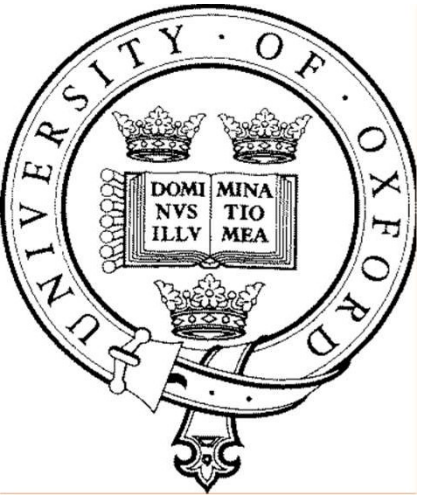
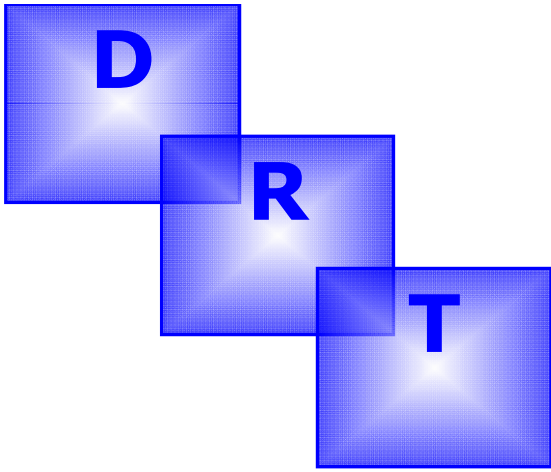


Oxford Dyslexia Association
13/10/2017

John Stein, Magdalen College, Oxford



‘Wobbles, Warbles & Fish’ - the Magnocellular Theory of Dyslexia

The real work was done by Sue Fowler, Tricia Riddell, Piers Cornelissen, Joel Talcott, Priti Kashyap, Joe Taylor, Ceris Mumford, Silvia Paracchini, Anna Pitt

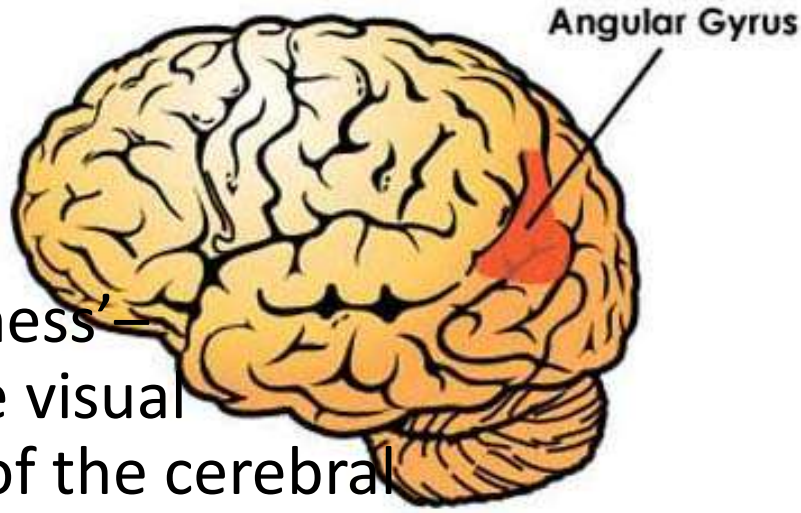
Supported by The Dyslexia Research (www.dyslexic.org.uk), Dyers & Colourists, Esmee Fairbairn, Garfield Weston, Tolkien and Wellcome Trusts, BBC Children in Need

ARGUMENT

- What is dyslexia – discrepancy between low reading v. high oral intelligence; genetic
- Visual sequencing –visual magnocellular system
- Auditory Sequencing – auditory magnocells
- Genetic Basis – KIAA0319, MCR5
- Immunity
- Nutrition – low omega3s

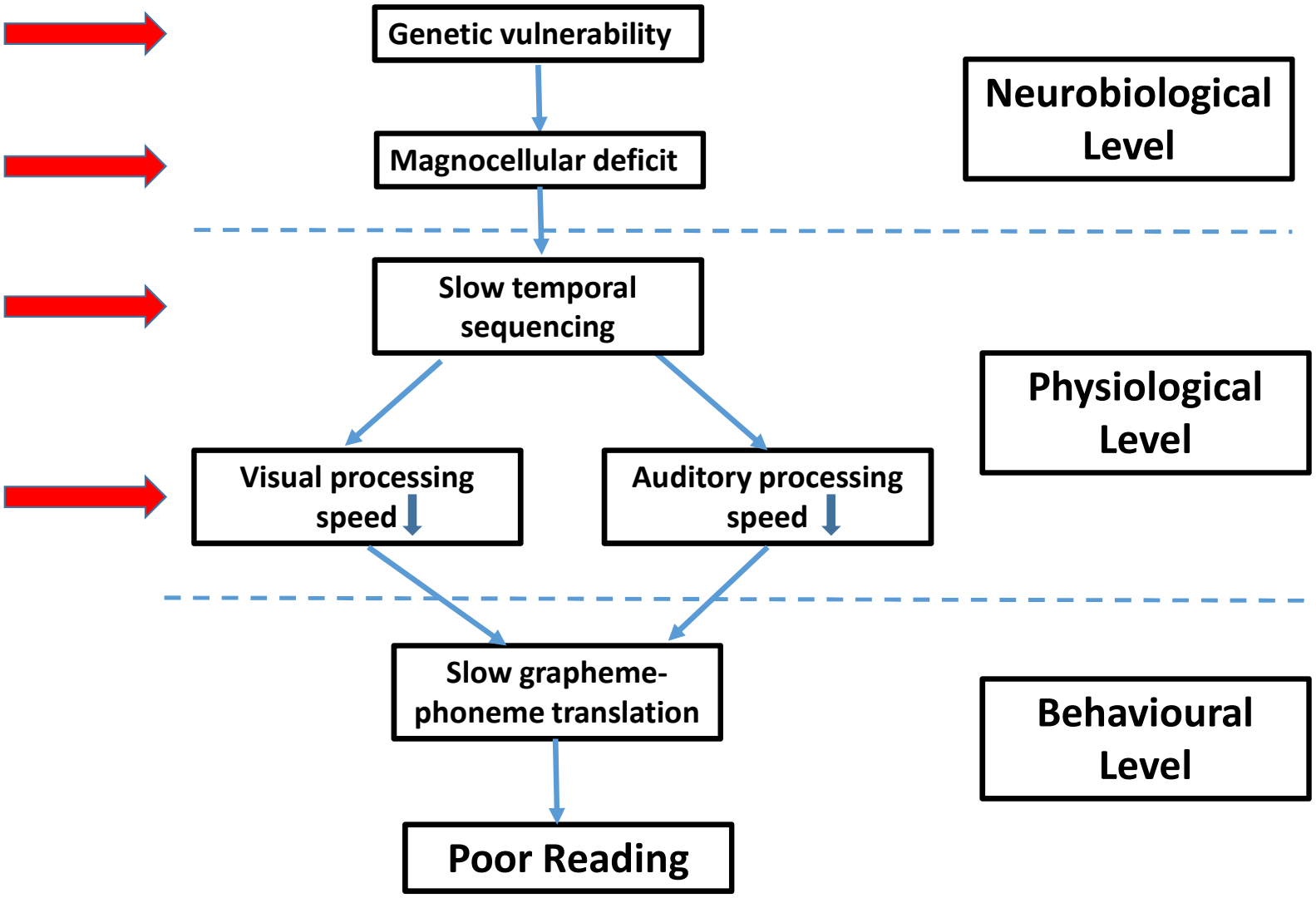
What is Dyslexia?

- The word ‘dyslexia’ was coined by Rudolf Berlin in 1887 to describe ‘acquired’ dyslexia - stroke patients who had lost the ability to read, but retained their sight, hearing and other cognitive skills
- It was a selective loss, specific to reading, implying a discrepancy between reading and other skills.
- Ascribed by Dejerine to visual ‘word blindness’ – loss of the neural representations of the visual form of words in the left angular gyrus of the cerebral cortex



Developmental Dyslexia

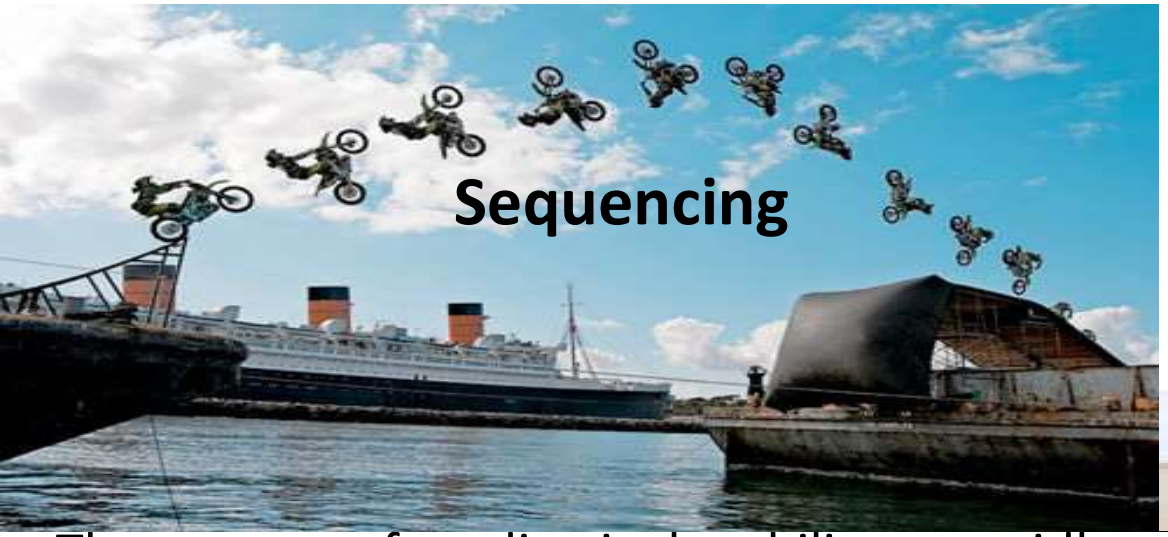
- 1896 – Pringle Morgan first described ***developmental*** 'word blindness'
  a) v. *poor reading* – Percy could not even read his own name
  b) orally he was the 'most intelligent boy in the class',
  ie. *discrepancy* between his reading and intelligence
  c) probably 'congenital' – hereditary/*genetic*.
- These are still the 3 cardinal features of the ***neurobiological*** view of developmental dyslexia
- Now however, many people believe that dyslexia is a 'purely phonological' problem; hence this 'neurological model' is not appropriate
- So everything I say will be deemed **controversial** by some people!


Genetic vulnerability
Magnocellular deficit
Slow temporal sequencing
Visual processing speed
Auditory processing speed
Slow grapheme-phoneme translation
Poor Reading
Neurobiological Level
Physiological Level
Behavioural Level

Dyslexia is a ‘neurobiological syndrome’

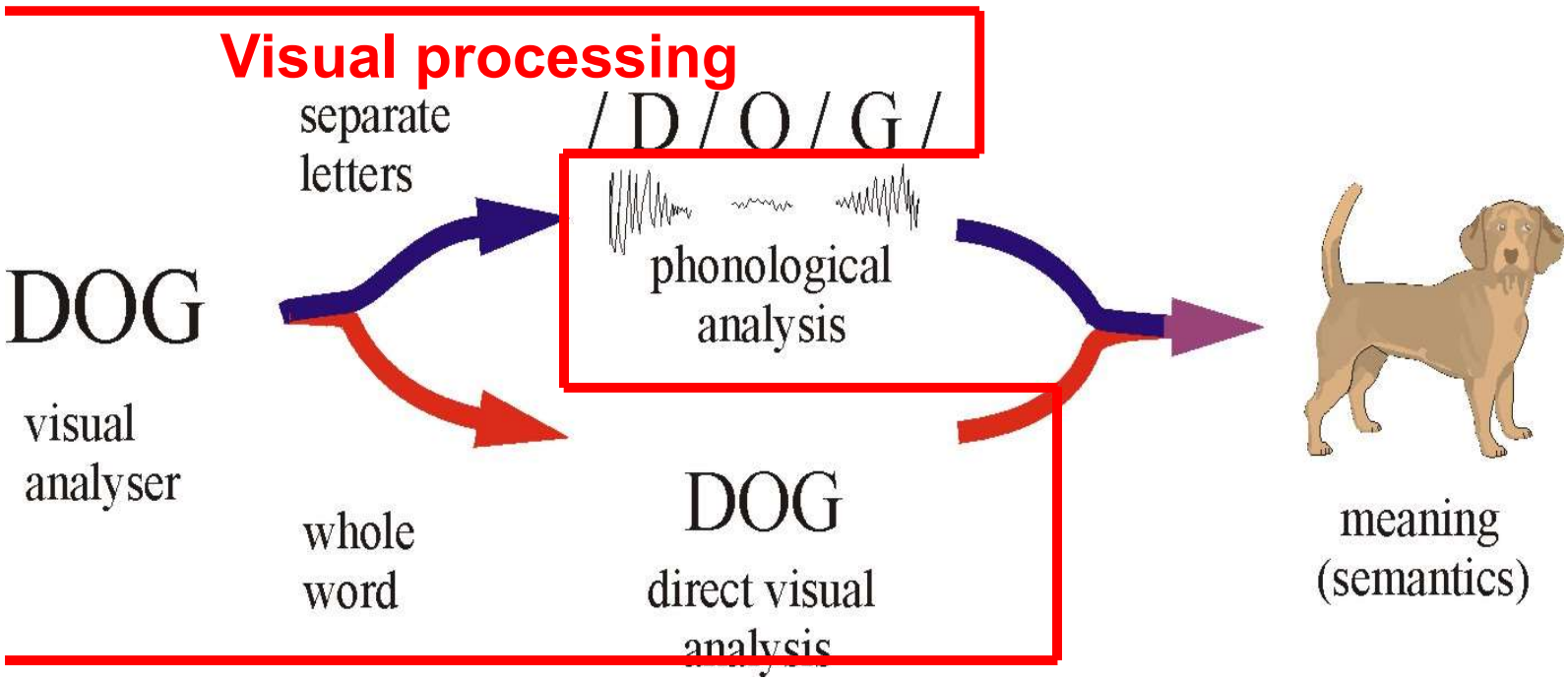
- Genetic basis – family history, 60% heritability, 2-4x greater prevalence in **males**
- Structural brain differences – cortical ectopias, smaller thalamic m- cells, left arcuate, right cerebellum
- Physiological differences: *slow temporal processing*
- ∴ *poor sequencing*, bad eye control & poor pronunciation

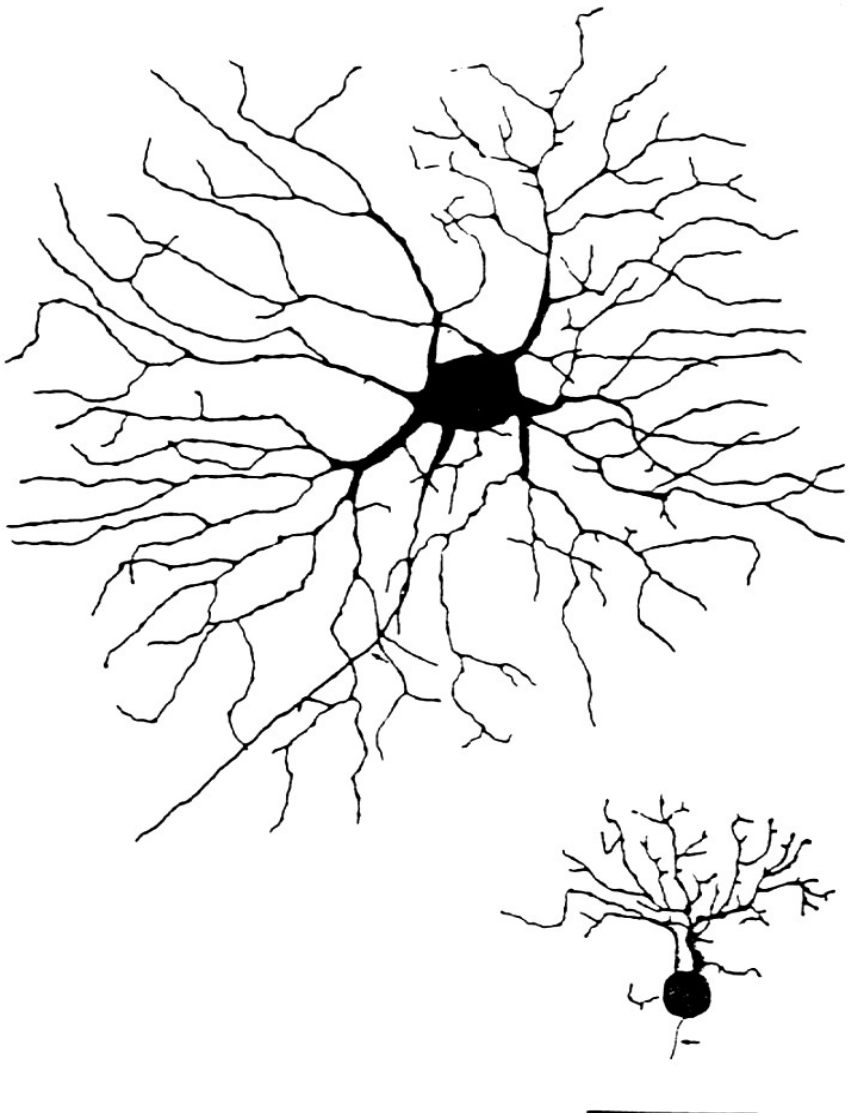
- Delayed crawling, walking, speaking
- Missequencing order of letters
- Missequencing sounds: mispronunciations, spoonerisms, Left/right confusions
- Overlap with other **neurodevelopmental** disorders: dysphasia, dyspraxia, ADHD, ASD
- Association with **autoimmunity**



- The essence of reading is the ability to rapidly **sequence** the seen letters in a word in the correct order
- Then we have to translate this **visual sequence** into an **auditory sequence** of the sounds they represent
- We also have to build up a background knowledge of how each spoken word can be split into a unique **sequence** of separate sounds (**phonemes**)
- These processes require **rapid temporal processing** to shift visual attention, move the eyes across the letters and attend to the **order of the sounds** in a word
- Visual and auditory temporal processing (‘**magnocellular**’) neural systems mediate these **sequencing** computations

Reading is primarily a visual process



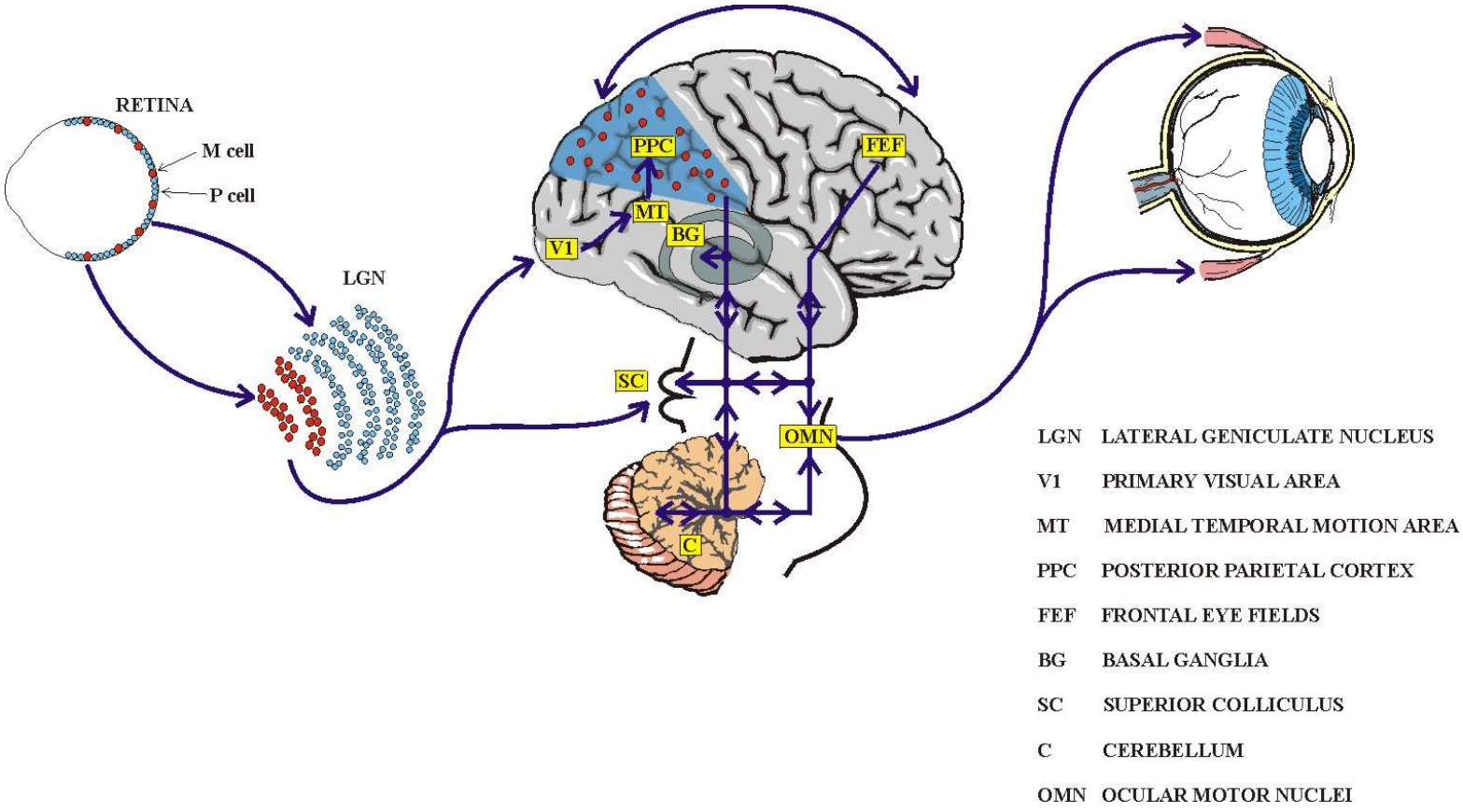


Magnocellular & parvocellular cells in the retina

10% are large **magnocellular** cells (>10x larger area than p-cells) - they time visual events: fast responses, high sensitivity to contrast, flicker & motion; they control the focus of visual attention & eye movements. They are highly vulnerable

Most retinal ganglion cells are **parvocellular** (small): for colour, fine detail, need high contrast (less vulnerable)

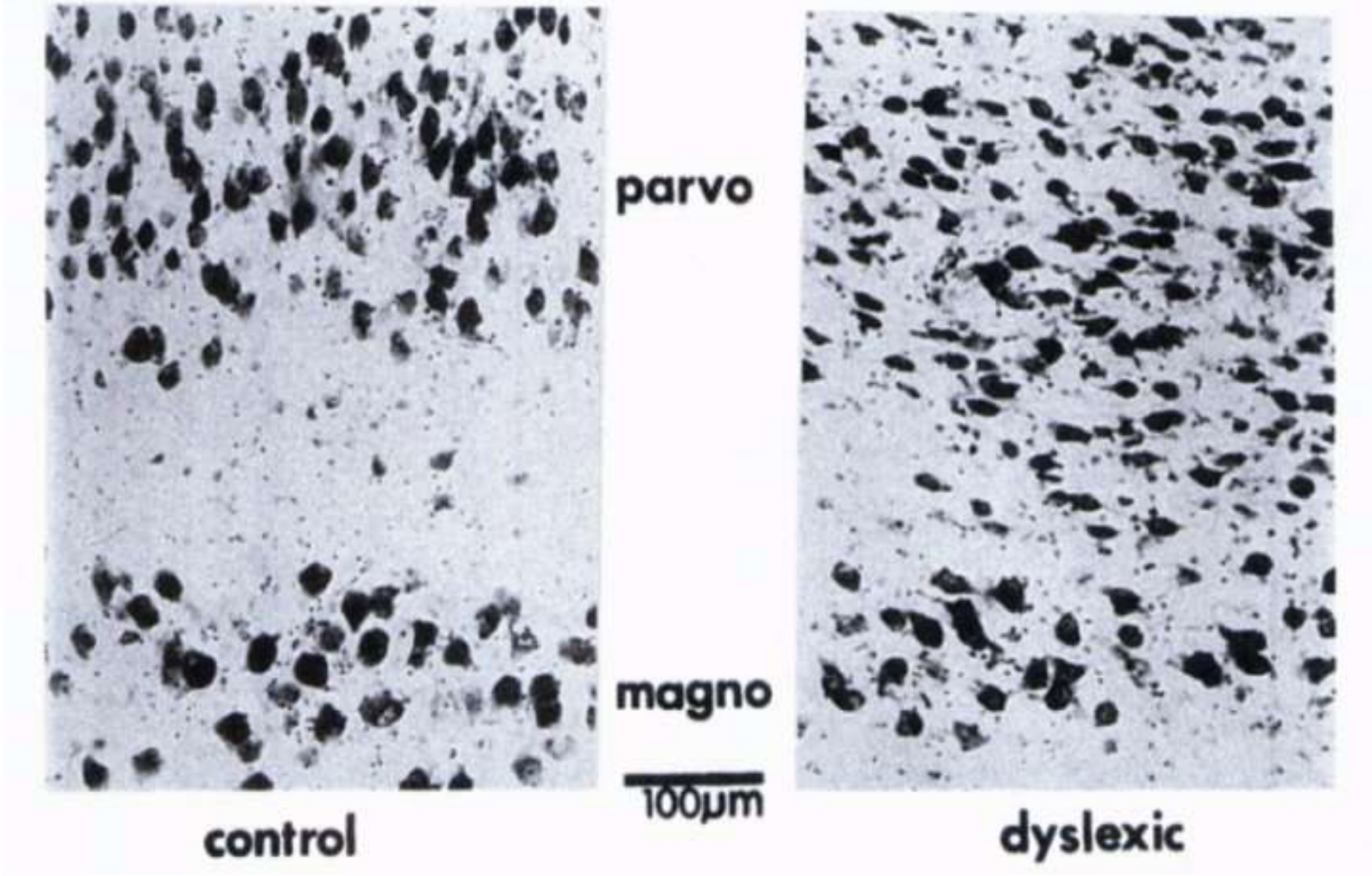
The visual magnocellular system provides the main input to the 'dorsal visuomotor stream' which guides the sequencing of visual attention & eye movements for reading.



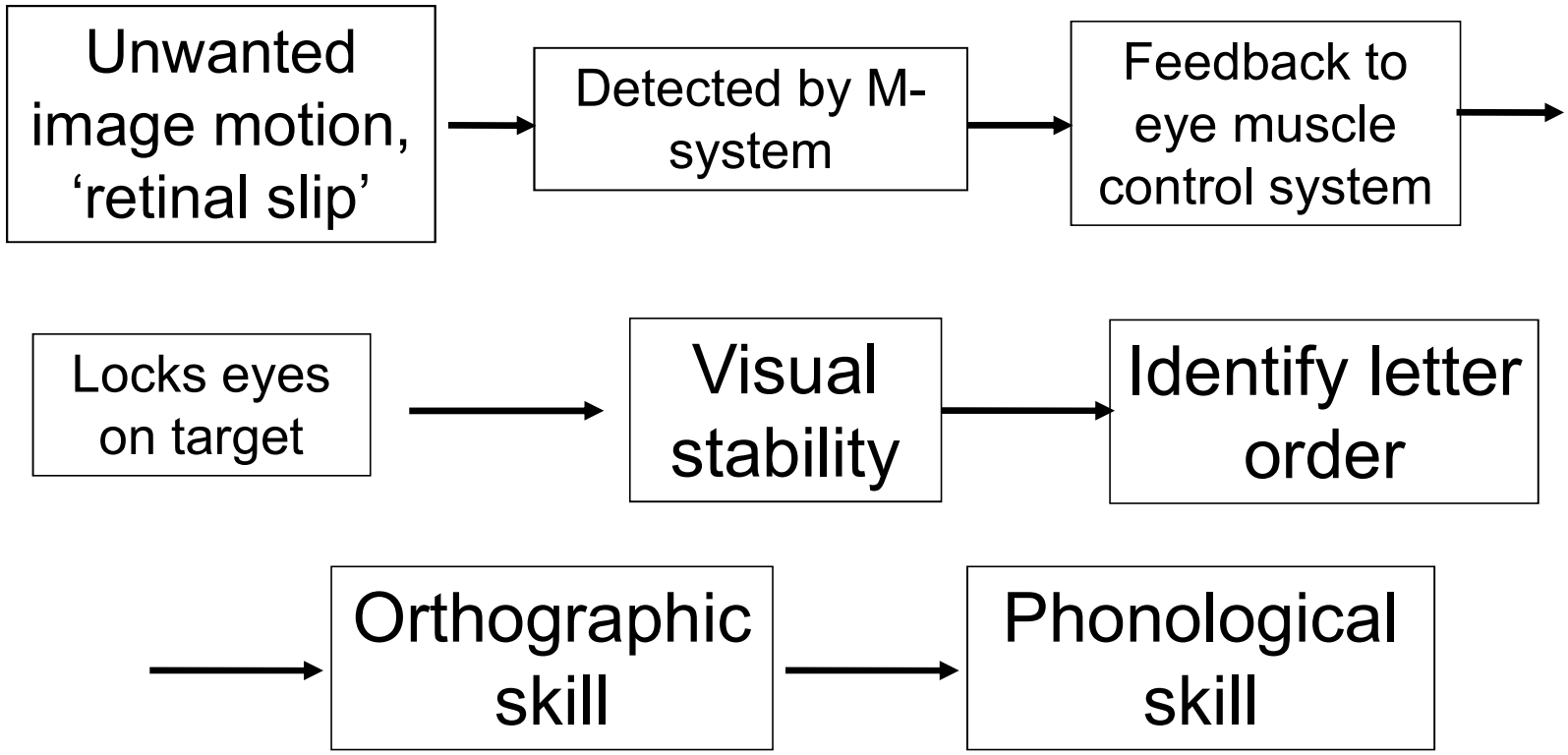
The visual magnocellular system is impaired in dyslexics

- 30% smaller LGN magnocells, *post mortem* and MRI
- Reduced and delayed evoked brain waves
- Reduced visual motion sensitivity
- Unstable eye control
- Reduced activation of cortical motion areas (fMRI)
- Lower sensitivity to contrast & flicker
- Lower stereoacuity
- Reduced visual jitter
- Poor visual attention - slower visual search
- Visual crowding
- Left neglect - clock drawing
- Prolonged line motion illusion
- Reduced Ternus effect

Abnormal visual magnocells in a dyslexic brain – confirmed by MRI



Why is high magnocellular sensitivity so important? Because it prevents letters blurring and moving around



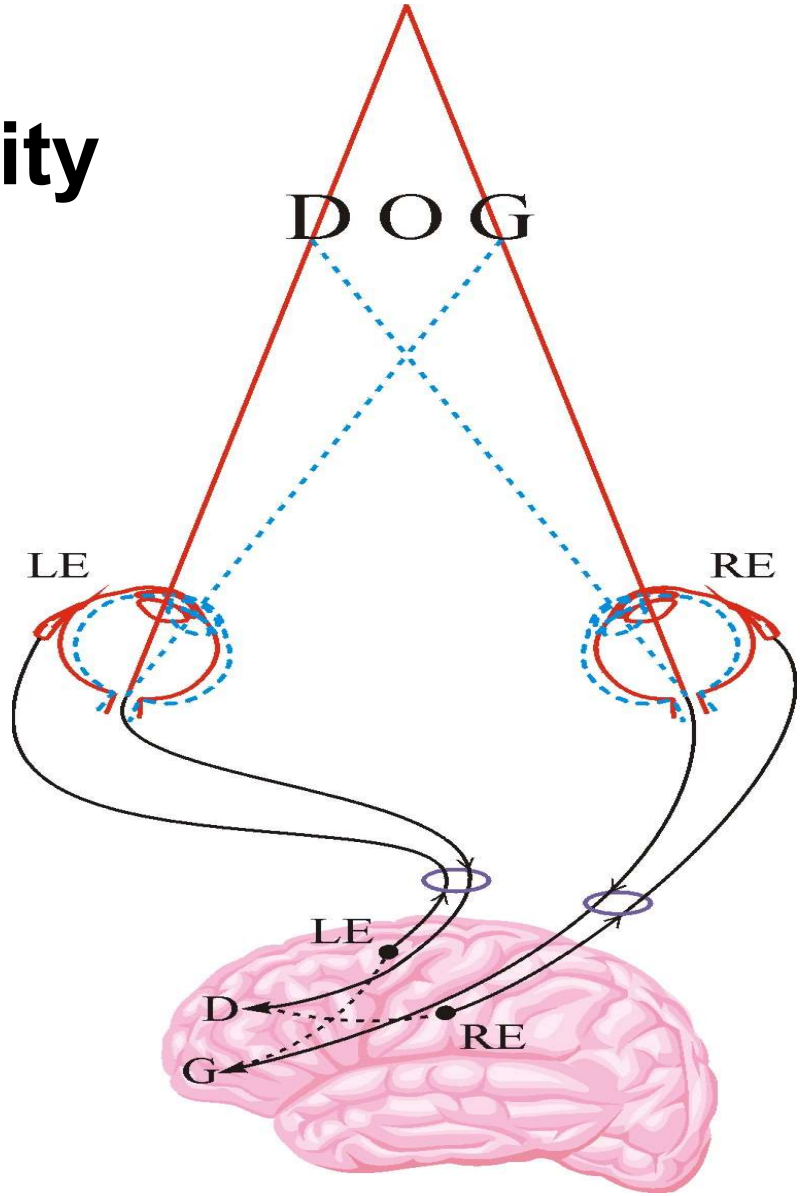

Unstable eyes\blur vision

Unstable visual perception

Four children in every classroom see print this way. They can't control their eye movements at close distances, making reading and attention almost impossible. As the print blurs and moves, they stumble over words, lose their place, and can't comprehend. Out of desperation, they give up and quit. Is it any wonder they struggle in school?

Vergence instability

- When reading the eyes also have to **converge** for near vision
- Control of **vergence** eye movements is dominated by the visual magno system
- The vergence eye movement control system is the most vulnerable to drugs and disease
- **Many poor readers have unstable vergence control**



A weak magnocellular system causes unstable vision - oscillopsia

"The letters go all blurry"

"The letters move over each other, so I can't tell which is which"

"The letters seem to float all over the page"

"The letters move in and out of the page"

"The letters split and go double"

"The c moved over the r, so it looked like another c"

"The p joined up with the c"

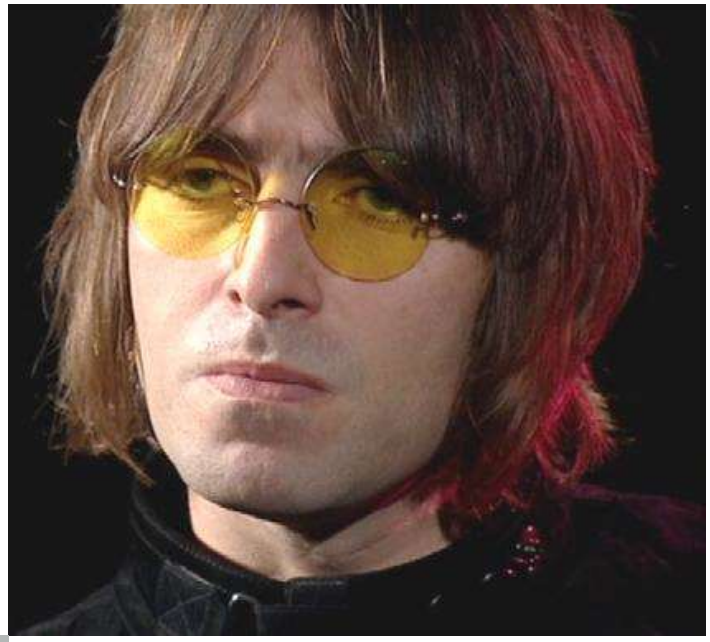
"d's and b's sort of get the wrong way round"

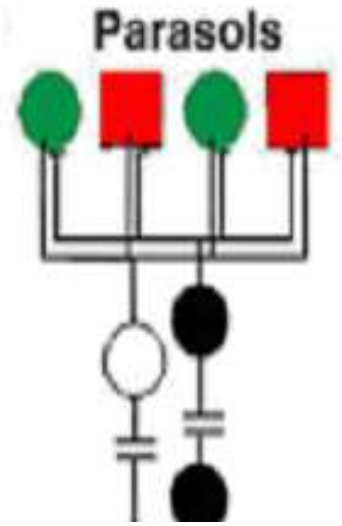
"The page goes all glary and hurts my eyes"

"I keep on losing my place"

How can we improve visual magnocellular function?

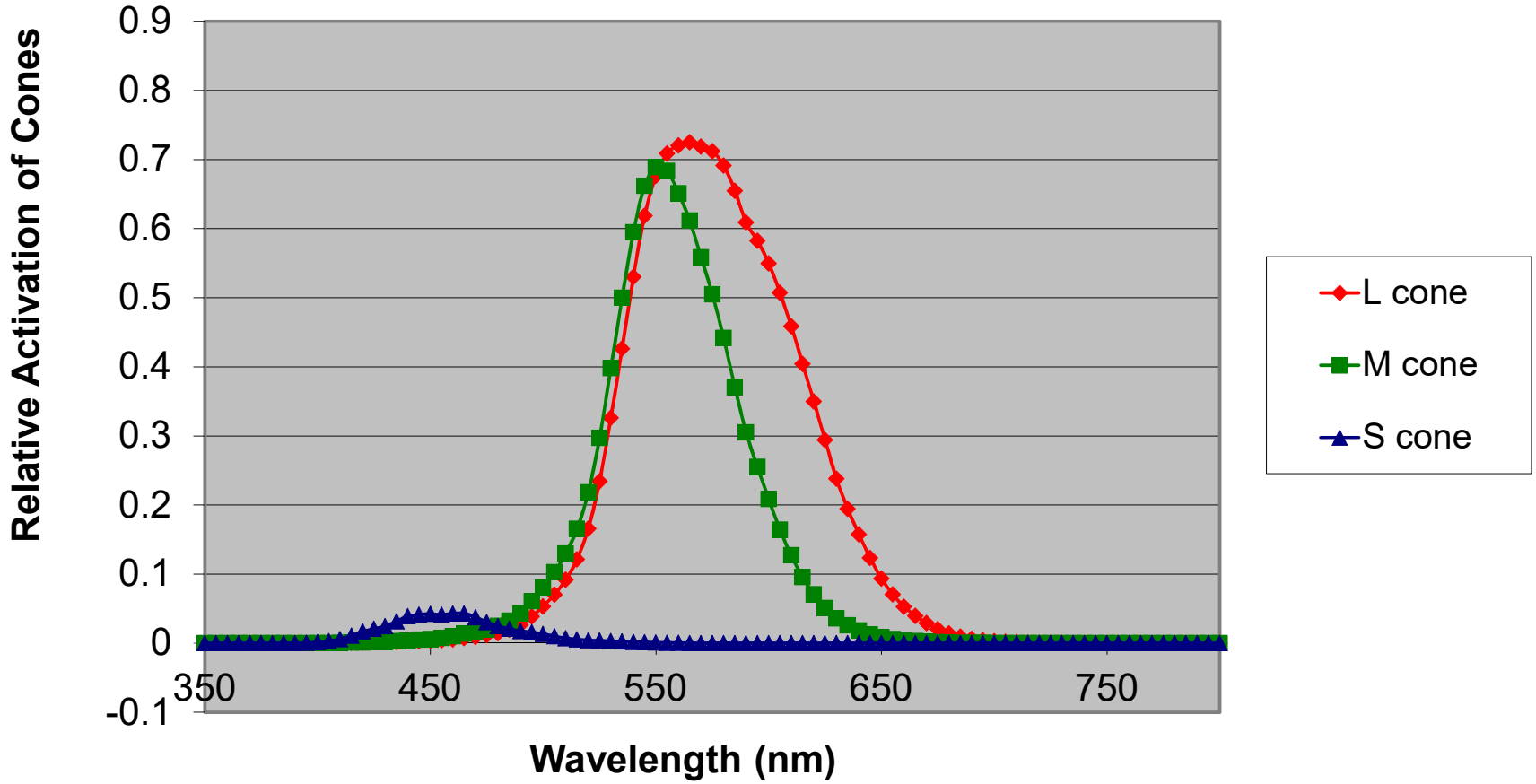
- Magnocells do not mediate colour vision, but they receive mainly from red and green cones.
- ∴they are most sensitive to yellow light
- In ¼ of dyslexics viewing text through yellow filters can improve magnocellular function, visual motion sensitivity and binocular control, hence improve reading





Oxford Yellow Lenses

Oxford yellow filters (negative blue) cut short wavelengths (blue) most

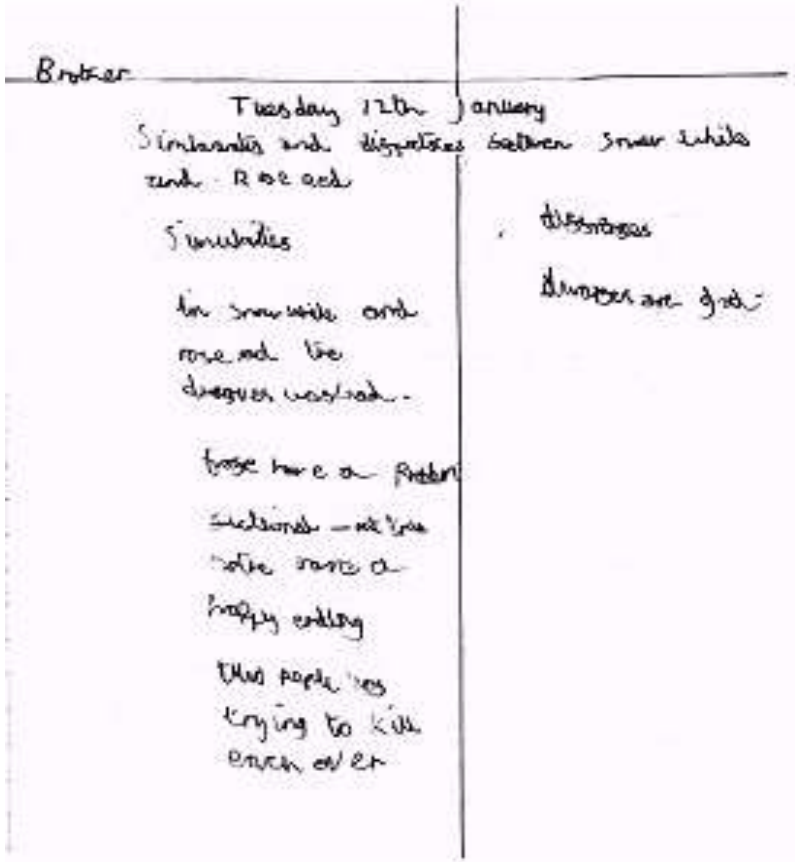


<¼ of dyslexics can be helped by viewing text through yellow filters

Their magnocellular function improves and their reading advances by av. 6 months in 3 months

Yellow Glasses

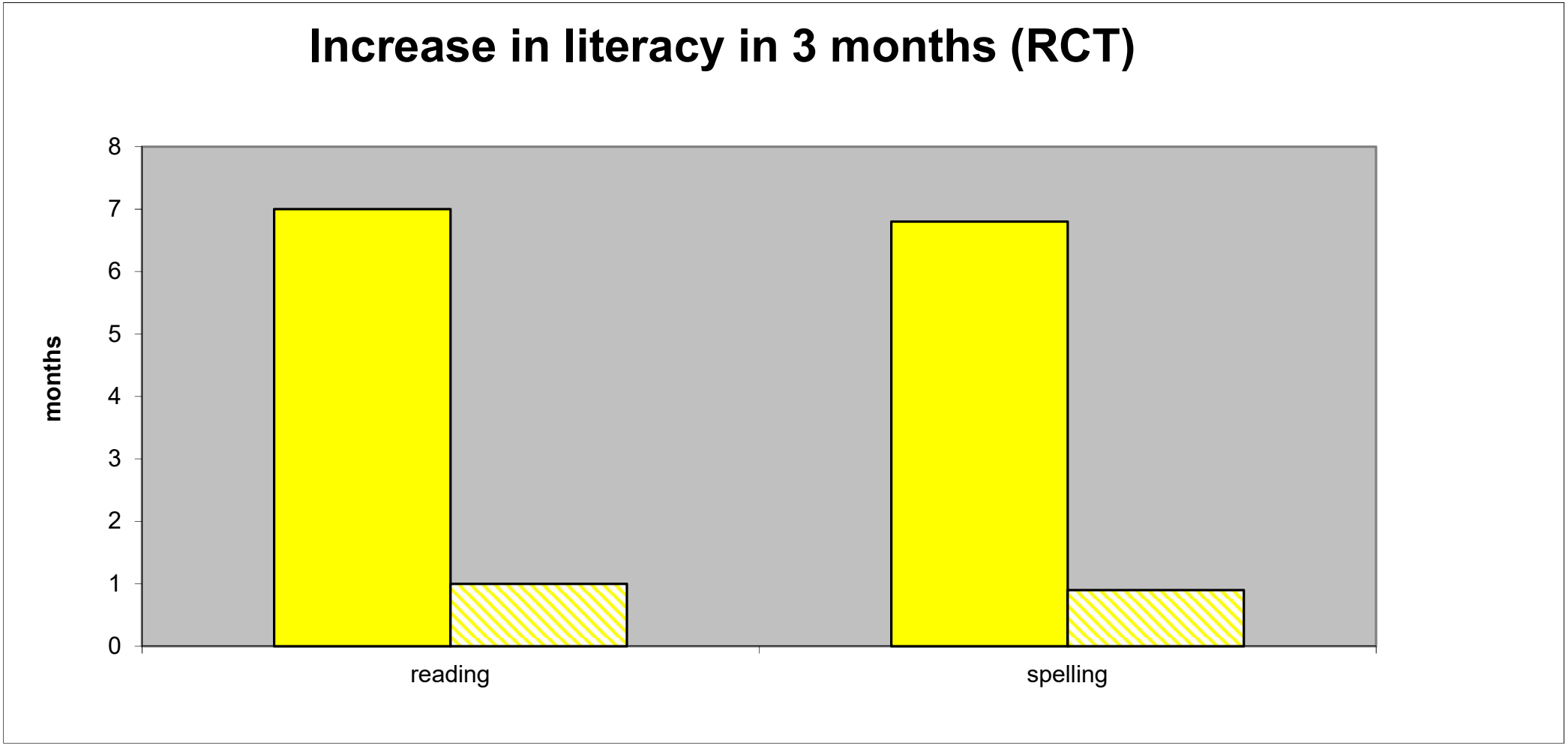
Before



Only 1 *week* later

1. In which county is castleton? Derbyshire Village overlooked by mam tor
2. Which mountain is it overlooked by? mount mam it has land slides and very big.
3. When was the village first founded? in 1198 many old custom mes survive such as the garland.
4. Which industries has castleton had in the past? such as Cam milling candle and rope making
5. Why do you think castleton is called this? because it has a Castle and it is on top of a hill
6. Who built peveril castle and when? William conquer it was in 1066.
7. What are the names of the four caverns? blue john speed well peak cavern treak cliff cavern
8. What was made in treak cliff cavern? mad slate used for houses and other places.
9. discribe what blue jhon looks like? blue] horite made from Stones and have different colours like red yellow pink purple
10. Can you find out more about the old Customs that survived in castleton? its the most valuable since blue jhon.

Yellow filters can improve reading



Visual symptoms can be alleviated by either yellow or blue filters

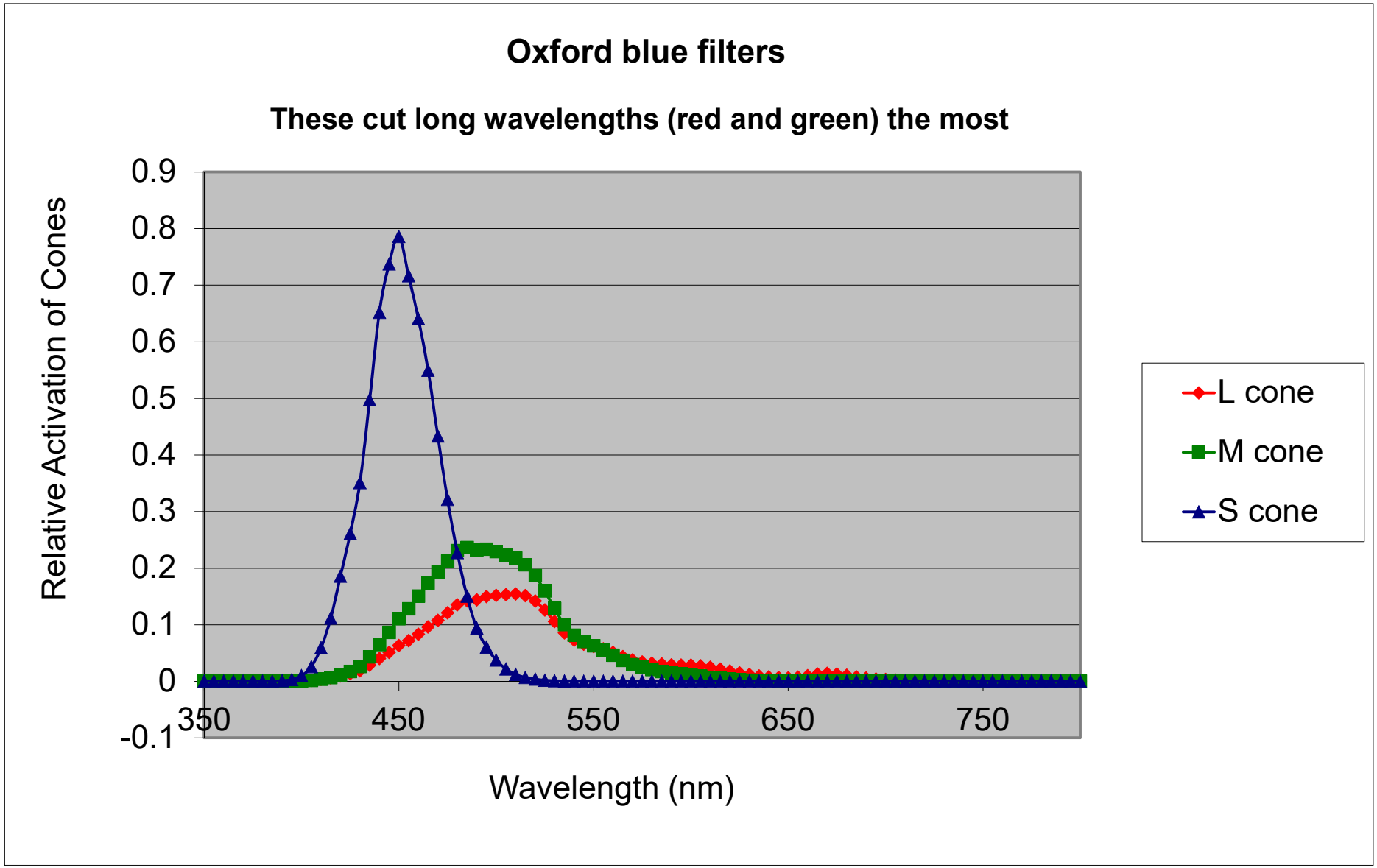
Yellow filters may help the 1/4 of dyslexics for whom :

- Letters blur due to failure to achieve precise focus (accommodation) - static ‘defocus blur’
- Double vision after a few minutes, due to failure to maintain accurate convergence

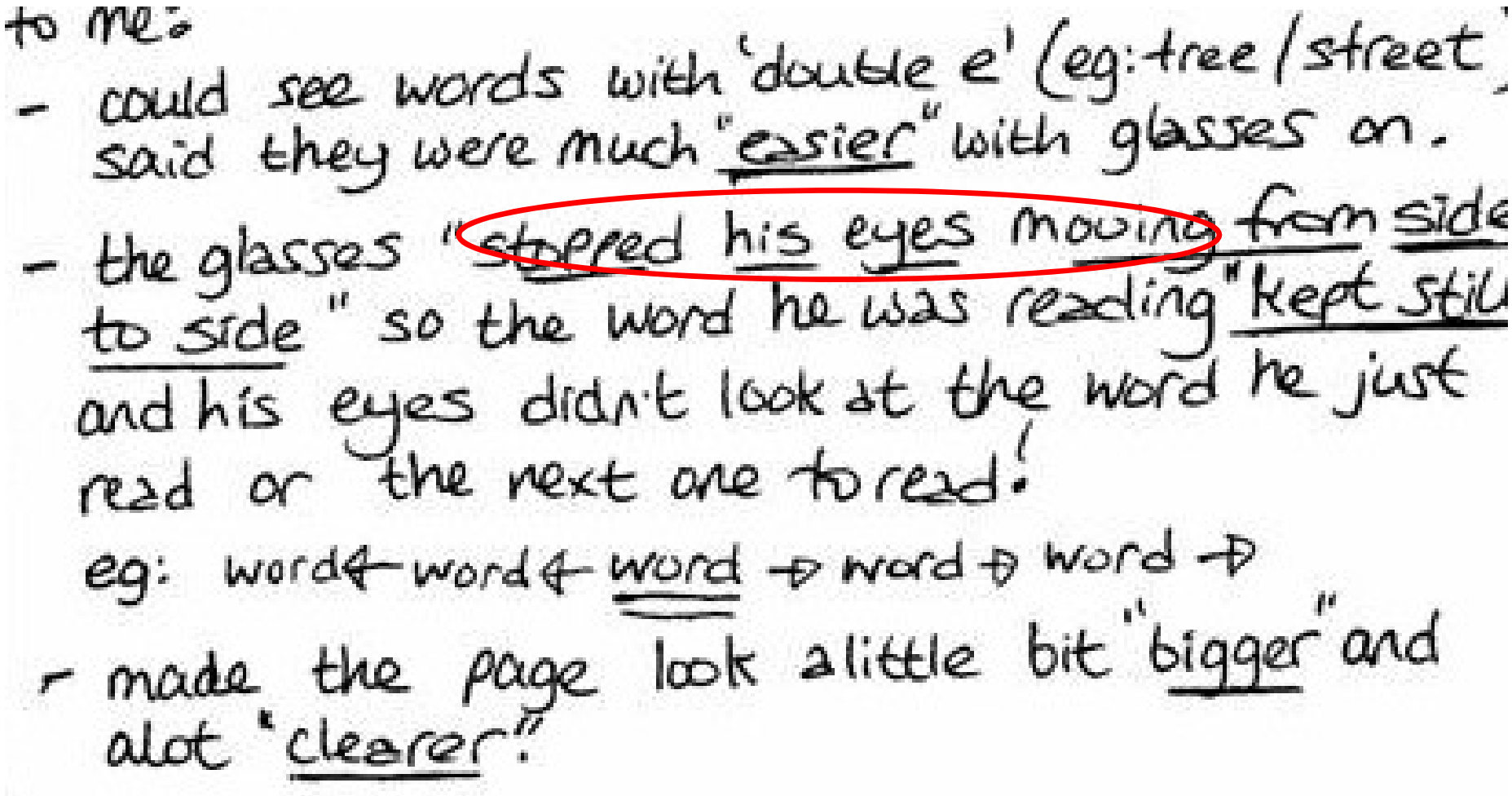
Blue filters may help another ¼ for whom:

- Letters ‘fizz’ and move around due to failure to maintain stable fixation
- Poor concentration
- Headaches
- Poor sleeping
- Travel sickness

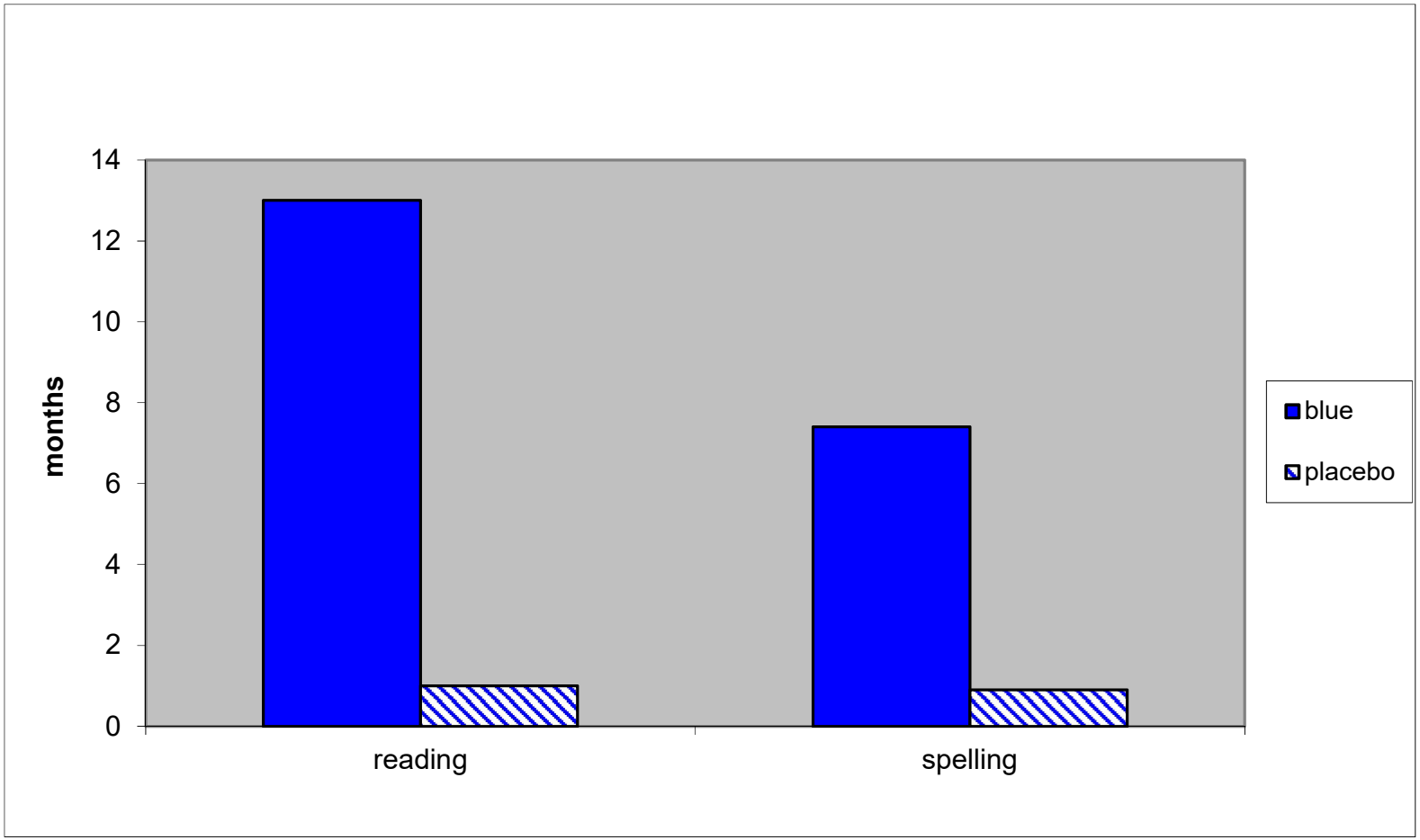

A different 1/4
of dyslexics can
benefit from
Oxford blue
filters


Oxford blue filters
These cut long wavelengths (red and green) the most
Relative Activation of Cones
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
350
450
550
650
750
Wavelength (nm)
L cone
M cone
S cone

Blue filters made the letters keep still!

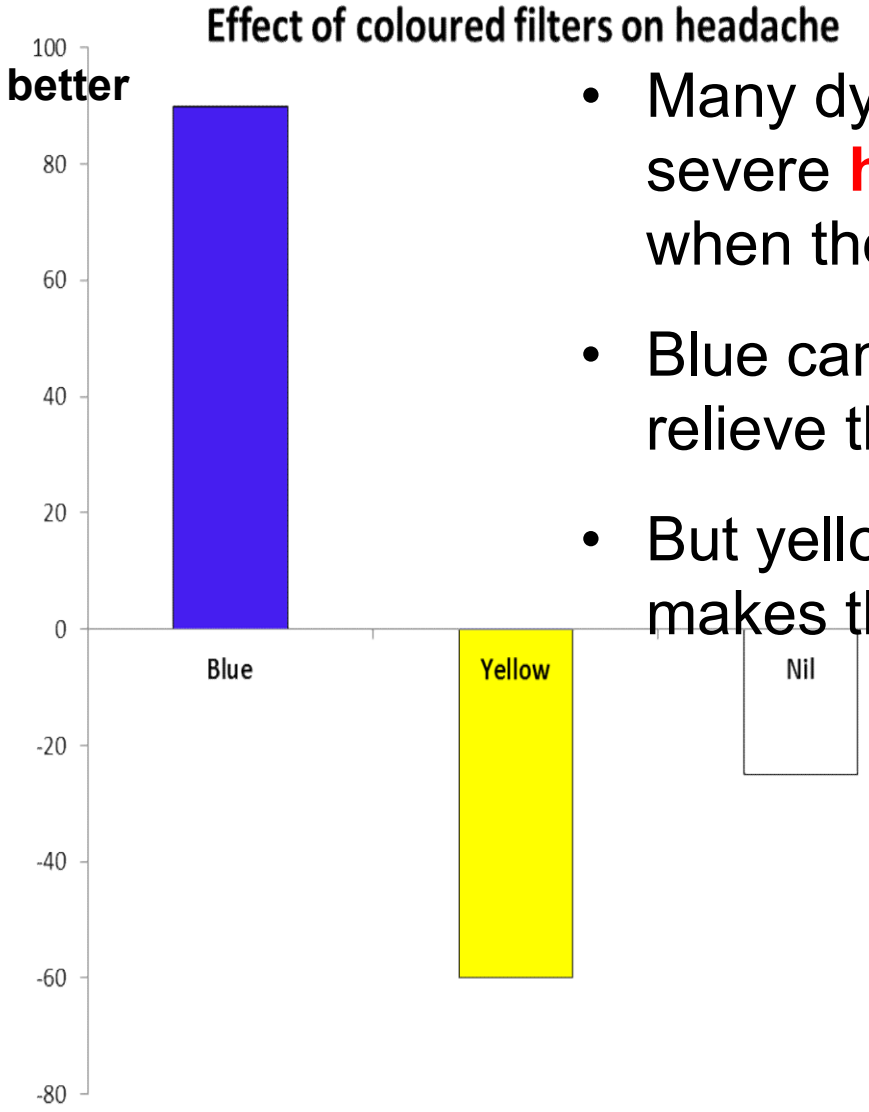


Blue filters can greatly improve reading

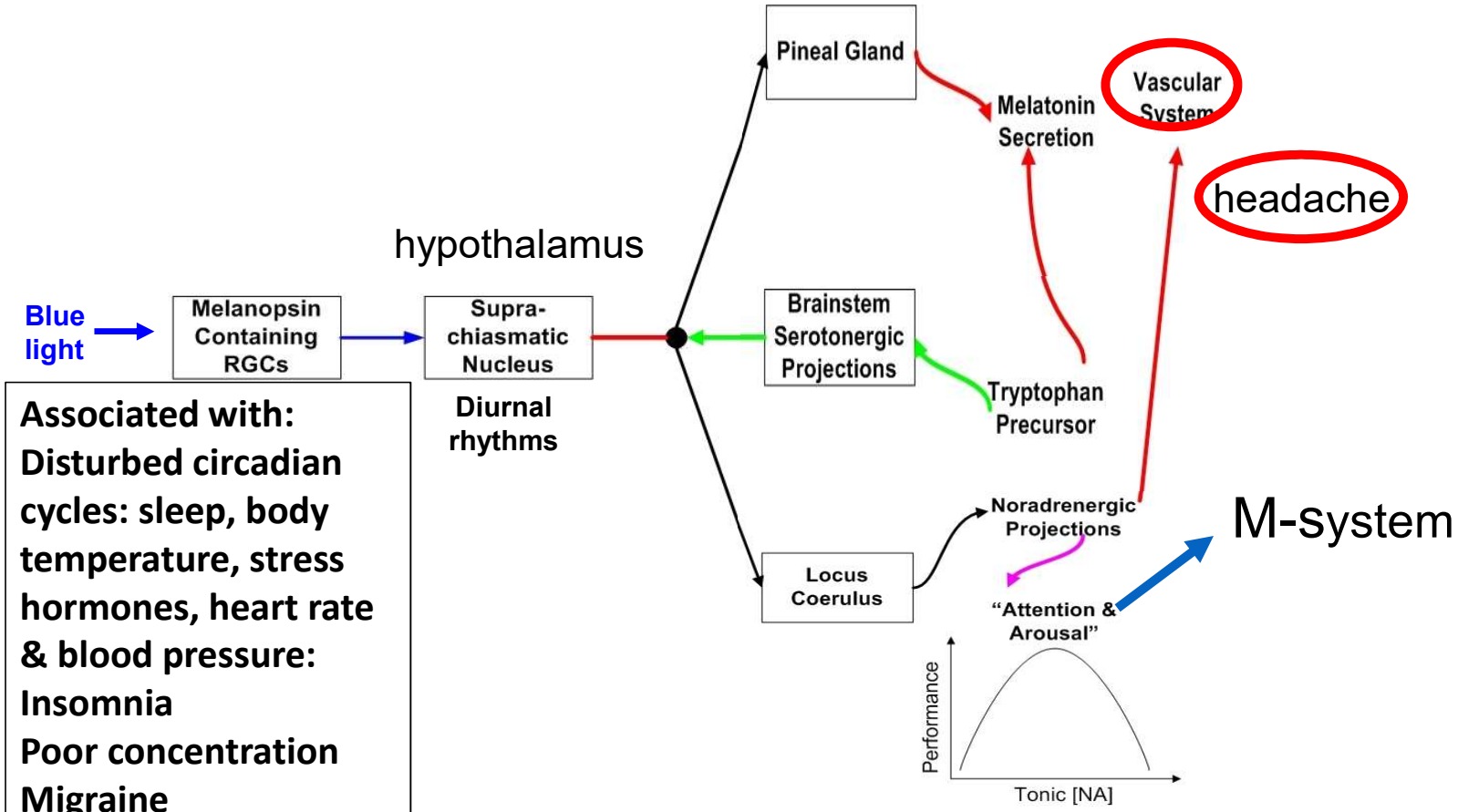


Blue filters probably work via the brain's clock in the hypothalamus

B - Dull Shifting Y - Highly Labile



- Many dyslexics get severe **headaches** when they read
- Blue can often relieve these
- But yellow often makes them worse!



Associated with:
Disturbed circadian cycles: sleep, body temperature, stress hormones, heart rate & blood pressure:
Insomnia
Poor concentration
Migraine
Travel sickness
Depression
ME

B - Dull Shifting Y - Highly Labile

DRT yellow or blue filters improved reading and spelling more than Harris multicoloured filters

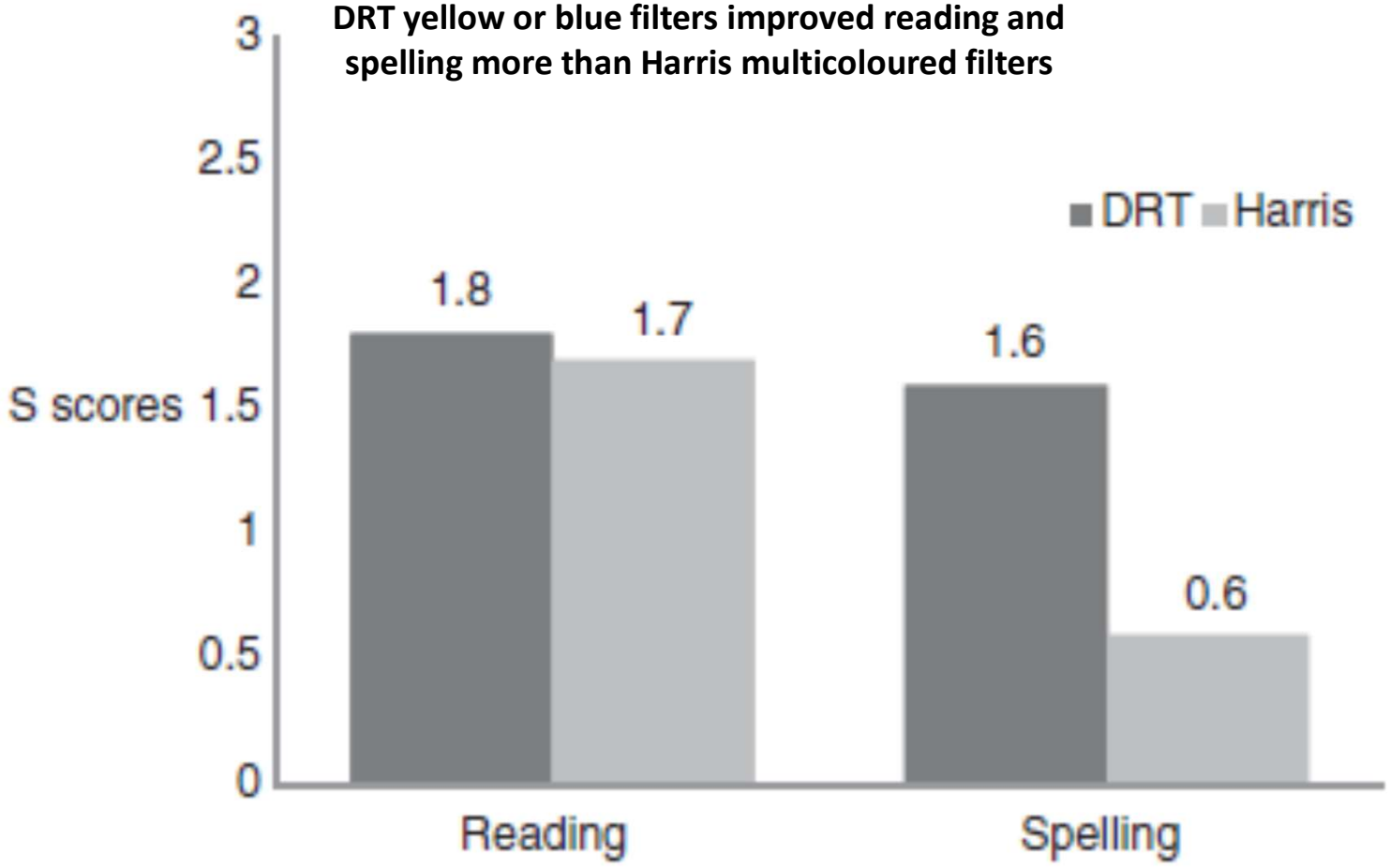
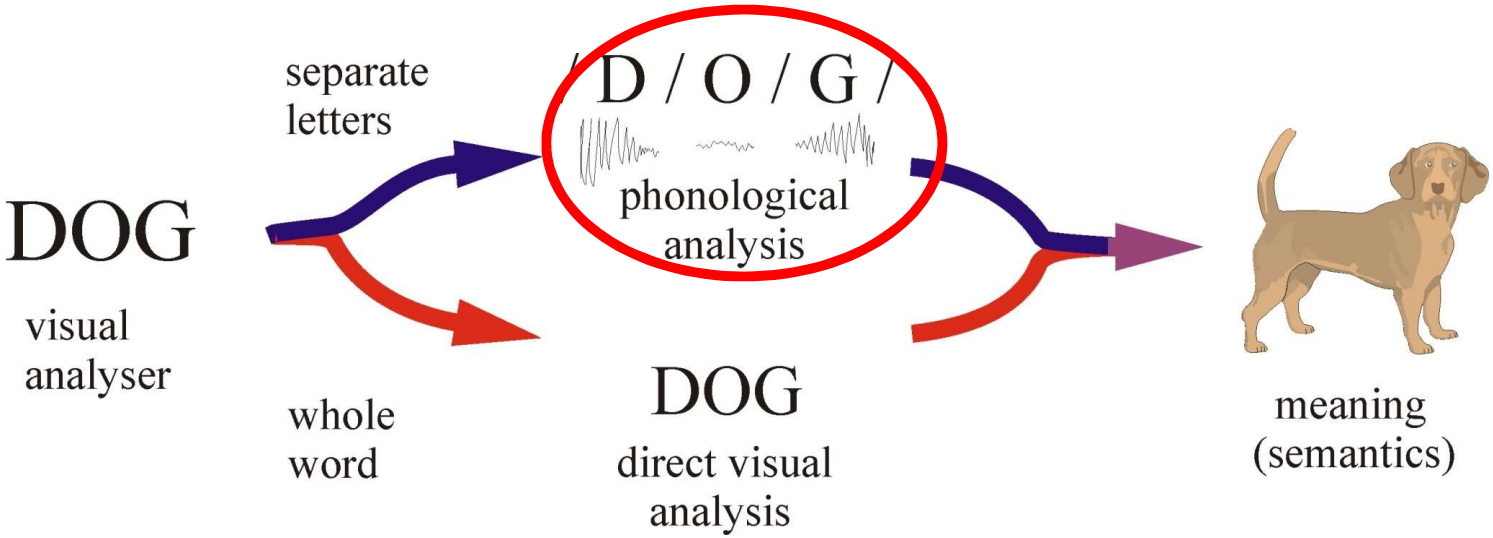


Figure 1. Increase in reading and spelling BAS II "*s*" scores after 3 months use of DRT or Harris filters.

Summary (vision)

- For reading the visual system needs to be able to identify letters *and their order in a word*
- M- temporal processing stabilises vision and times when the eyes move
- Thus a well developed M- system is crucial for sequencing the letters in a word correctly; the M- system is impaired in dyslexics
- Hence their sequencing of letter order, hence orthographical memory, is impaired
- These problems can be alleviated by viewing text through yellow or blue filters

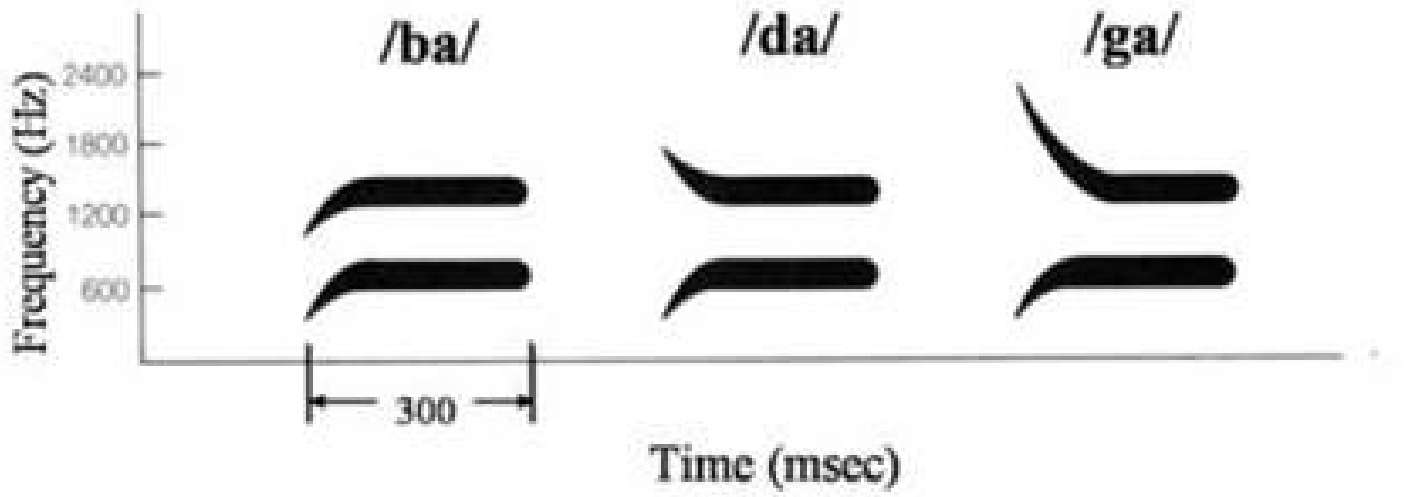
The auditory/phonological pathway



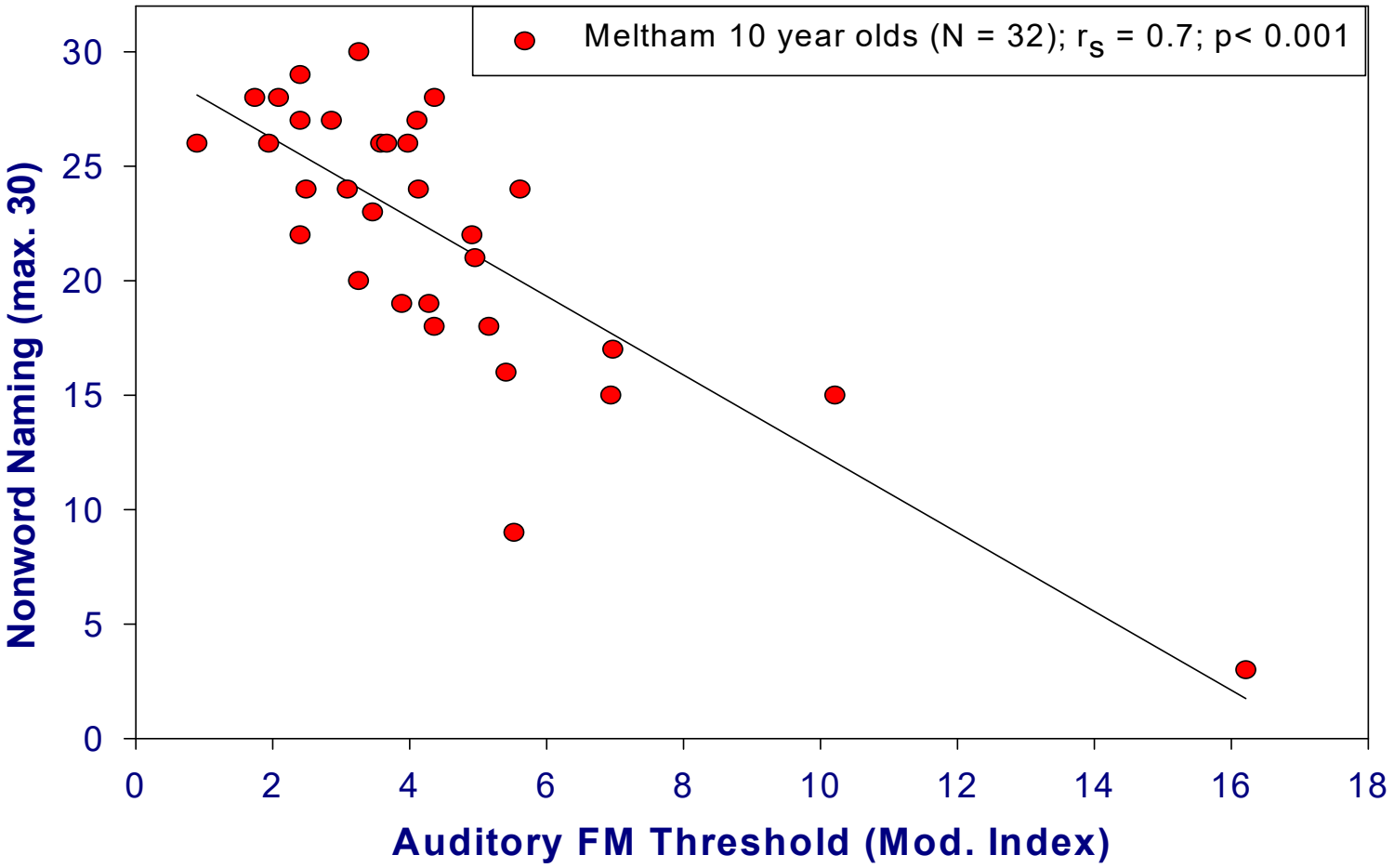
Auditory Sequencing for Reading

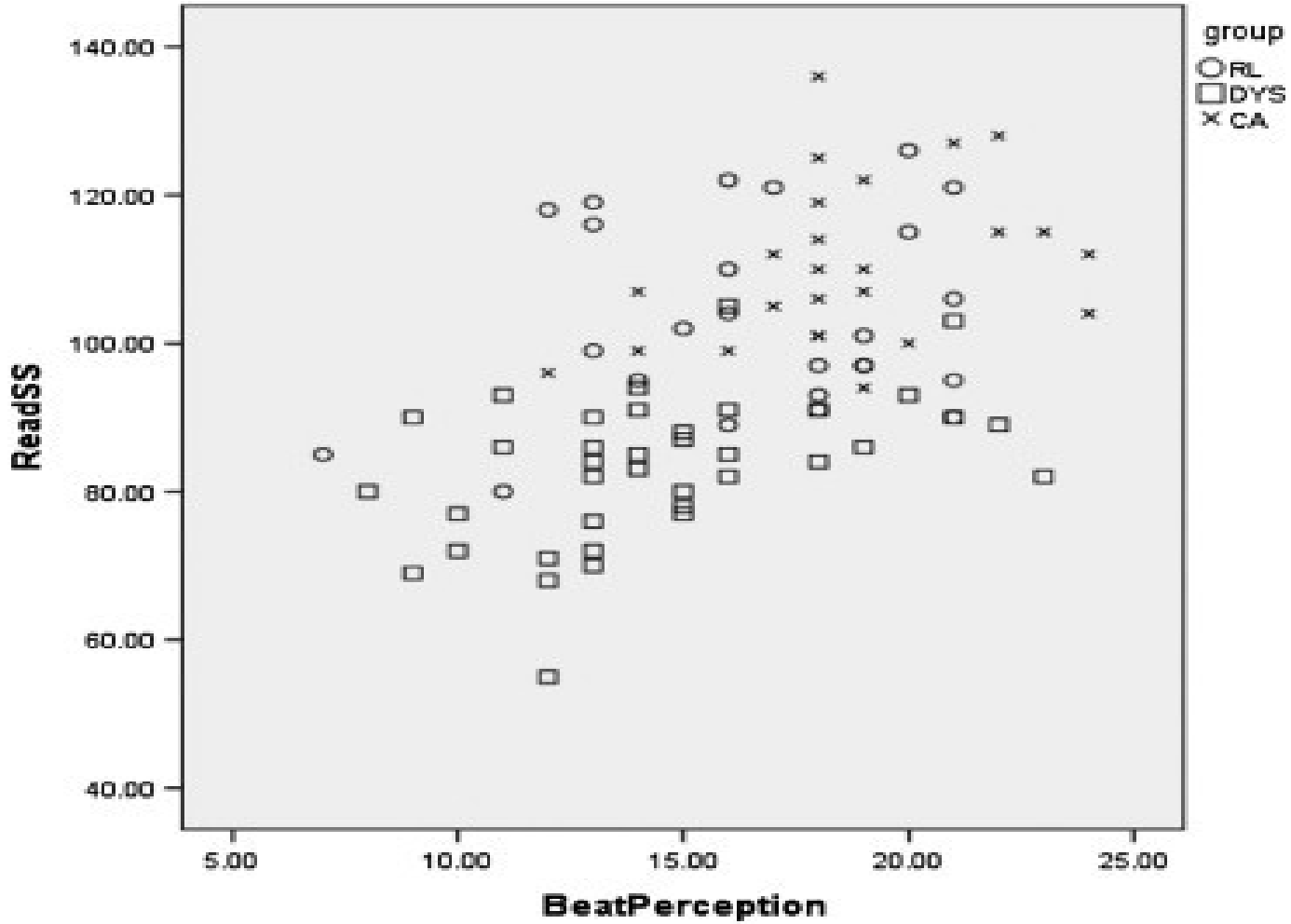
- Need to be able to track the order of phonemes in syllables, syllables in words and words in sentences
- Requires tracking the changes in the amplitude and/or frequency of the sounds
- These enable you to sequence the sounds correctly
- Dyslexics are slower and less accurate at this sequencing
- Probably due to impaired development of their auditory magnocellular system
- Improving their detection of AM & FM improves their reading

2nd formant ascends in frequency for ‘b’;
but descends for ‘d’ & ‘g’.
Subtle auditory processing impairments in dyslexics may reduce sensitivity to these changes in sound frequency, hence underlie their phonological problems



Sensitivity to sound frequency changes determines phonological skill

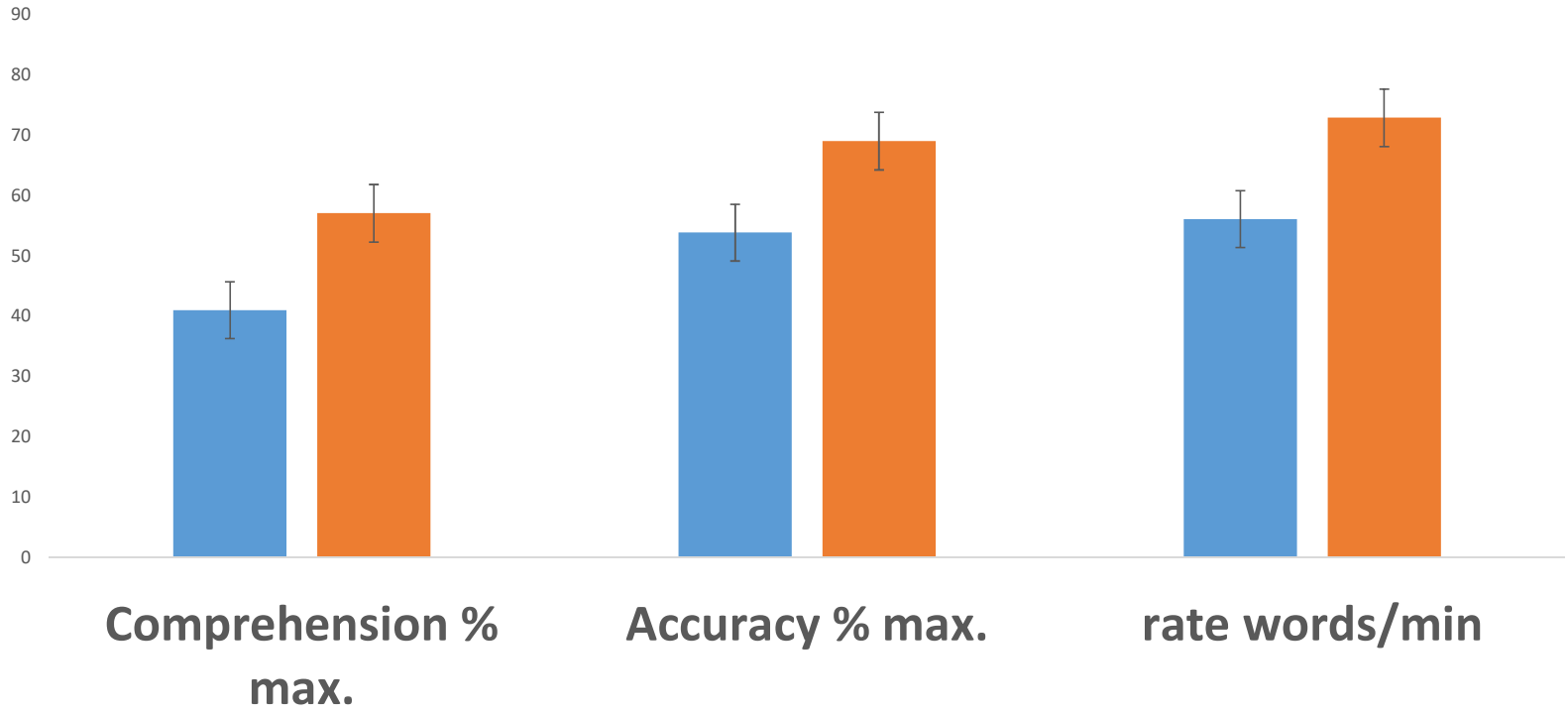




Sensitivity to rhythm (regular amplitude modulations) predicts reading skills in both dyslexics and controls

Rhythm Training improves Reading-

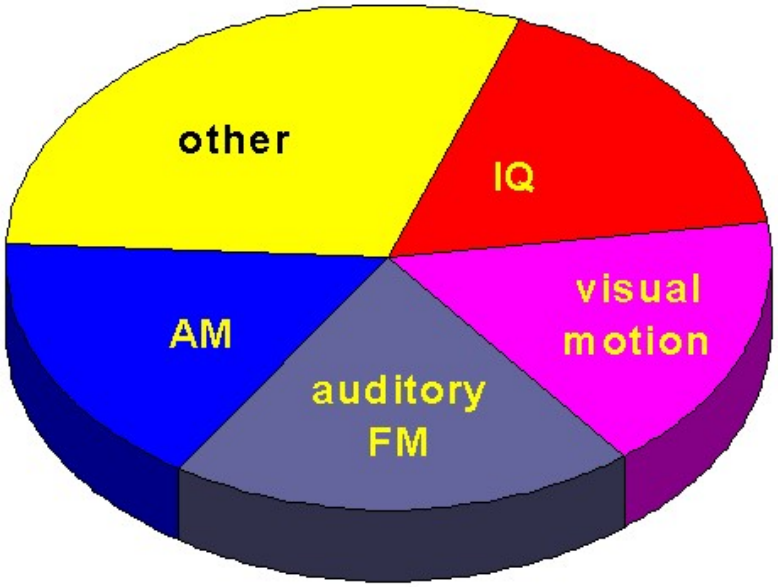
Moreno et al. 2009



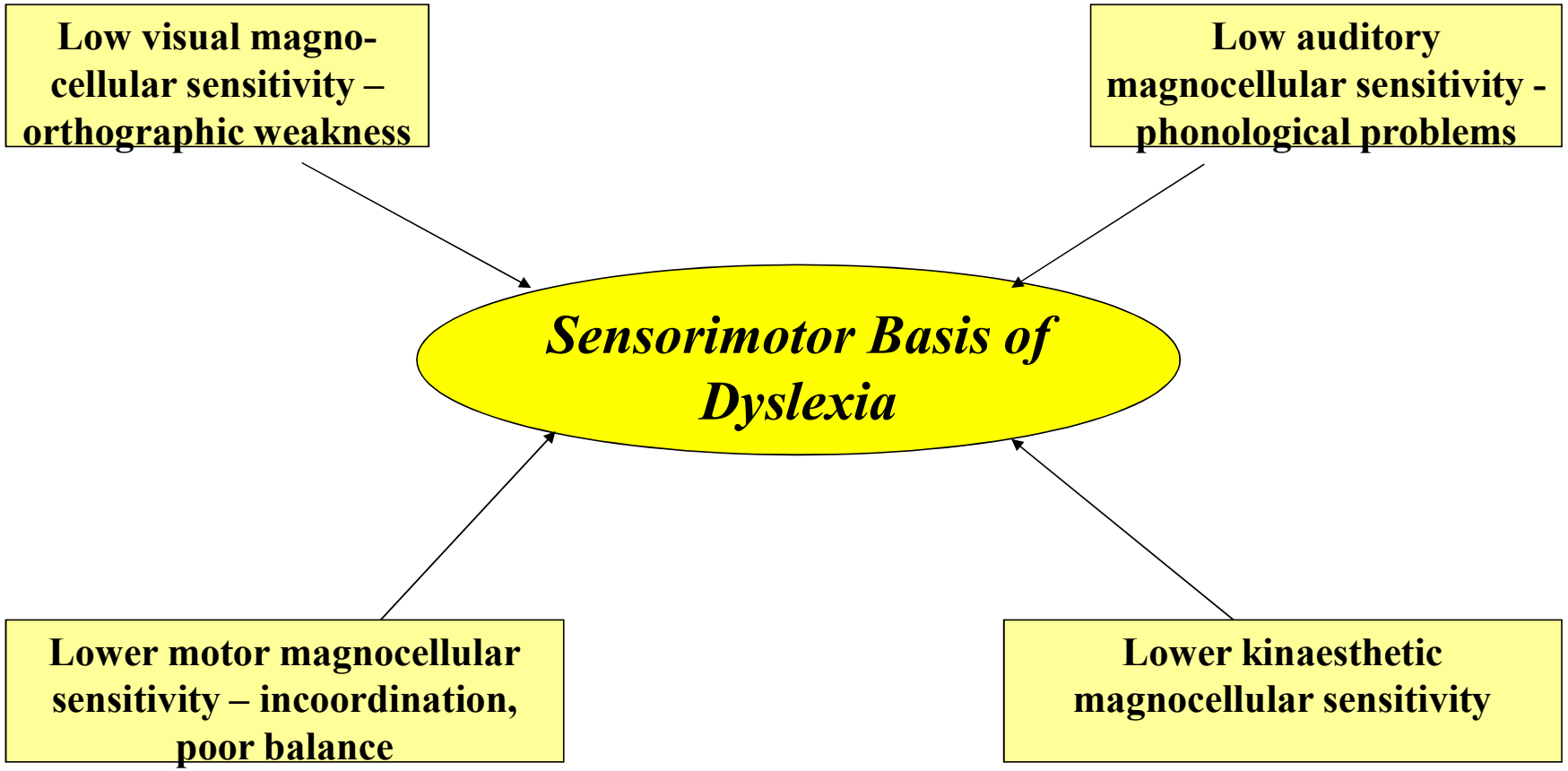
Impaired auditory magnocells in dyslexics?

- Large ‘magnocellular’ neurones in the auditory brainstem signal changes in sound frequency and amplitude
- Dyslexics have smaller magnocellular neurones in the medial geniculate nucleus
- They have lower frequency, AM & FM sensitivity
- Frequency sensitivity predicts their non word reading skills
- Poor phonological skill may result from impaired development of **auditory magnocells**
- **Musical** training, particularly in rhythm, may improve auditory m- cell responses, hence improve reading

Auditory (AM & FM) and visual (motion) magnocellular sensitivity explains over half of the differences between individual children's reading abilities

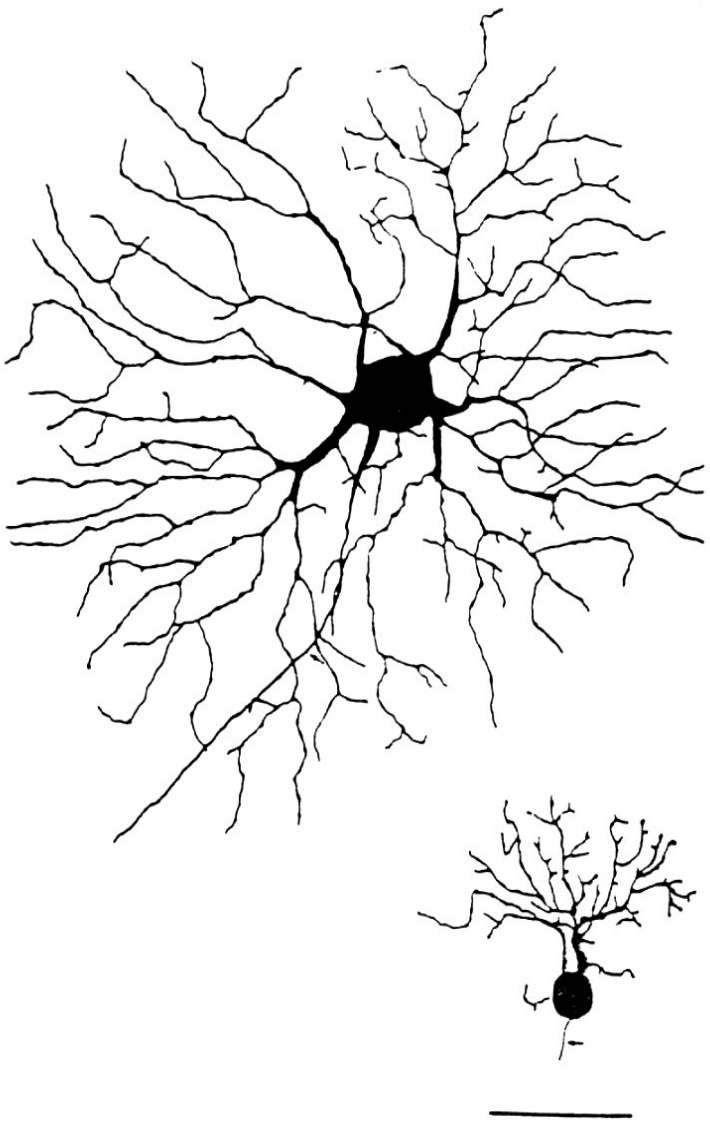


Thus magnocellular sensitivity seems to be the most important determinant of overall reading ability; this is v. encouraging because M- sensitivity can be improved by simple techniques: coloured filters, rhythm training


Low visual magno-cellular sensitivity – orthographic weakness
Low auditory magnocellular sensitivity - phonological problems
Sensorimotor Basis of Dyslexia
Lower motor magnocellular sensitivity – incoordination, poor balance
Lower kinaesthetic magnocellular sensitivity

Magnocellular Neurones

- A system of large neurones specialised for temporal processing – tracking changes in light, sound, position etc. for direction of attention
- Large, fast axonal conduction, fast synaptic transmission
- All derive from same lineage; they all express the same surface antigen, CAT 301
- Found throughout the whole brain: visual, auditory, skin, muscle proprioceptors, cerebral cortex, hippocampus,
- Very vulnerable. Impaired m- cell development has been found in prematurity, foetal alcohol syndrome, developmental dyslexia, dyspraxia, dysphasia, ADHD, ASD, Williams syndrome, schizophrenia, depression
- M- cell high dynamic sensitivity requires high membrane flexibility provided by local environment of essential fatty acids, particularly **omega 3s**, found in fish oils



What causes this general magnocellular impairment?

Genetic

Immune System

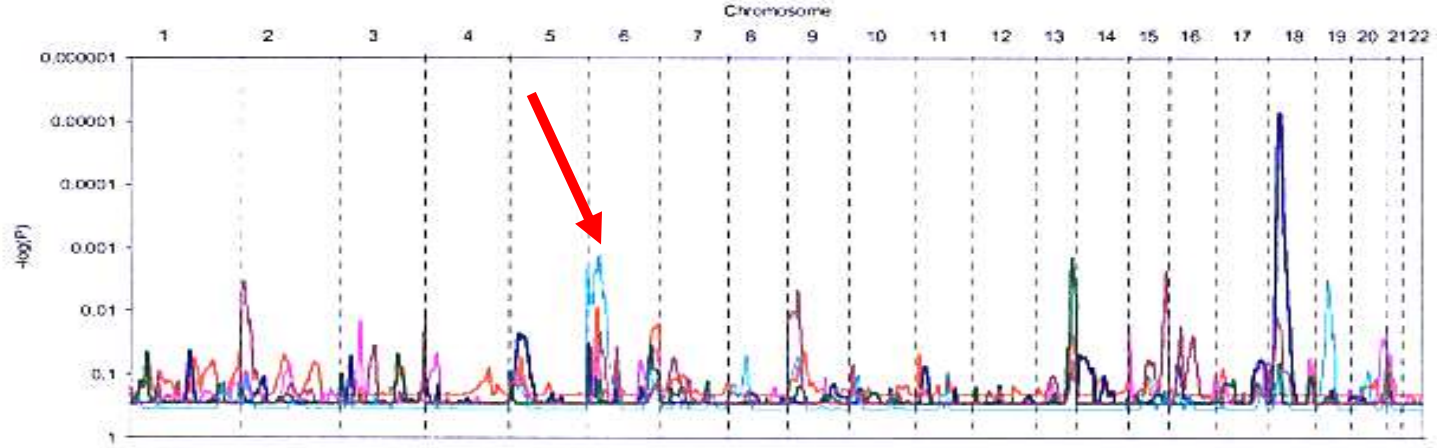
Nutrition

Genetic linkage/association

- Are particular chromosomal markers/sites associated with poor reading?
- Analyse the DNA of father, mother and their poor and normally reading children
- >500 Oxford (UK); 100 Boulder (US) families
- EU consortium; 1000 families, 2000 cases, 2000 controls, 50,000 markers per case

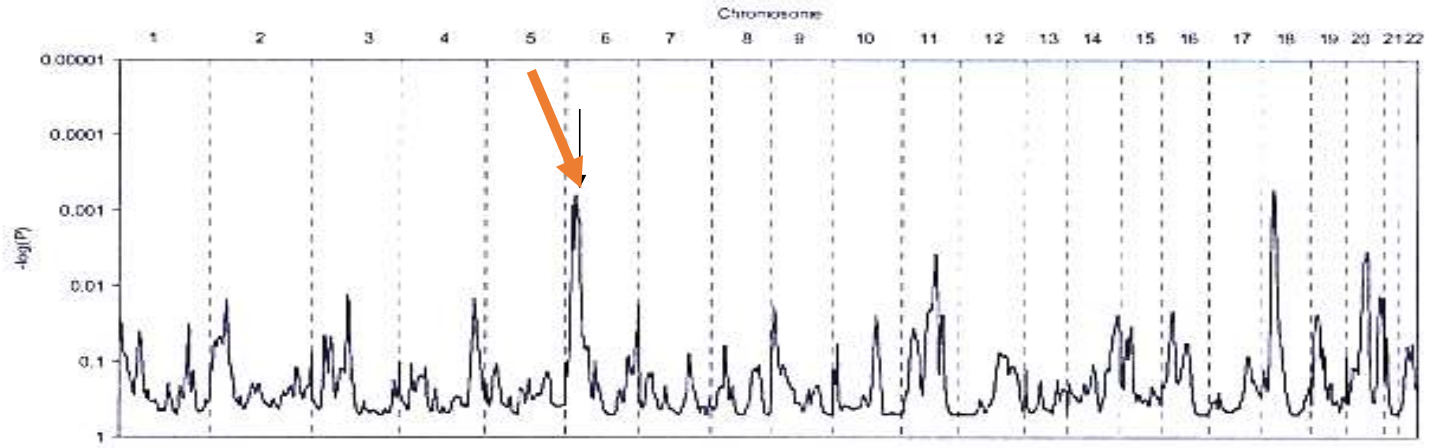
(A)

Genetic Linkage in 400 Oxford Families



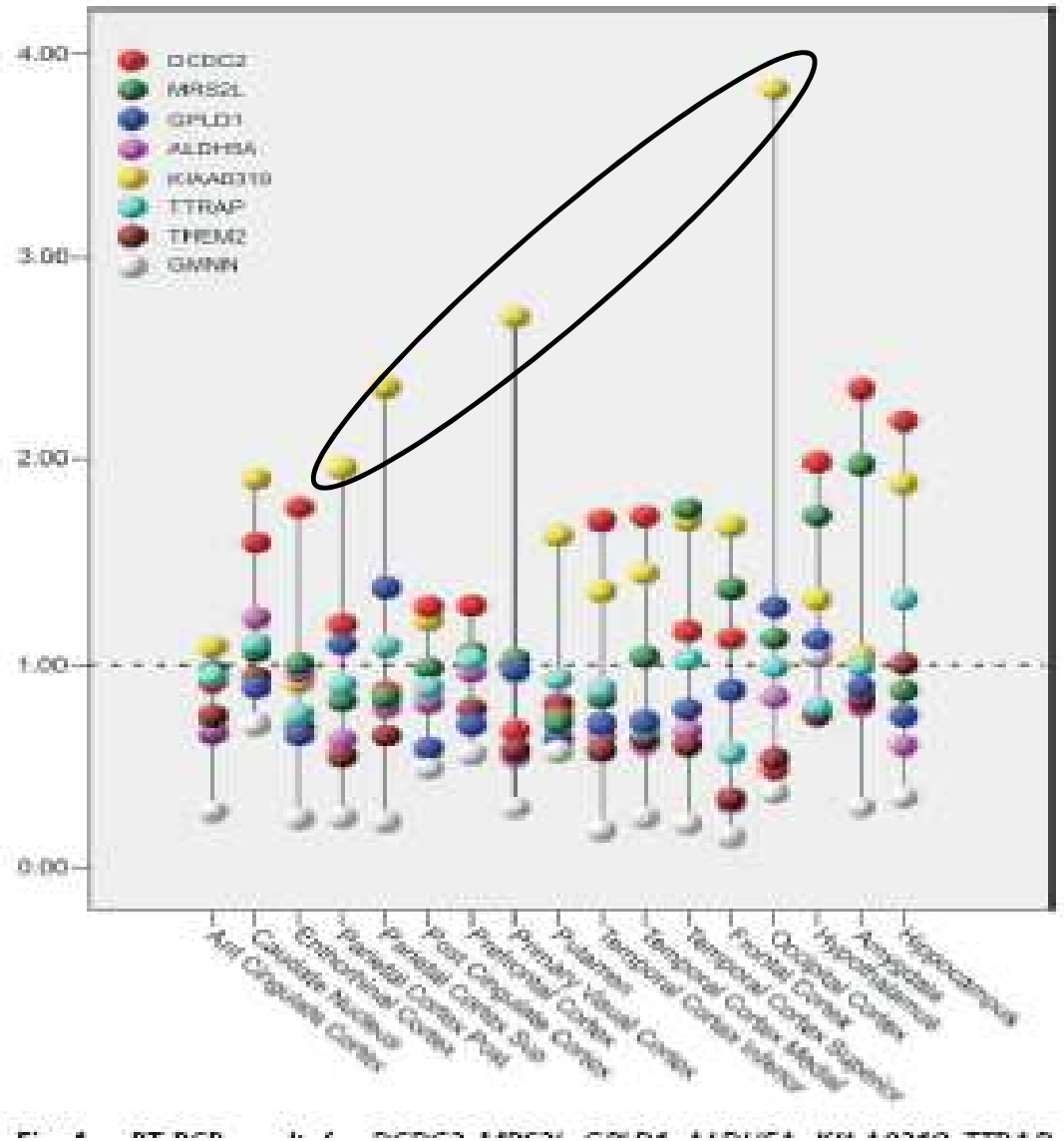
(B)

Chromosome 6p21, KIAA 0319, DCDC2

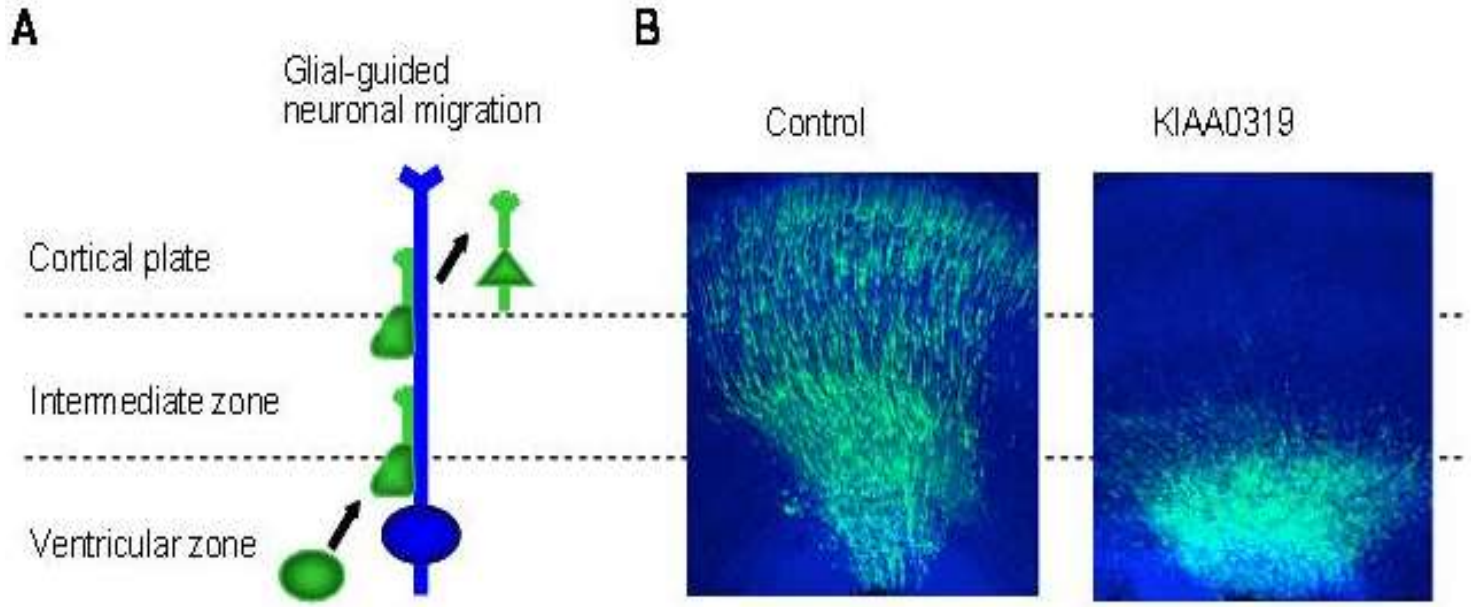


Monaco et al 2000

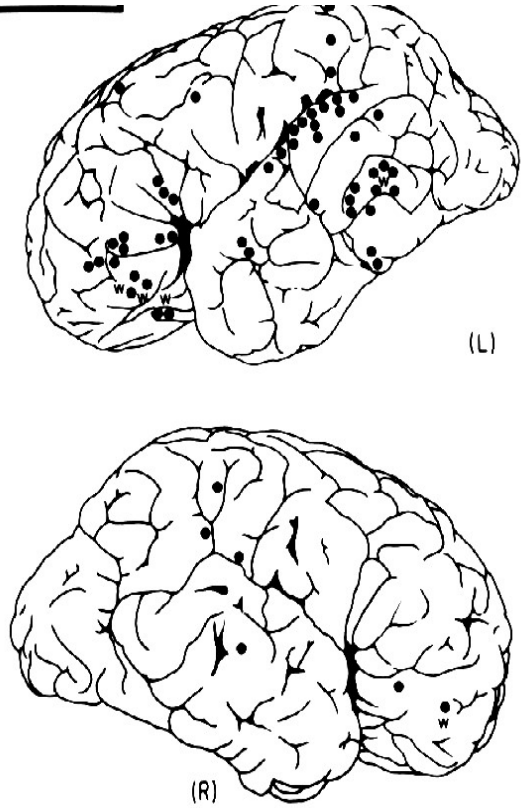
One gene we've discovered, KIAA 0319, is strongly expressed in the visual magnocellular system

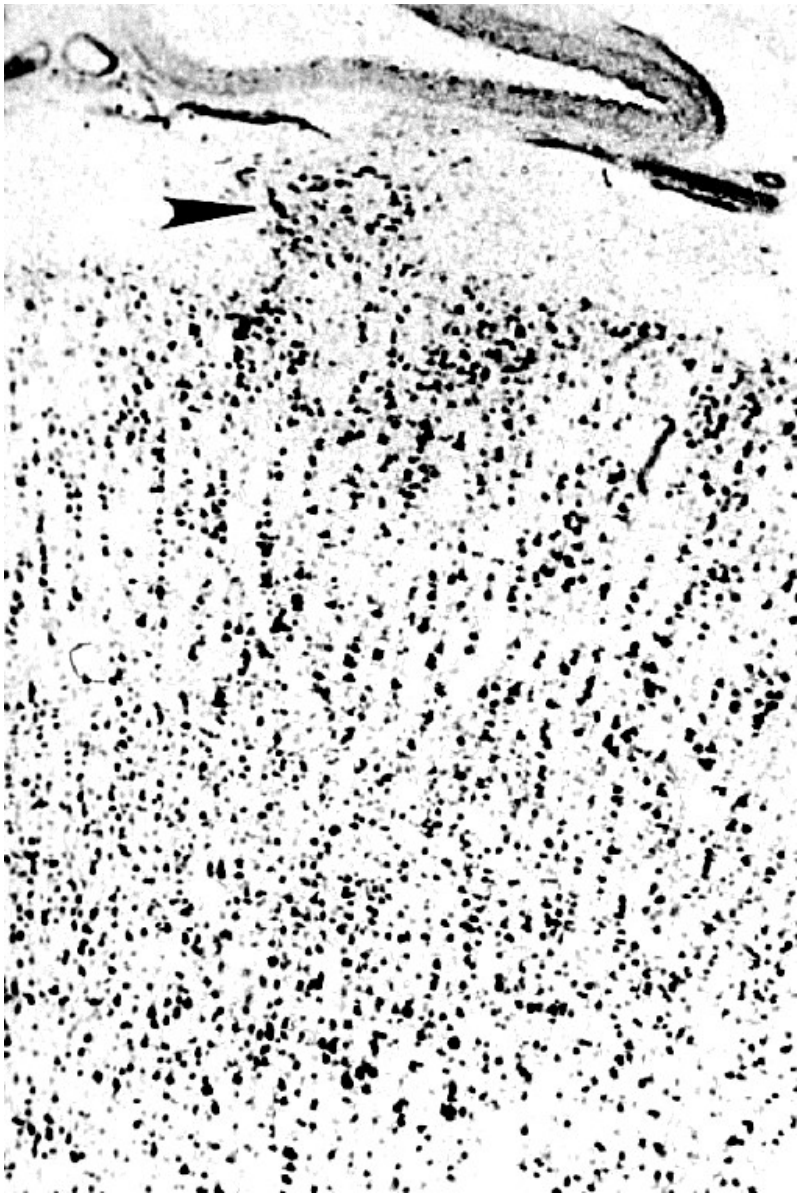


C6 KIAA 0319 gene controls neuronal migration during early brain development *in utero.* Underexpression in dyslexics may explain their ectopias and the impaired development of their magnocellular neurones

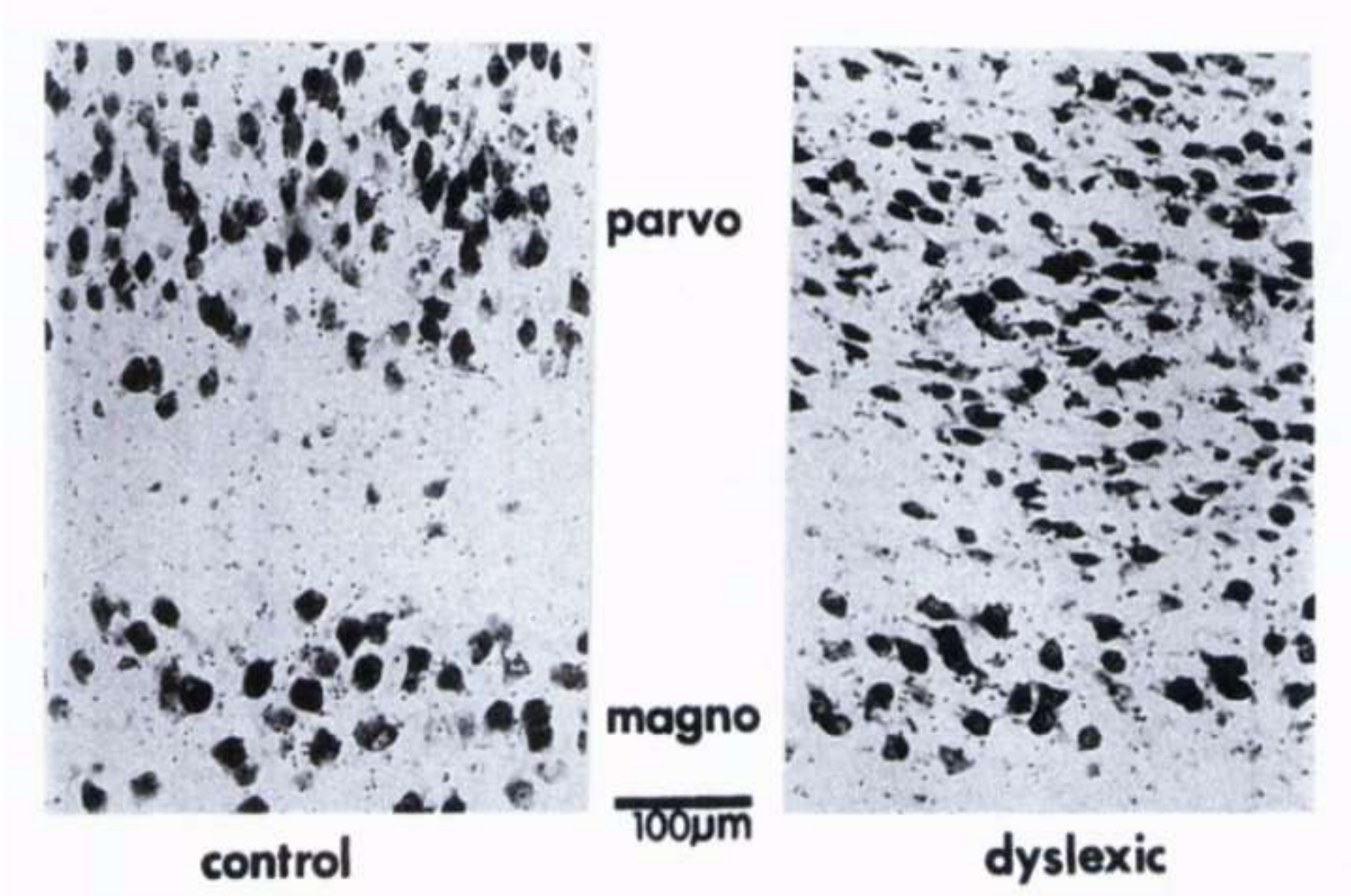


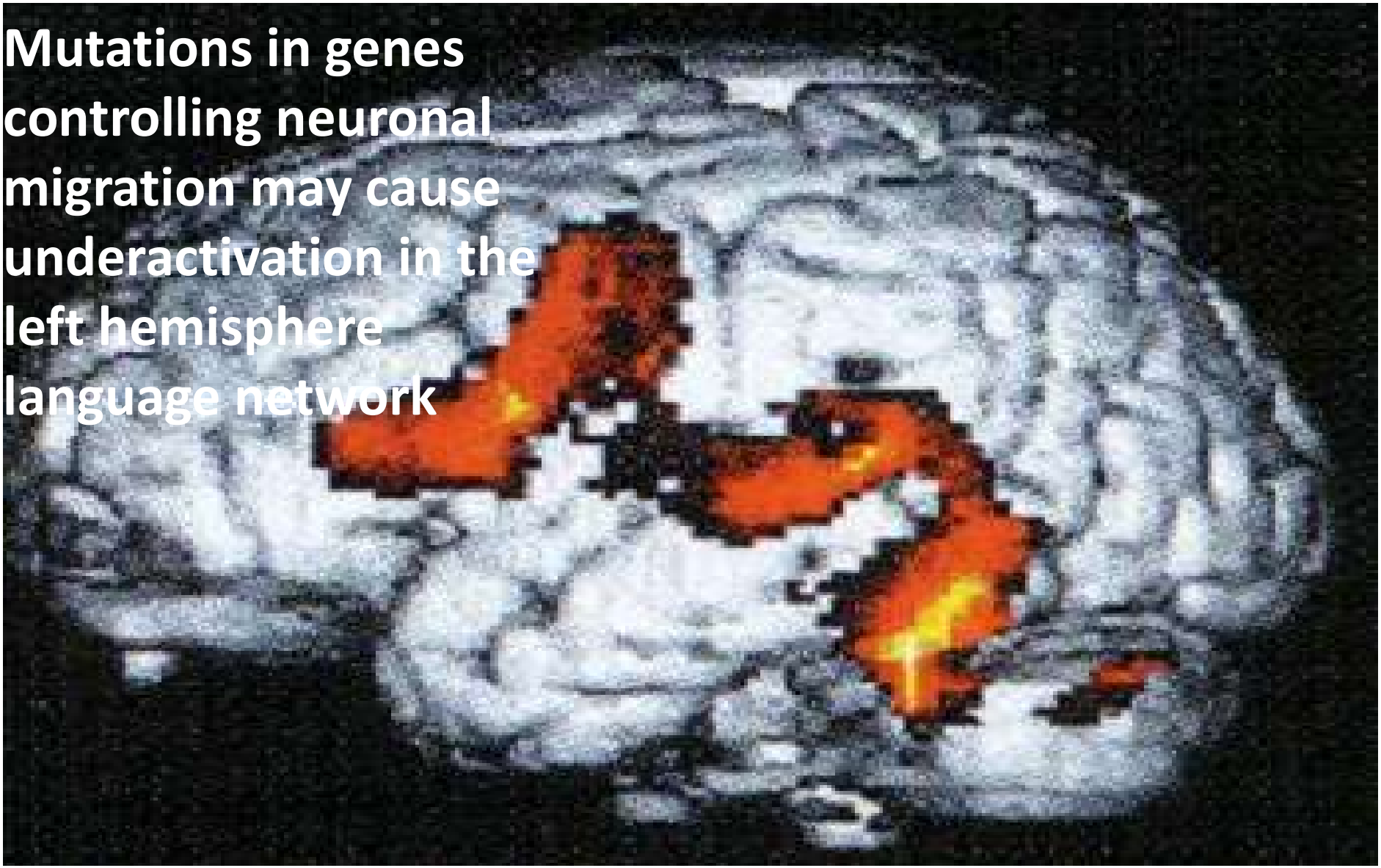
3 dyslexia genes (KIAA, DCDC2, ROBO) control neuronal migration and may cause these ectopias. KIAA 0319 is also involved in immunity, setting up speech laterality and whether you are right or left handed





Abnormal and mismigrated magnocells in dyslexic brain

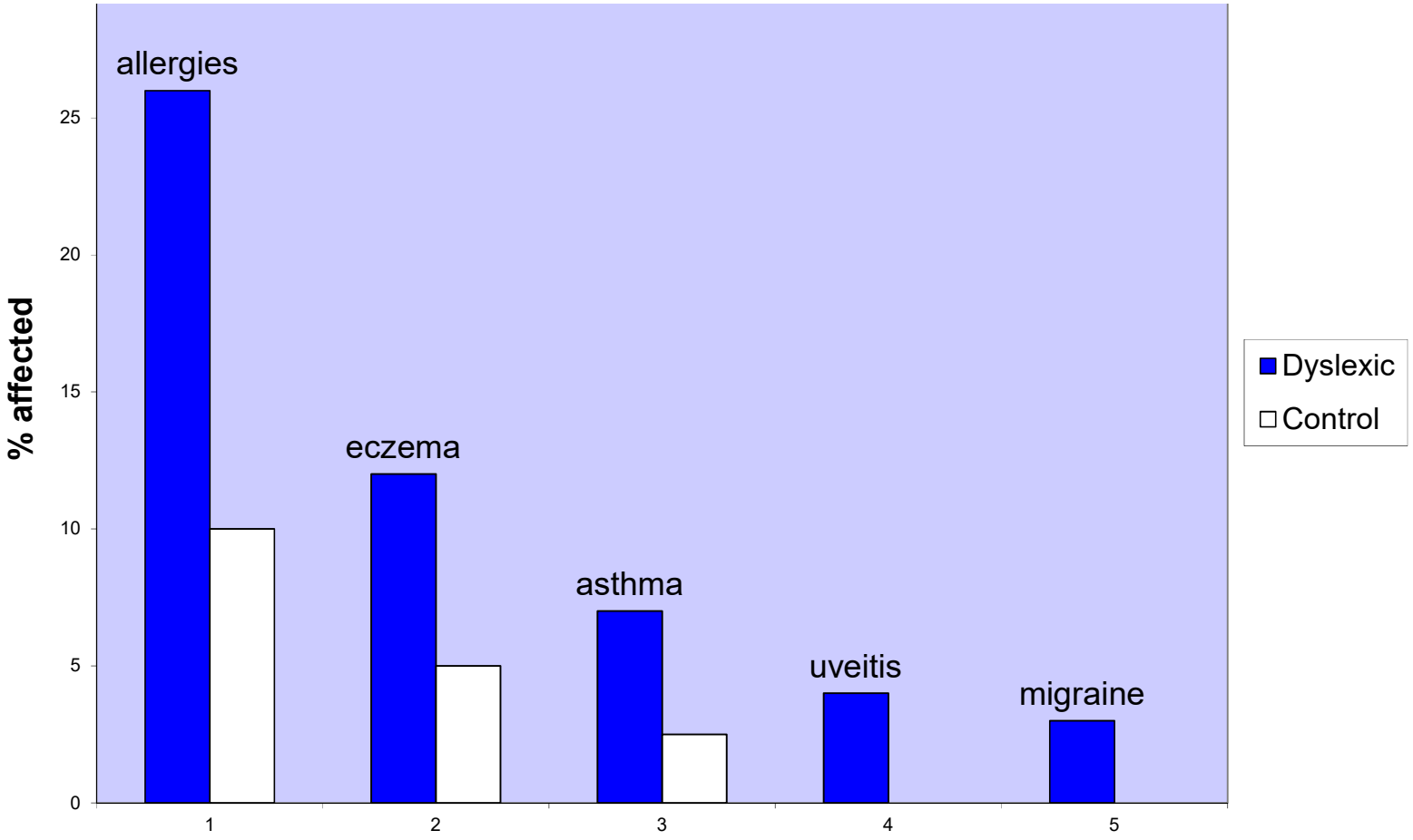


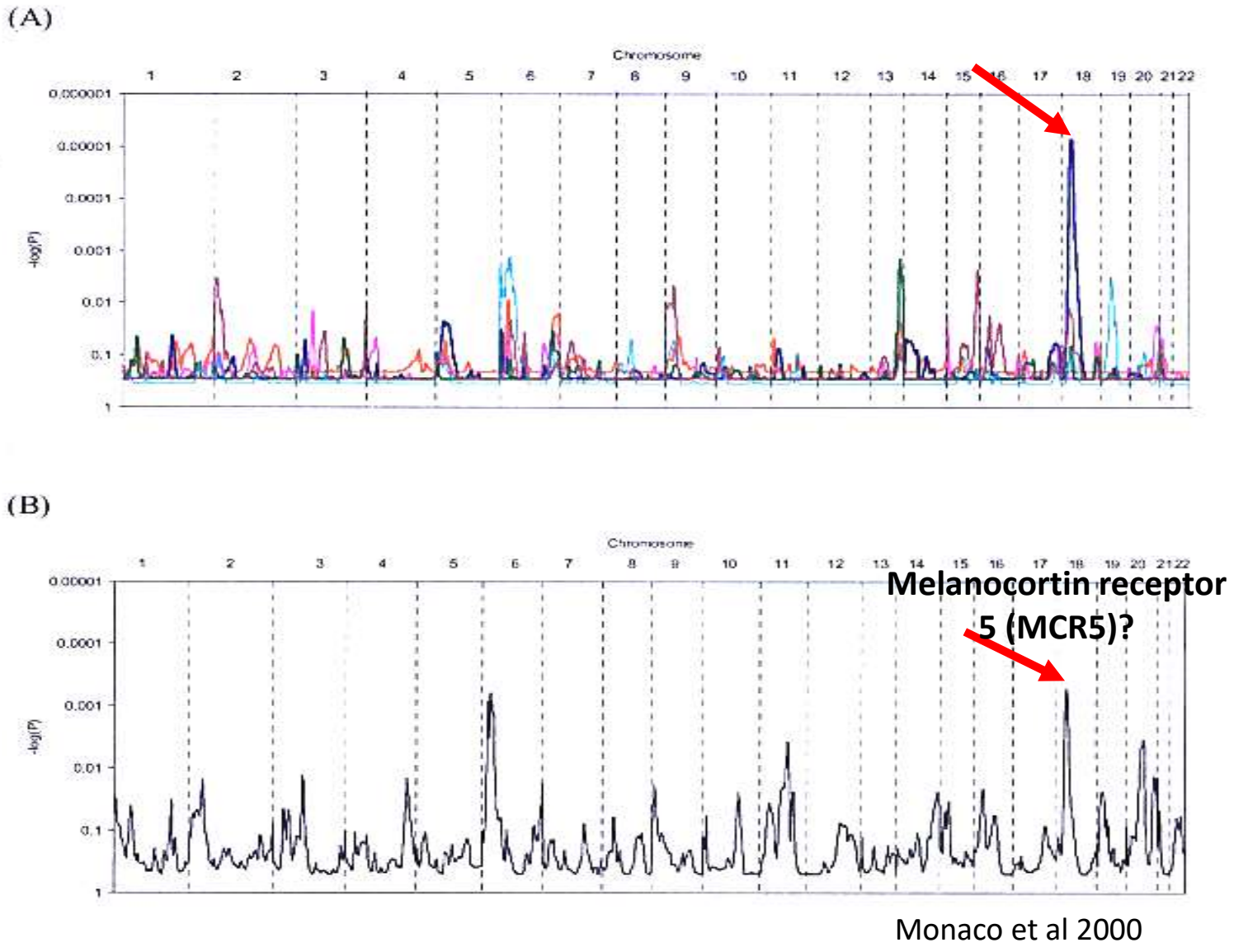

Mutations in genes controlling neuronal migration may cause underactivation in the left hemisphere language network

Dyslexia genes, neuronal migration & immune function

- Underexpression of KIAA0319, DCDC2, ROBO genes all disrupt neuronal migration early in brain development
- KIAA0319 controls the expression of cell surface recognition (signature) molecules such as CAT 301
- **Later** many of these genes seem to help to control **immune** function
- This may cause magnocells to fail to develop properly, to successfully contact with other magnocells, and to remain <u>immunologically highly vulnerable</u>

High incidence of immune anomalies in dyslexics & their families





Monaco et al 2000

MCR5? - Cod Liver Oil Queue, 1949

‘Most Britons were better fed in 1943 at the height of the German blockade, than in 1983’

***Dr Hugh Sinclair**, Magdalen College, Oxford*

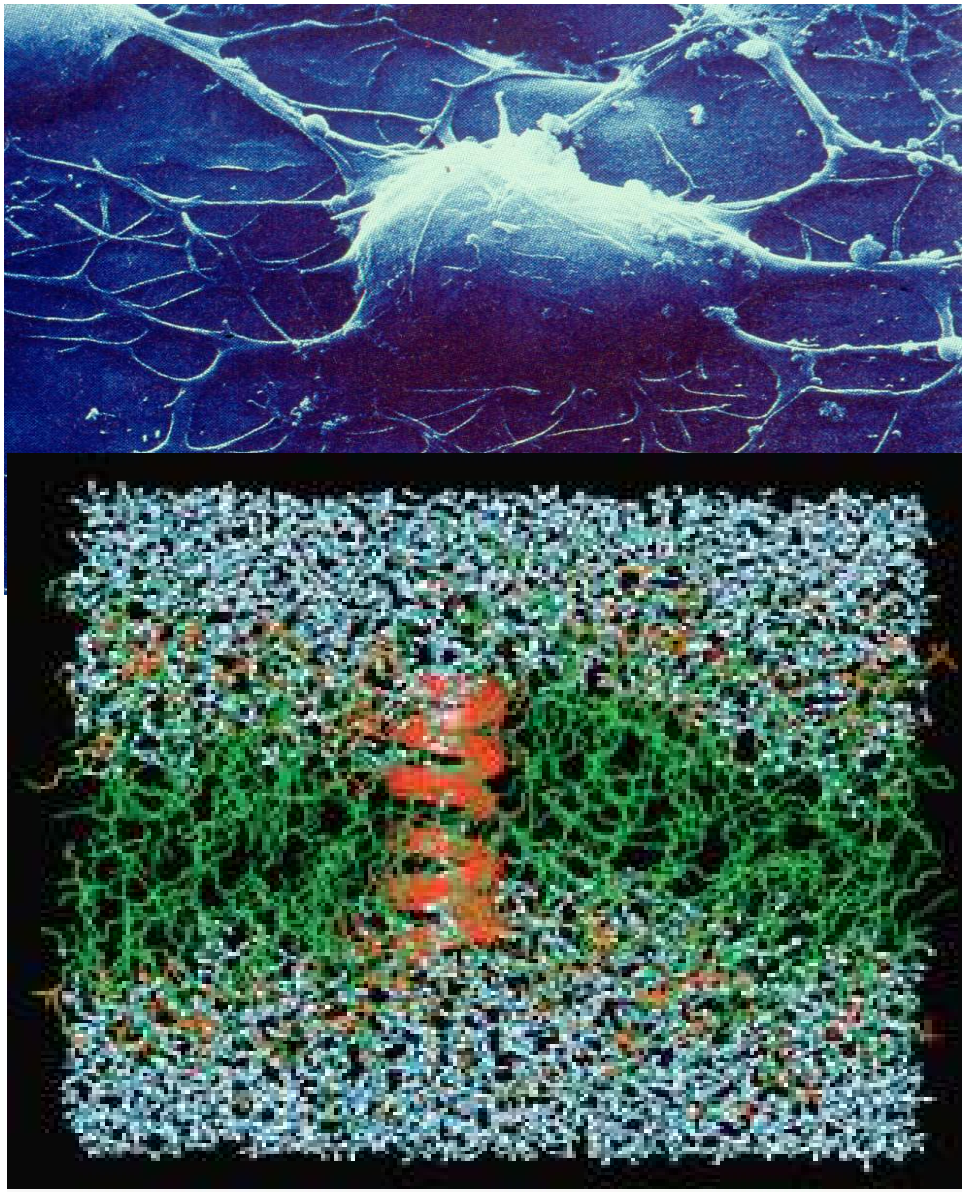
- Aged only 28, he persuaded the WWII government to provide free cod liver oil, malt and orange juice to all pregnant mothers and young children
- 20% of yr. brain membranes (5 G) is docosahexanoic acid (DHA –22,6 n-3)
- Essential for flexible and electrostatic membranes – rapid neural responses
- You lose 5 mgm DHA/day
- **But 75% of 18 yr olds eat no fish at all.**

Fish Diet

- Humans evolved in or near water, providing a plentiful supply of fish. This was their main source of calories & protein, not meat.
- Fish oils were incorporated into our nerve membranes
- This allowed our 100 fold expansion of brain connections compared with chimpanzees.
- Even 100 years ago, fish was our main source of protein

But now most eat very little fish at all!

- The long chain omega 3 poly-unsaturated fatty acid, DHA, found in fish oil, is the backbone (20%) of this nerve membrane
- In order to open and signal fast, magnocellular membrane ionic channels need to be surrounded by these flexible n-3 fatty acids
- Fast magnocellular neurones are therefore especially vulnerable to lack of fish oil omega 3 (n-3) fatty acids

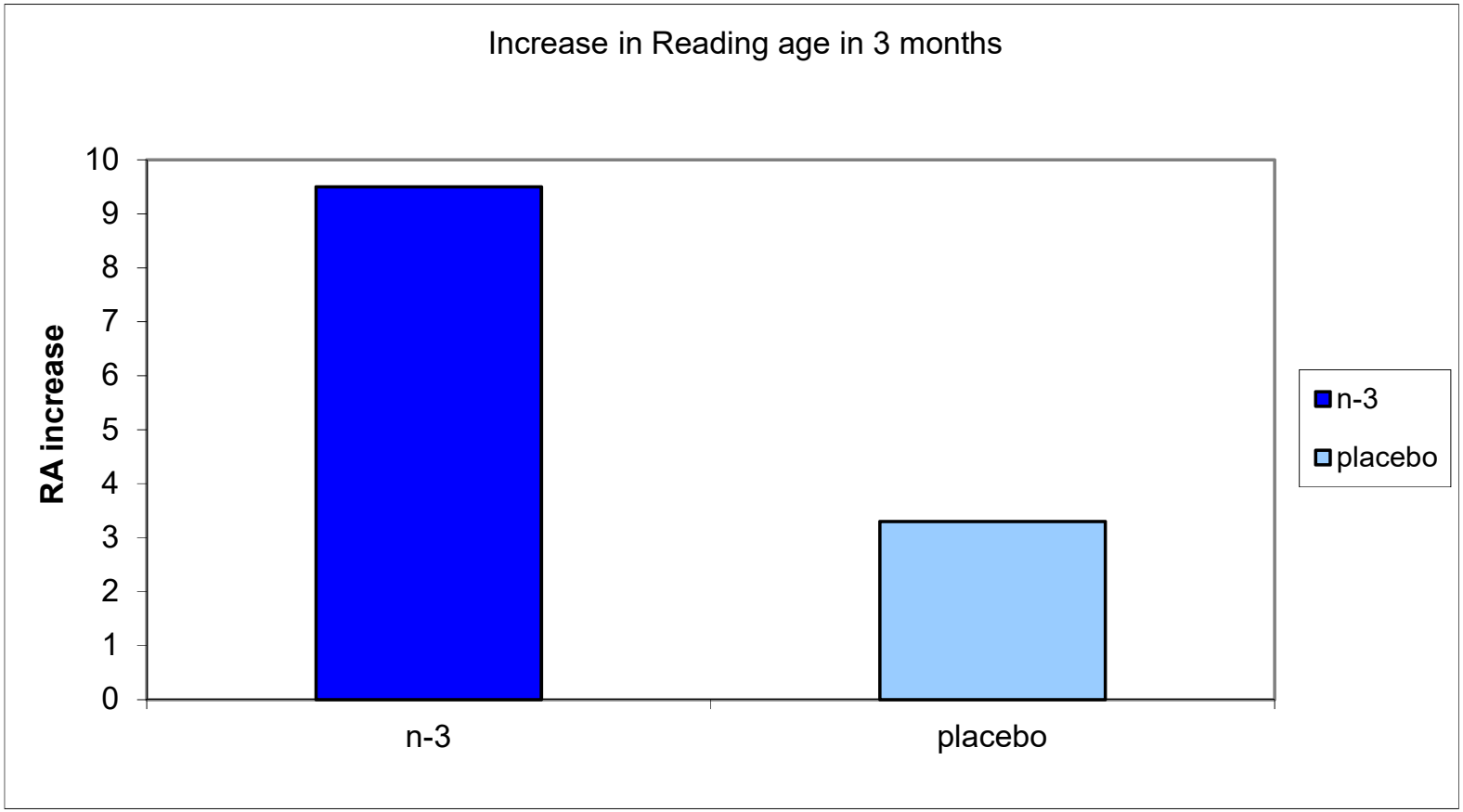


Fish is essential for the whole body!

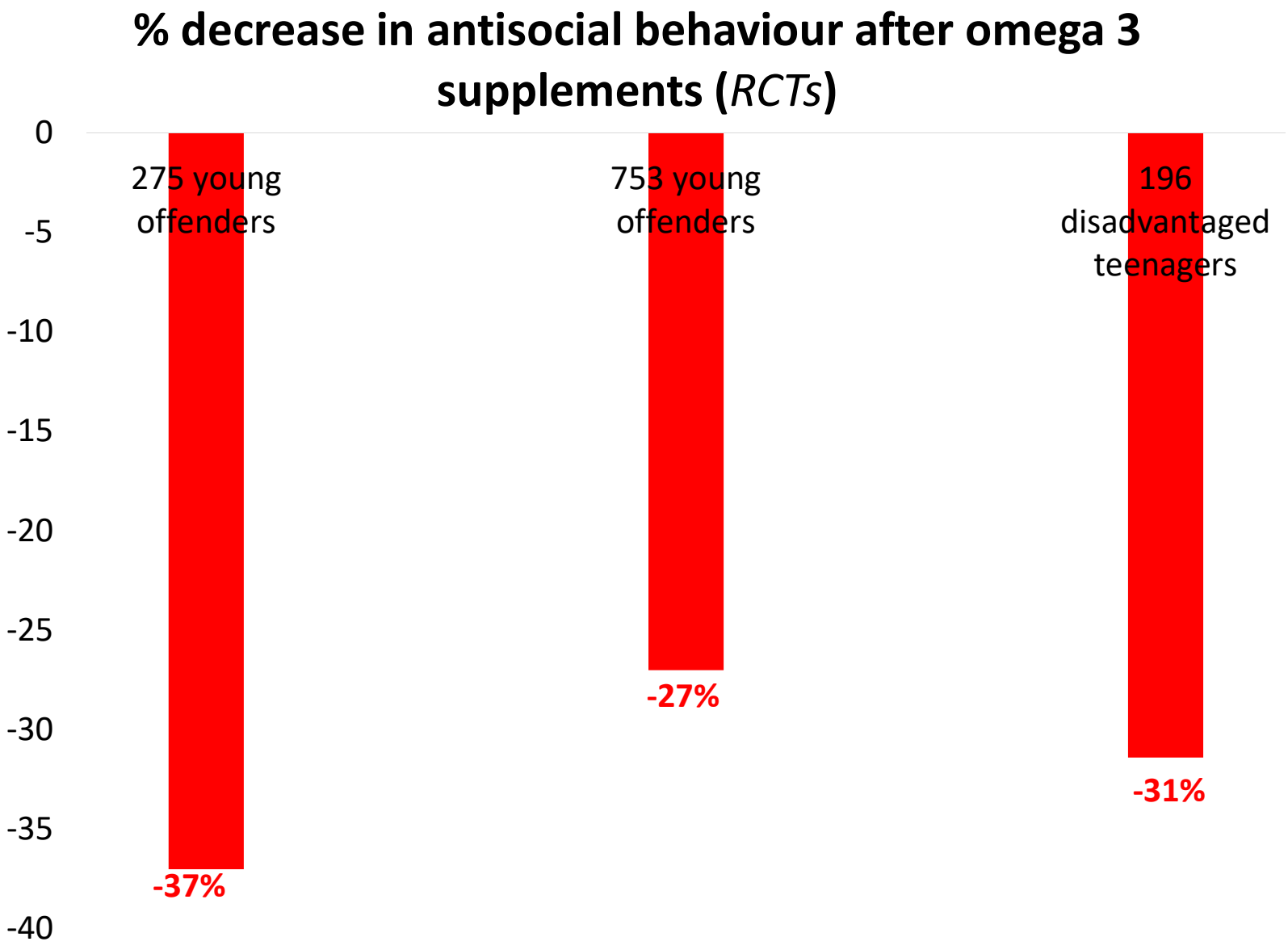
- DHA & EPA increase membrane flexibility, speed up neuronal Na, K, NMDA, GABAa currents; ie they accelerate magnocellular timing functions
- Increase neurogenesis; decrease cell death (apoptosis – Alzheimer's)
- Increase neurite outgrowth and synapse formation, hence improve memory
- Strengthen hemispheric lateralisation
- Reduce inflammation in arthritis, arteriosclerosis, Alzheimer's
- Reduce pain transmission (Capsaicin (TrpV1) receptors)
- Prevent accumulation of insoluble amyloid precursor protein (Alzheimer's)
- Improve gut flora (microbiome)

Correlations do not prove causation, but interventions can!

Fish oil Omega 3 DHA & EPA supplements helped these dyslexic children to improve their concentration and their reading (RCT)



RM4
RMRM6


% decrease in antisocial behaviour after omega 3 supplements (*RCTs*)
0
-5
-10
-15
-20
-25
-30
-35
-40
275 young offenders
753 young offenders
196 disadvantaged teenagers
-37%
-27%
-31%

Slide 60

RM4 I think the tone of this needs lightening.
Richard Marsh, 9/20/2015

RM5 Much more conversational
Richard Marsh, 9/20/2015

RM6 Is there a way that we can rework this so that it doesnt feel backward looking but picks out the interesting things we've learned and says how they should be applied?
Richard Marsh, 9/20/2015

Fatty acid deficiency in poor readers and young offenders?

- Many people with neurodevelopmental problems and young offenders have very low n-3 long chain polyunsaturated fatty acids (LCPUFAs) in their brains
- **Omega 3 FA (fish oil) supplements can greatly improve their magnocellular function; hence improve their attention, reading, mood and violent behaviour**

The Brain and Fish Oils

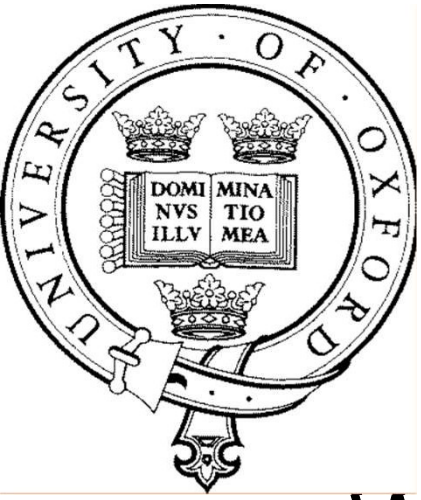
- Communication (speech, reading, social interactions) all depend upon accurate **temporal processing and sequencing** of speech sounds, letters and facial expressions by **magnocellular** neurones
- **Impaired development** of magnocellular neurones is found in most neurodevelopmental conditions
- Magnocellular neurones need omega 3 fish oils **(DHA and EPA)** in their membranes to work properly
- This makes them exceptionally vulnerable to lack of omega 3s
- But fish is expensive and 3/4s of population eat **no fish** at all
- **DHA and EPA supplements** should be used to help people woth low omega 3s to improve their attention, speech, reading and social interactions

Take home messages

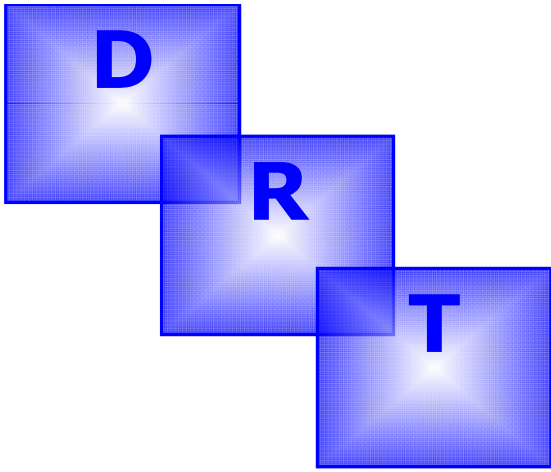
- Suspect dyslexia in any pupil who is much better at talking than reading or spelling, has dreadful writing, avoids reading out loud, has poor attention and tends to make errors on visual & sound sequences
- Due to poor temporal sequencing by magnocellular neurons
- Visual reading problems can often be improved by simple blue or yellow filters – try them
- Blue filters often help sleep, car sickness, headaches and depression as well
- Auditory magnocellular function can often be improved by musical training, especially rhythm
- Magnocellular function in general can often be improved by eating oily fish or supplement capsules of DHA and EPA (>1/2 G every day)

BUT…..

Dyslexia ‘genes’ would not be so common if they did not endow selective advantage. Many dyslexics are unusually creative and excel when ‘holistic’ thinking is required



John Stein, Magdalen College, Oxford



Wobbles, Warbles & Fish - the Magnocellular Theory of Dyslexia

Thank you for listening

The real work was done by Sue Fowler, Tricia Riddell, Piers Cornelissen, Joel Talcott, Priti Kashyap, Joe Taylor, Ceris Mumford, Tony Monaco, Anna Pitt

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