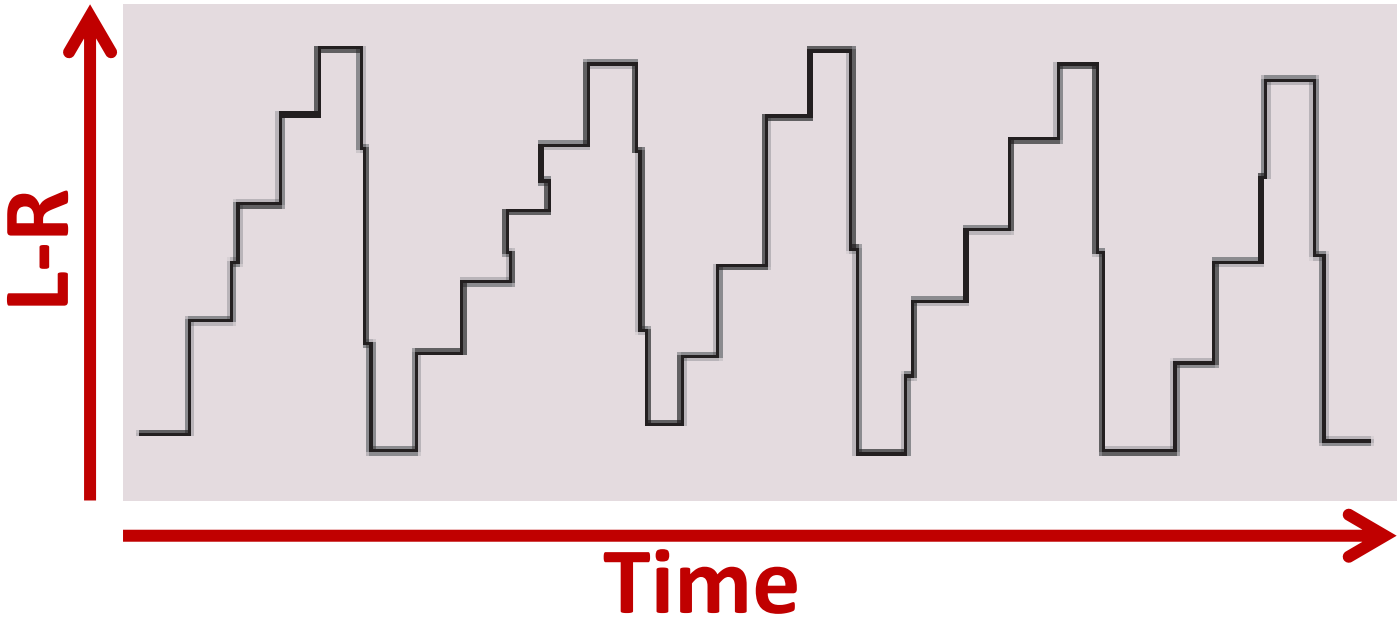
How do you read text?



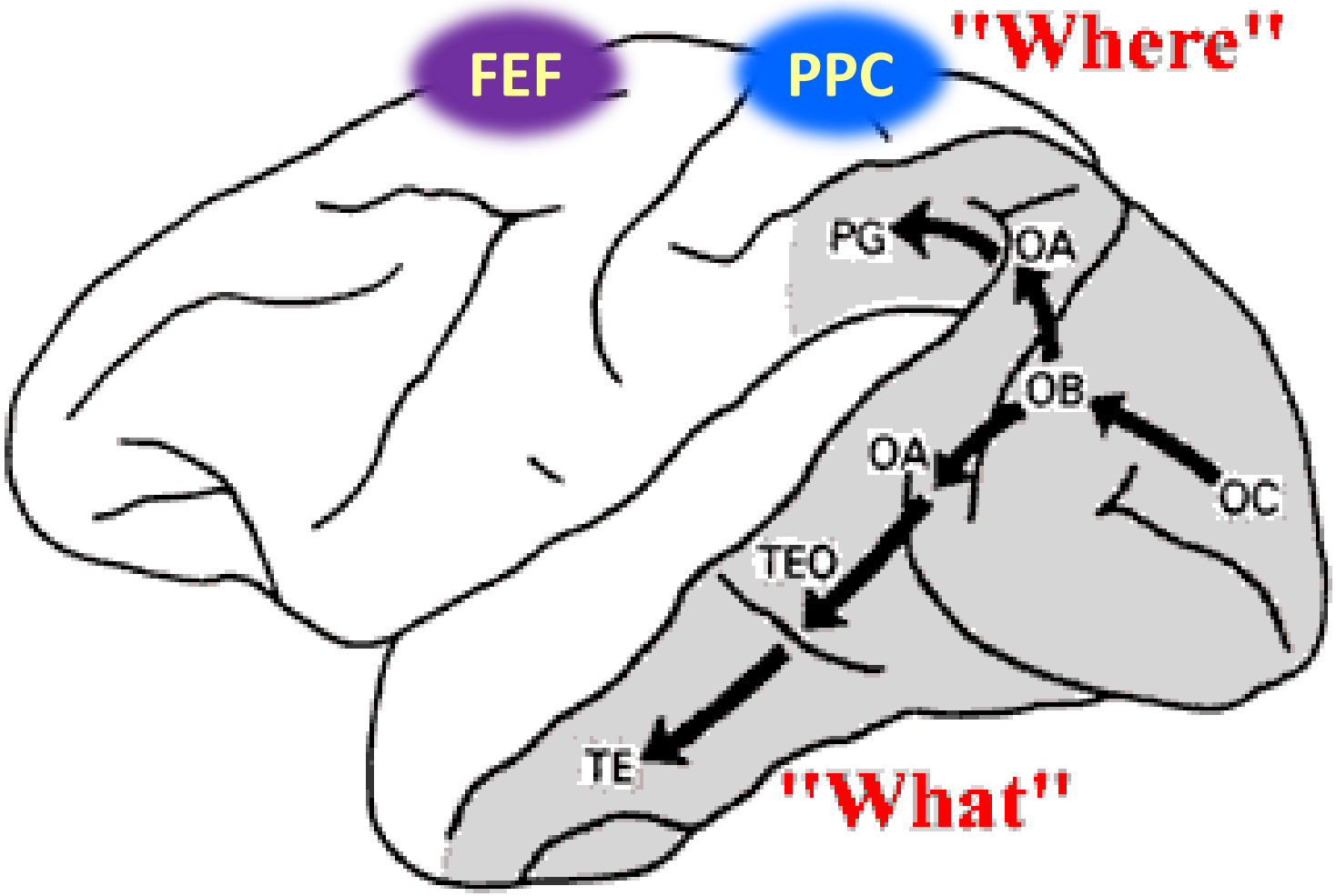
Eye movements limit reading speed

Reading eye movements

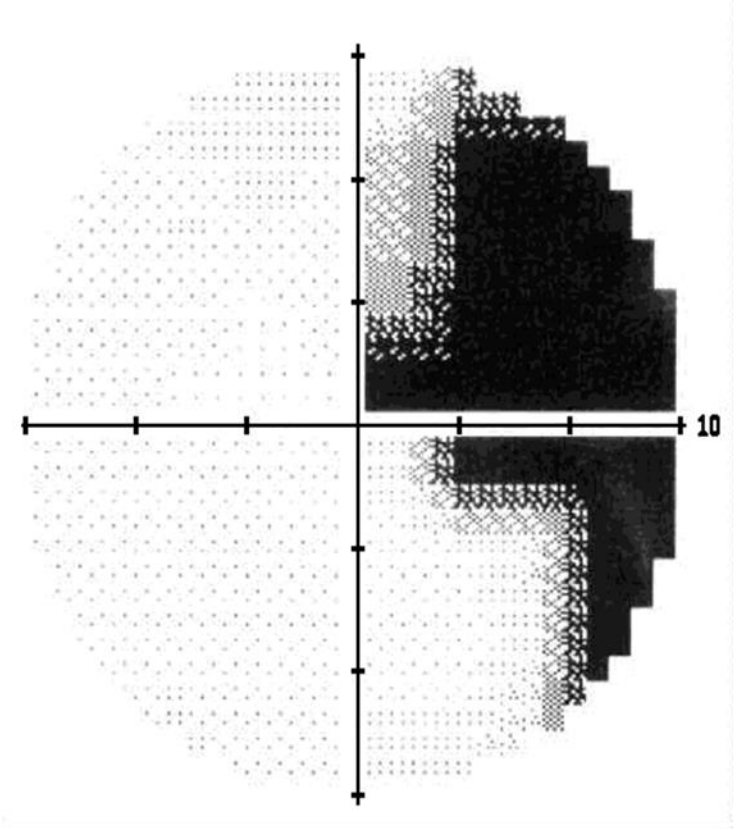
Hemianopic dyslexia is an acquired reading disorder whereby patients with homonymous visual field defects have persistent and severe reading difficulties, despite having intact language functions. The term 'hemianopic dyslexia' derives from the fact that hemianopia is the



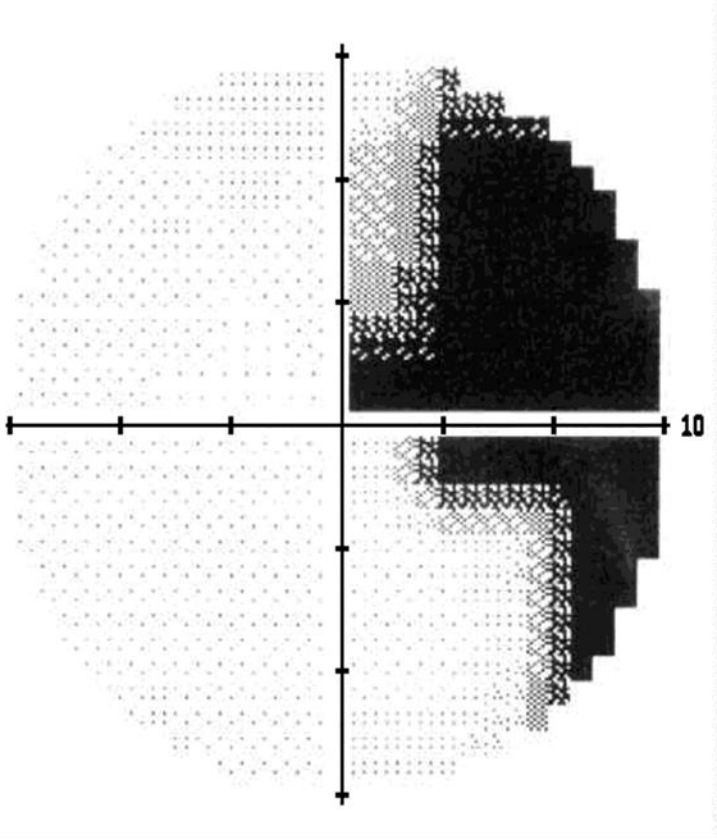
Beyond primary visual cortex: what, where and EMs



Hemianopia robs the reader of upcoming info

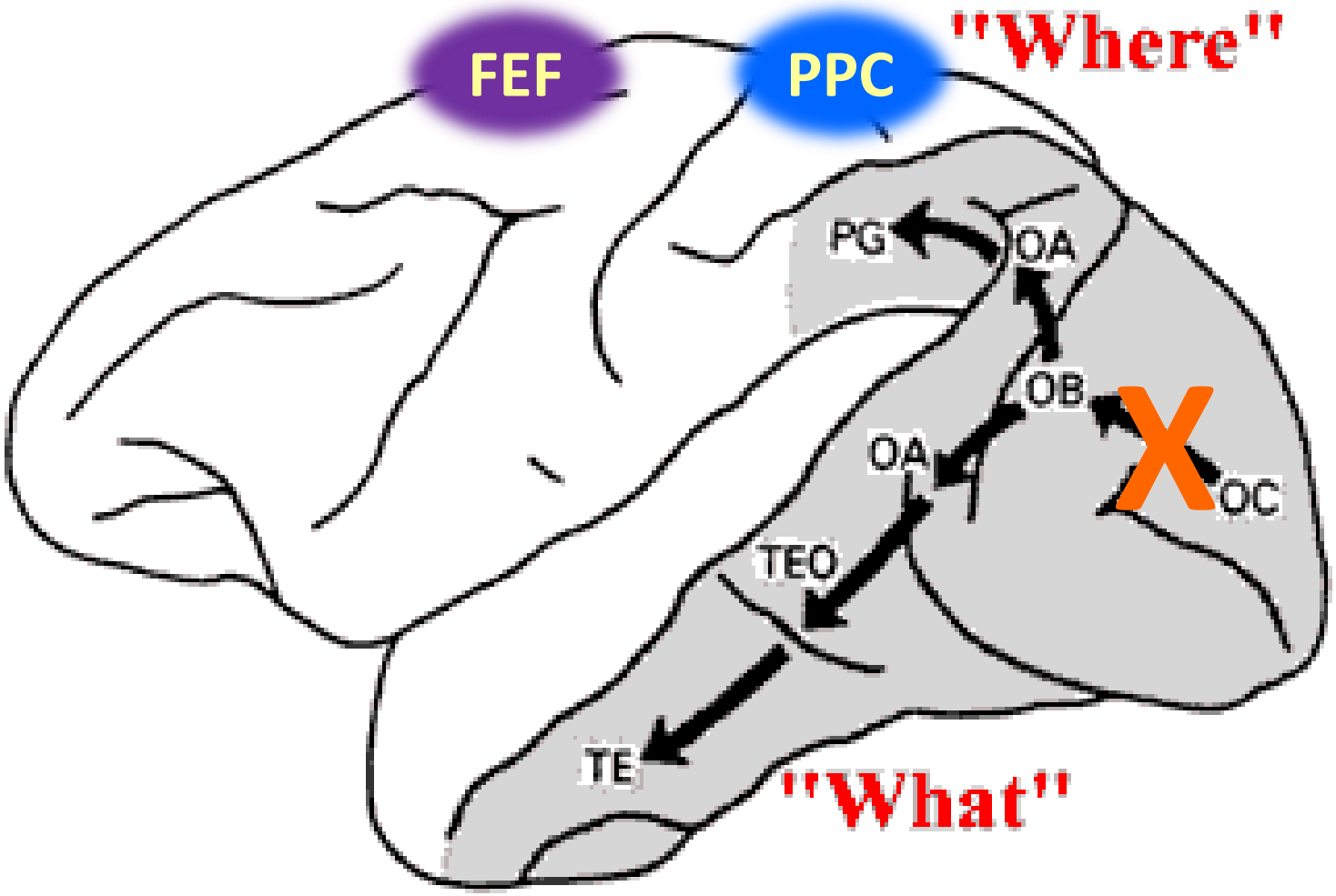


Left Eye

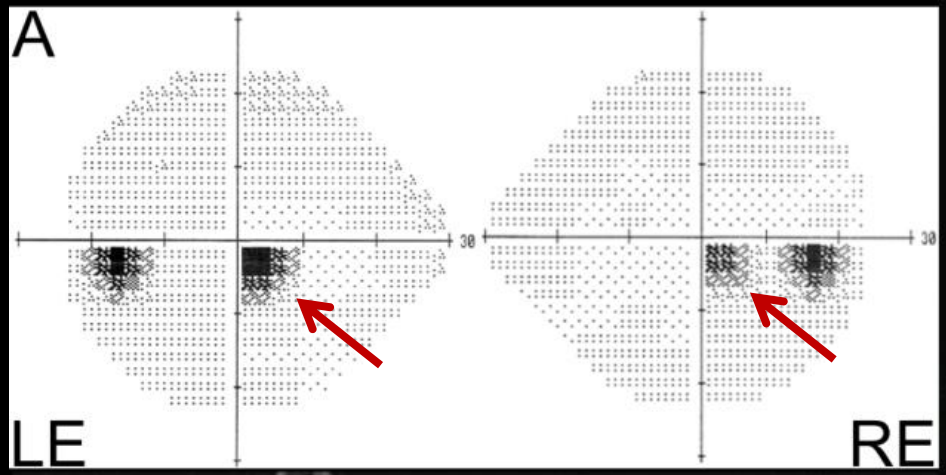


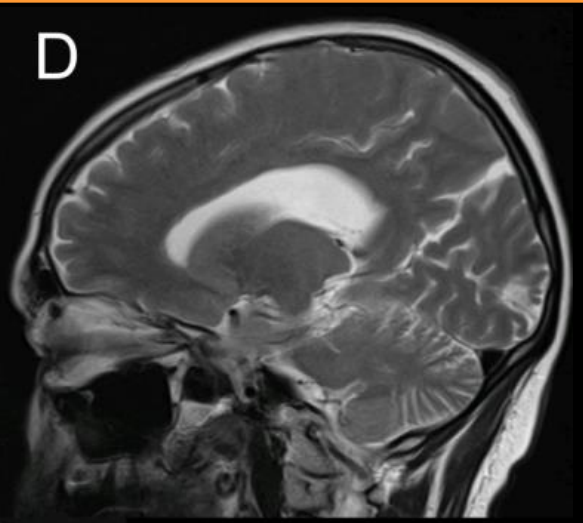
Right Eye

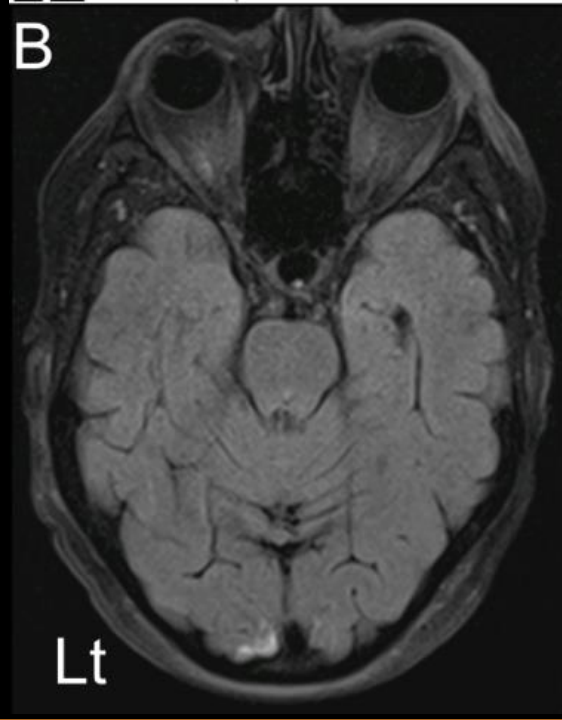
Hemianopic Alexia: stroke affects co-ordination of “where”

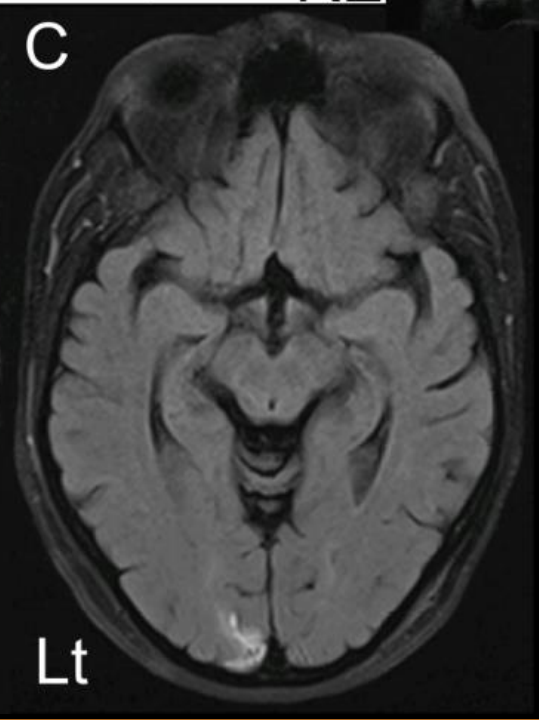


Right-sided, parafoveal homonymous scotoma

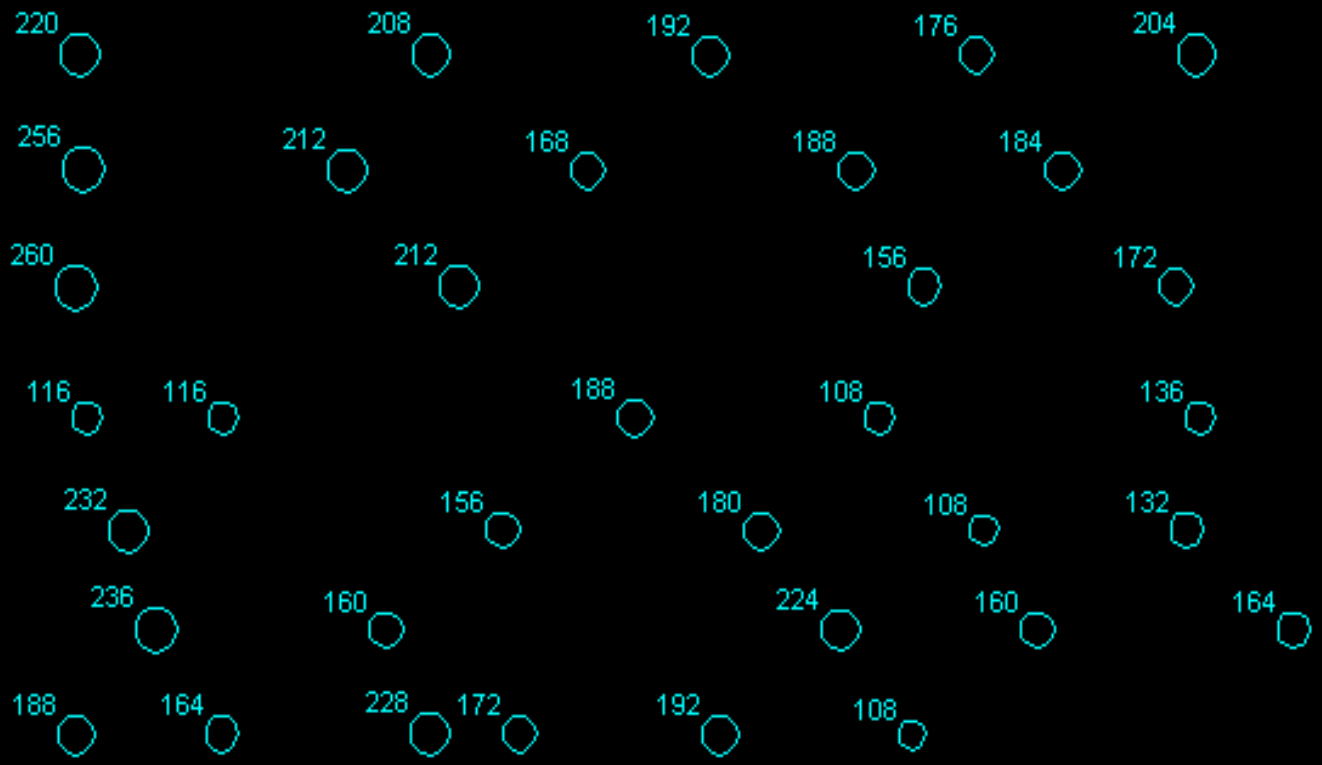




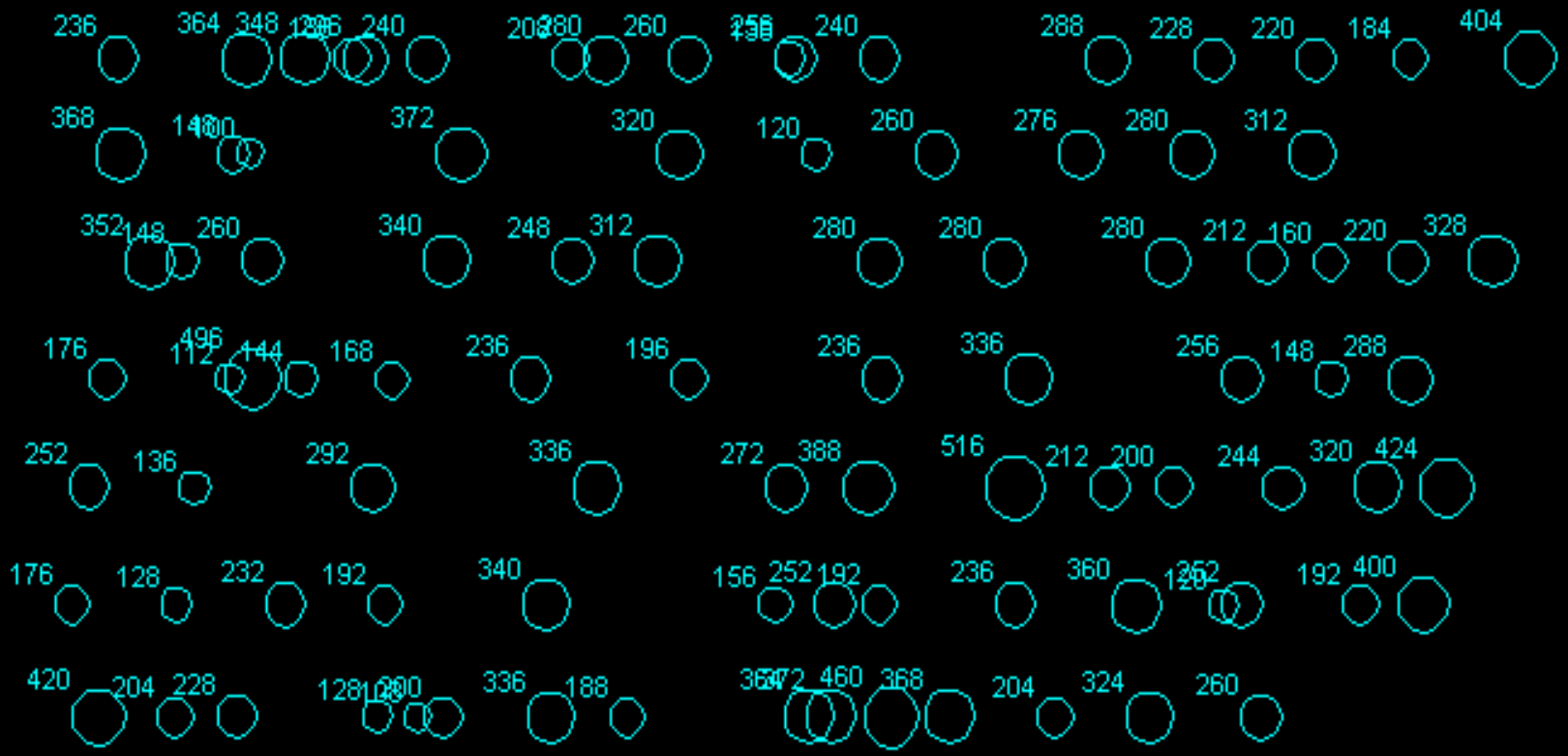




Passenger Paul Lynch stunned airport security staff when he proved his identity by showing them the cover of a Guinness Book of Records. Paul did not have any photo ID with him when he checked in at Stansted for a no-frills GO flight to Edinburgh.



Normal text reading fixations:
36 fixations 45 words, ratio = 0.8



Hemianopic alexia text reading fixations:
93 fixations 45 words, ratio = 2.1

Hemianopia: recovery curve

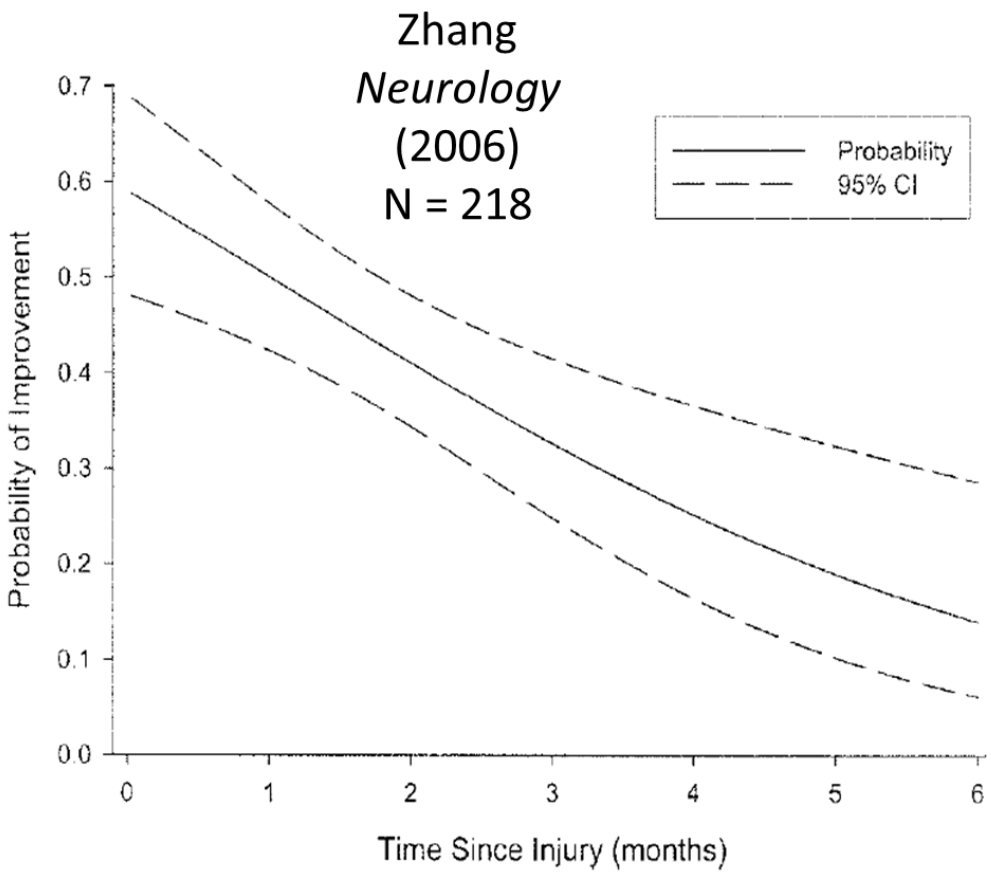


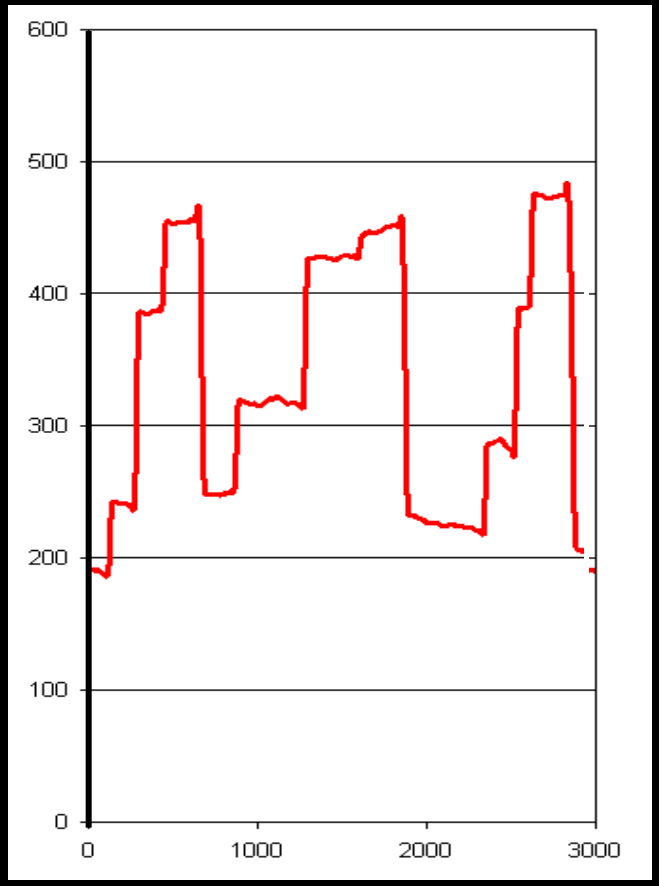
Figure. Graph showing the probability of improvement vs time since injury. Only cases initially tested within 6 months after the injury are included (83% of the 263 patients seen in follow-up). The estimated logistic regression function is $1/(1+\exp(0.3657 - 0.36449 \times \text{Time}))$.

Ground rules/Assumptions

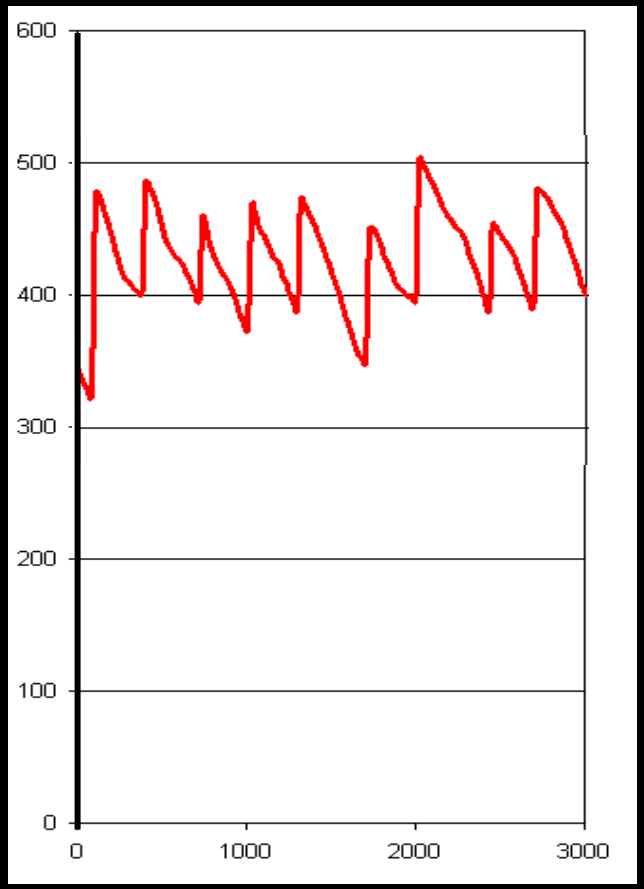
- Behavioural therapy does not improve high-acuity vision in patients with homonymous hemianopia
- My techniques rely on inducing compensatory strategies - changes in eye-movement behaviour
- At least five published studies showing the efficacy of EM training in hemianopic alexia

Therapy:
induces small-field optokinetic nystagmus

Why does moving text work?



Static text – “staircases”



Moving text – OKN

Why put it on the web?

1) Improve access

2) More user friendly

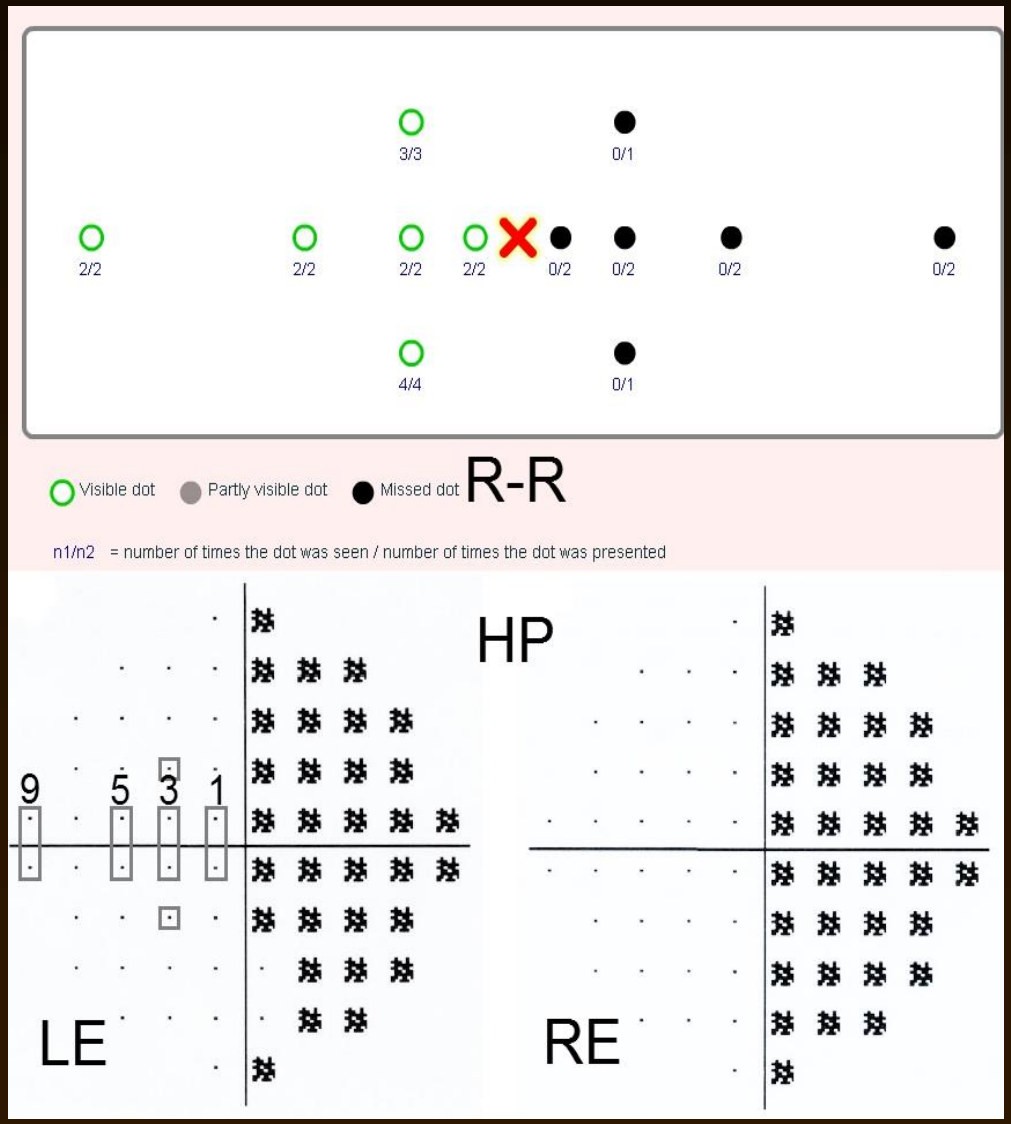
3) Research tool

Provide these for free to anyone with internet access

Can be used by patients/carers/therapists

Demo: visual field test

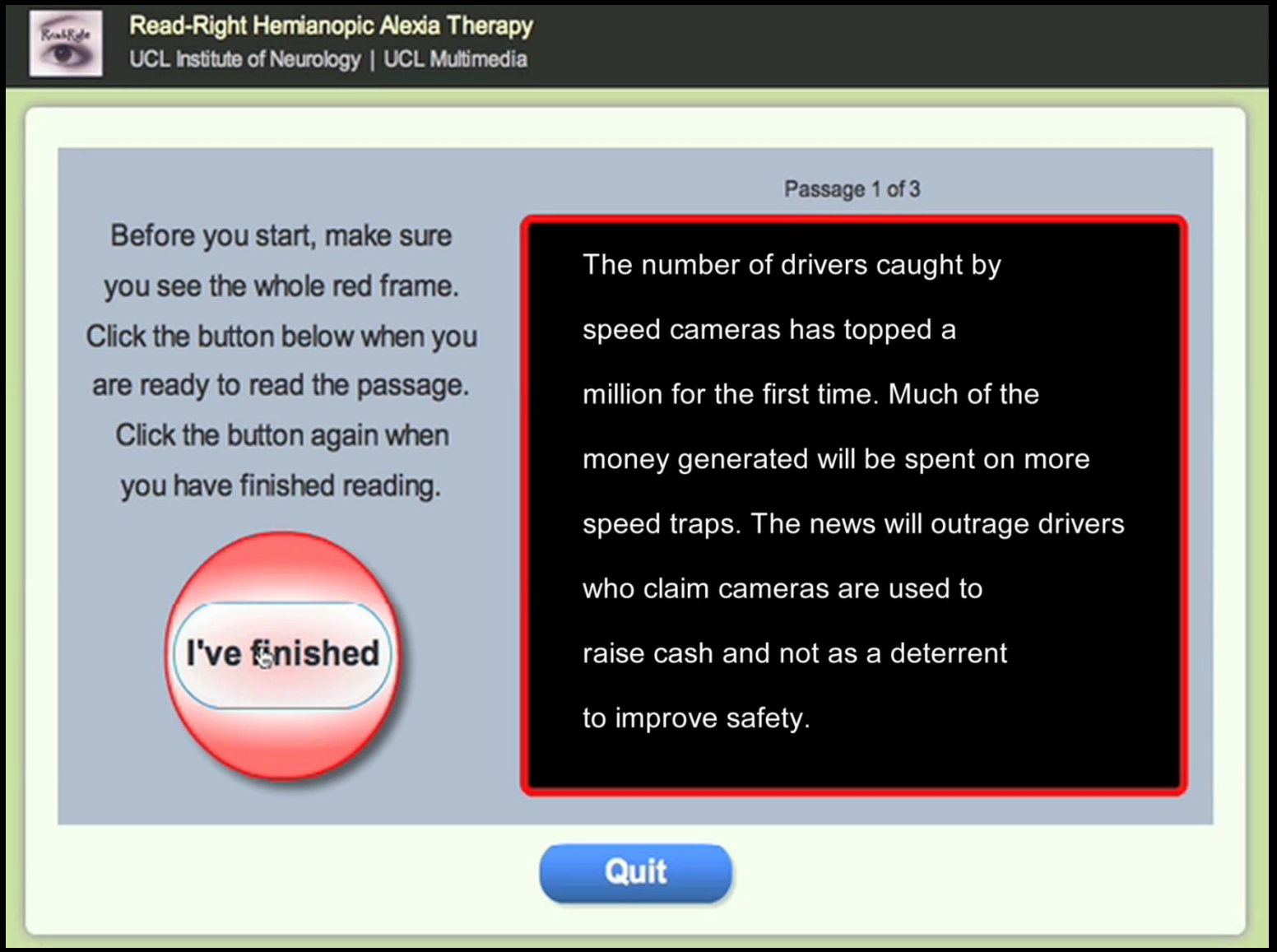
Criterion validity of R-R visual field test



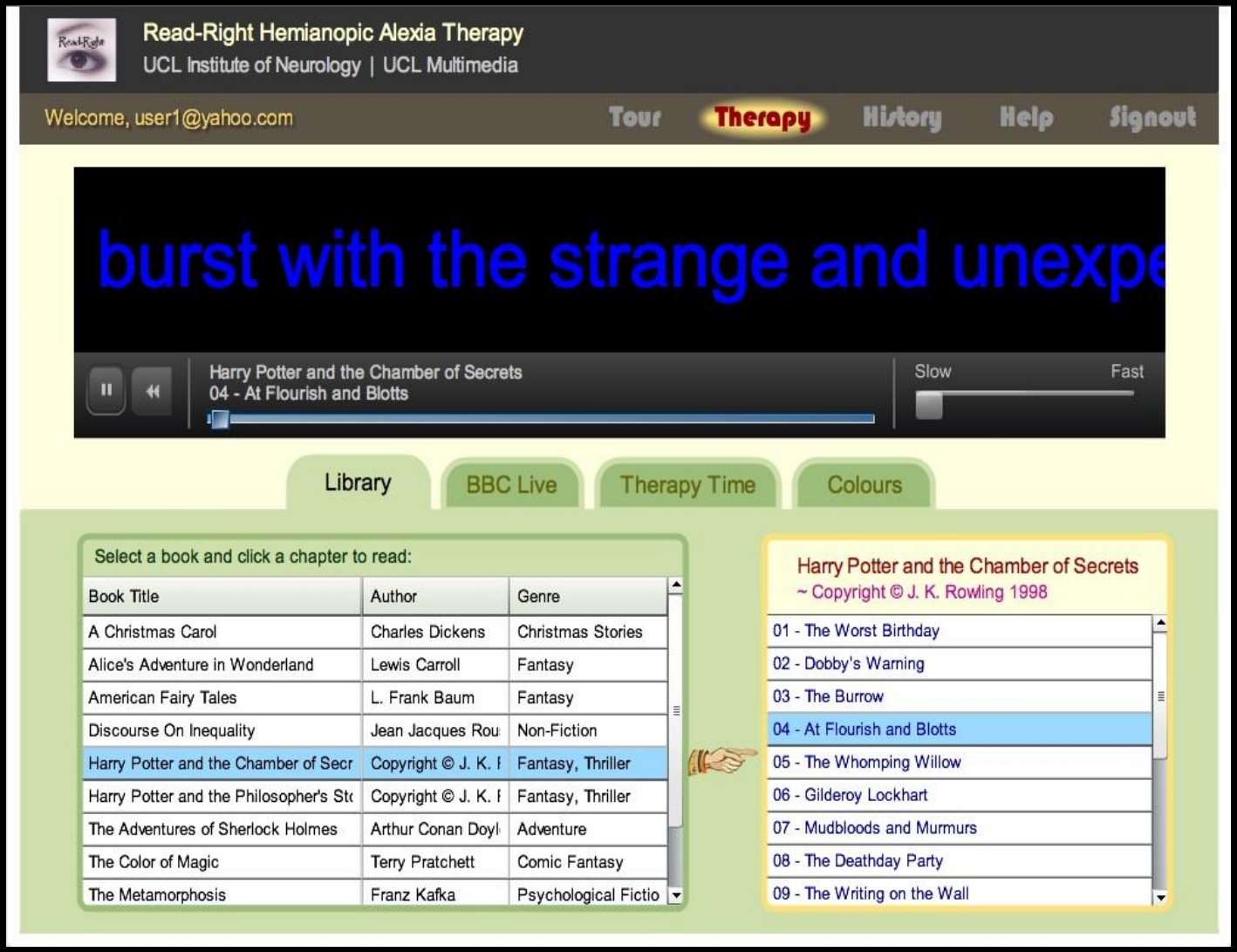
- 22 subjects took part
- average age = 56.0 years
- All had unilateral homonymous visual field defects
- All were in the chronic phase more than 5 months post event
- 'Gold-standard' = HAF 10-2
- sensitivities and specificities
- kappa values
- intra-class correlations

Koiava *Journal of Neurology Neurosurgery and Psychiatry* 2012

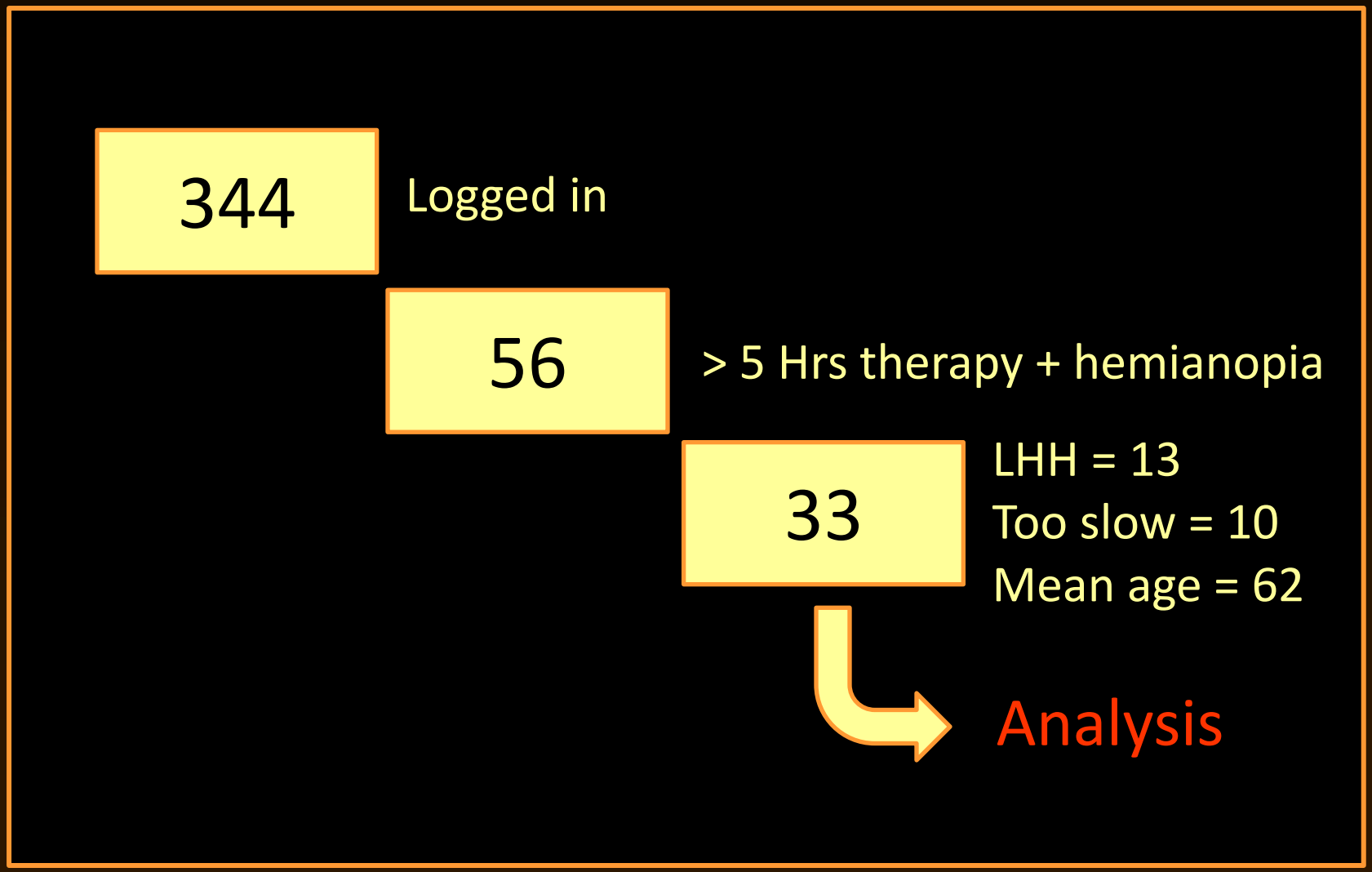
Demo: text reading test (outcome)



Therapy: options



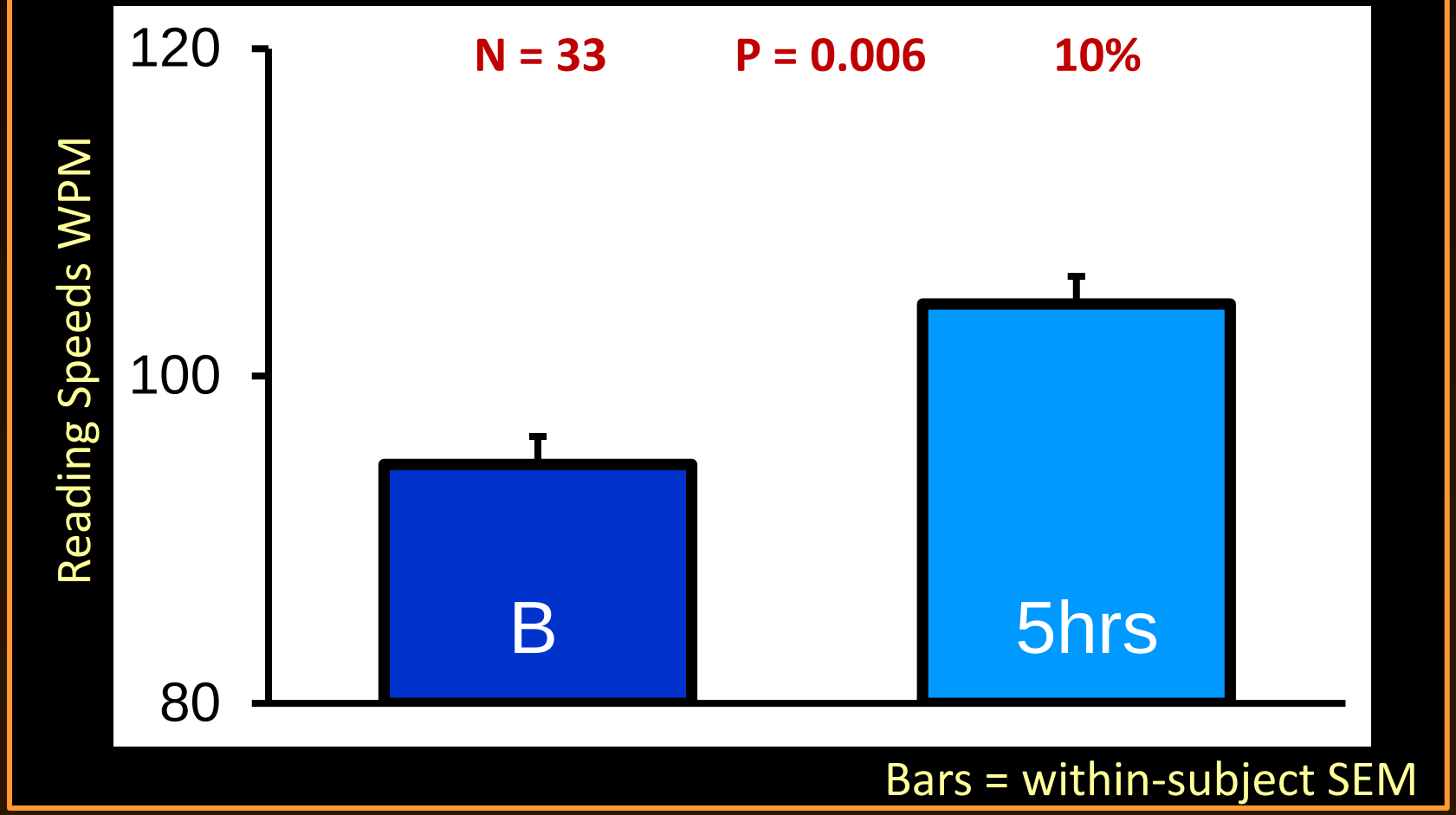
Subjects



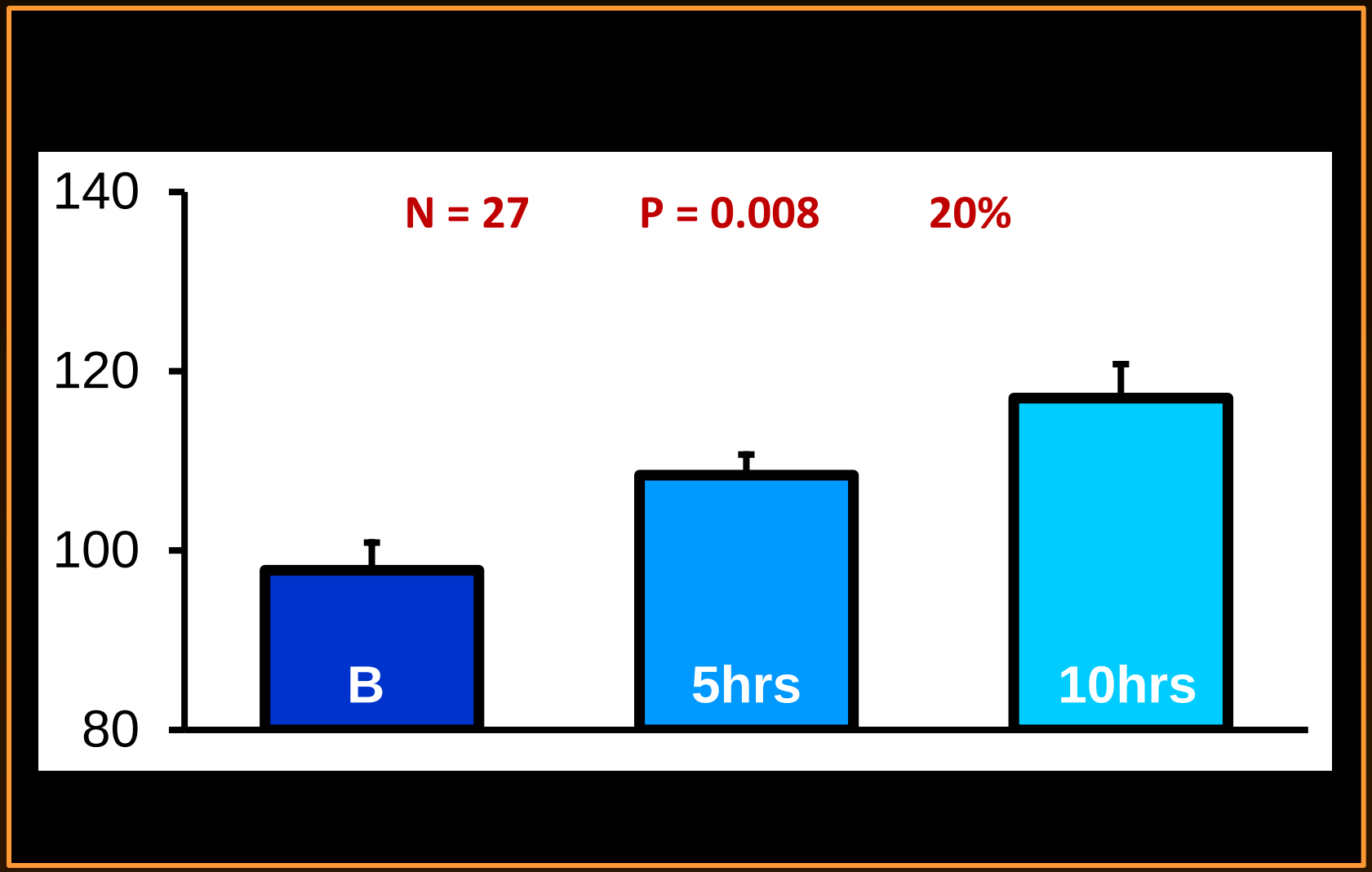
Ong *Journal of Neurology* 2012

Results after 5 hours of therapy

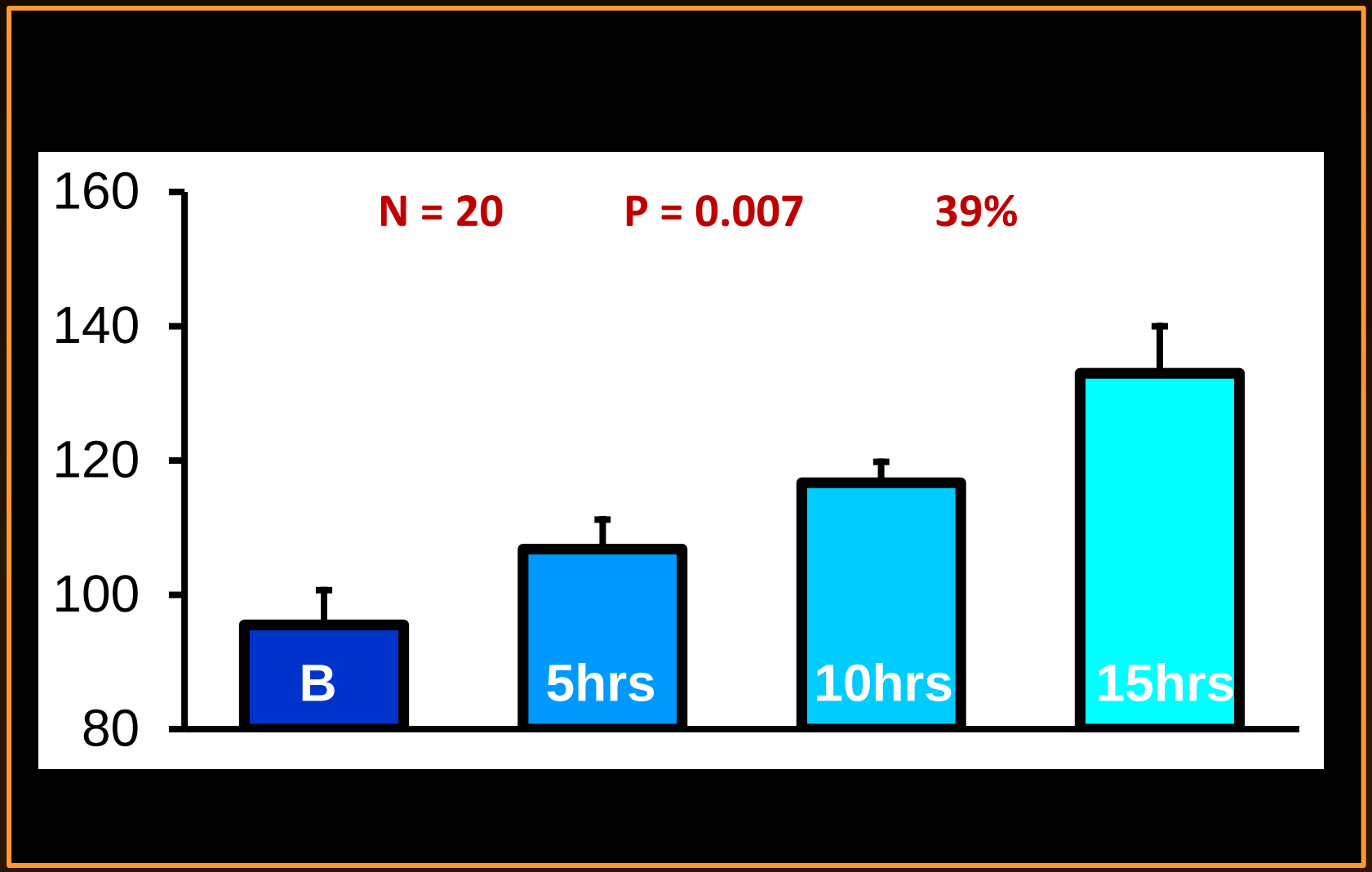
Normal reading speed (38 age-matched controls) = 302 wpm [80] SD



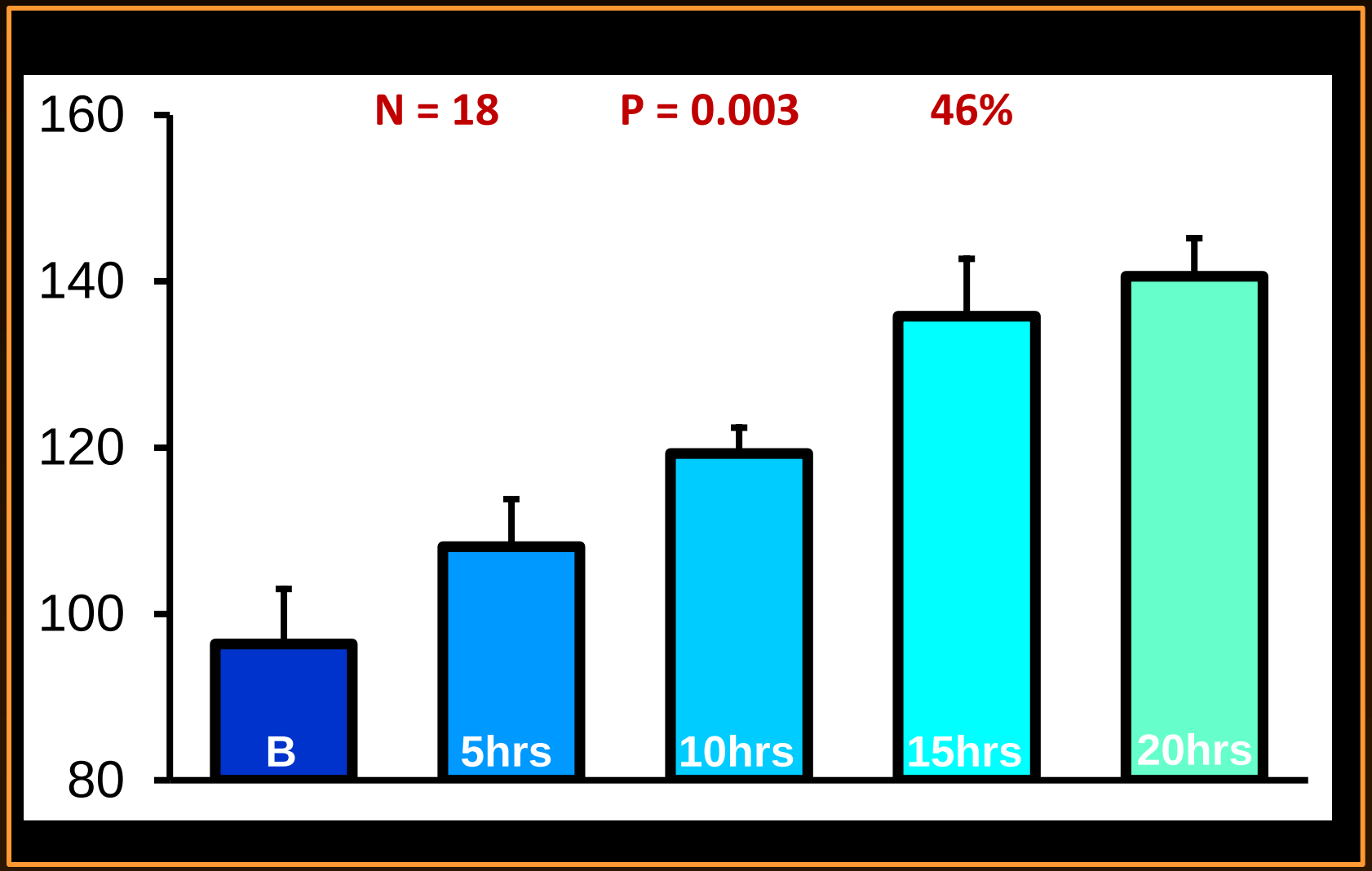
Results after 10 hours of therapy



Results after 15 hours of therapy



Results after 20 hours of therapy



Second analysis: with controls

All new data (exclude all previous RH subjects). Compare RHA with LHA and controls
Who are the controls? No hemianopia, reading speed above 40 wpm.

201 > 5 Hrs therapy

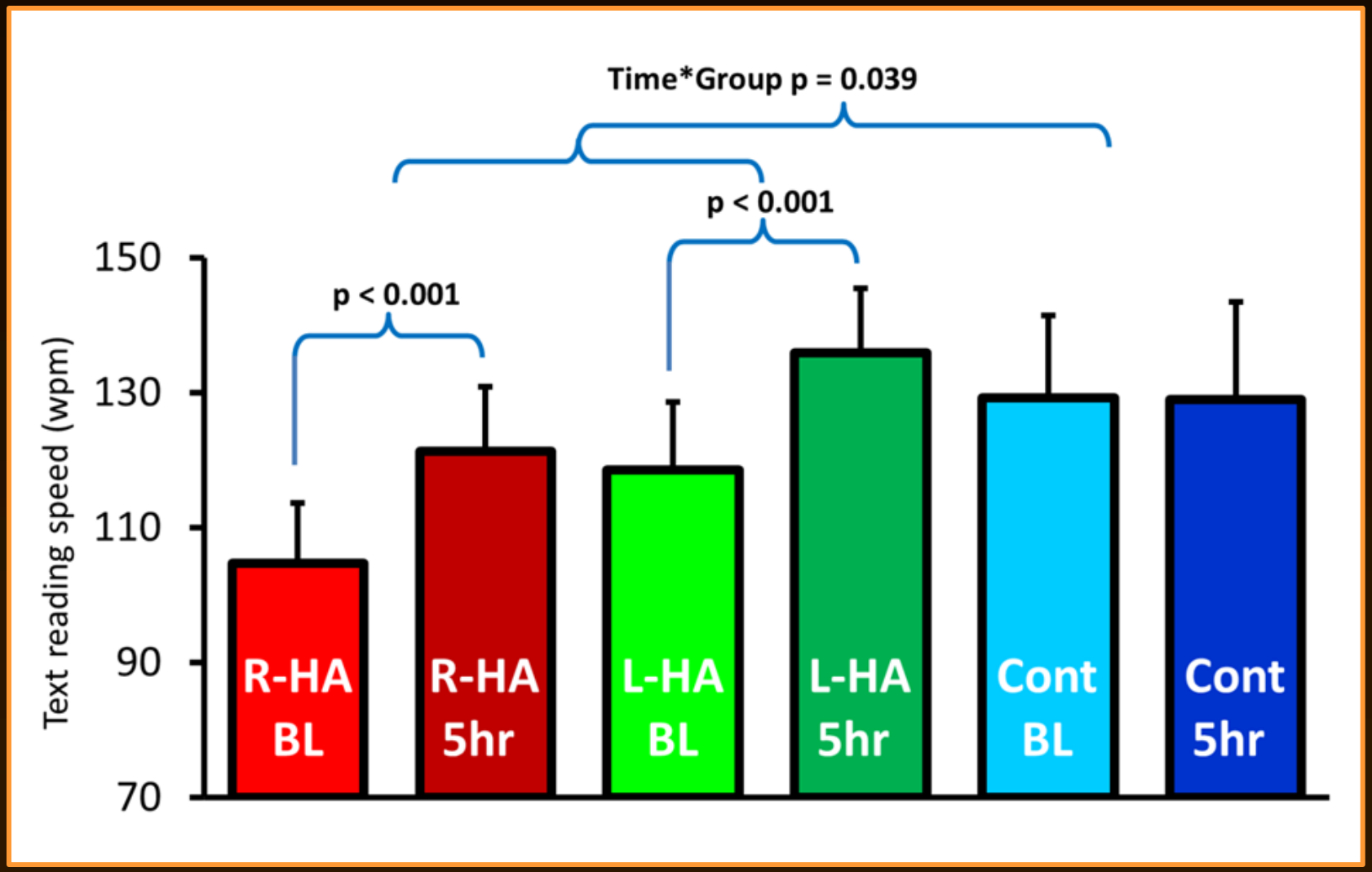
Reject 96
Too slow = 60 (almost all RHH)
Bilateral HH = 36

105
RHA = 47
LHA = 36
Controls = 22

Analysis

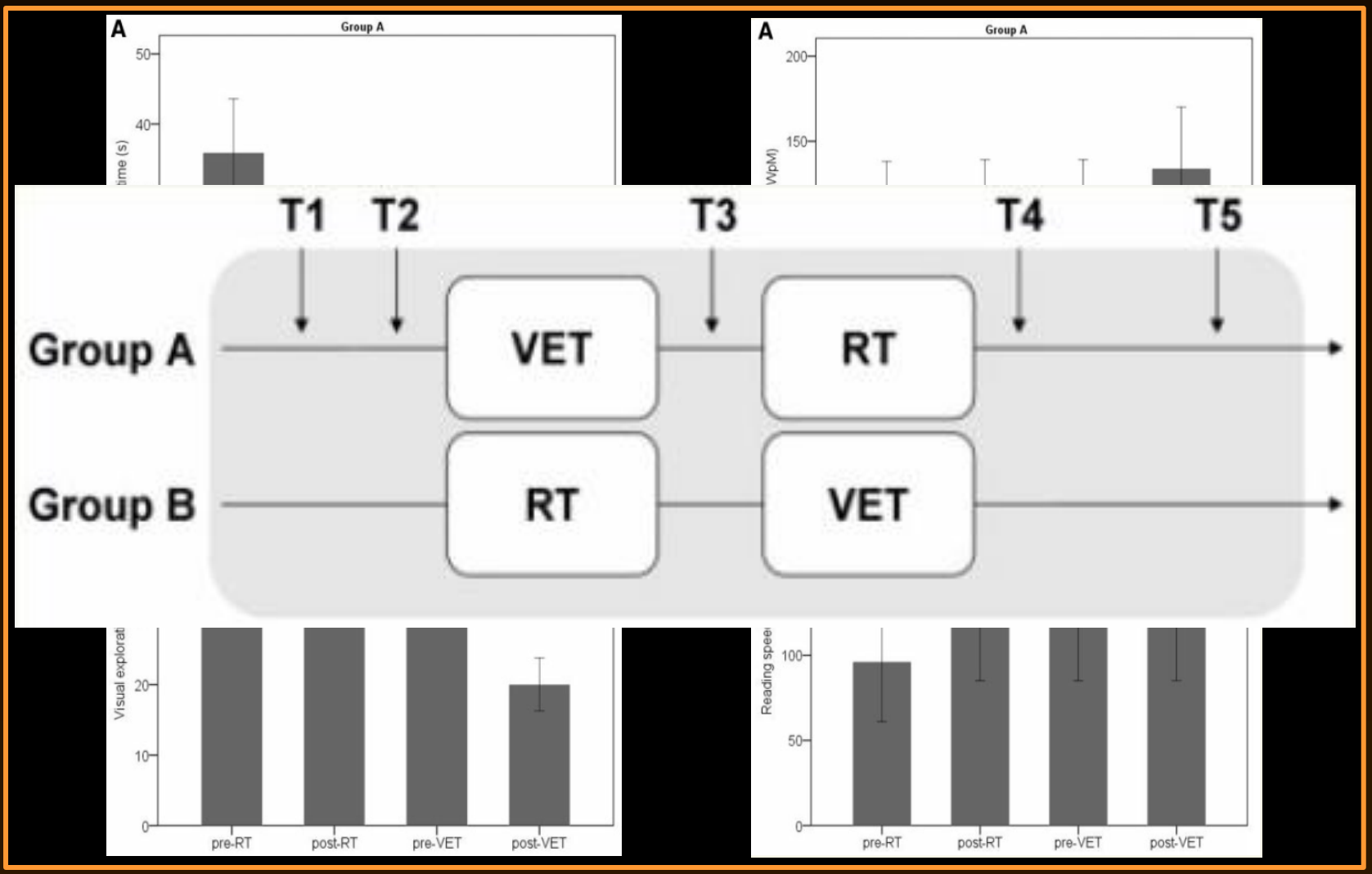
Woodhead et al. *BMJ Innovations* 2015

Results after 5 hours of therapy



Woodhead et al. *BMJ Innovations* 2015

EM therapy is very task-specific



Schuett *Brain* 2012

EM therapy works for old and young

Research report

Does age matter? Age and rehabilitation of visual field disorders after brain injury

Susanne Schuett [a,b,*] *and Josef Zihl* [c,d]

Table 1 – Demographic and clinical details and behavioural measurements for the younger and older treatment groups [mean (SD, range)]. Statistical comparisons were made between treatment groups; *p*-values for two-tailed independent t-tests are given.

	Younger patients ($n = 19$)	Older patients ($n = 19$)	
Age (years)	27.8 (4.3, 20–34)	77.2 (4.4, 70–84)	$p < .001$
Sex			
Female	10 (52.6%)	5 (26.3%)	
Male	9 (47.4%)	14 (73.7%)	
Education (years)	13.5 (2.9, 8–18)	11.5 (3.9, 6–18)	$p = .075$
Occupation[a]			
Lower-skilled	14 (73.7%)	13 (68.4%)	
Higher-skilled	5 (26.3%)	6 (31.6%)	
Time since lesion (weeks)	19.1 (13.5, 6–51)	16.2 (13.3, 4–56)	$p = .510$
Aetiology			

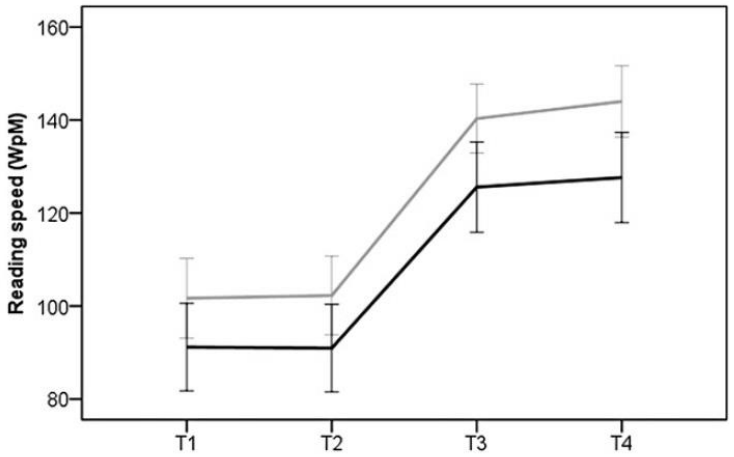


Fig. 1 – Mean reading performance (in wpm) in younger patients (grey line) and older patients (black line). T1: at initial assessment [0 weeks] T2: before treatment [6 weeks] T3: after treatment [2 weeks] T4: at follow-up [11 weeks]. Vertical bars indicate ±1SE.

Arabic version of Read-Right

Sharifa AlRagam
MSc Speech-Language Pathologist
MSc Cognitive Neuroscience
PhD student at ICN/UCL

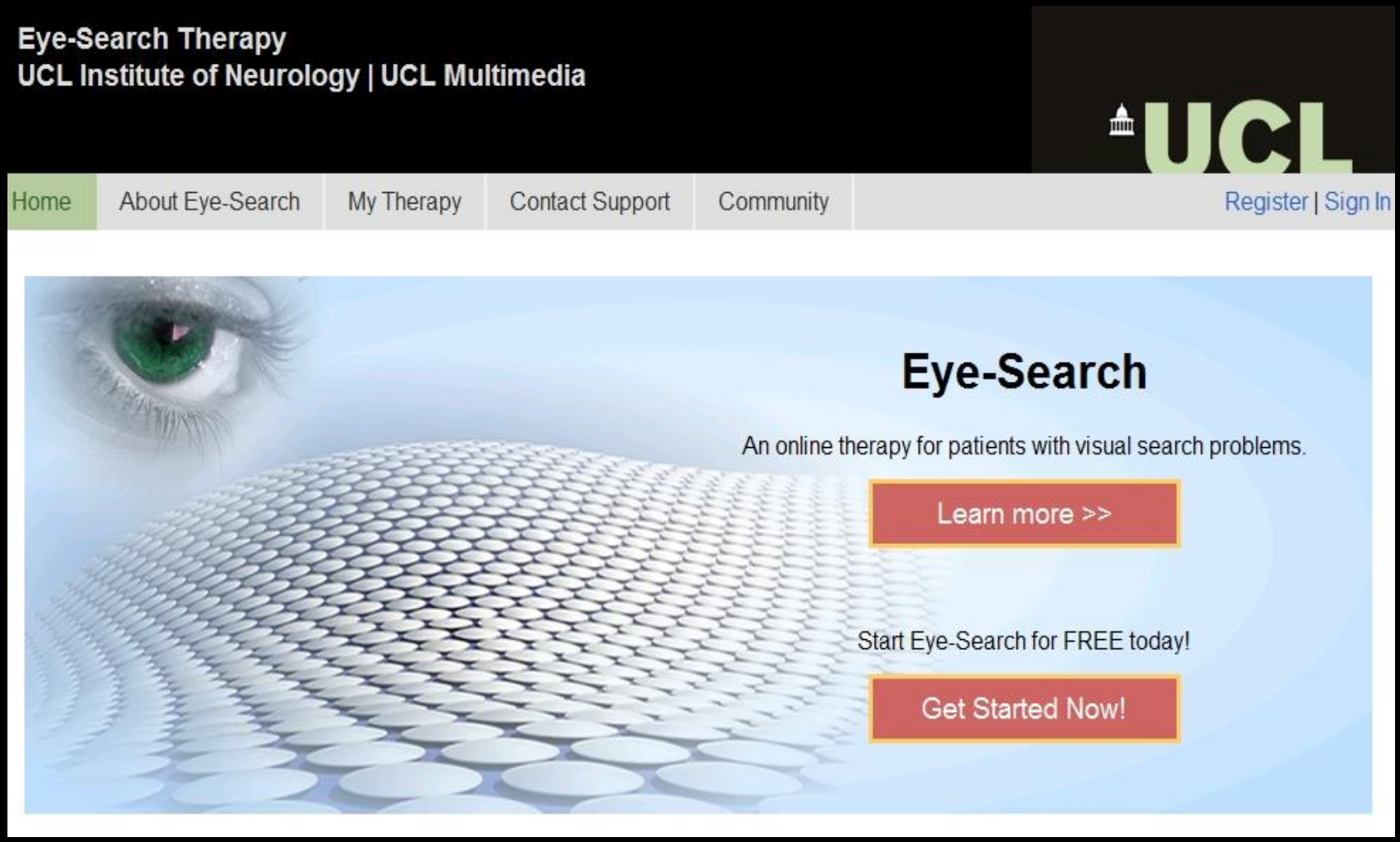
اقرأ لتكون

Ikrʌ lɪtəkʊ:n

"read to become"

300 million Arabic readers

Web app for visual search

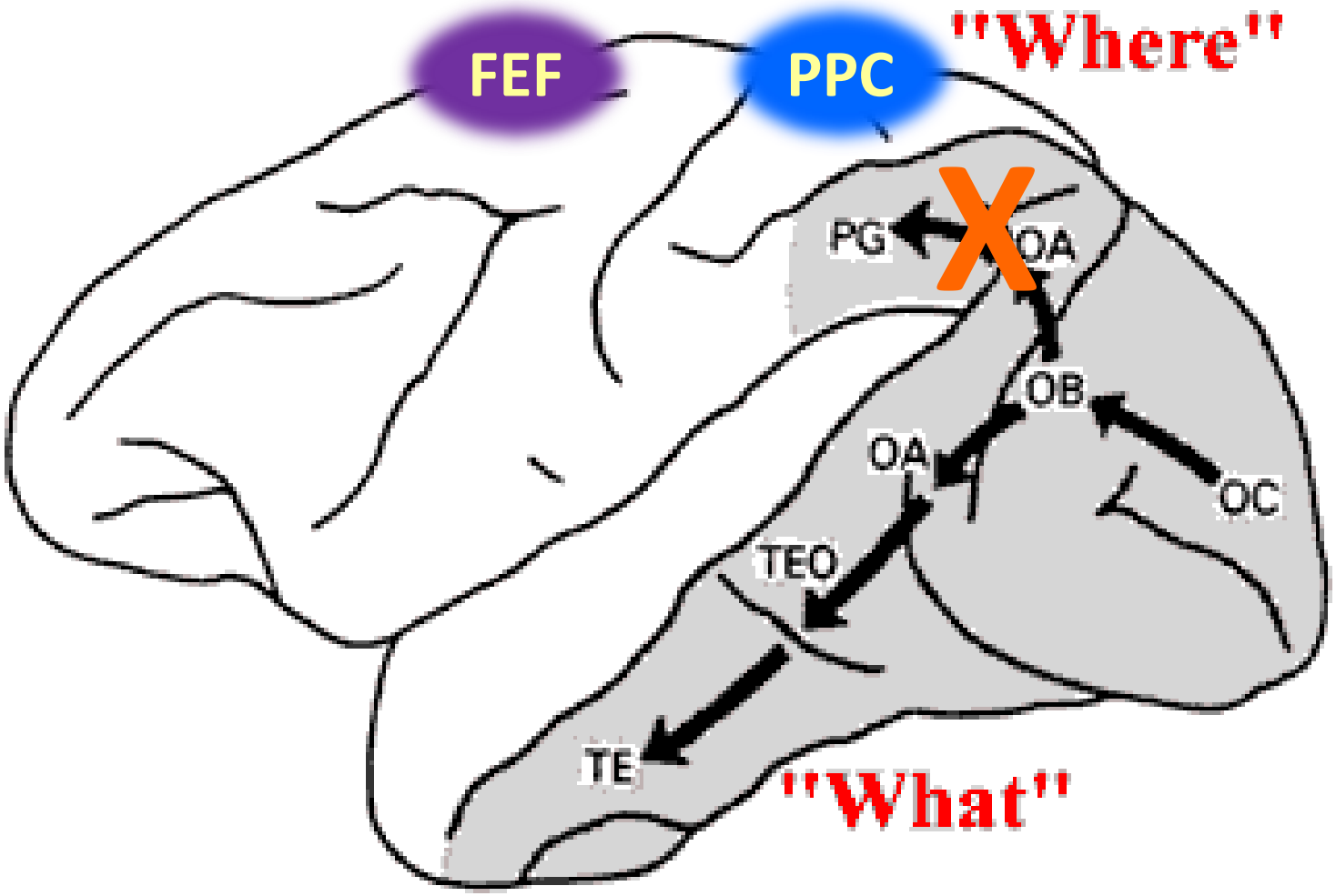


www.eyesearch.ucl.ac.uk

Summary

1. Hemianopic alexia causes inefficient reading eye movements because the dorsal stream is robbed of important visual information
2. Rehabilitation $\rightarrow$ change in reading behaviour for new texts
3. Different types of EM therapy but all are task-specific
4. Assessment, therapy and outcome measures can be delivered via a web-app

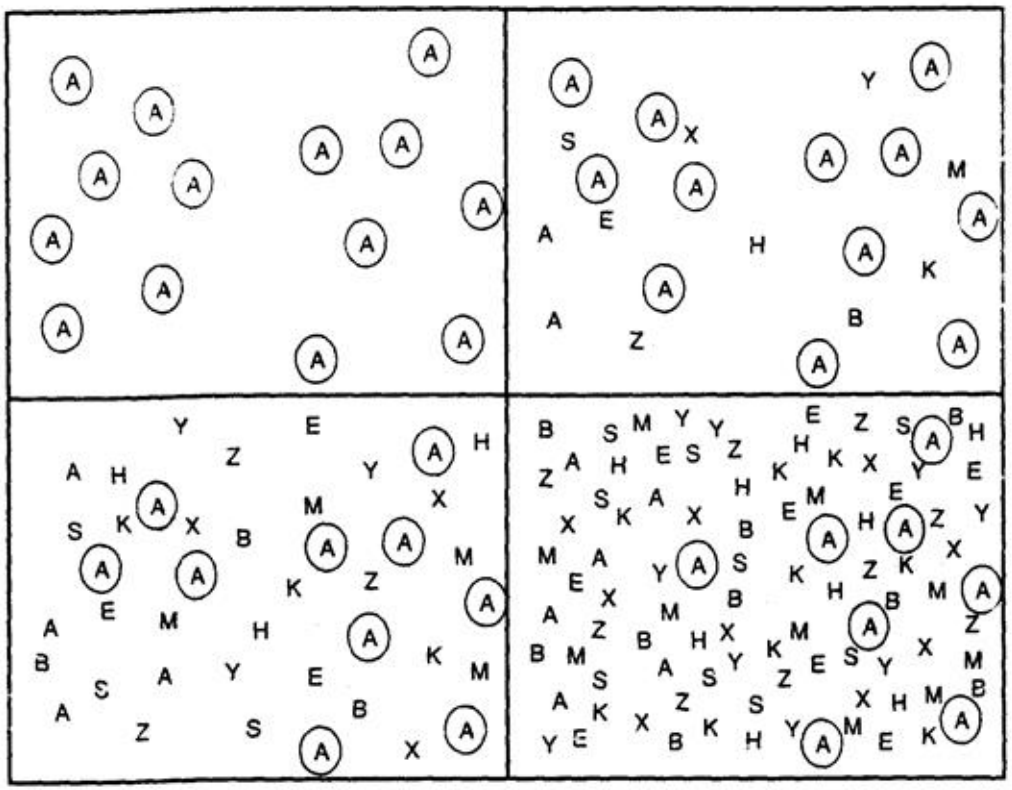
Neglect Dyslexia: affects “where”



Spatial neglect occurs in about 25–30% of all stroke-affected individuals (an estimated 3–5 million a year, worldwide). It is a complex syndrome characterized by a failure to attend to, look at and respond to stimuli (objects, food, people) located on the side of space or of the body opposite to the side affected by a brain lesion… Over 90% of individuals with spatial neglect have right hemisphere injury and neglect of the left side of space or body

Corbetta *Nat Neurosci* 2005

Greater competition for selection leads to more neglect



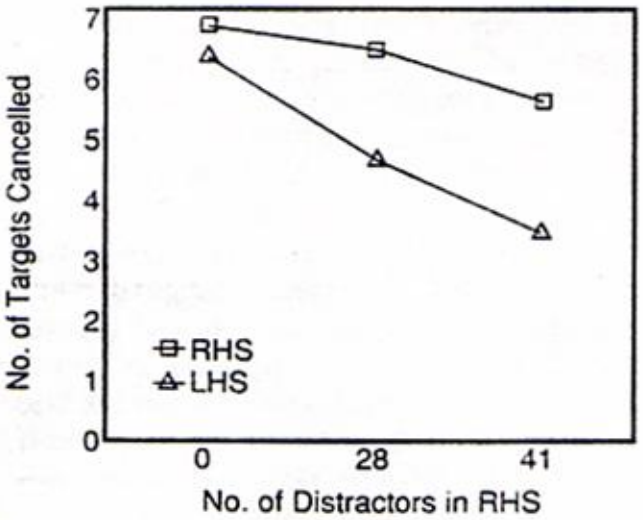
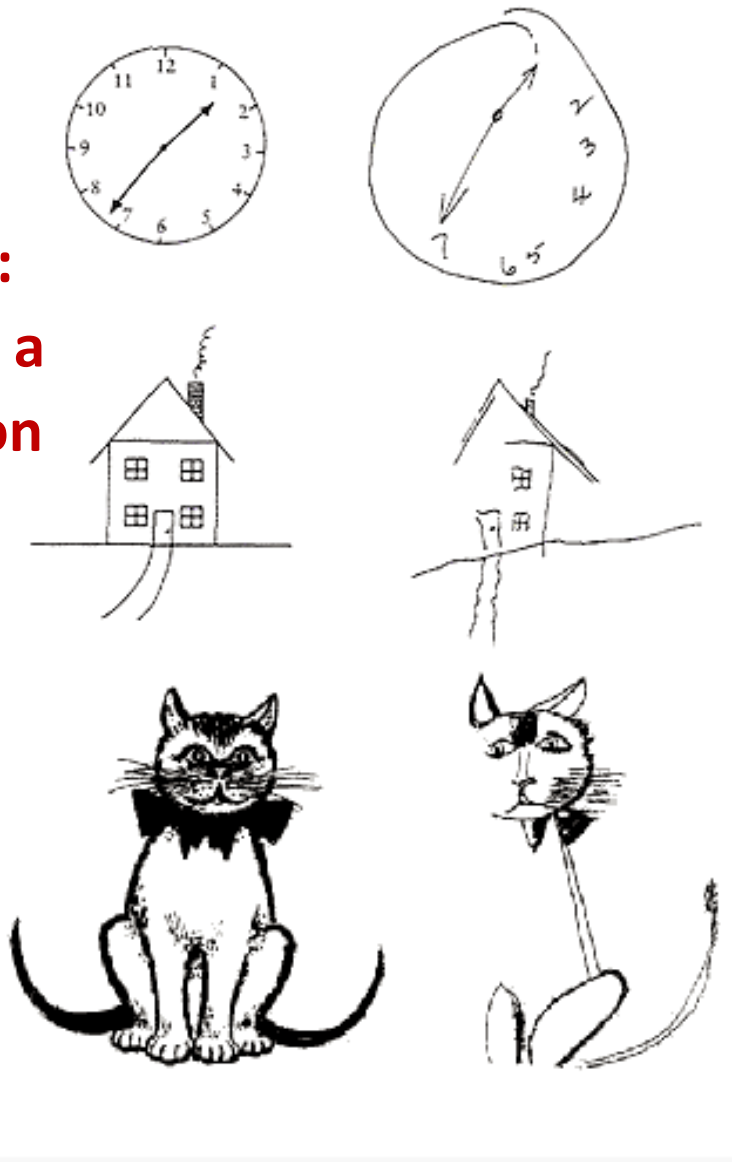


Fig 3.—Mean number of targets canceled at each distractor level for the left (LHS) and right (RHS) hemispace when distractors were presented only in RHS.

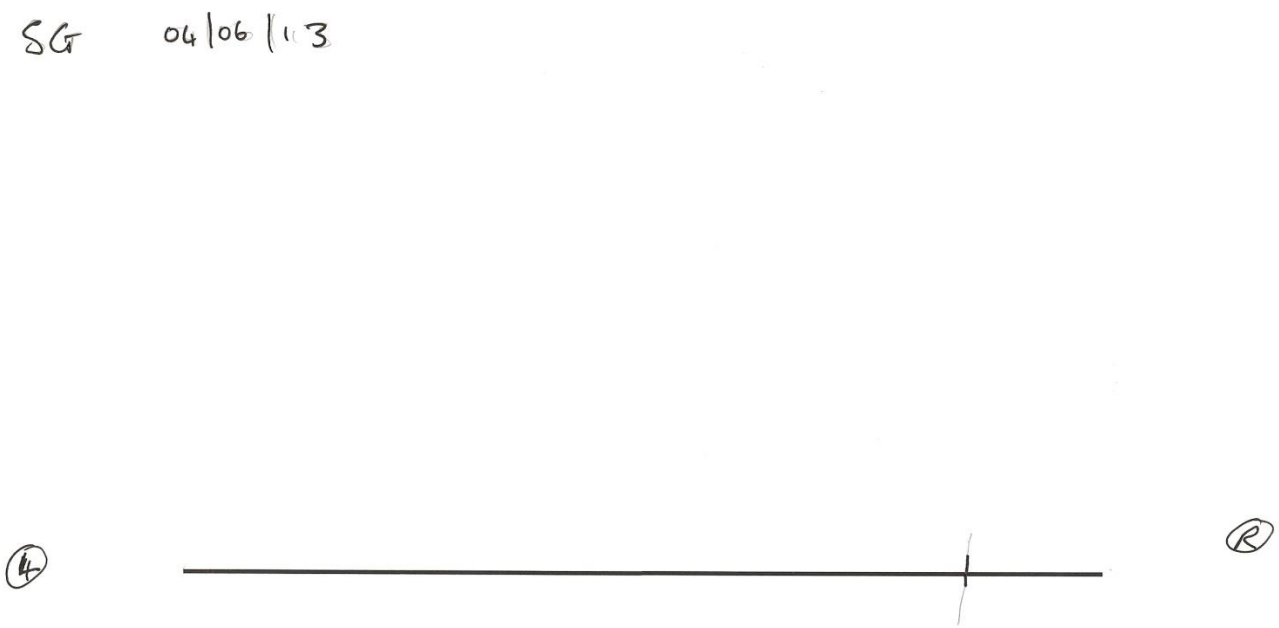
Kaplan *JAMA Neurology* 1991

What happens when the ‘where’ pathway goes wrong?

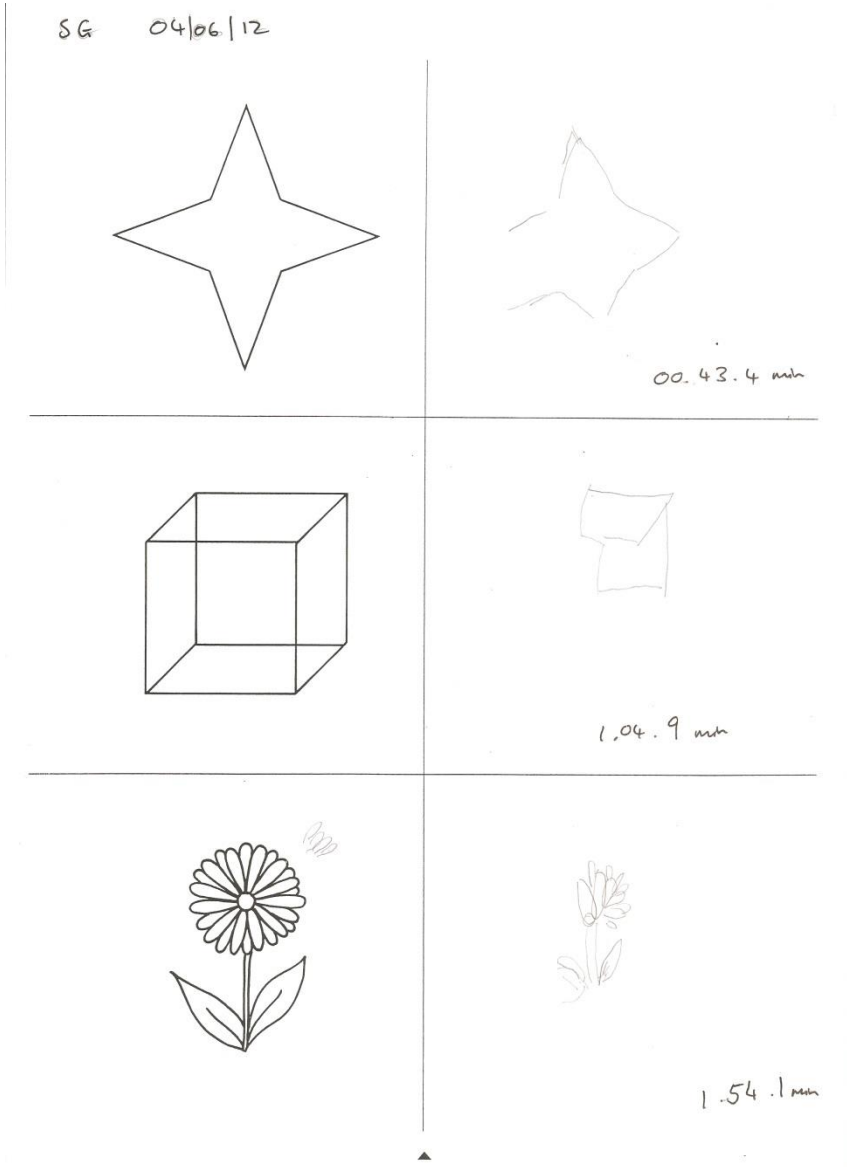
Unilateral neglect:
Usually caused by a right parietal lesion



Behavioural Inattention Test (BIT): line bisection

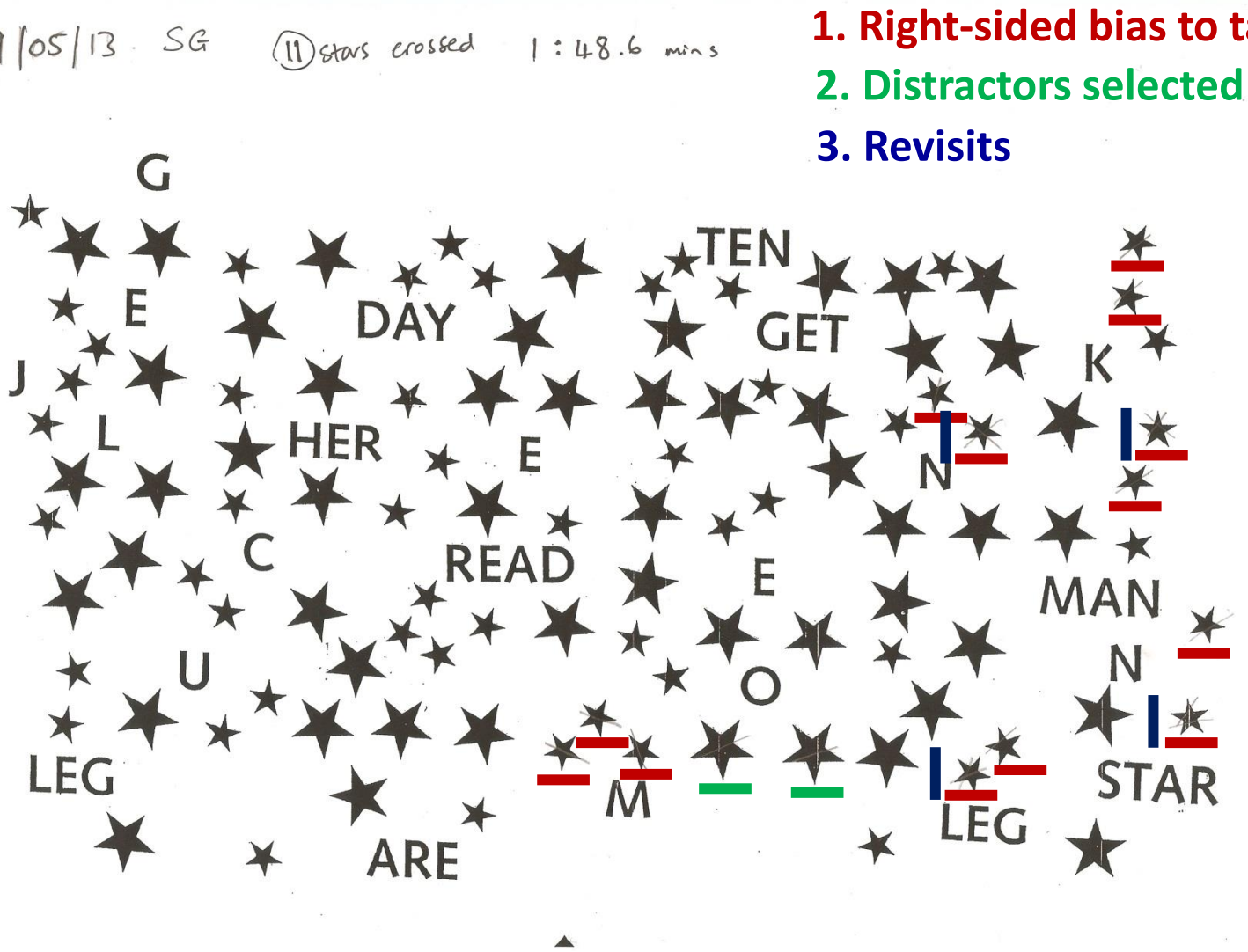


Behavioural Inattention Test (BIT): figure & shape copying

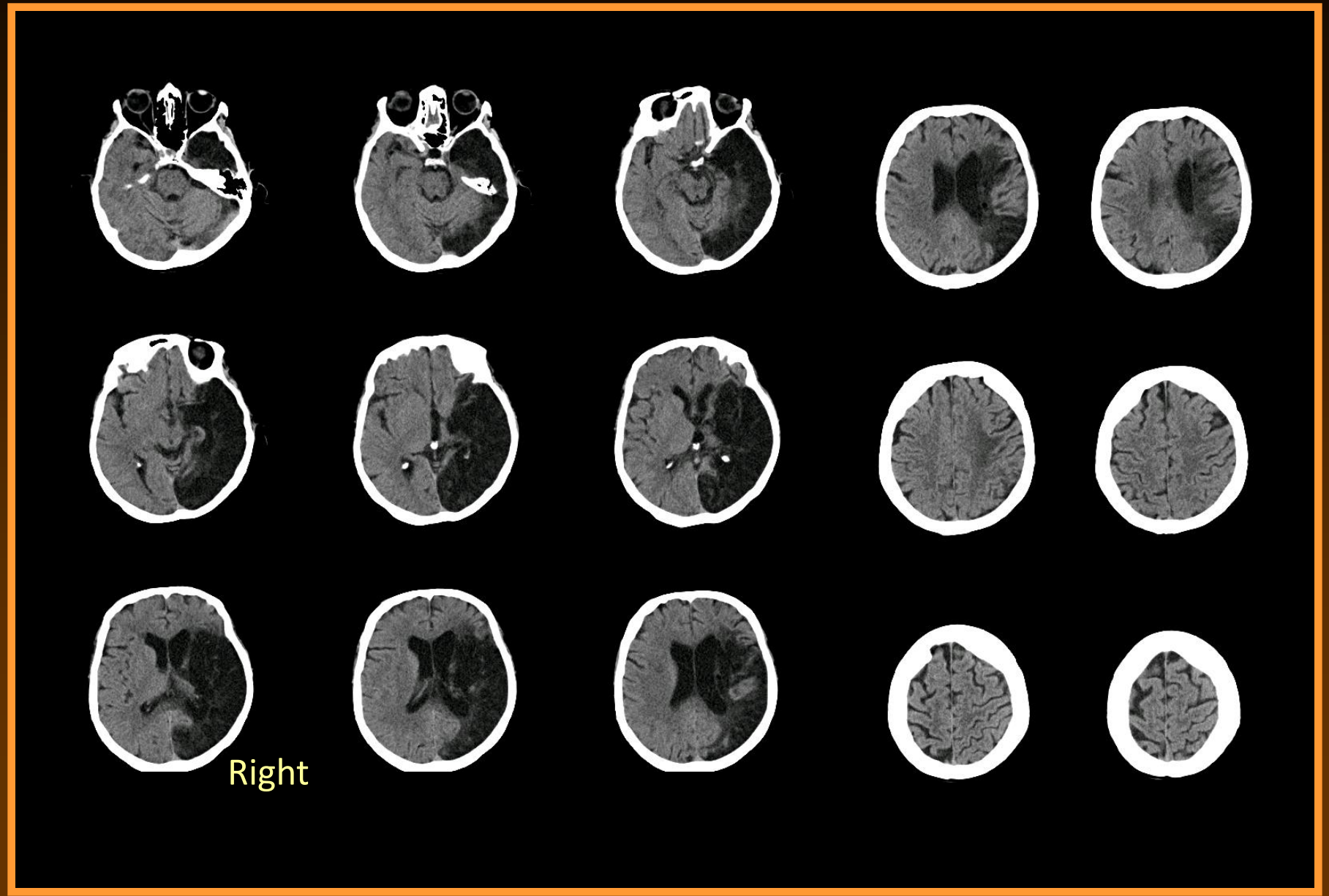


1. **Poorly formed**
2. **Slow**
3. **Spatial bias to errors**

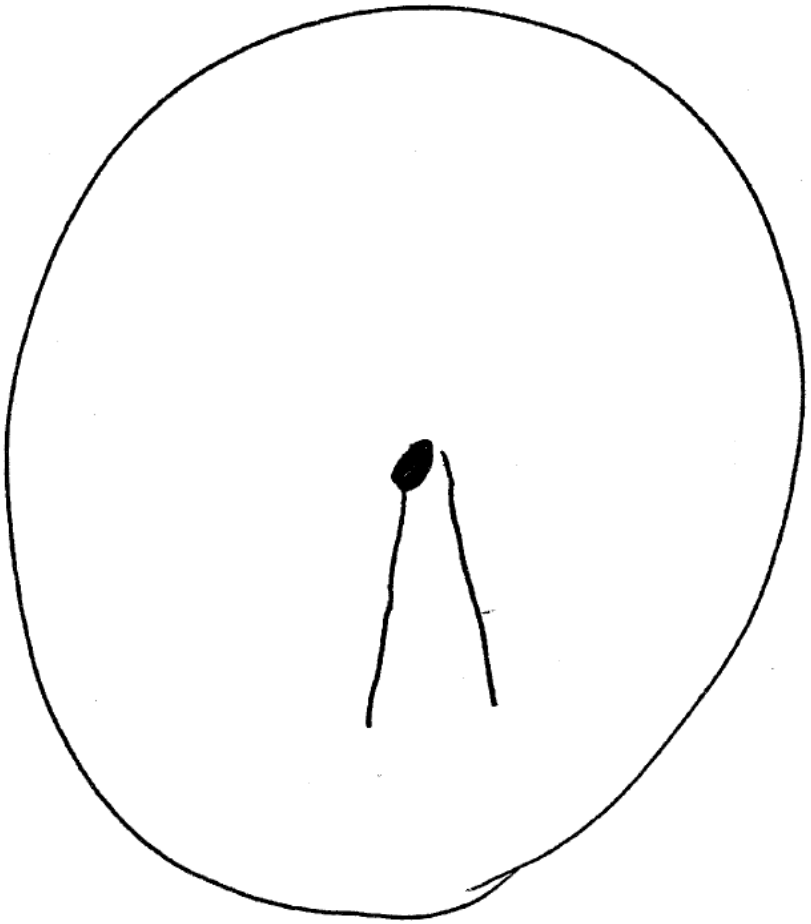
Behavioural Inattention Test (BIT): star cancellation

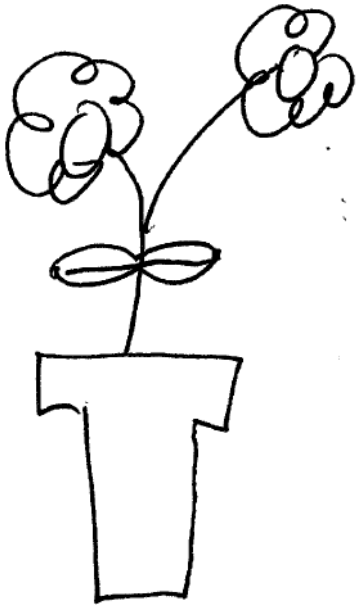


CT scan

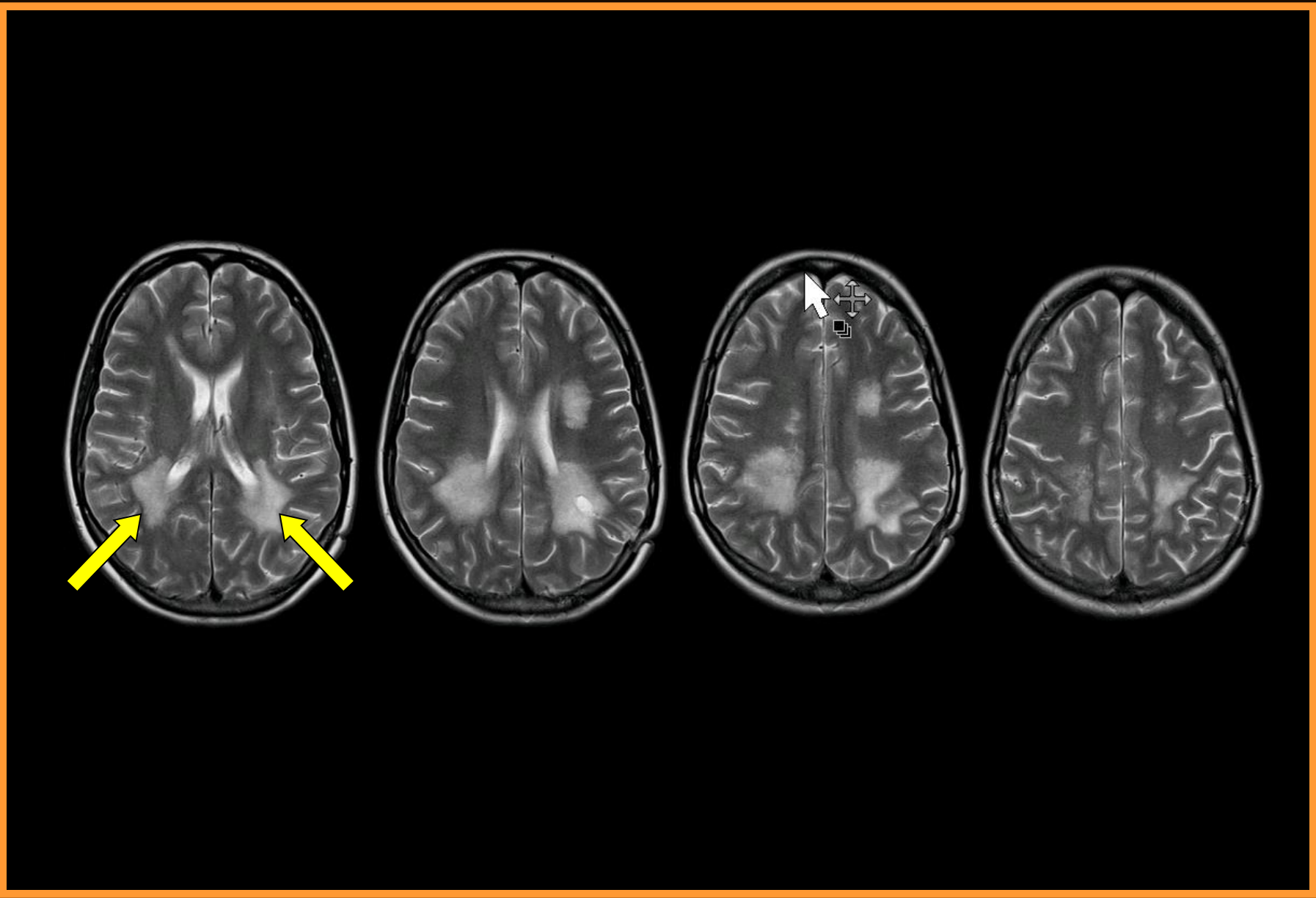


What happens when the ‘where’ pathway goes wrong?

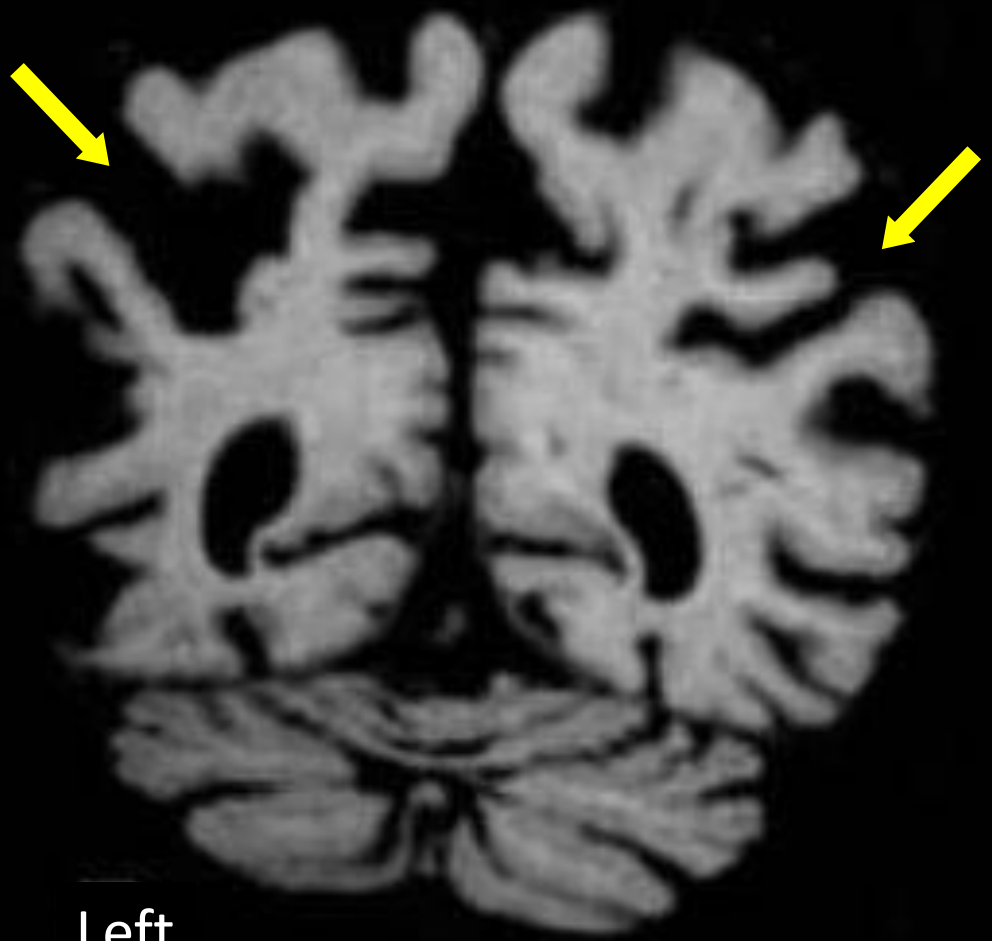




Biparietal damage: dorsal simultanagnosia



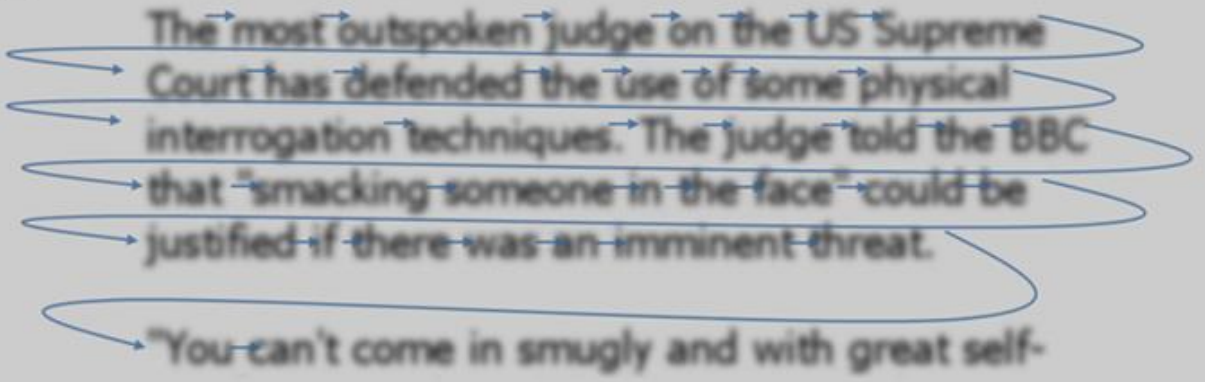
Patient with Posterior Cortical Atrophy: Damage to the dorsal “where” stream



Left

Posterior Cortical Atrophy: getting lost on the page

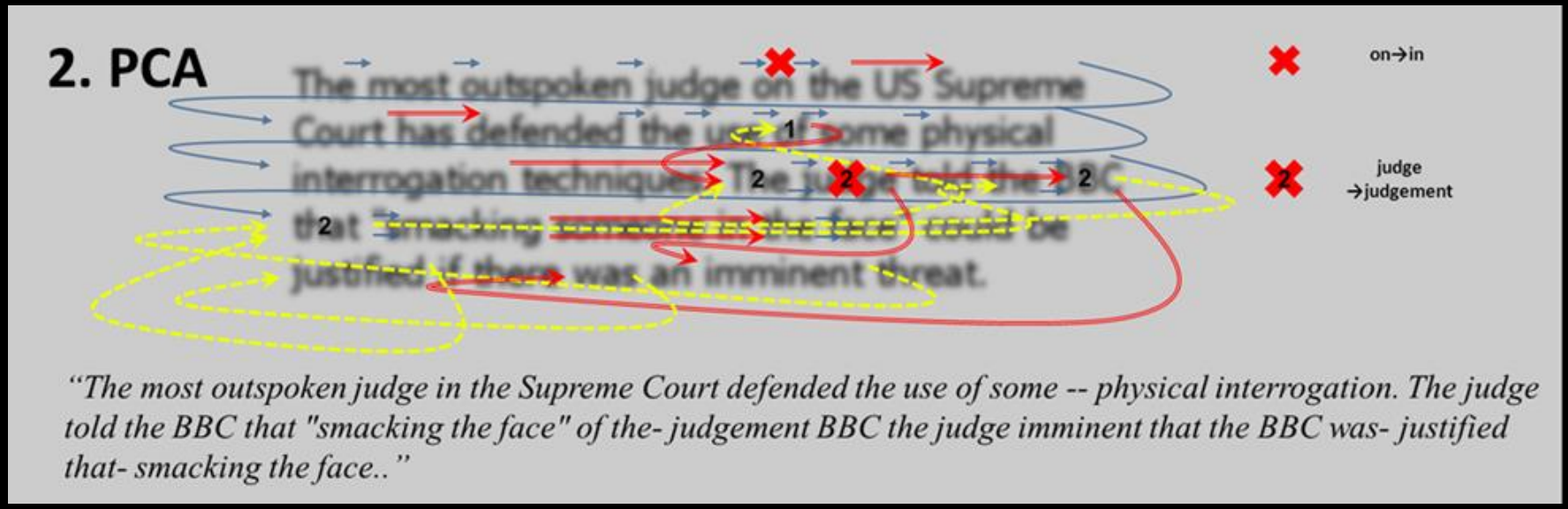
1. tAD



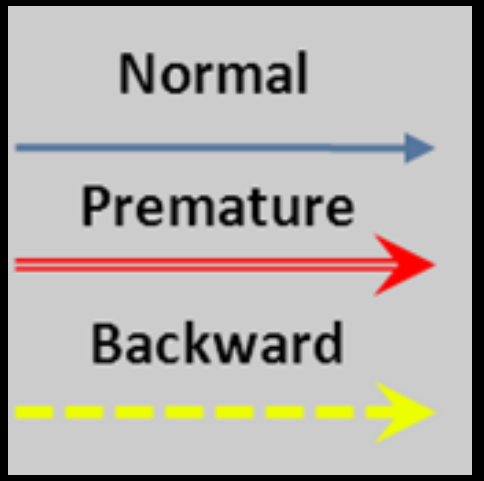
"The most outspoken judge on the US Supreme Court has defended the use of some physical interrogation techniques. The judge told the BBC that "smacking someone in the face" could be justified if there was an imminent threat. You can't…"

tAD = typical Alzheimer's Disease patient, control

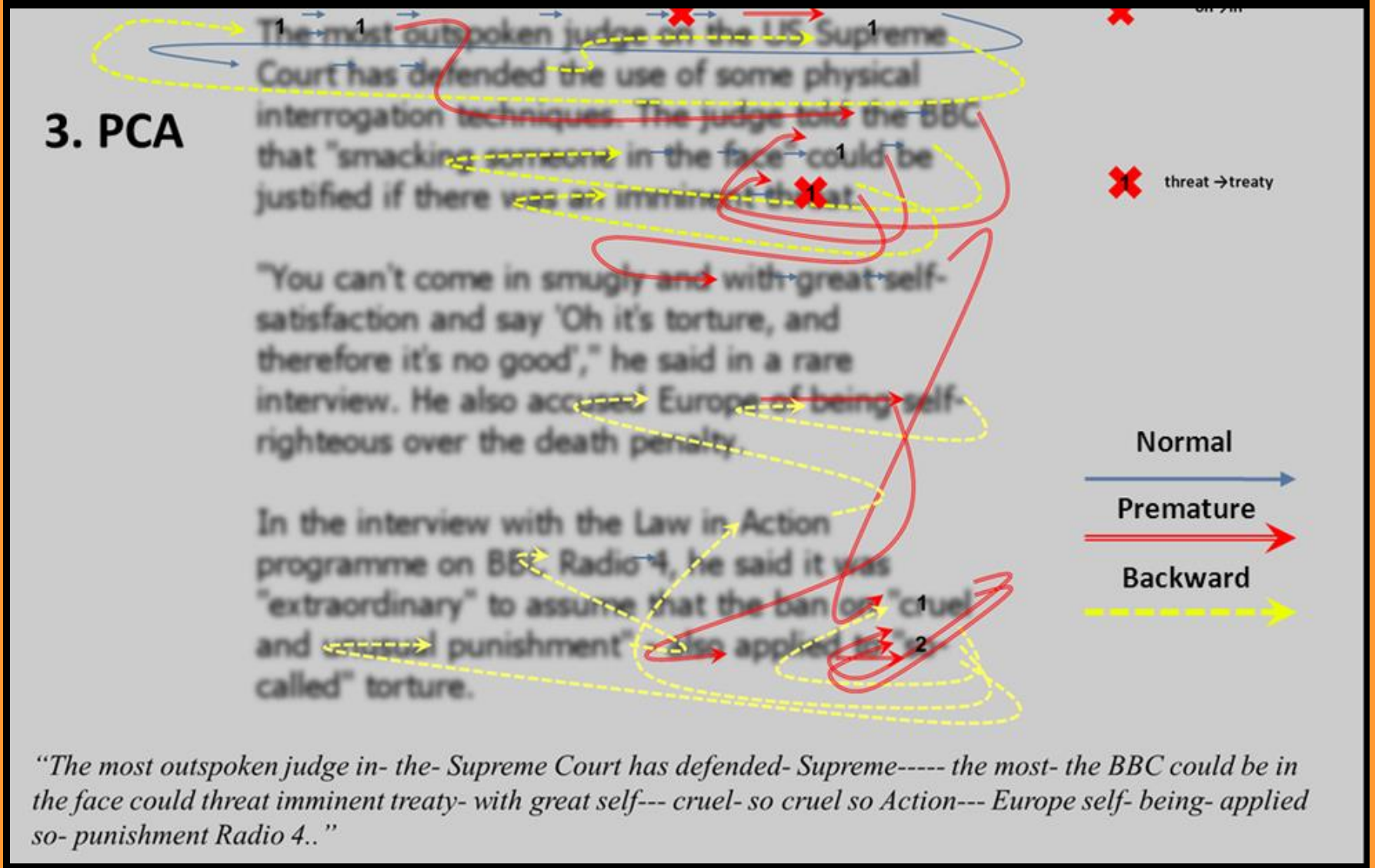
Posterior Cortical Atrophy: getting lost on the page



"The most outspoken judge in the Supreme Court defended the use of some -- physical interrogation. The judge told the BBC that "smacking the face" of the- judgement BBC the judge imminent that the BBC was- justified that- smacking the face.."

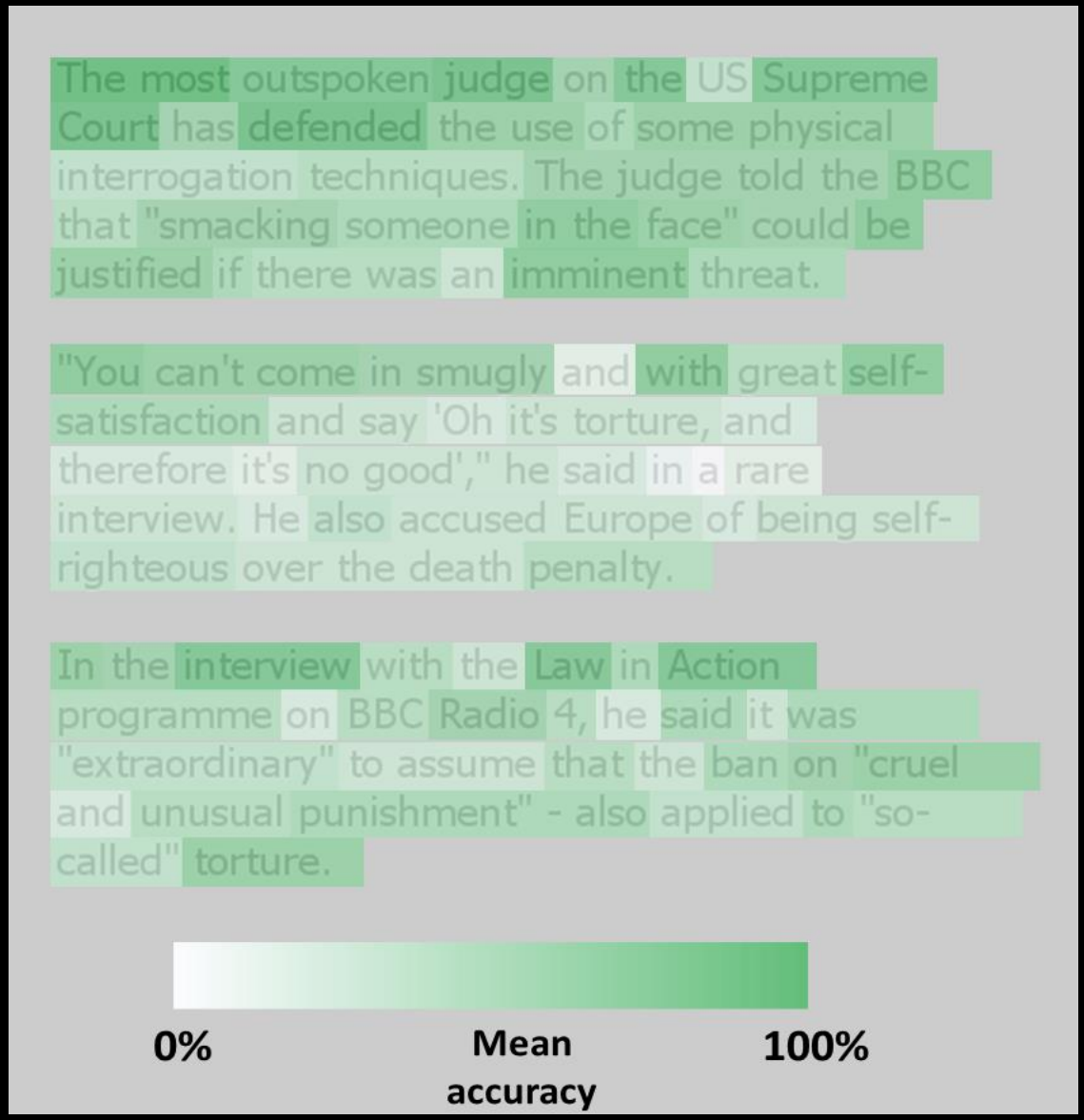


Posterior Cortical Atrophy: getting lost on the page

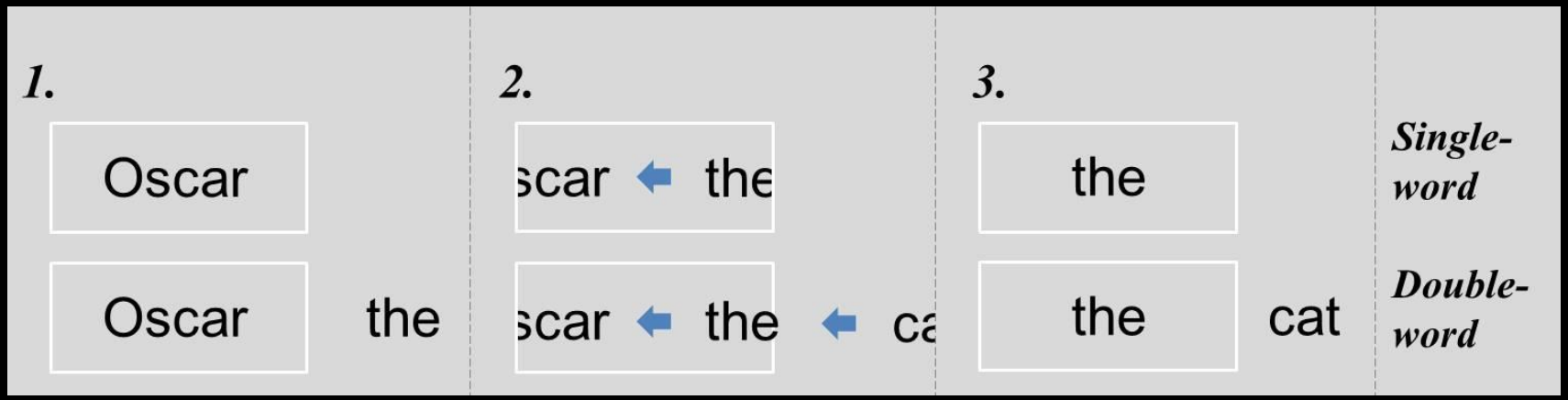


"The most outspoken judge in- the- Supreme Court has defended- Supreme----- the most- the BBC could be in the face could threat imminent treaty- with great self--- cruel- so cruel so Action--- Europe self- being- applied so- punishment Radio 4.."

Posterior Cortical Atrophy: getting lost on the page

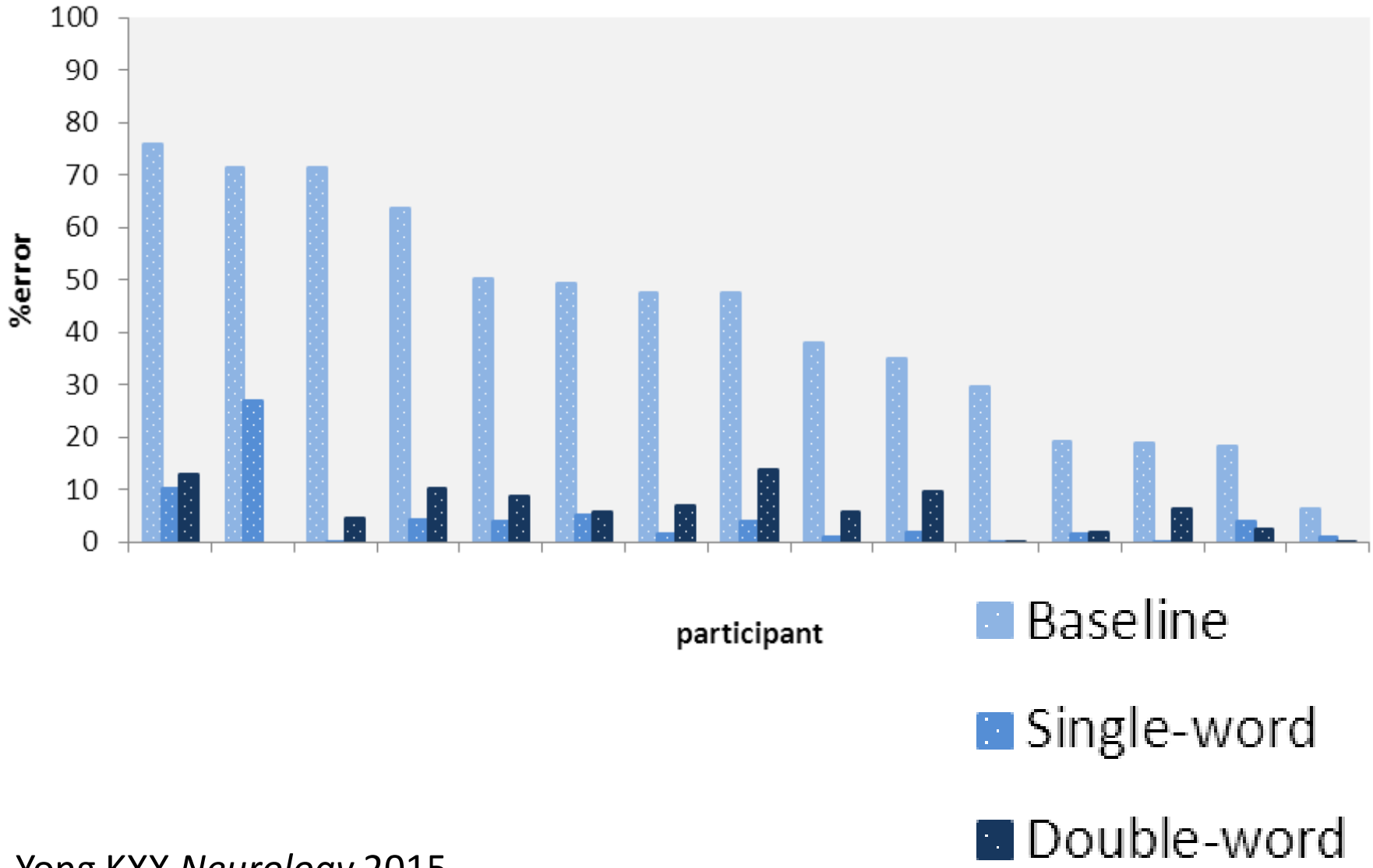


Posterior Cortical Atrophy: therapy



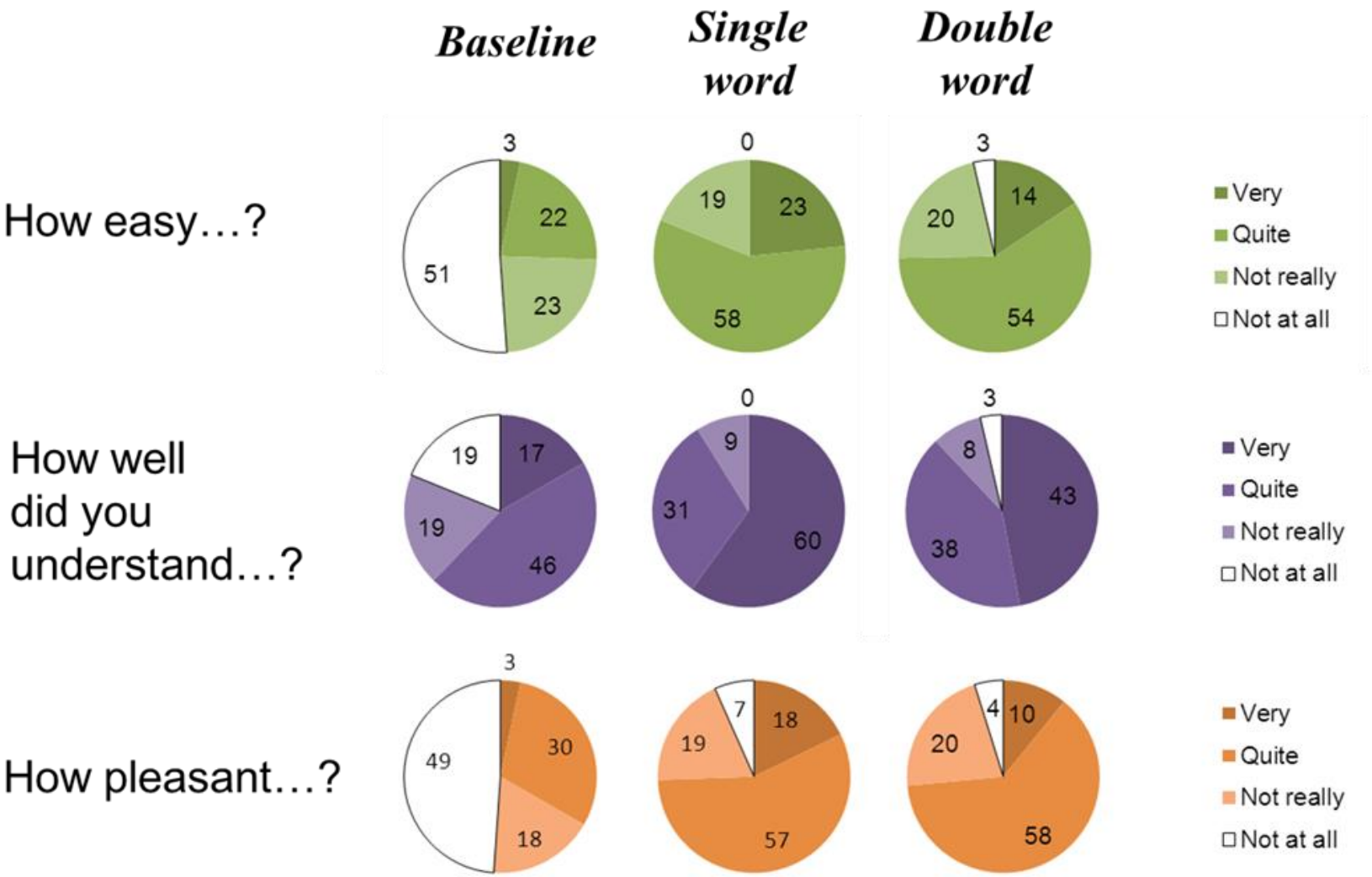
Posterior Cortical Atrophy: therapy video

PCA aid benefit: accuracy



Yong KXX *Neurology* 2015

PCA aid benefit: patient report



Yong KXX *Neurology* 2015

Reading aid for PCA: in development

Reading aid for PCA: in development

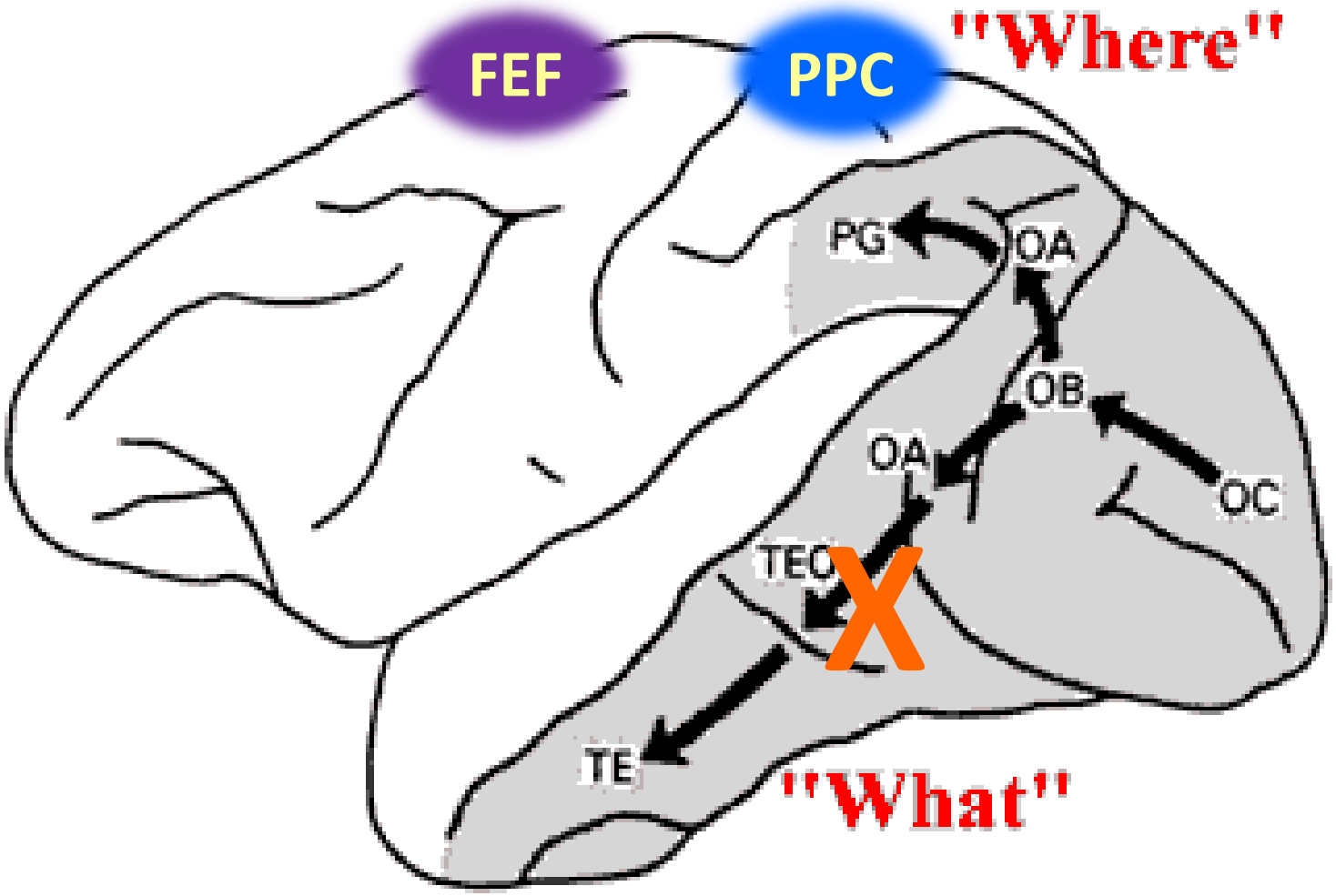
Summary

1. PCA disrupts the dorsal stream making the visuospatial challenge of text reading insurmountable
2. Aid $\rightarrow$ improves reading but only when text is streamed through the viewer

   (so this is not rehabilitation)
3. Working on a reading app for PCA

   (with lots of patient involvement)

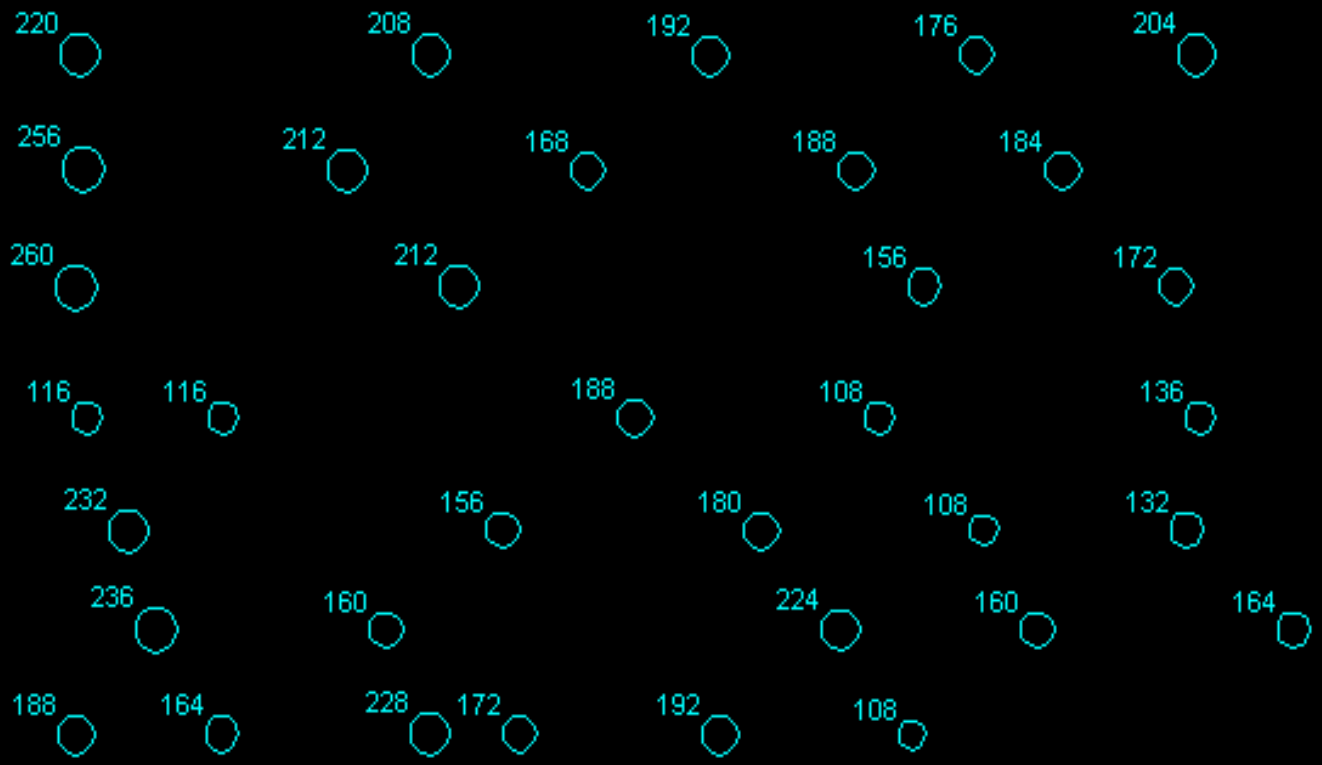
Word-form Alexia: stroke affects “what” pathway



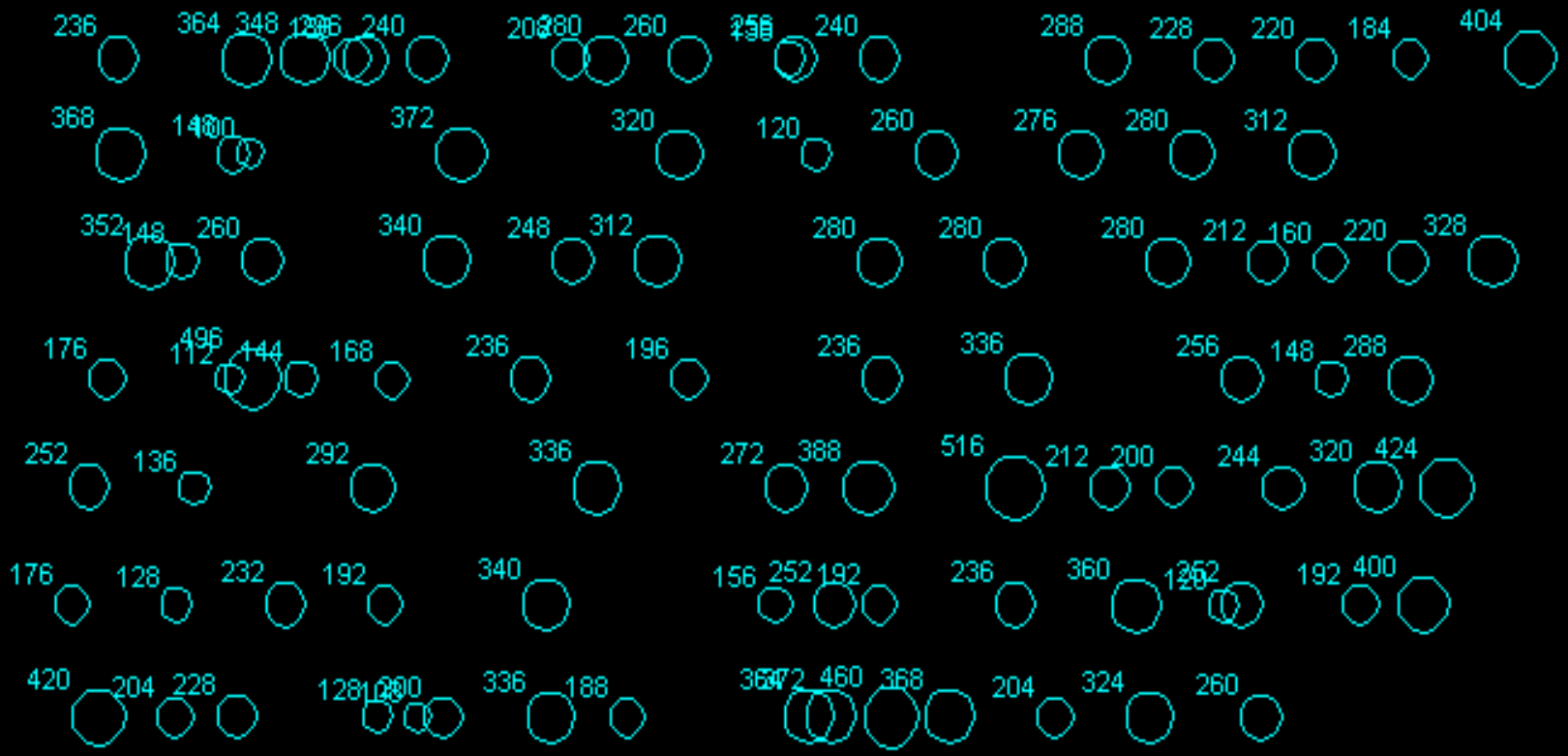
What is pure alexia?

- 20th century term synonymous with “Alexia without agraphia” or ‘peripheral’ alexia
- Means that general language functions (speaking, writing and speech comprehension) are normal
- Also come to mean that there is a category-specific visual impairment (words *only* affected)
- It is caused by a problem with ‘word form recognition’
- Area of brain damage causing pure alexia = “visual word-form area”
- Patients have a word-length effect
- Patients sometimes read “letter-by-letter”
- Letter processing (and perhaps number processing) are intact

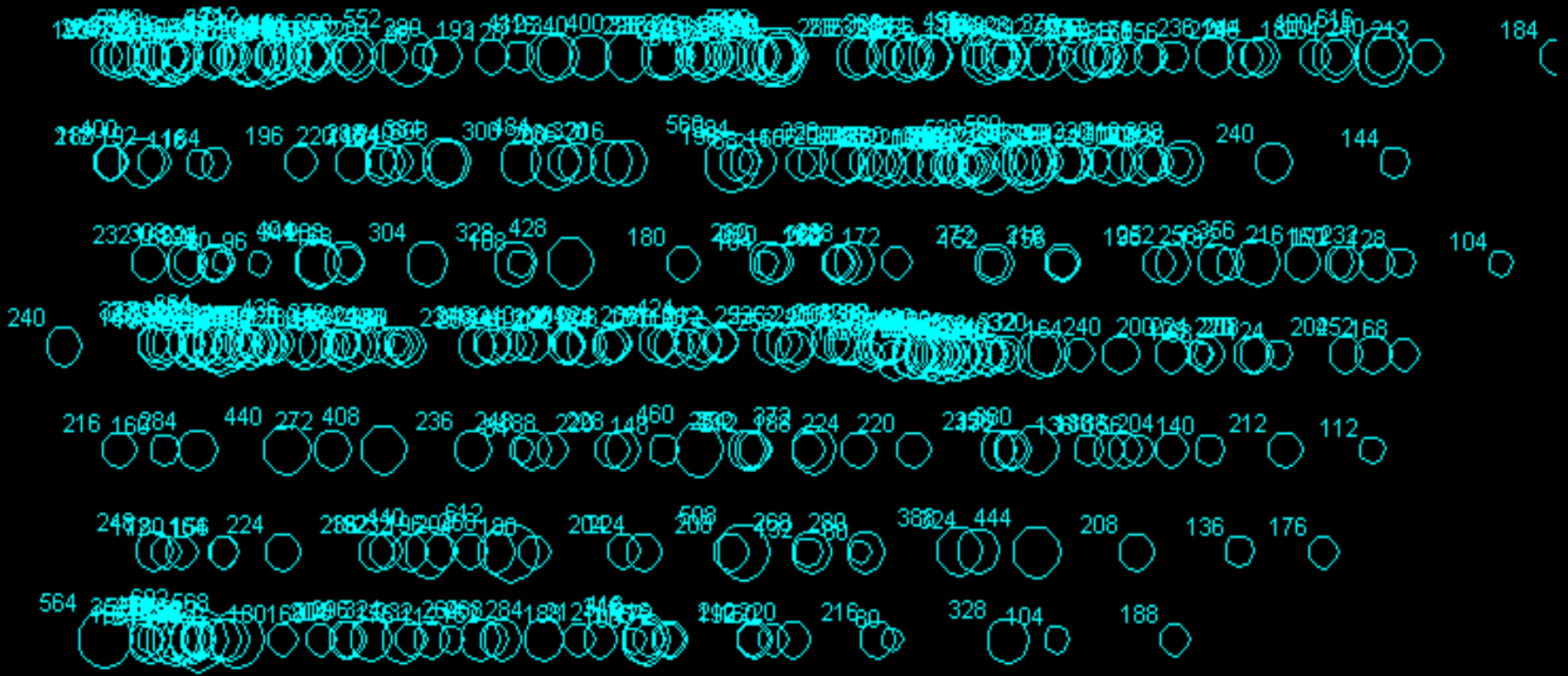
Passenger Paul Lynch stunned airport security staff when he proved his identity by showing them the cover of a Guinness Book of Records. Paul did not have any photo ID with him when he checked in at Stansted for a no-frills GO flight to Edinburgh.



Normal text reading fixations:
36 fixations 45 words, ratio = 0.8

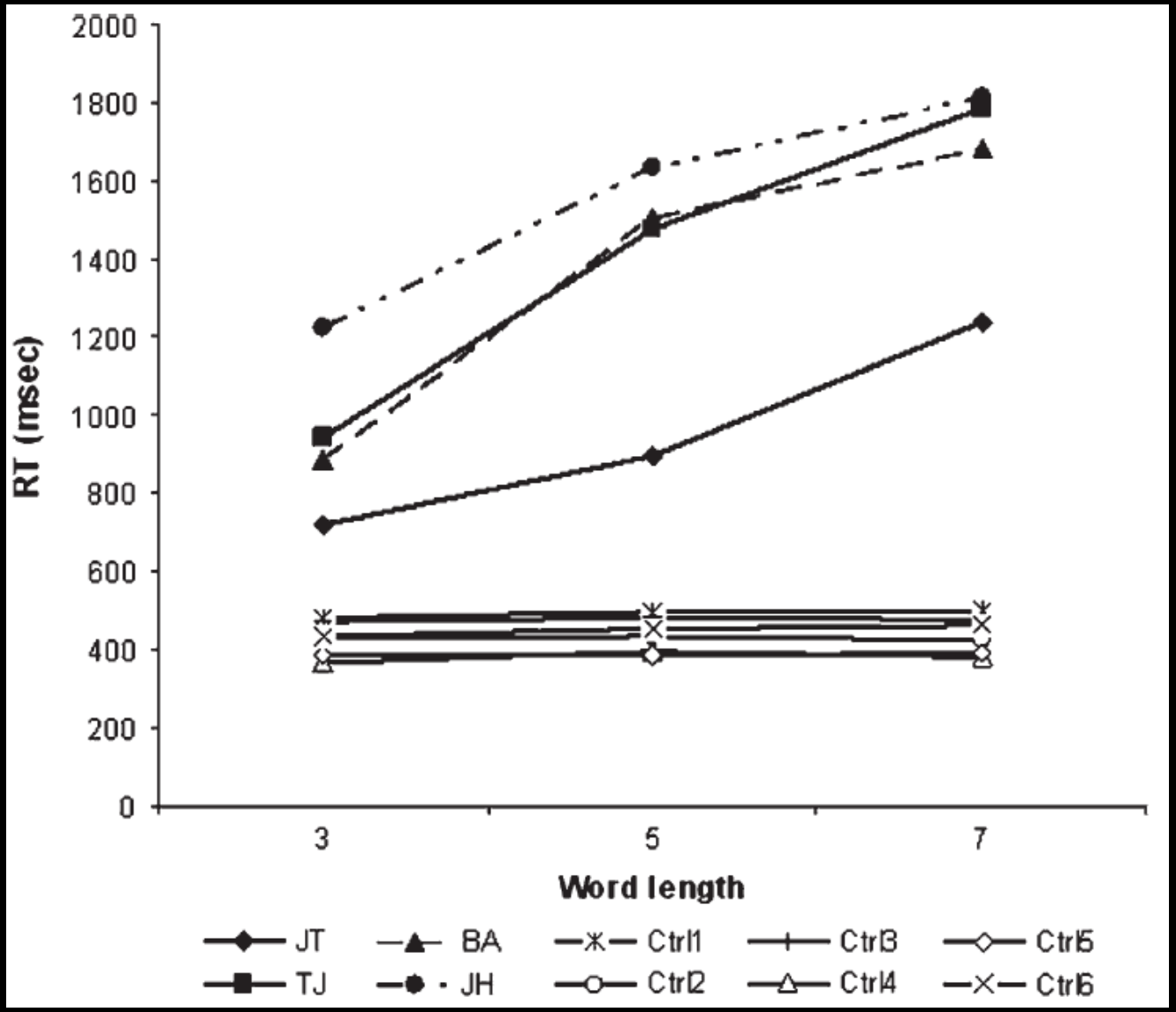


Hemianopic alexia text reading fixations:
93 fixations 45 words, ratio = 2.1

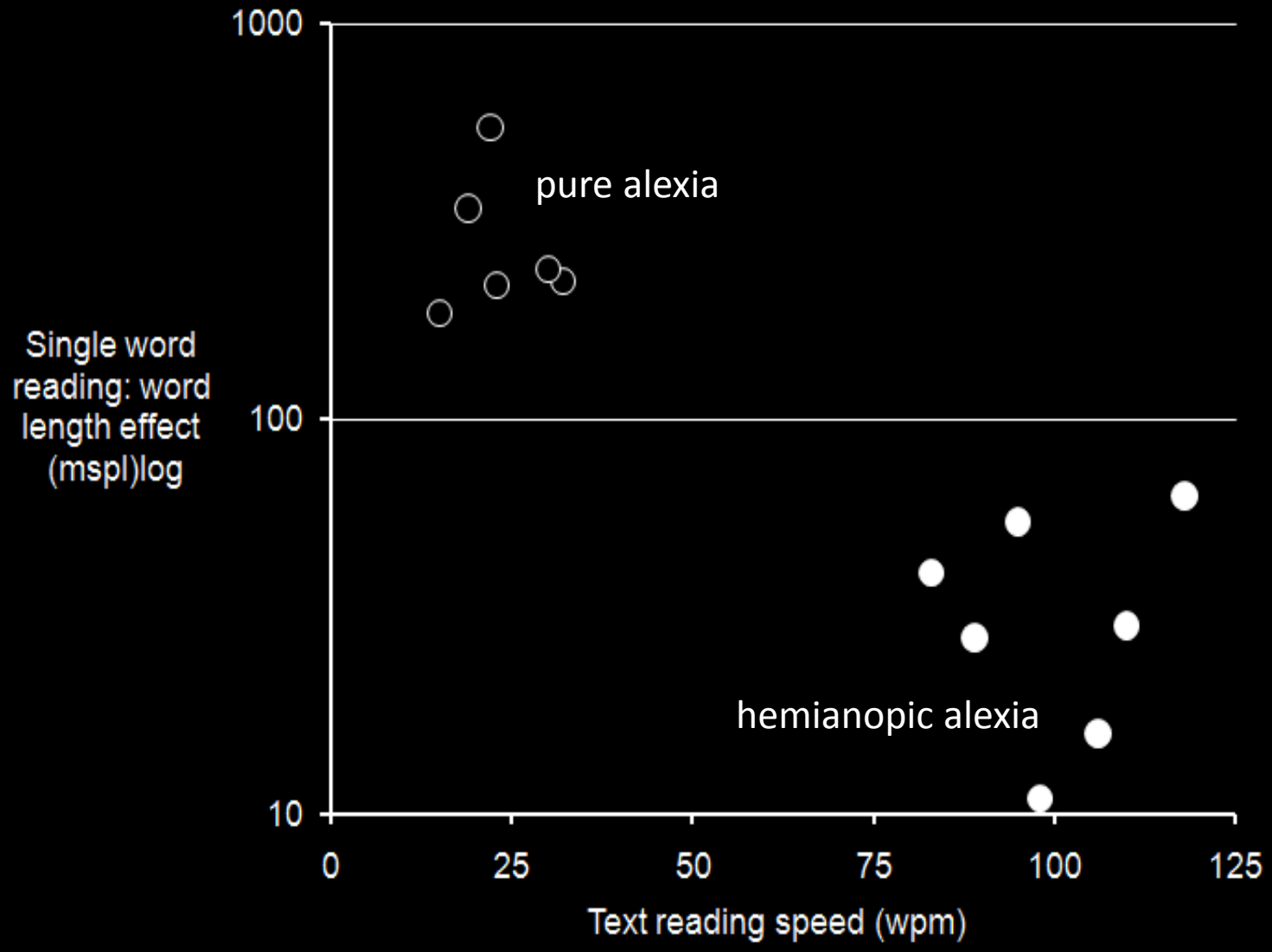


text reading fixations – pure alexia

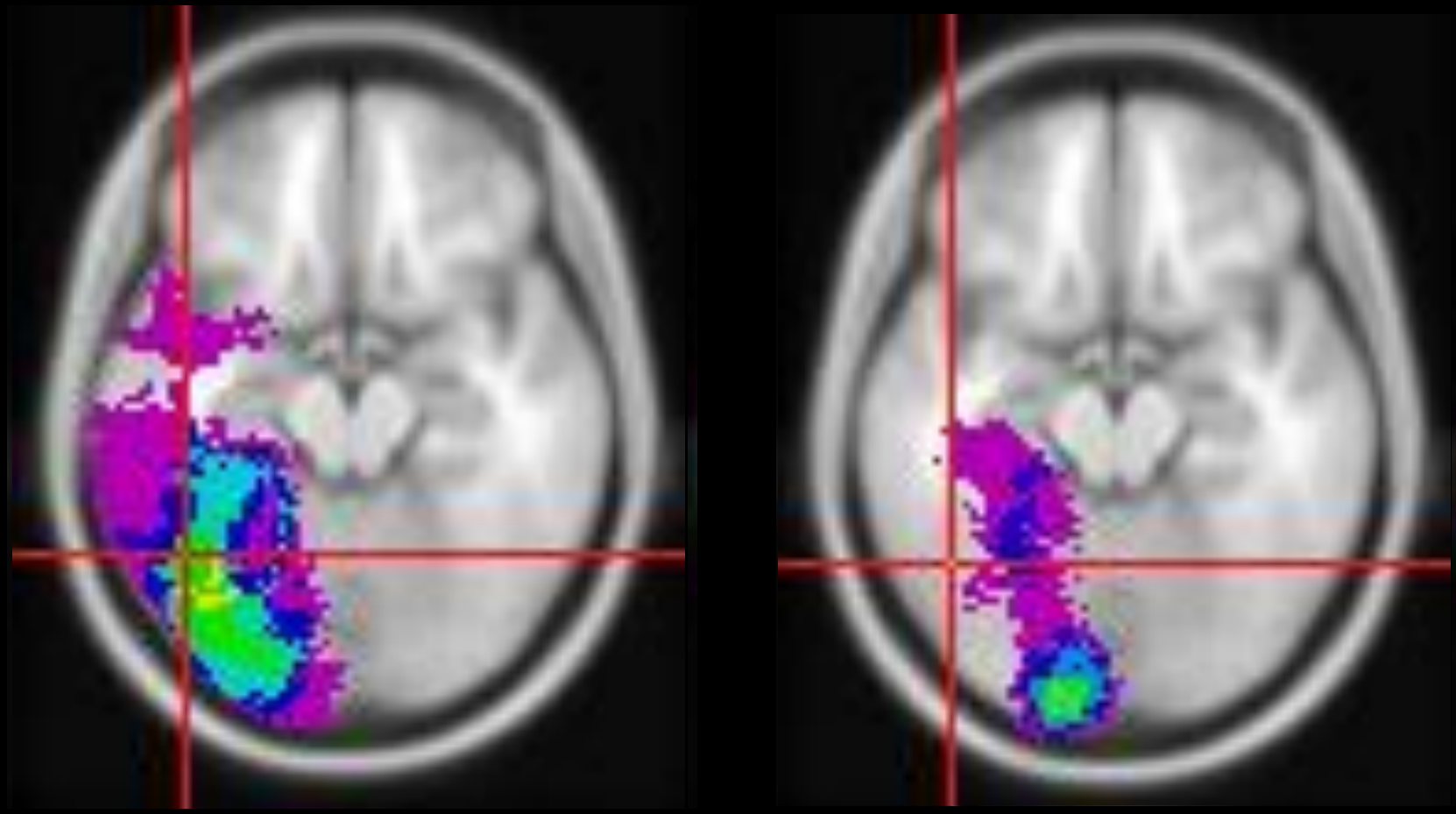
Word-length effect



Pure alexia vs. HA: WLE

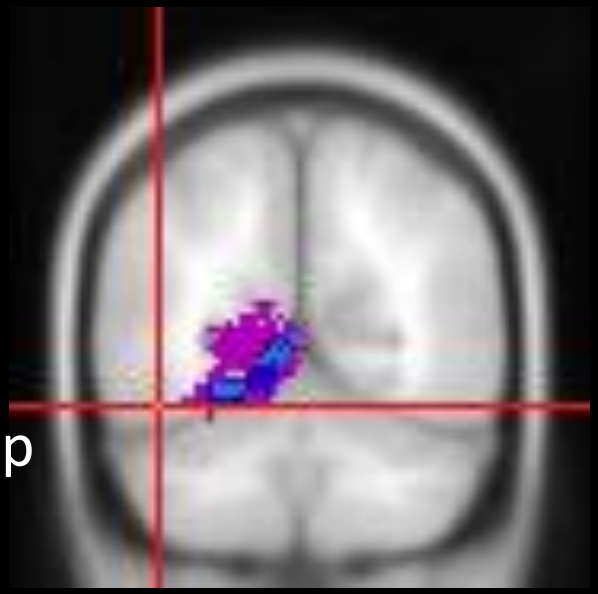


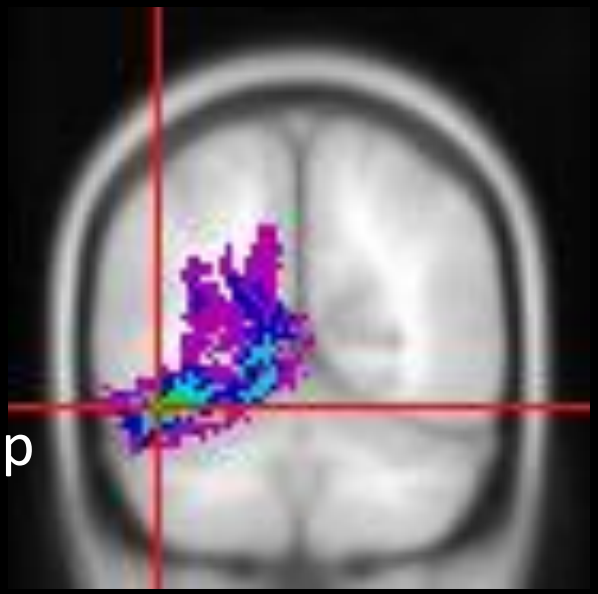
Where is the lesion in pure alexia?

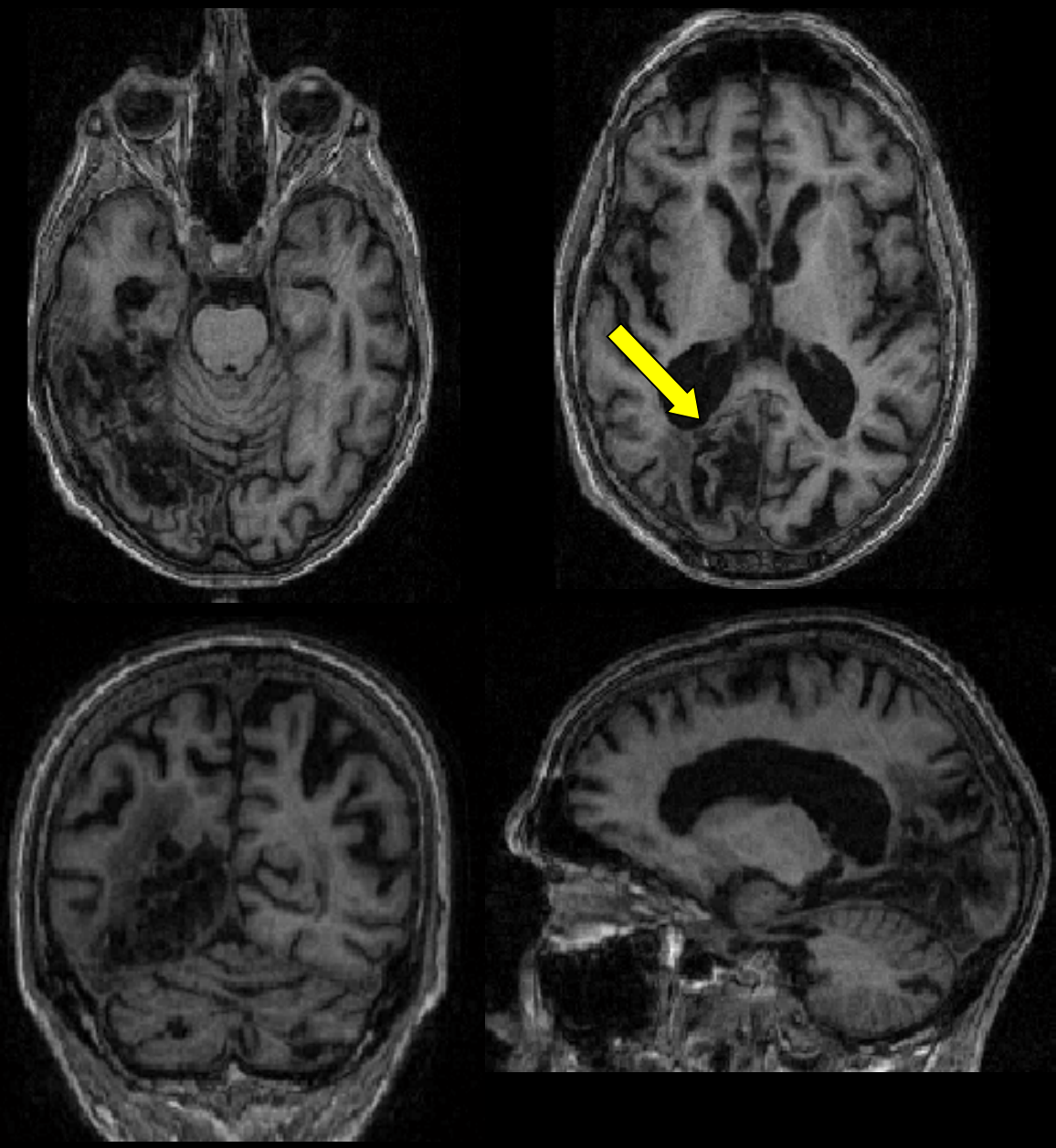


HA group

PA group







Anatomical overlay map
Leff *JNNP* 2006

MRI Video Pt with global alexia
damage to VWFA and CC

How ‘pure’ is pure alexia?

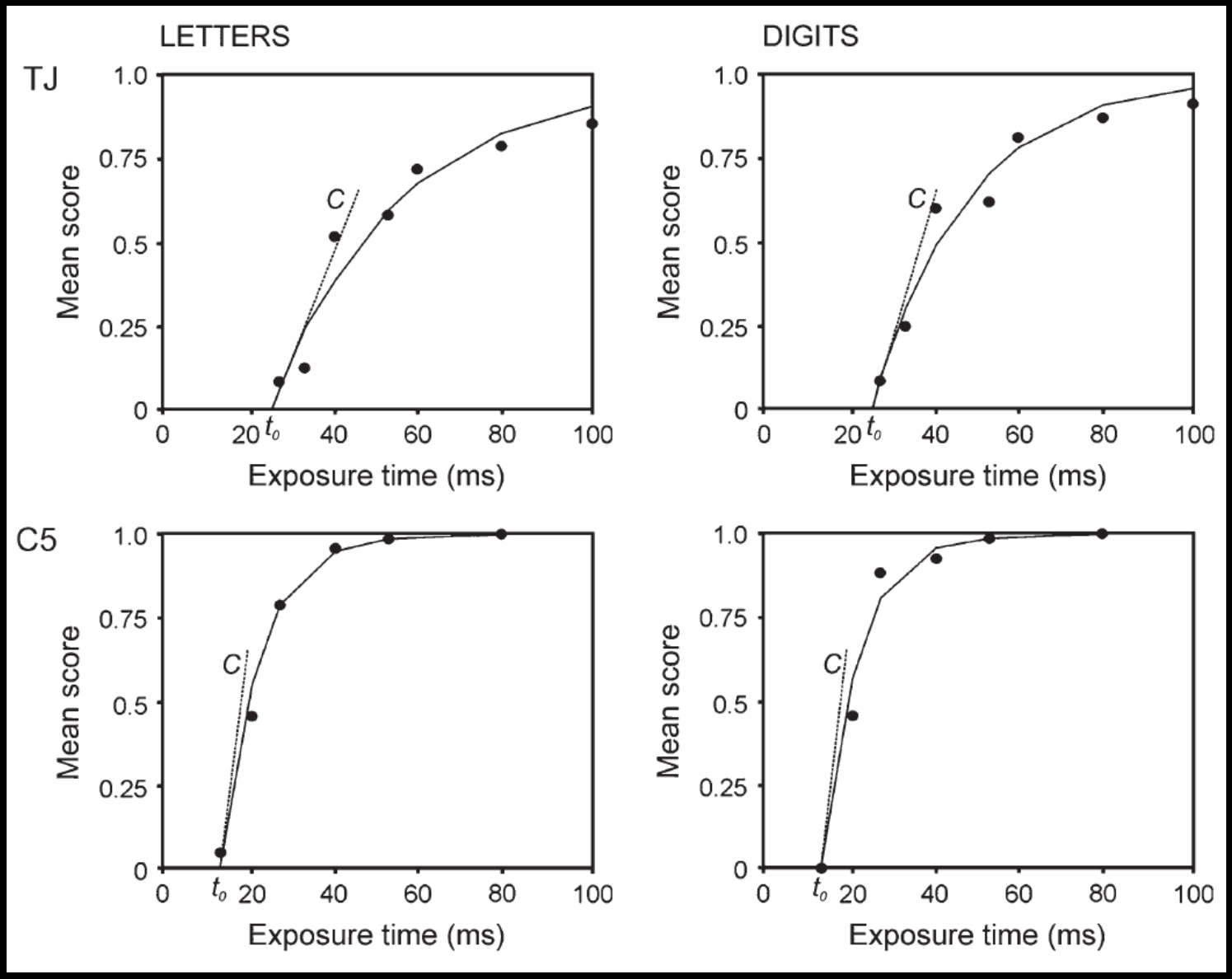
- We tested this using a theory of visual attention (TVA) paradigm
- Instead of measuring RT, vary exposure time
- Subjects report stimuli and can take as long as they like to do this
- Multiple repetitions at multiple exposure times: produce a curve
- Slope, C = “the speed of visual processing”

How ‘pure’ is pure alexia?

Stimuli and mask used in TVA experiment

Starrfelt *Cerebral Cortex* 2009

How ‘pure’ is pure alexia?



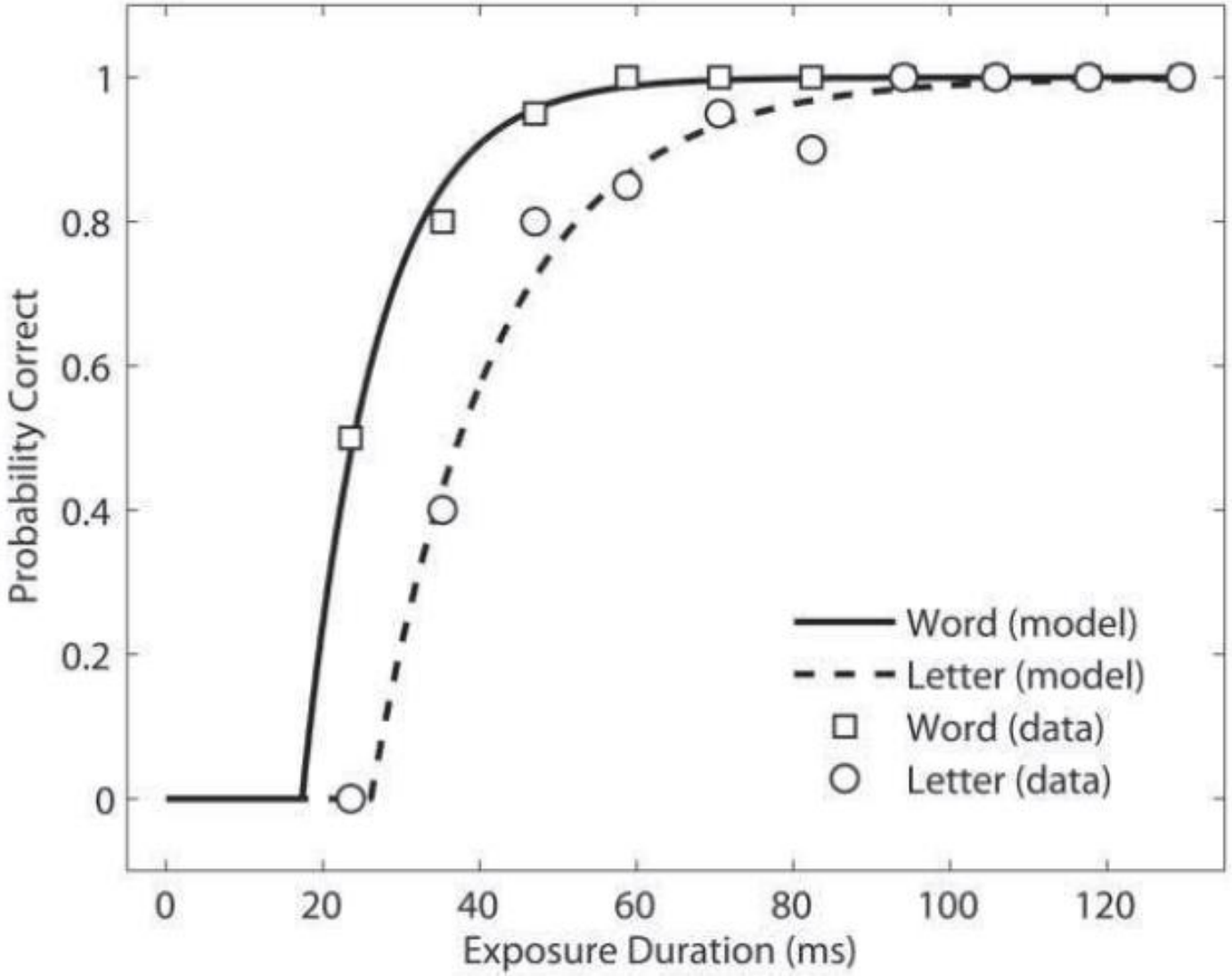
How ‘pure’ is pure alexia?

	TJ	JT	BA	JH	Control mean (SD)
Single letter $C_{central}$	31**	27**	25**	22**	117 (23)
Single letter $t_{0\ central}$	25**	31**	17	10	13.0 (3.1)
Single digit $C_{central}$	44**	47**	29**	79*	119 (16)
Single digit $t_{0\ central}$	25**	26**	20*	15	11.9 (2.8)

Note: Processing speed ($C_{central}$ given in s^{-1}) and perception threshold (t_0, given in milliseconds) for single letters and digits presented at fixation for individual patients, and control group ($N = 9$) mean results (SD in brackets).
*$P < 0.05$; **$P < 0.01$ by Crawford and Garthwaite’s test.

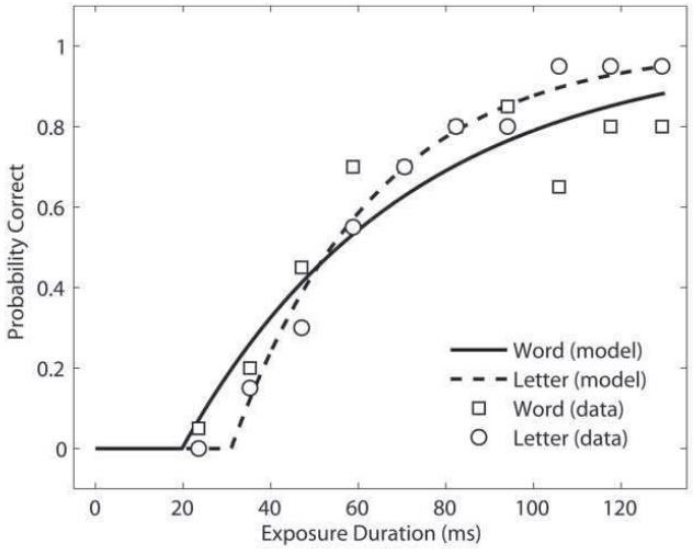
- These patients have degraded sensory perception that impacts their visual recognition of individual letters and digits
- Reading is a high capacity skill that places different demands on the visual system than other visual tasks

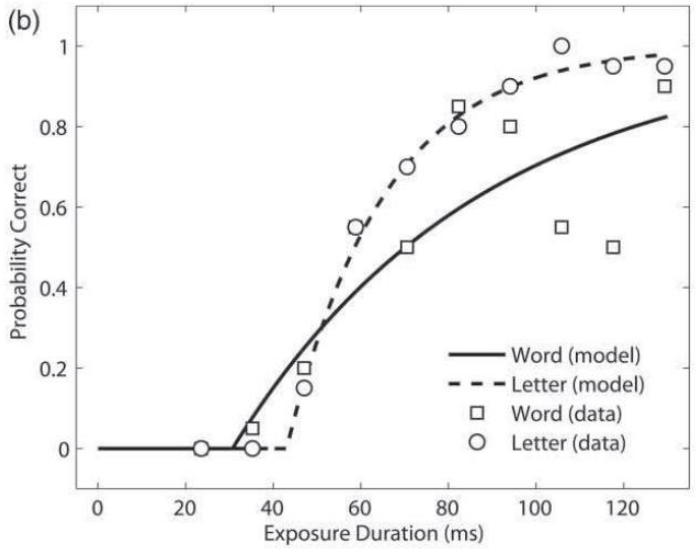
Word superiority effect: controls



Word superiority effect: patients

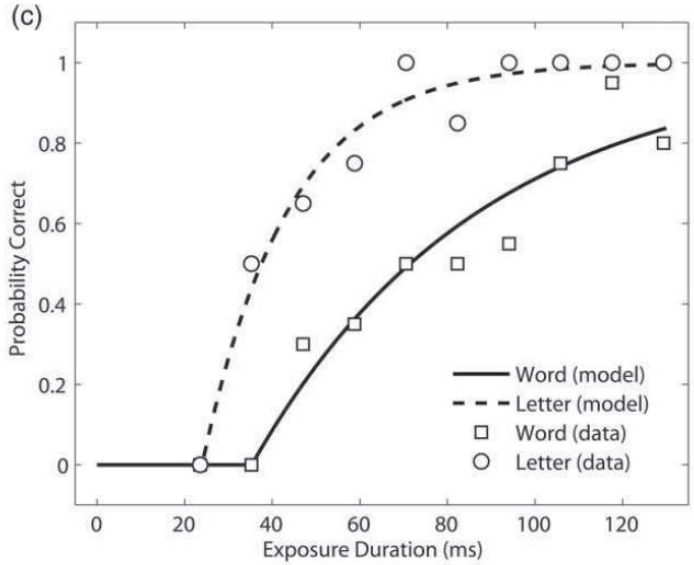
PA1

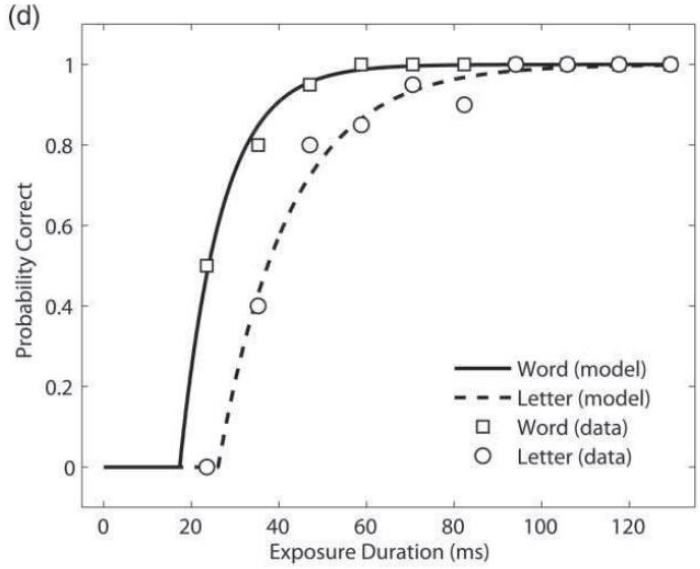




PA2

PA3





Con

Interim summary

- Pure alexia probably is ‘pure’ with regard to other language domains being spared

  (visual language affected)

- Pure alexia probably is not ‘pure’ with regard to other visual abilities being spared (not a category-specific deficit affecting only words)
- Mechanistic explanation is still not clear
- Difficult to treat

Therapy for pure alexia

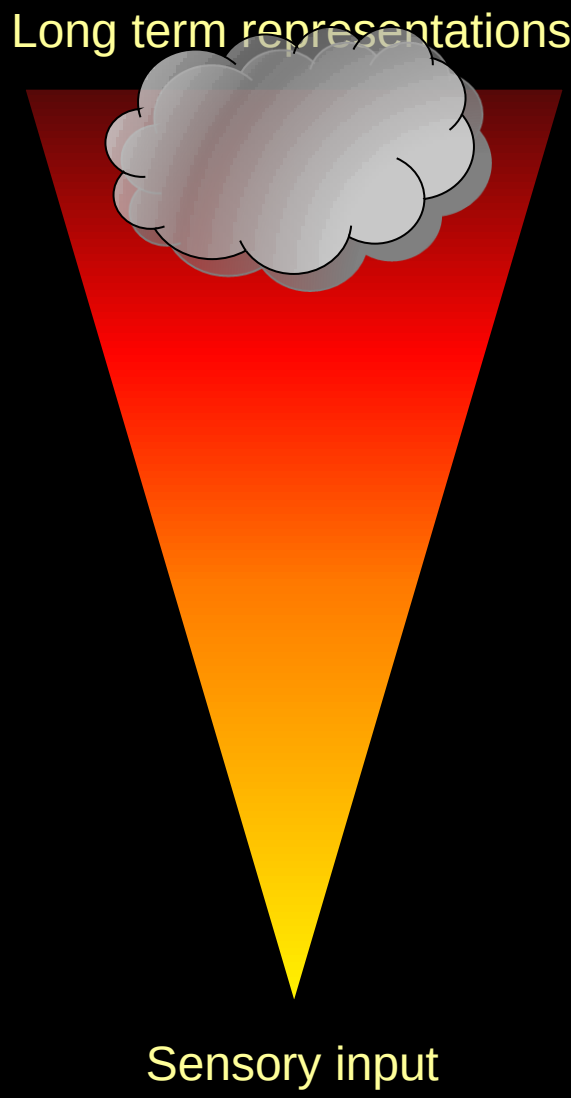
Zoe Woodhead

Zoe is a post-doctoral fellow researching the neural networks supporting reading in both healthy controls and patient groups, using fMRI and MEG. She has also developed a behavioural therapy for patients with pure alexia. She is testing an adapted version of this therapy 'iREADmore' in patients with central alexia.

- Therapy study n=9 patients with pure alexia
- Computer-based, mass-practice, reading therapy
- No control group, rather we had control items (trained vs. untrained)
- Structural imaging: delineate lesion
- Functional imaging (MEG): therapy effects in the surviving reading network

Language hierarchy

Hierarchical mismatch between symptoms and pathophysiology

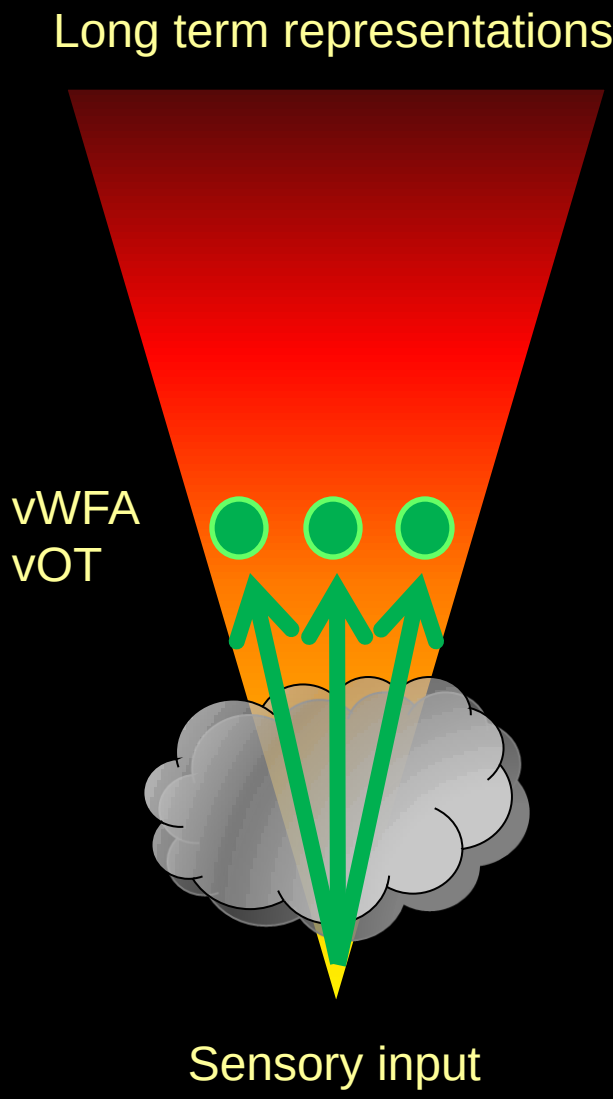


Patients with perceptual language problems (pure alexia) usually only notice their language impairments and not other, associated non-language impairments.

But there is good evidence that there is no such thing as a purely perceptual language syndrome.

Conclusion 1:
patients with language impairments have damage lower in the hierarchy than you might expect from their symptoms

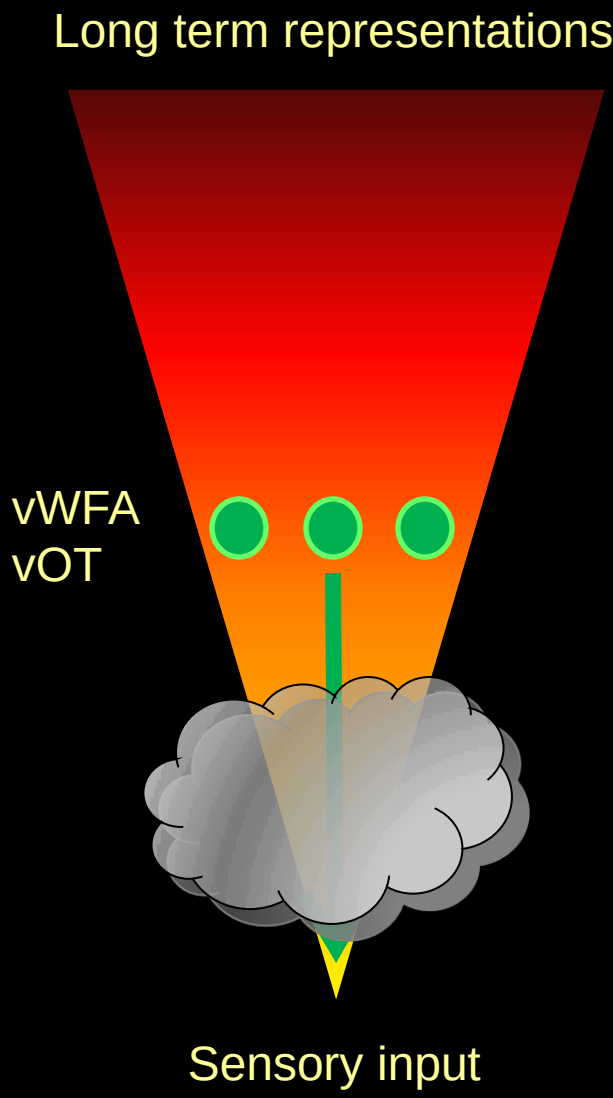
Bottom-up model of recovery



Behaviourally-induced restoration of function occurs at the hierarchical level below the lesion

Behavioural prediction:
If we can improve the perceptual deficit, therapy effects will generalize to all stimuli.

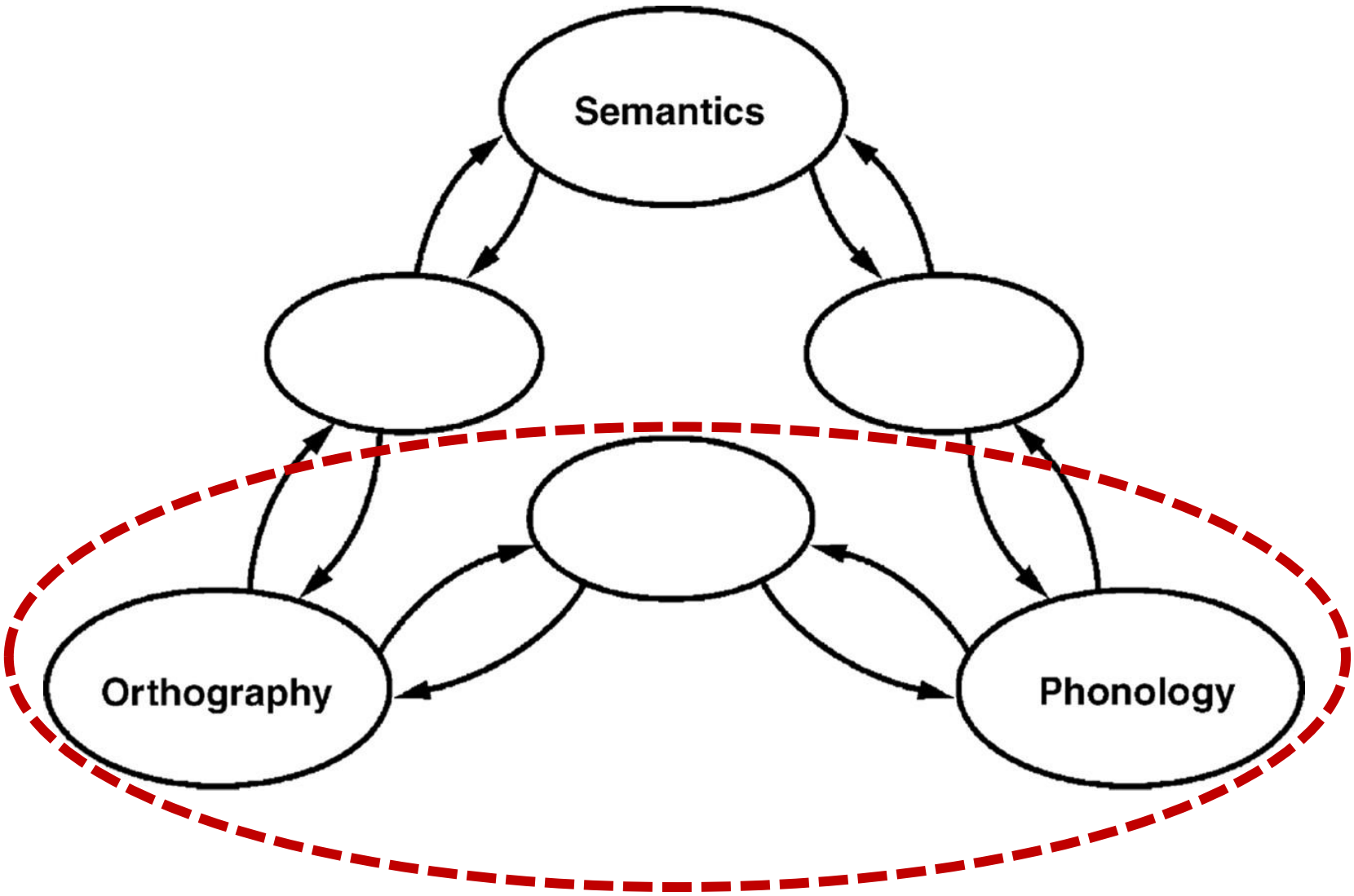
Top-down model of recovery



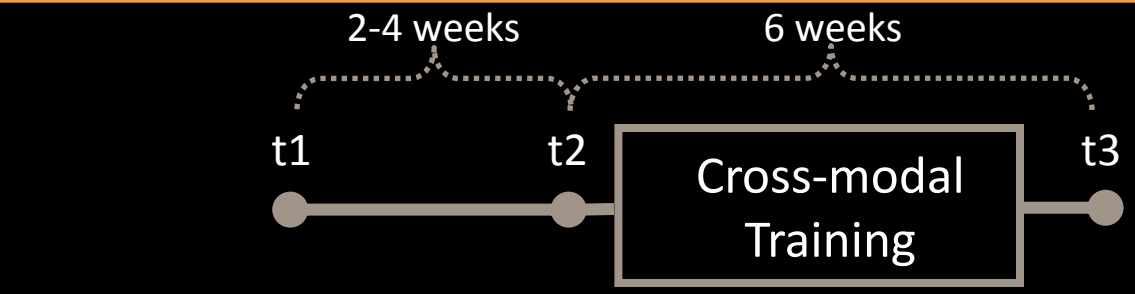
Behaviourally-induced restoration of function occurs at the hierarchical level above the lesion

Behavioural prediction:
Because we are training discreet, higher-level representations, therapy-effects will be item specific

Pure Alexia Rx: based on triangle model of reading



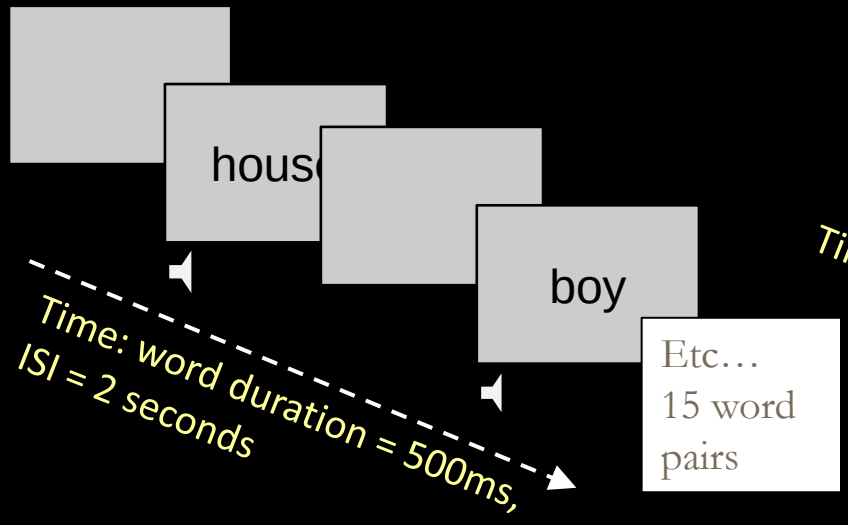
MEG: cross-modal reading therapy



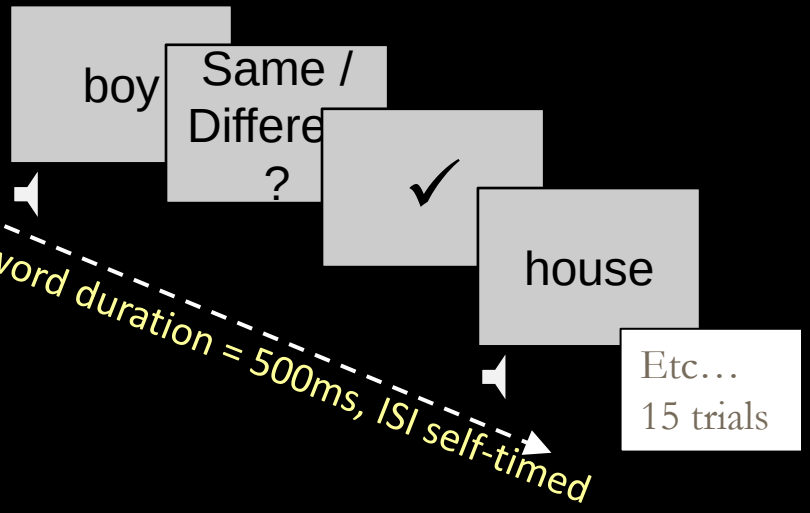
Training stimuli:

- 2 matched word lists
- 500 words each
- Short words (3-6 letters)
- High written frequency
- Word list allocation counterbalanced

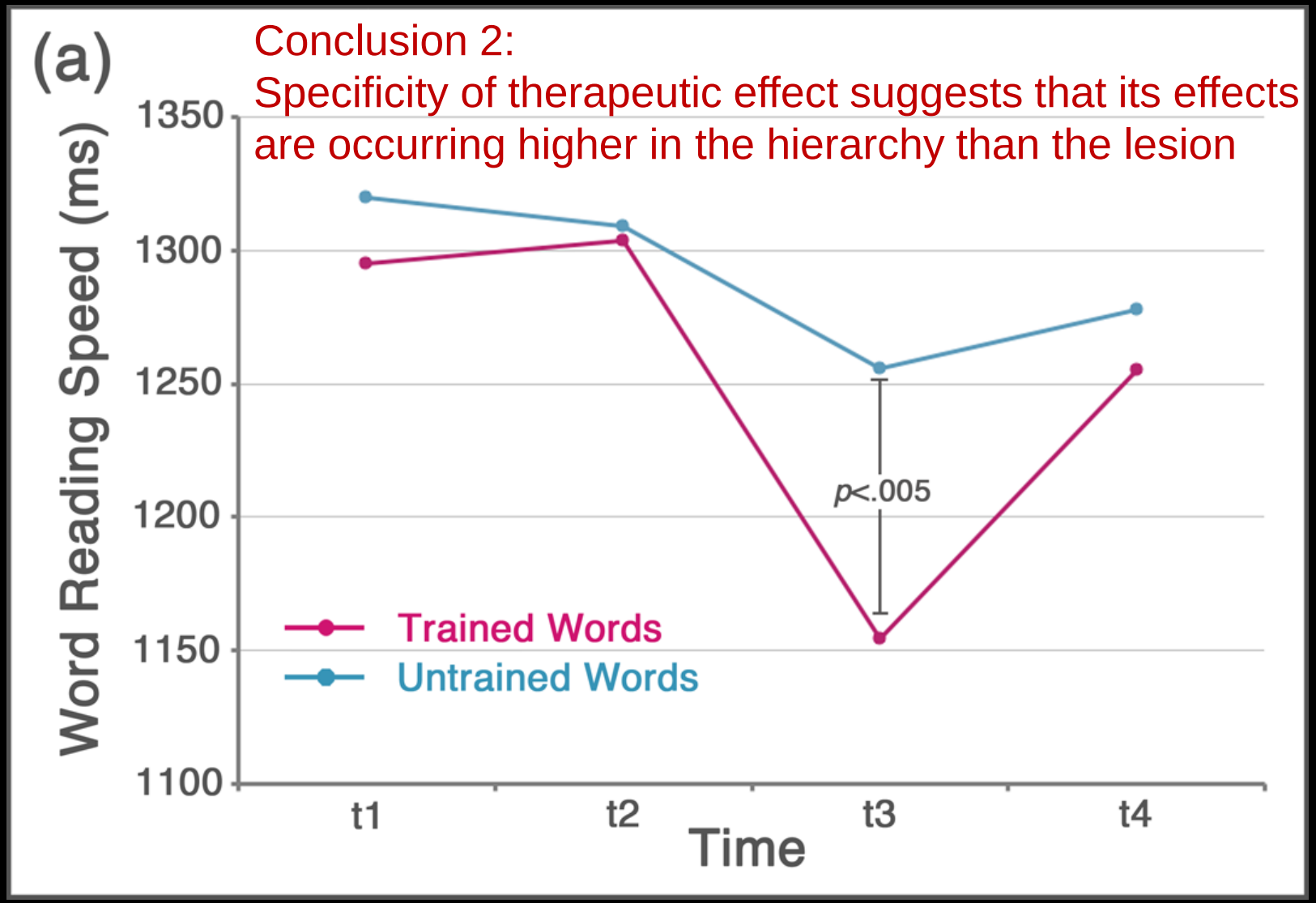
Training phase:



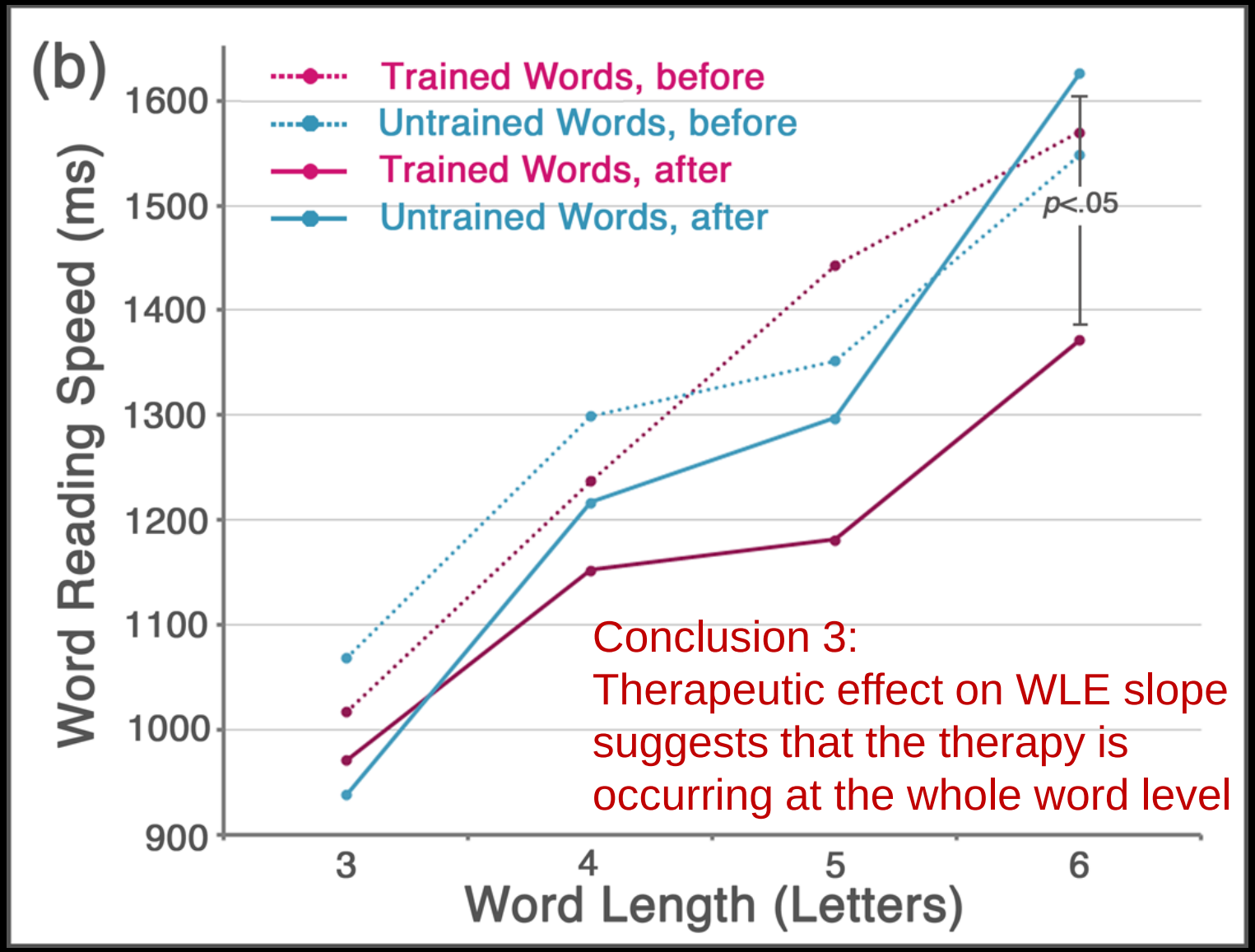
Testing phase:



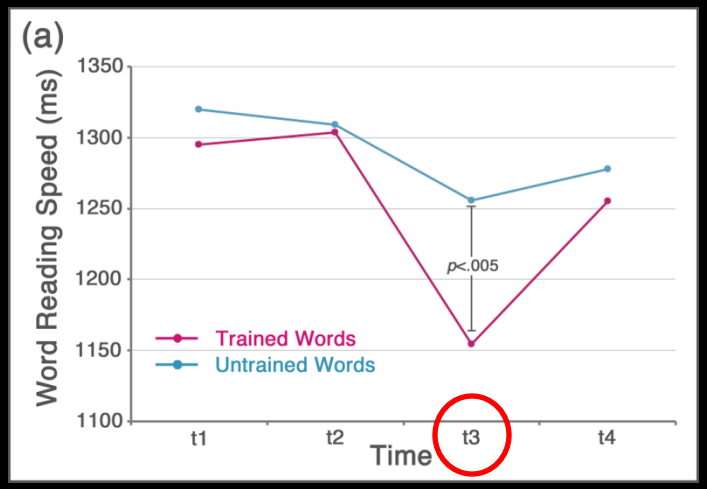
Behavioural results: all word lengths



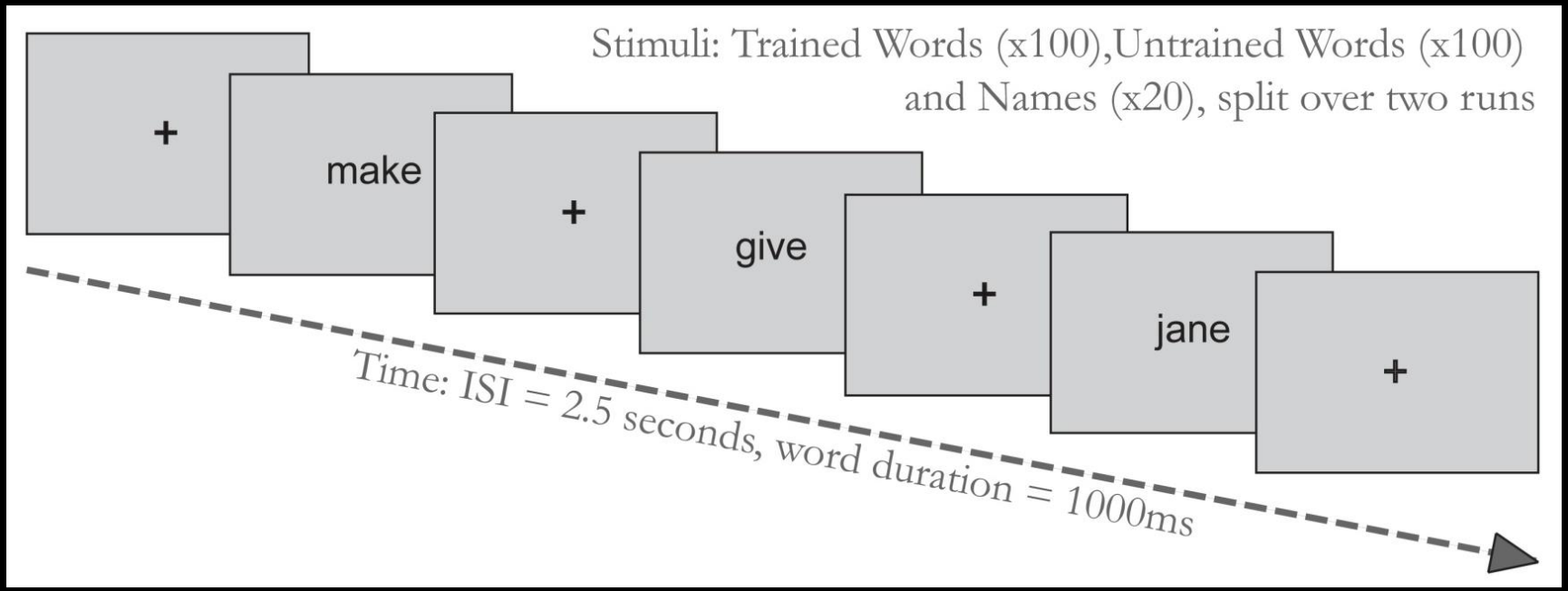
Word length effect



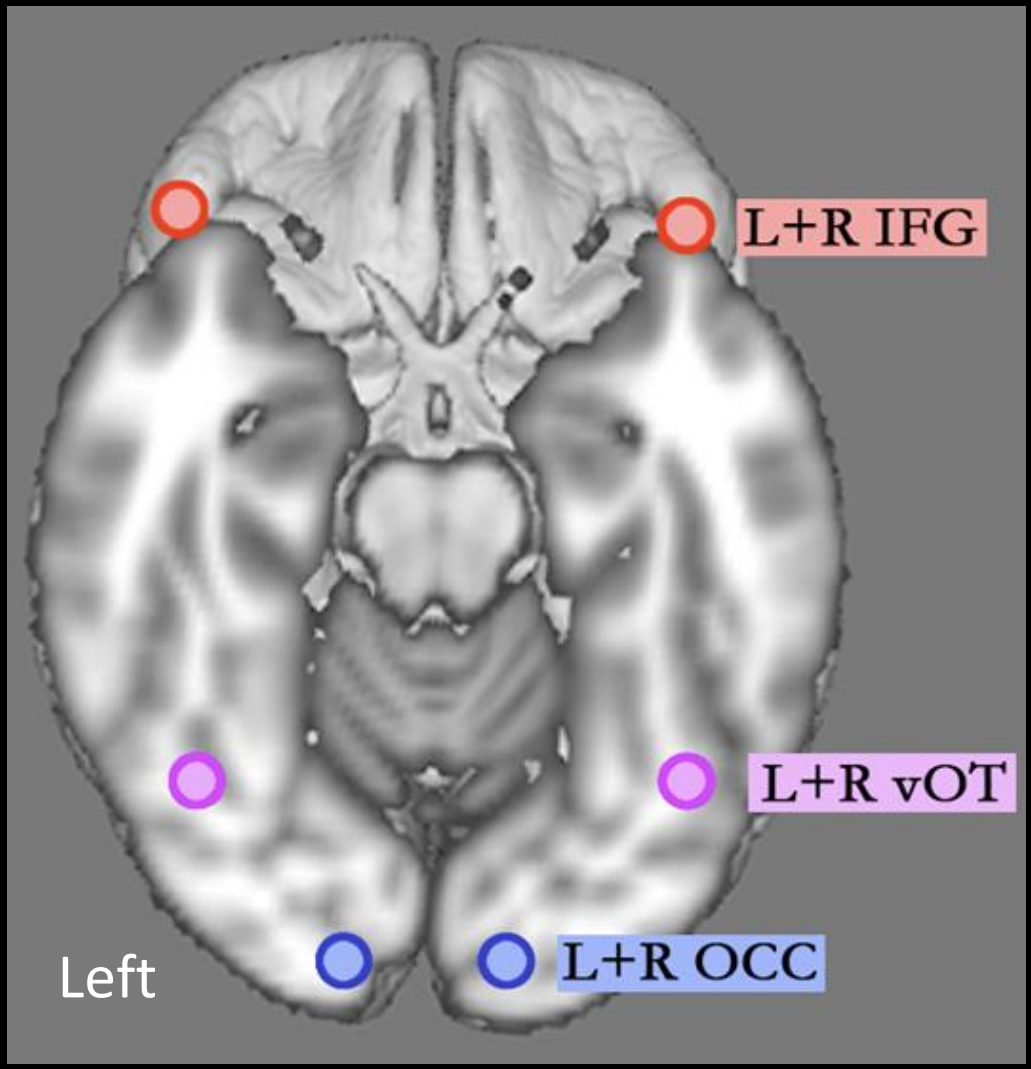
MEG: patients



What differences in network connectivity underlie the differences in reading speed for trained and untrained words AFTER training (t3)?



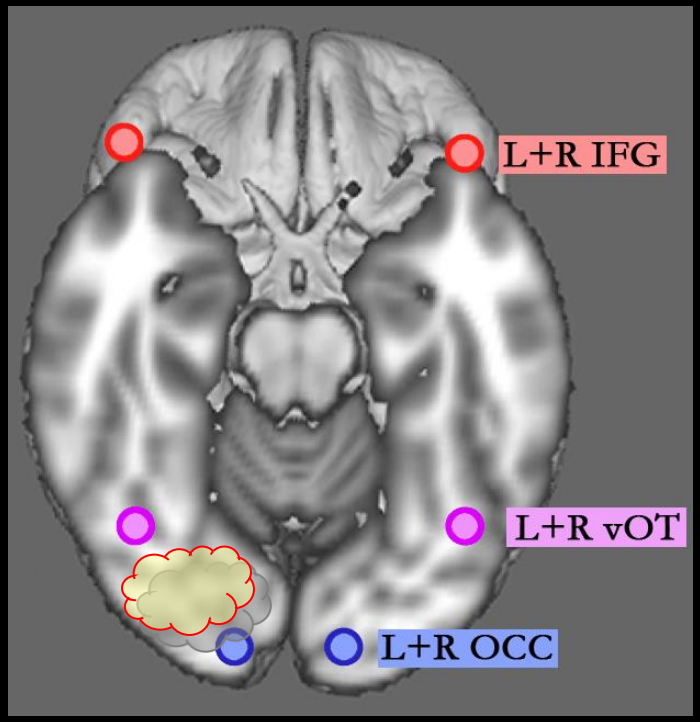
MEG

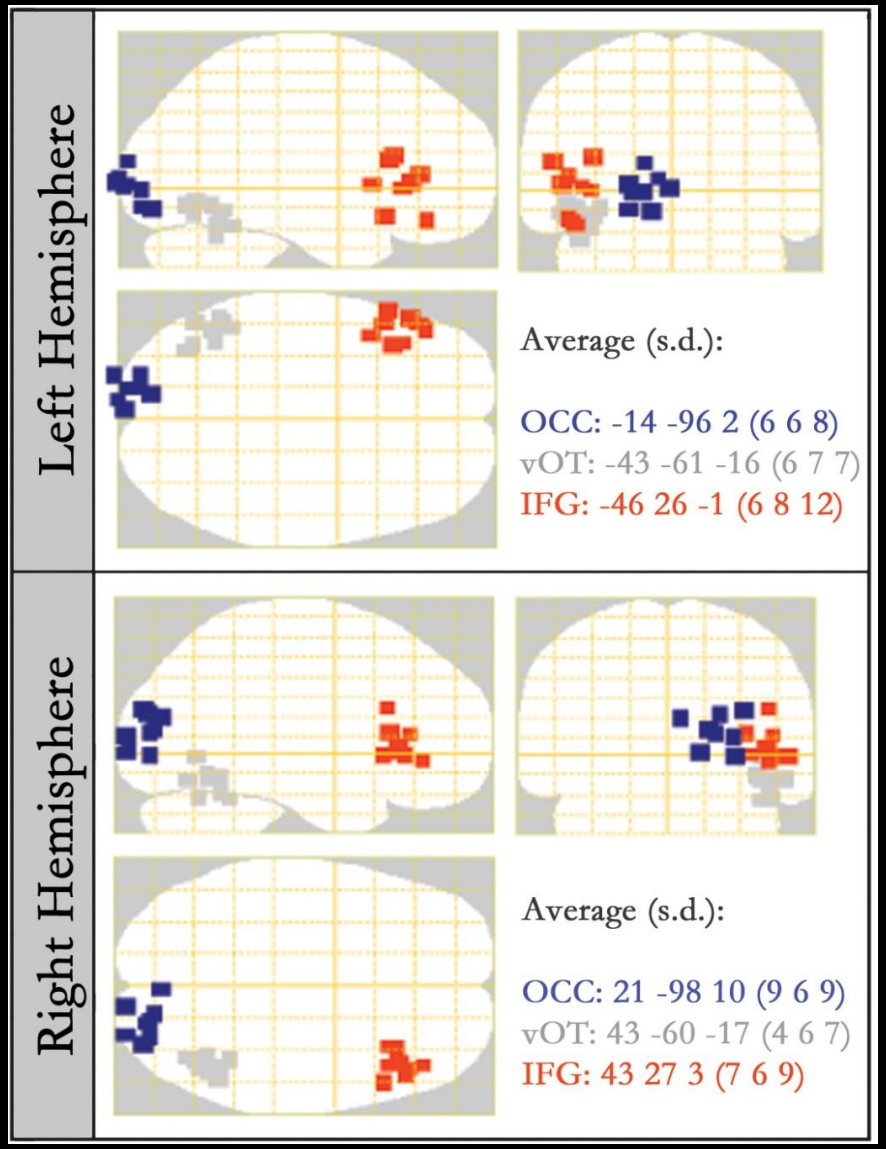


How does connectivity differ between trained and untrained words?

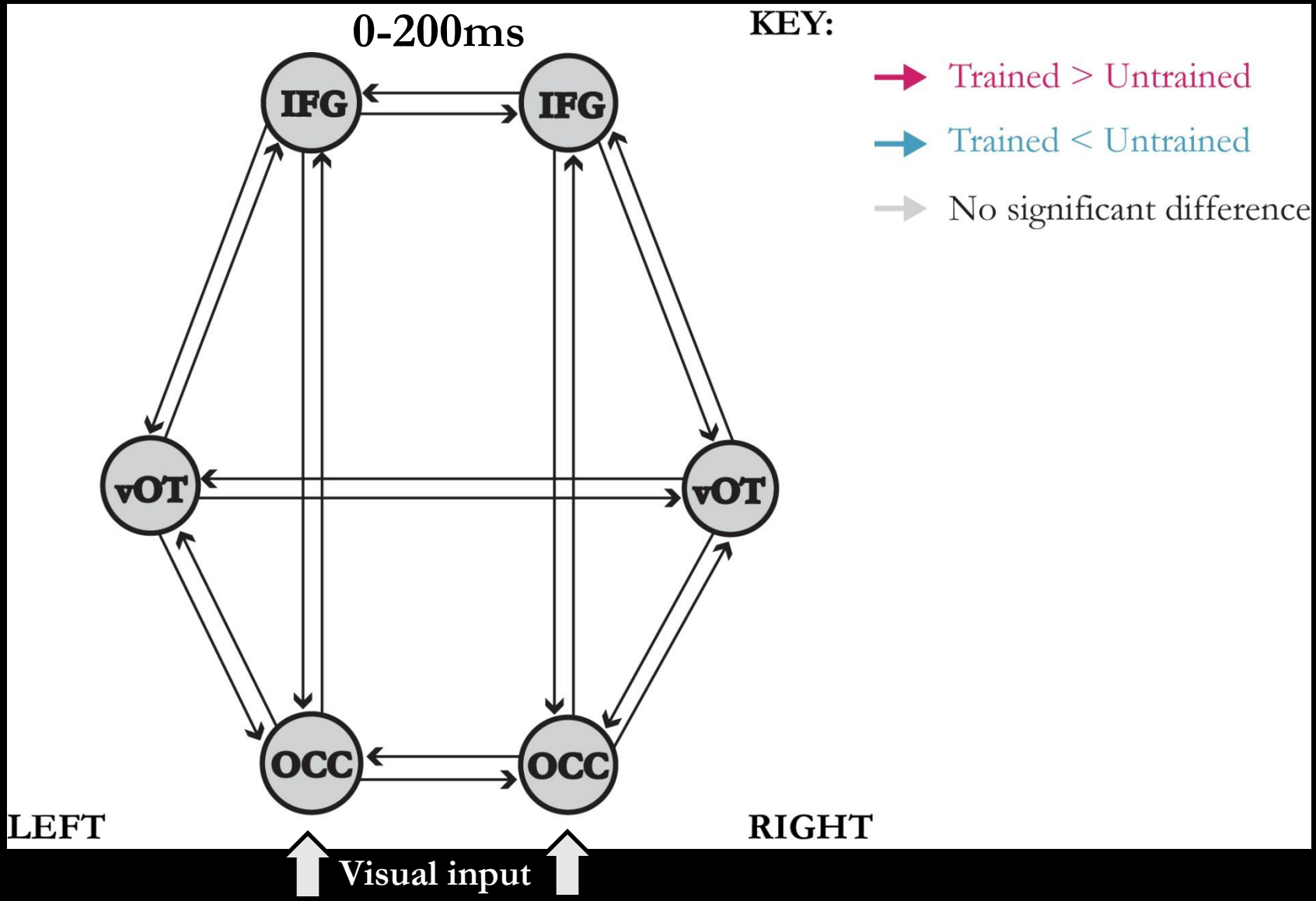
Patients: source localization

- Variational-Bayesian Equivalent Current Dipoles (VB-ECD)
- Dipole fits were subject-specific
- All dipoles fell within intact cortex, not lesion
- Woodhead *Brain* 2013

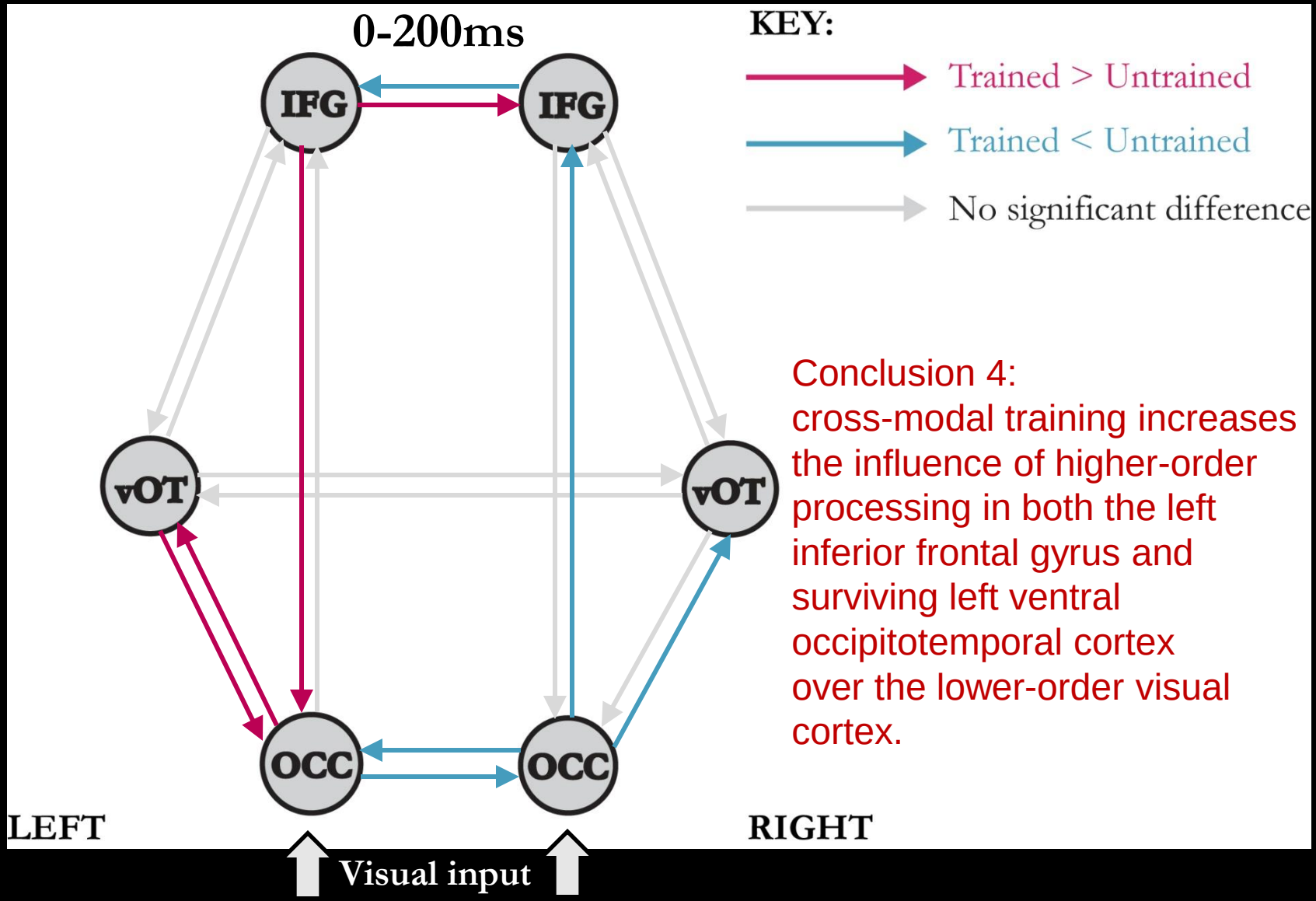




Patients: DCM results



Patients: DCM results

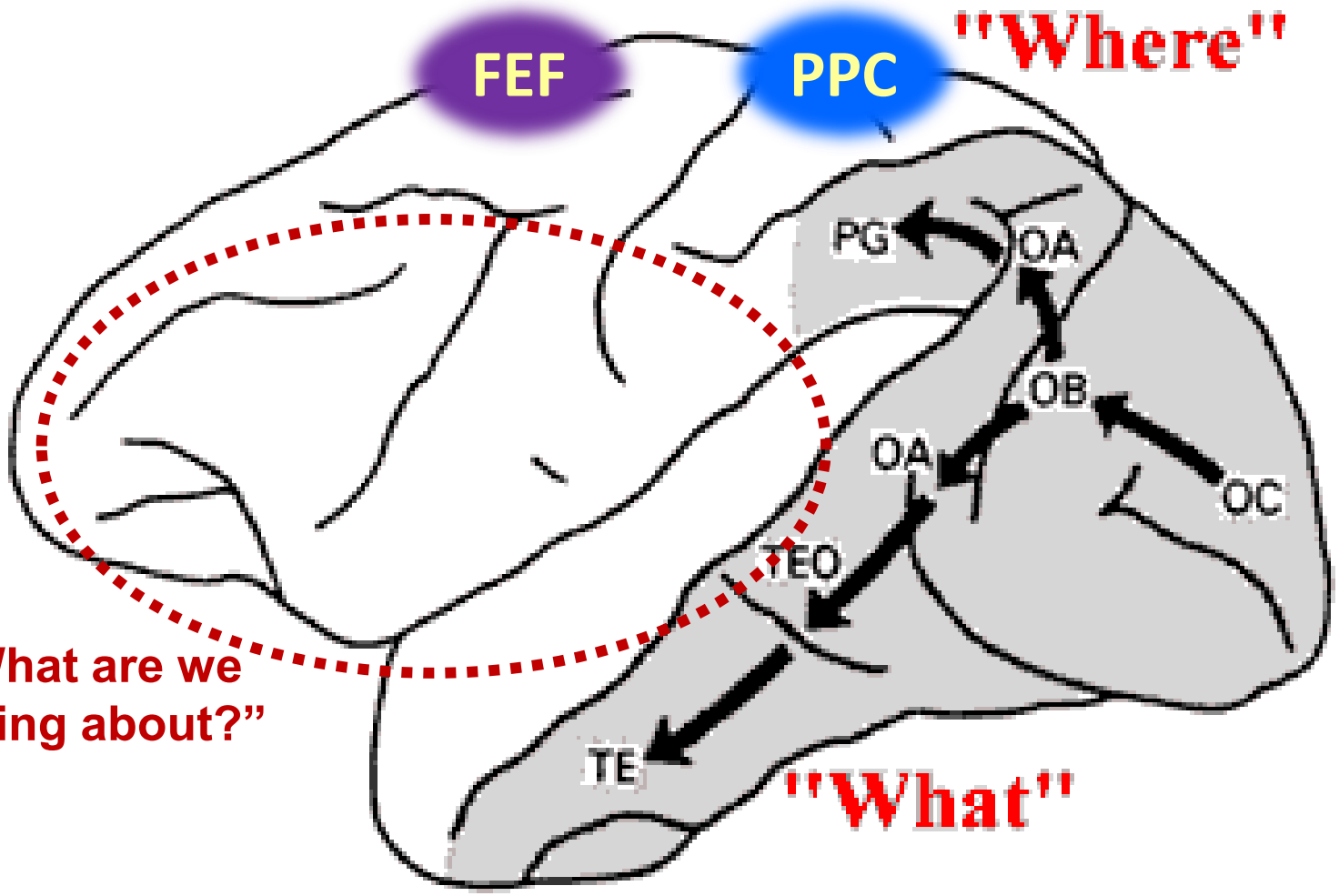


Conclusion 4:
cross-modal training increases the influence of higher-order processing in both the left inferior frontal gyrus and surviving left ventral occipitotemporal cortex over the lower-order visual cortex.

Conclusions

1. Psychophysical evidence: patients with pure alexia have damage lower in the visual hierarchy than you might expect from their symptoms
2. Cross-modal therapy: specificity of the therapeutic effect (trained items only) and effect on WLR slope suggests that its effects are occurring higher in the hierarchy than the lesion
3. Patient DCM: increased influence of higher-order processing over lower-order visual cortex

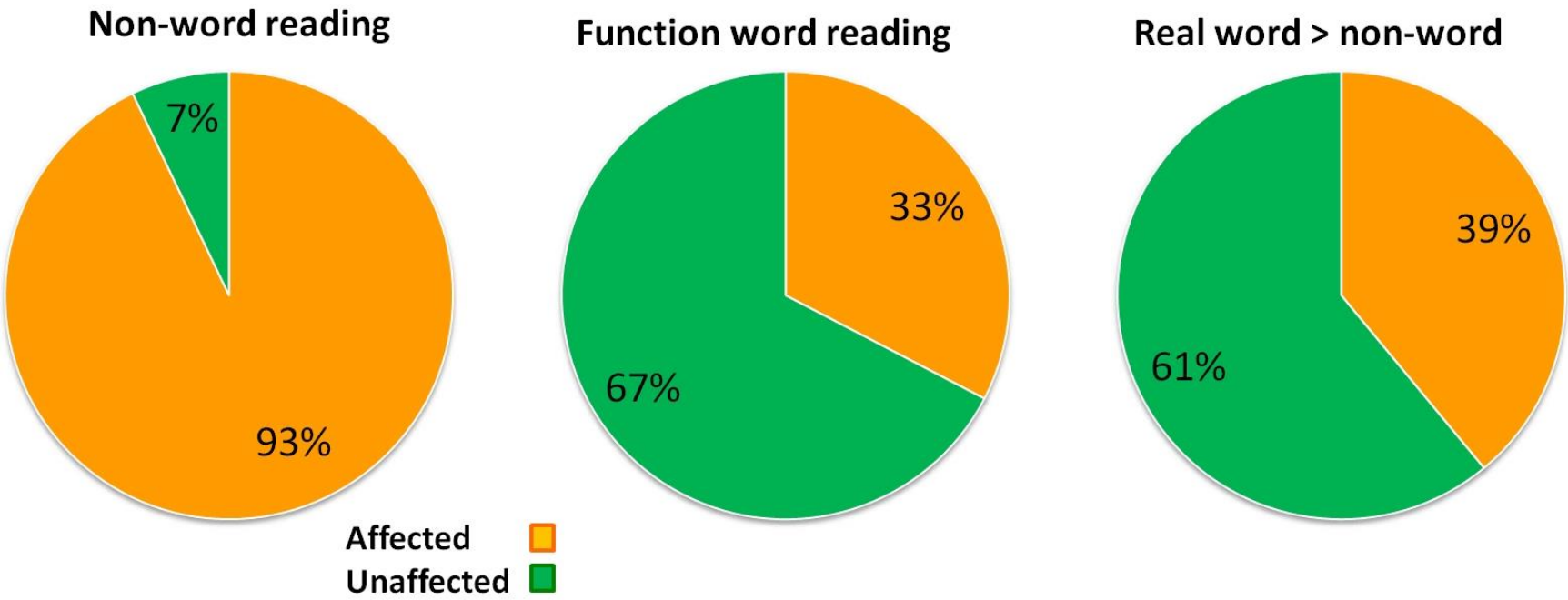
Central alexia



Central Alexia: Subtypes

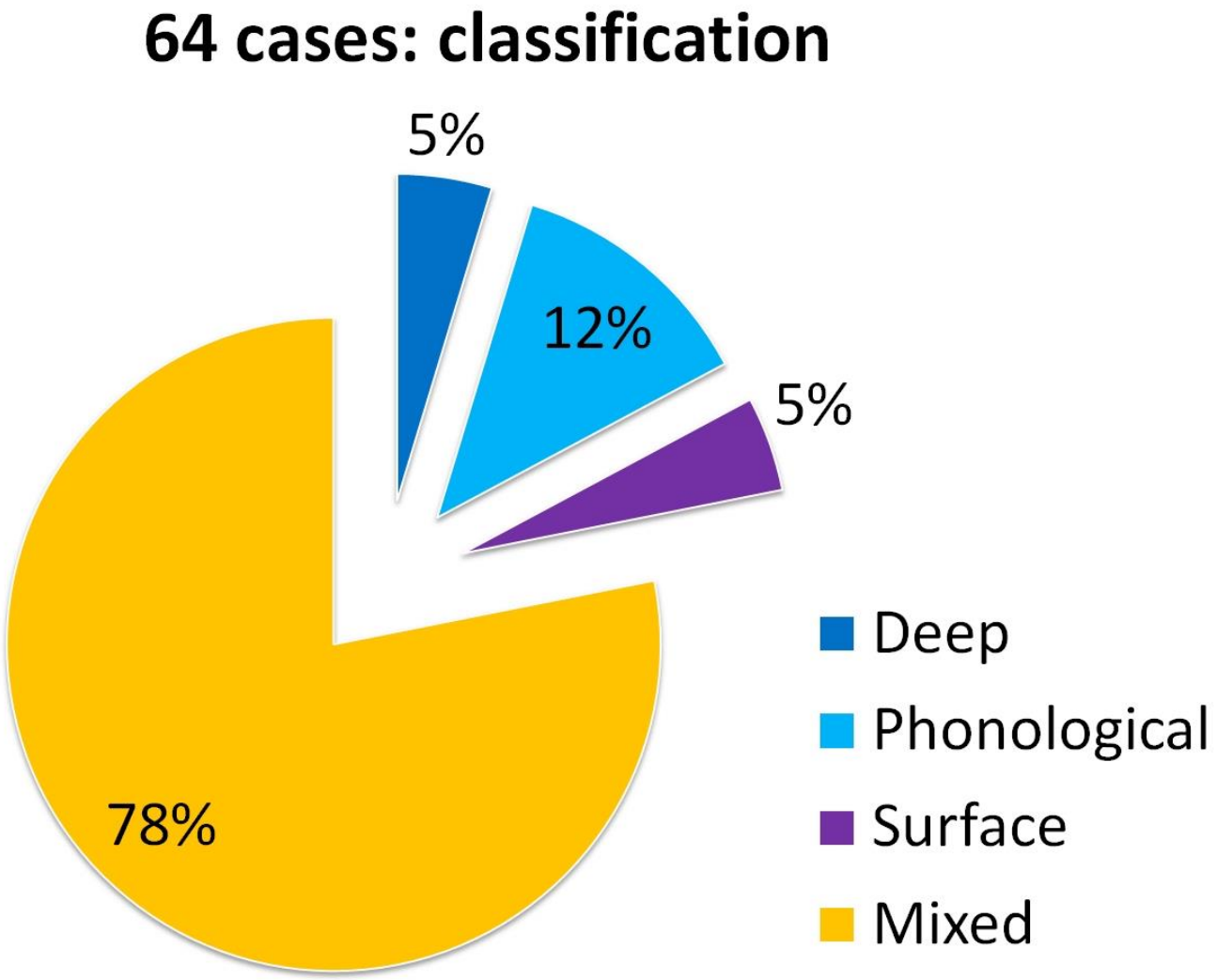
	Part of speech/Lexical class effects			Error types: reading aloud			
Dyslexia subtype	Irregular words	Non-words	Function words	Semantic	Morphological	Visual	Regularization
Surface	Errors*	OK	OK	Yes	Yes	No	Yes*
Phonological	OK	Errors*	OK	No	Yes	No	No
Deep	OK/Errors	Errors	Errors*	Yes*	Yes	Yes	No

Central Alexia: Reading errors 141 PLORAS patients

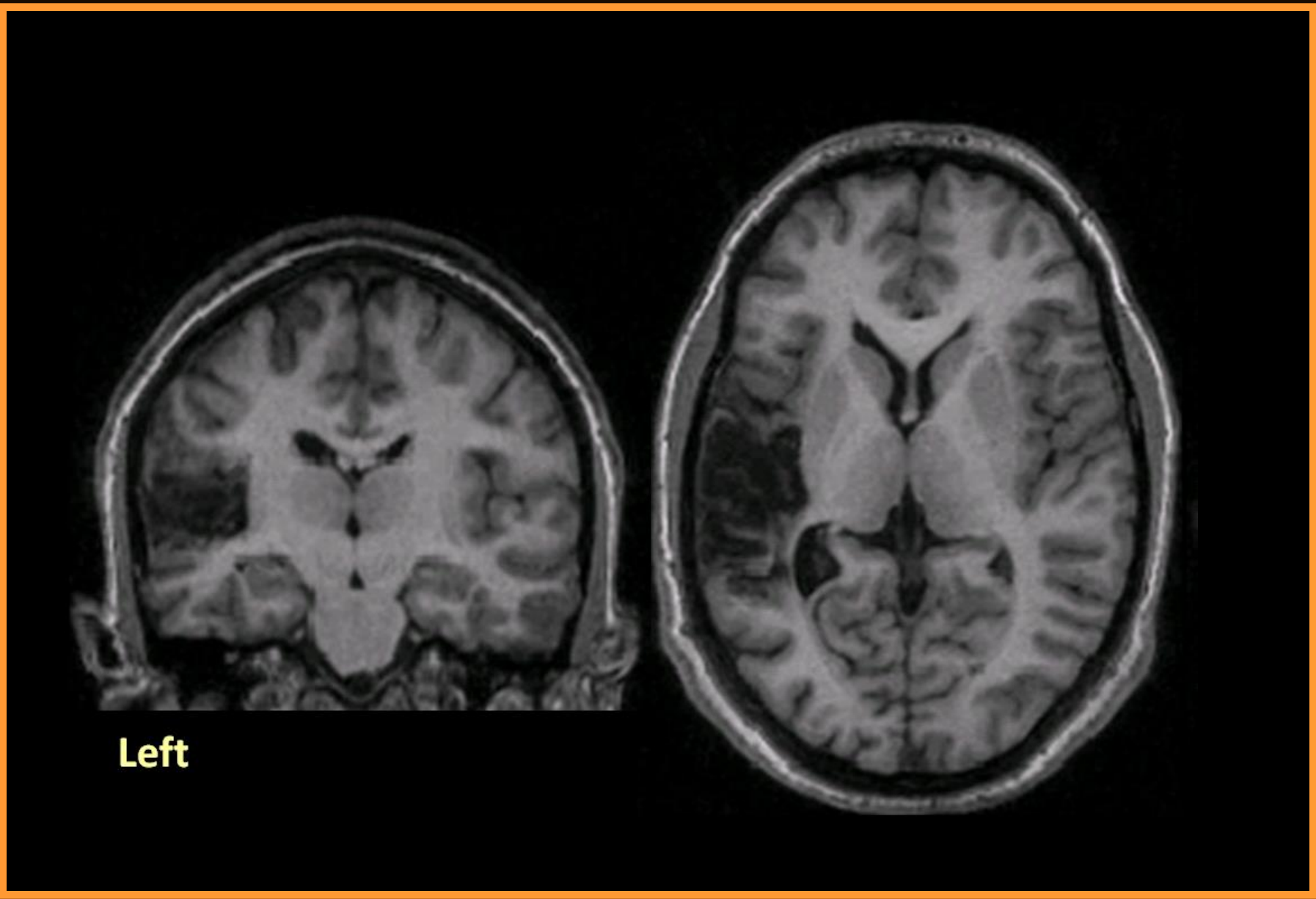


- 212 patients in PLORAS with aphasic speech
- 141/212 (67%) of aphasic patients in PLORAS had abnormal reading as well
- A more detailed analysis of 64 (fuller data set) of the 141

Central Alexia: ‘pure’ cases rare



Central Alexia: ‘lexico-semantic’ problems

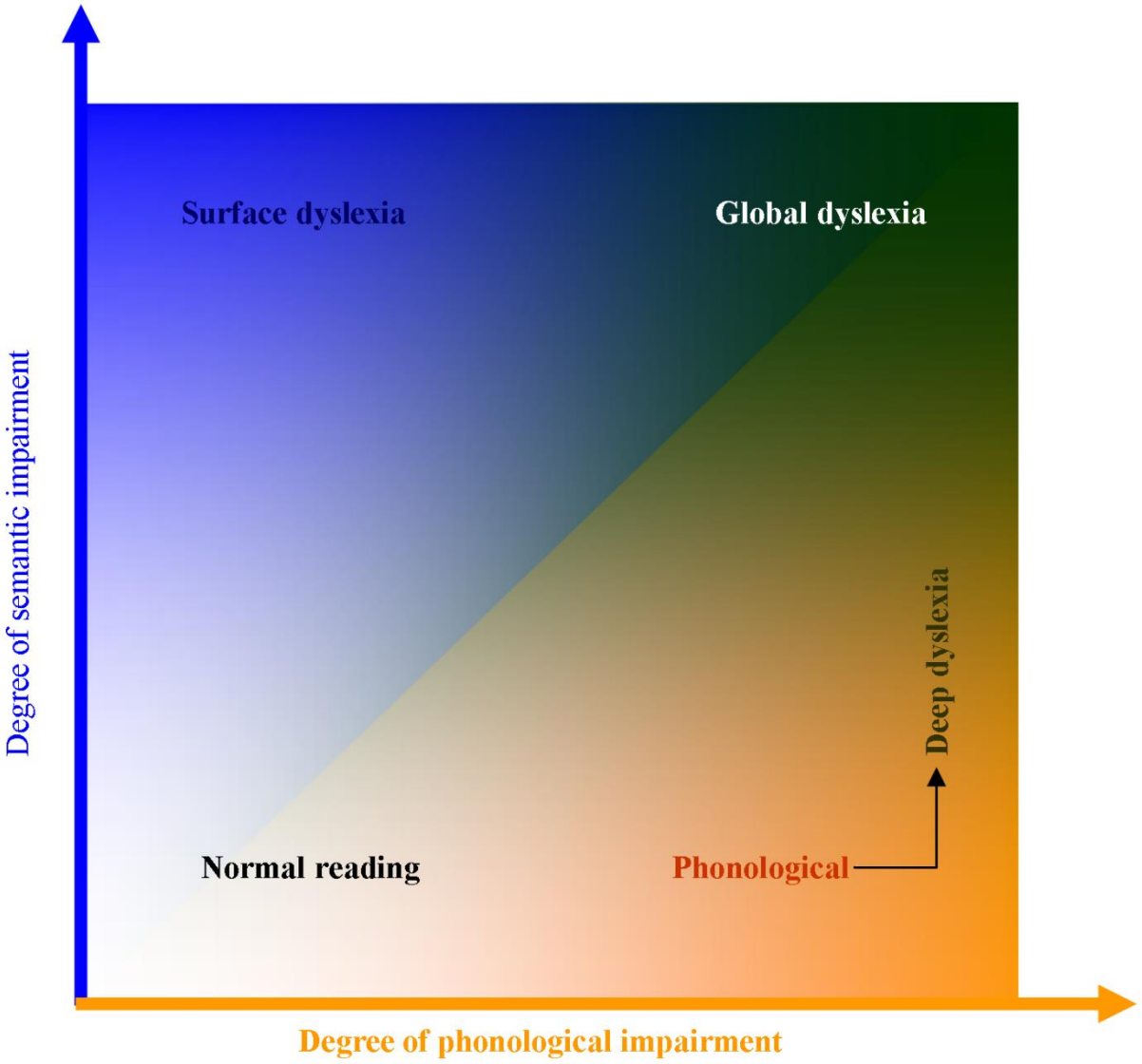


CA reading: phonological and surface errors

CA repetition: ASTM↓ deep dysphasic (semantic) errors

CA SPD: phonological, agrammatic (tense)

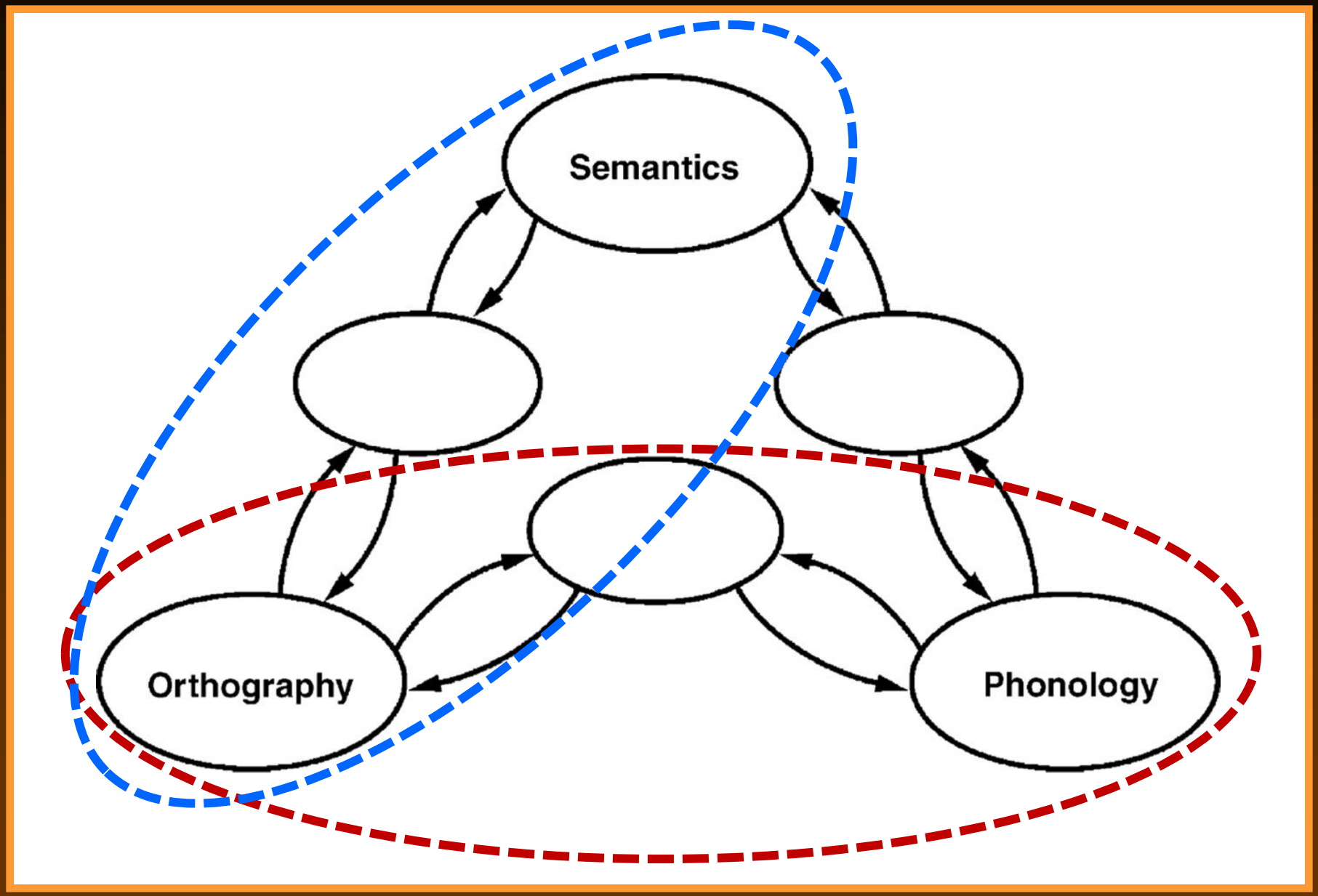
Perhaps different forms of CA are on a continuum?



Crisp *J Cog Neurosci* 2006

Central Alexia Rx: extension of pure alexia Rx

Central Alexia Rx: based on triangle model of reading

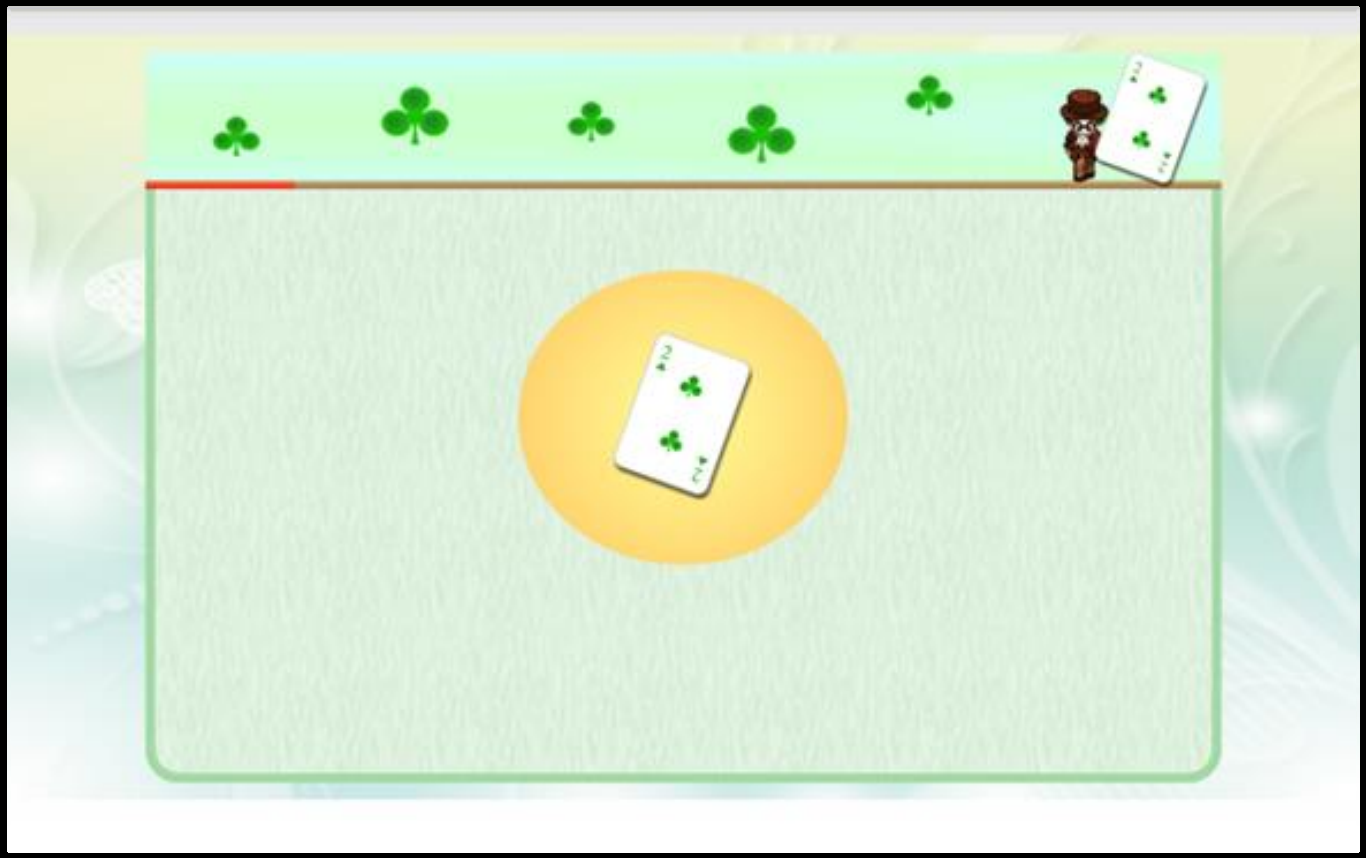


iReadMore

Key Design Features

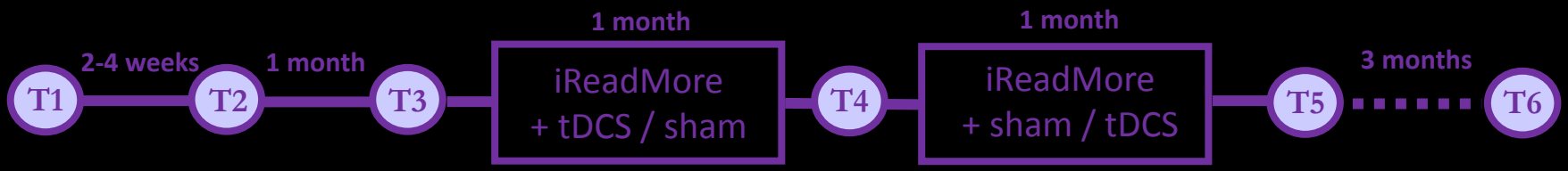
- Aims to improve patients' word reading accuracy
  - Repetitive Word-Picture-Sound pairings to rebuild associations
- Suitable for patients with different types / severities of central alexia
  - Adaptive difficulty
- Suitable for unassisted use via the internet
  - Intuitive design, with gamification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

iReadMore



CA Rx: reinforce grapheme-phoneme representations

iReadMore



2 x 4 week blocks of reading training

~35 hours of training per block

Double-blind real / sham tDCS crossover

Training Word Lists

3 word lists (A, B, C), 150 items per list

Matched for Freq, imageability, length, N-size and baseline performance

Counterbalanced word list allocation → Block1 / Block2 / Untrained

Primary Outcome Measure

Single word reading accuracy (reading aloud) tested at **all timepoints**

iReadMore

23 patients with central alexia

15 have finished the study

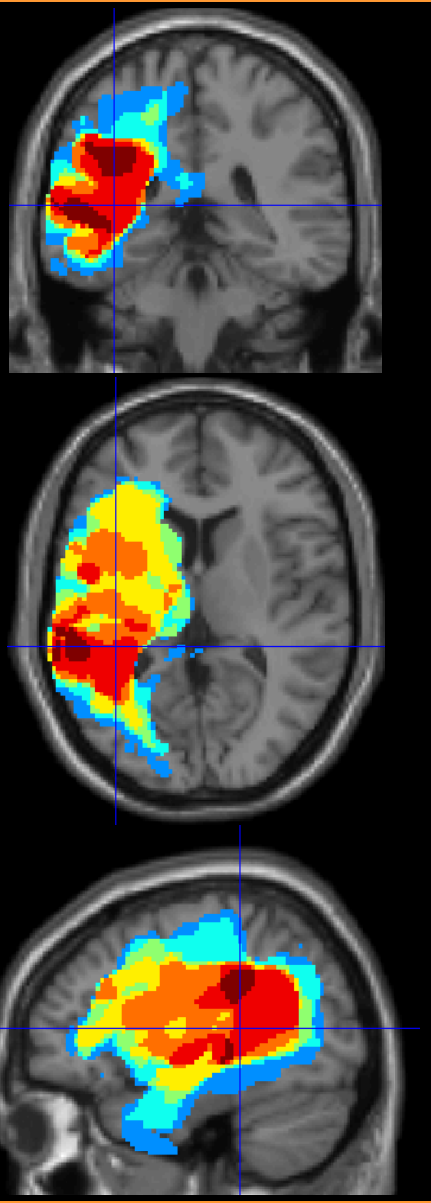
Recruited from PLORAS

Impaired speech output (aphasic)

Impaired word reading (alexic)

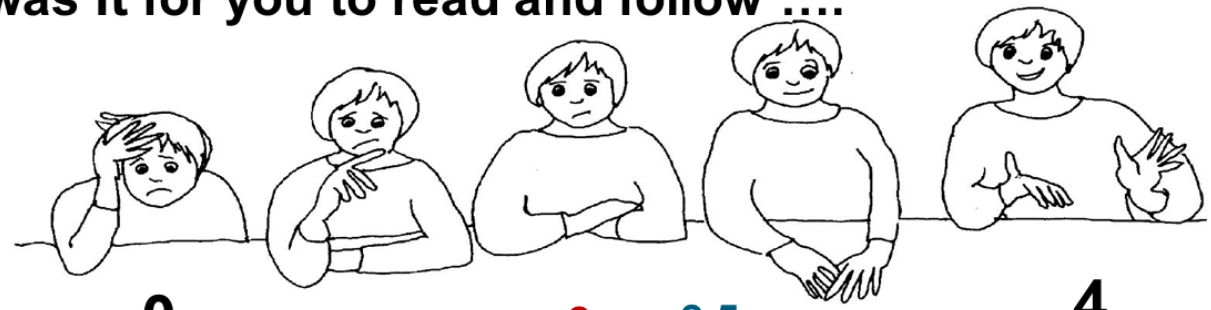
At least 1 year post stroke (chronic)

Sparing of left IFG



iReadMore: PROMS

How easy was it for you to read and follow ….



A word

0 — 2 (Before) — 2.5 (After) — 4

A headline

0 — 1.5 (Before) — 2.75 (After) — 4

An article

0 — 0.5 (Before) — 1.5 (After) — 4

An official letter

0 — After — Before — 4

iReadMore: Summary

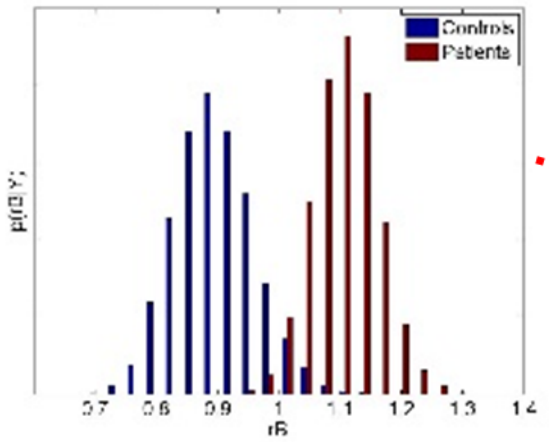
Preliminary Results

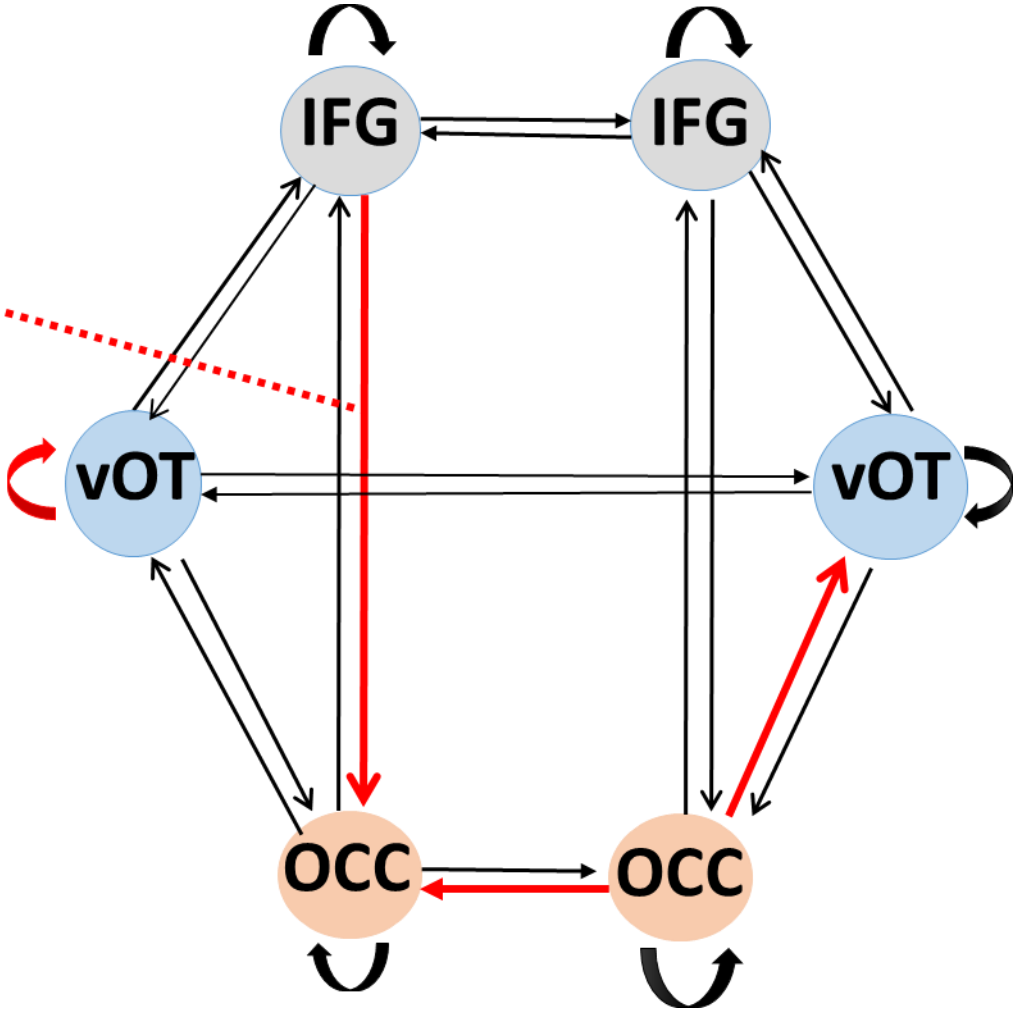
- iReadMore improves word reading accuracy
- Effects are item specific
- Longevity is better than the pure alexia study
- PROMS are positive

Still to come...

- Does tDCS facilitate learning?
- Does training result in structural changes (MPM)?
- Does training result in connectivity changes (MEG)?
- Explore individual variability

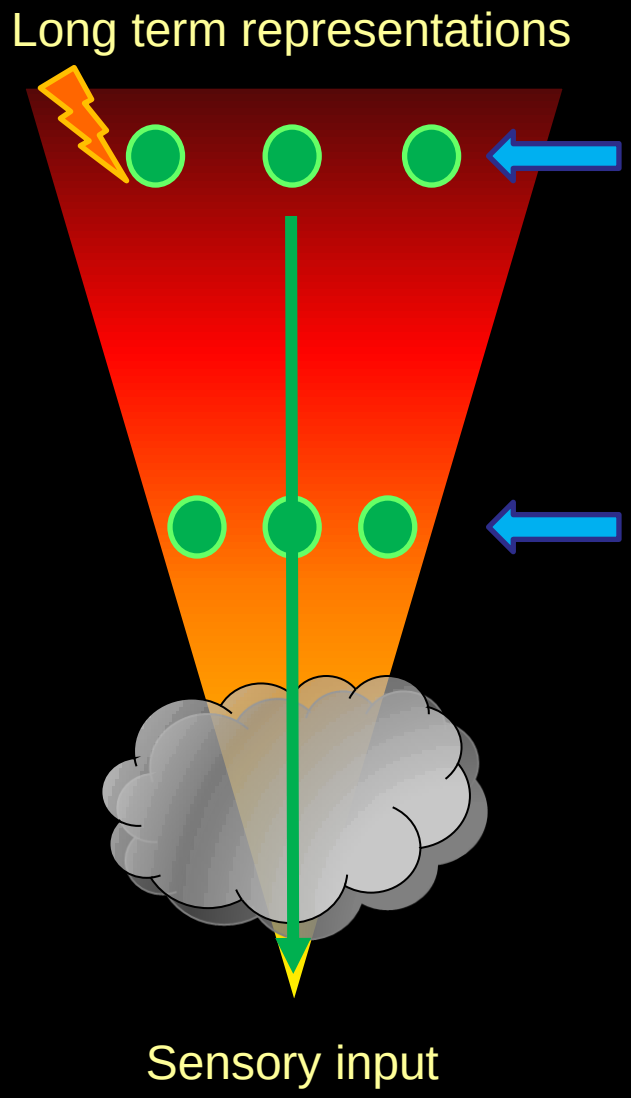
iReadMore: MEG Pts vs. Controls pre-Rx





Connections with significantly greater positive modulation (words vs false fonts) Patients than controls

How do these results inform therapy?



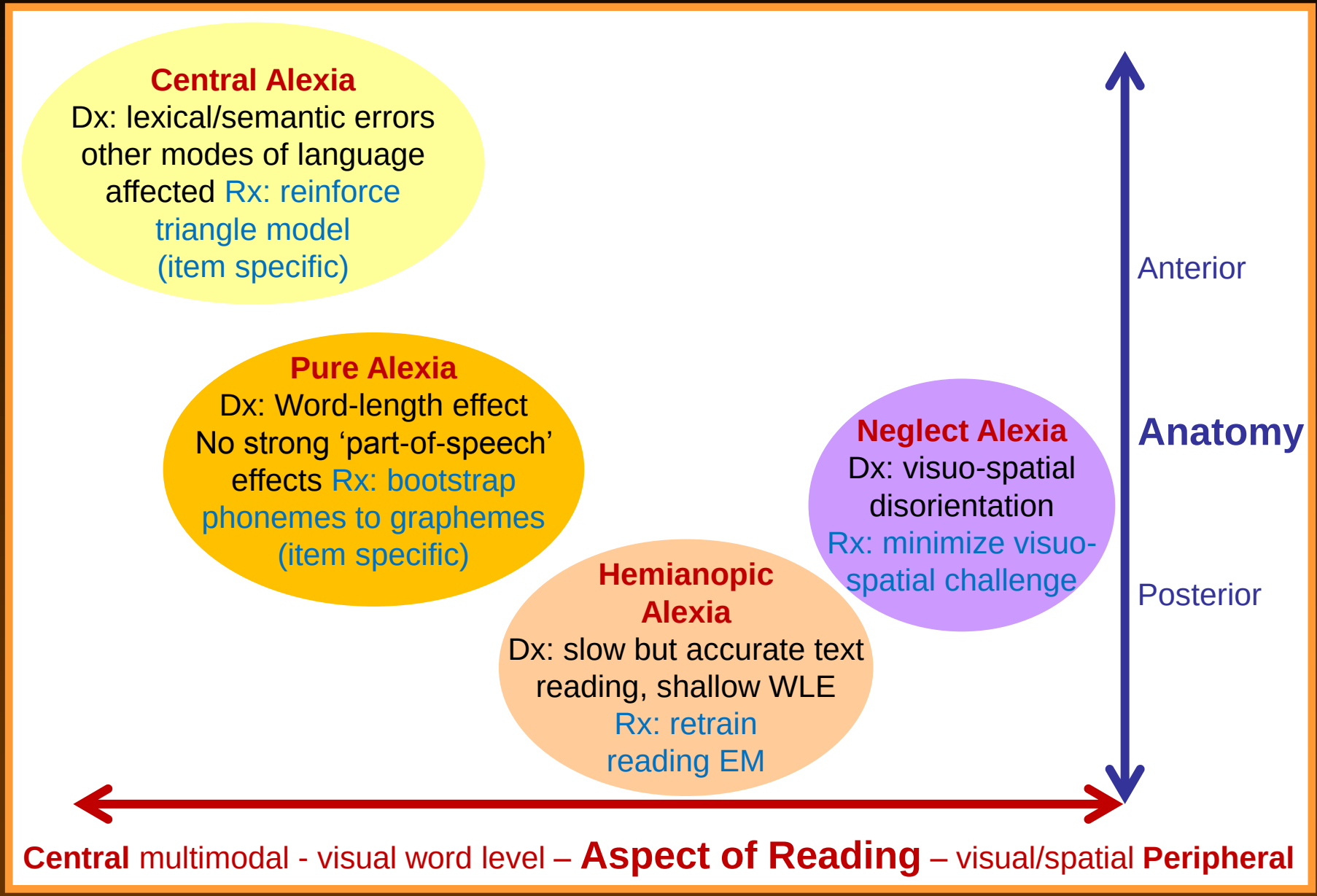
Psychophysical and functional imaging evidence points to top-down representations being the key to practice-based language recovery

Currently using paired associate learning with stimuli entering via the damaged route supported by another route (pure alexia) or routes (central alexia)

Augmenting behavioural therapy with focal stimulation (tDCS) to the top node in the language system (left IFG)

Therapy is hard to access, so we are developing self-supporting, web-based versions of proven language therapies

2D map of the four alexias



Corbetta, M., Kincade, M. J., Lewis, C., Snyder, A. Z., & Sapir, A. (2005). Neural basis and recovery of spatial attention deficits in spatial neglect. Nature neuroscience, 8(11), 1603-1610.

Crisp, J., & Lambon Ralph, M. A. (2006). Unlocking the nature of the phonological–deep dyslexia continuum: The keys to reading aloud are in phonology and semantics. Journal of Cognitive Neuroscience, 18(3), 348-362.

Dignam, J., Copland, D., McKinnon, E., Burfein, P., O'Brien, K., Farrell, A., & Rodriguez, A. D. (2015). Intensive Versus Distributed Aphasia Therapy A Nonrandomized, Parallel-Group, Dosage-Controlled Study. Stroke, 46(8), 2206-2211.

Habekost, T., Petersen, A., Behrmann, M., & Starrfelt, R. (2014). From word superiority to word inferiority: Visual processing of letters and words in pure alexia. Cognitive neuropsychology, 31(5-6), 413-436.

Koiava, N., Ong, Y. H., Brown, M. M., Acheson, J., Plant, G. T., & Leff, A. P. (2012). A 'web app' for diagnosing hemianopia. Journal of Neurology, Neurosurgery & Psychiatry, jnnp-2012.

Leff, A. P., Spitsyna, G., Plant, G. T., & Wise, R. J. S. (2006). Structural anatomy of pure and hemianopic alexia. Journal of Neurology, Neurosurgery & Psychiatry, 77(9), 1004-1007.

Leff, A., & Starrfelt, R. (2013). Alexia: diagnosis, treatment and theory. Springer Science & Business Media.

Miller, E. K. (2000). The prefontral cortex and cognitive control. Nature reviews neuroscience, 1(1), 59-65.

Ong, Y. H., Brown, M. M., Robinson, P., Plant, G. T., Husain, M., & Leff, A. P. (2012). Read-Right: a "web app" that improves reading speeds in patients with hemianopia. J Neurol.

Ong, Y. H., Jacquin-Courtois, S., Gorgoraptis, N., Bays, P. M., Husain, M., & Leff, A. P. (2015). Eye-Search: a web-based therapy that improves visual search in hemianopia. Annals of Clinical and Translational Neurology, 2(1), 74-78.

Rayner, K., Inhoff, A. W., Morrison, R. E., Slowiaczek, M. L., & Bertera, J. H. (1981). Masking of foveal and parafoveal vision during eye fixations in reading. Journal of Experimental Psychology: Human perception and performance, 7(1), 167.

Starrfelt, R., Habekost, T., & Leff, A. P. (2009). Too little, too late: reduced visual span and speed characterize pure alexia. Cerebral Cortex, 19(12), 2880-2890.

Woodhead, Z. V., Penny, W., Barnes, G. R., Crewes, H., Wise, R. J., Price, C. J., & Leff, A. P. (2013). Reading therapy strengthens top–down connectivity in patients with pure alexia. Brain, 136(8), 2579-2591.

Woodhead, Z.V. J, Ong, Y. H., & Leff, A. P. (2015). Web-based therapy for hemianopic alexia is syndrome-specific. BMJ Innovations.

Yong, K. X., Rajdev, K., Shakespeare, T. J., Leff, A. P., & Crutch, S. J. (2015). Facilitating text reading in posterior cortical atrophy. Neurology, 85(4), 339-348.

Zhang, X., Kedar, S., Lynn, M. J., Newman, N. J., & Biousse, V. (2006). Natural history of homonymous hemianopia. Neurology, 66(6), 901-905.