Neuroimaging studies of language development reading and reading disabilities

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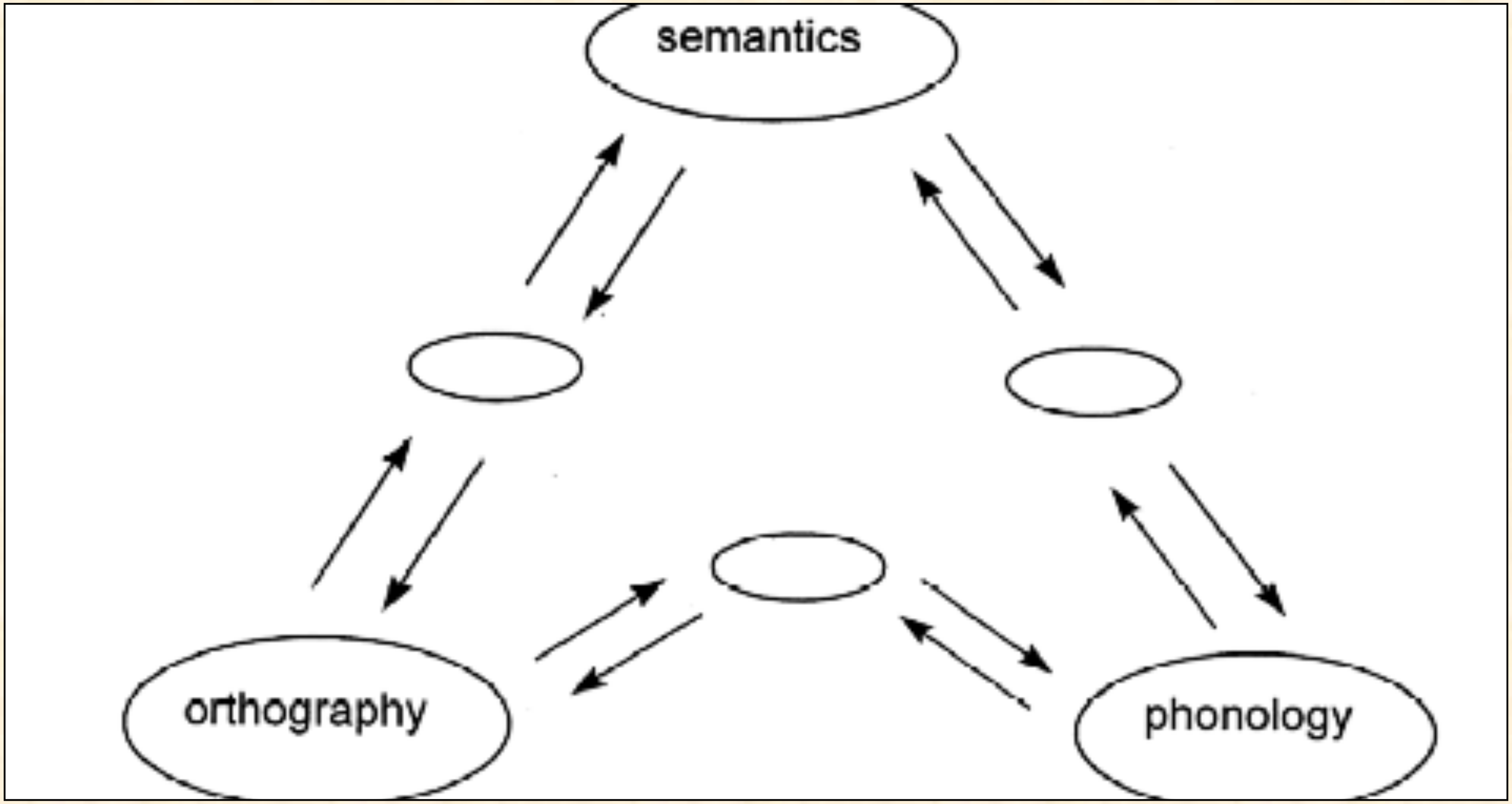
The importance of Reading

- The development of fluent reading skill is essential for success in the modern world.
- Significant numbers of children in all countries fail to acquire adequate literacy skills.
- For many this is due largely to lack of good learning opportunities
- But for some will reflect difficulties that are **brain-based** (Specific Reading Disability).

First Principles: Speech, Reading, and the Brain

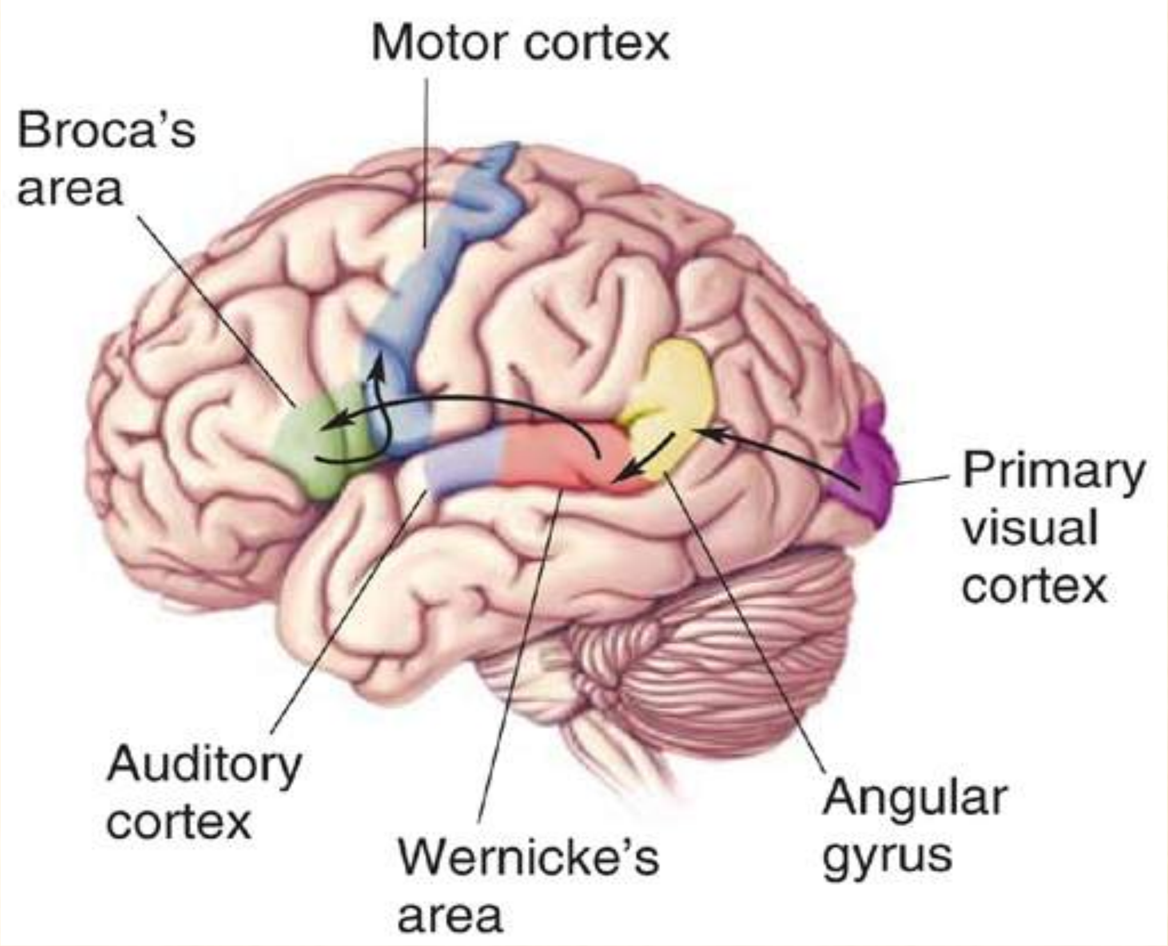
- Speech is a **biological specialization** but written language is largely a cultural invention.
- Speech is mastered naturally in almost all people, without direct instruction.
- But reading is difficult and reading failure occurs in large numbers of children across all written languages.
- **Explicit instruction is essential.**
- No brain specialization for reading.

The cognitive challenge of learning to read



What is the brain basis reading development?

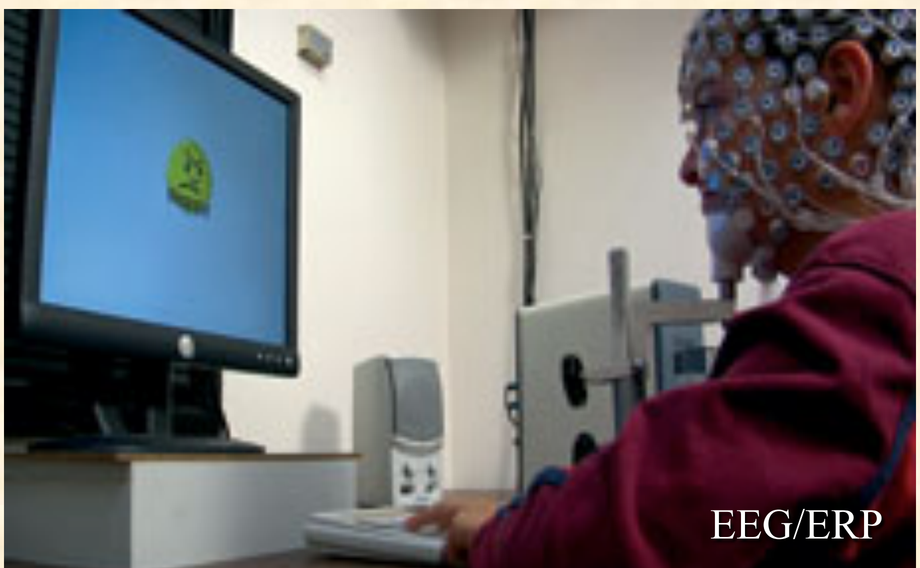
Fast and automatic word reading depends on finding most efficient brain pathways to support mapping from “vision to language”


Motor cortex
Broca's area
Primary visual cortex
Auditory cortex
Wernicke's area
Angular gyrus

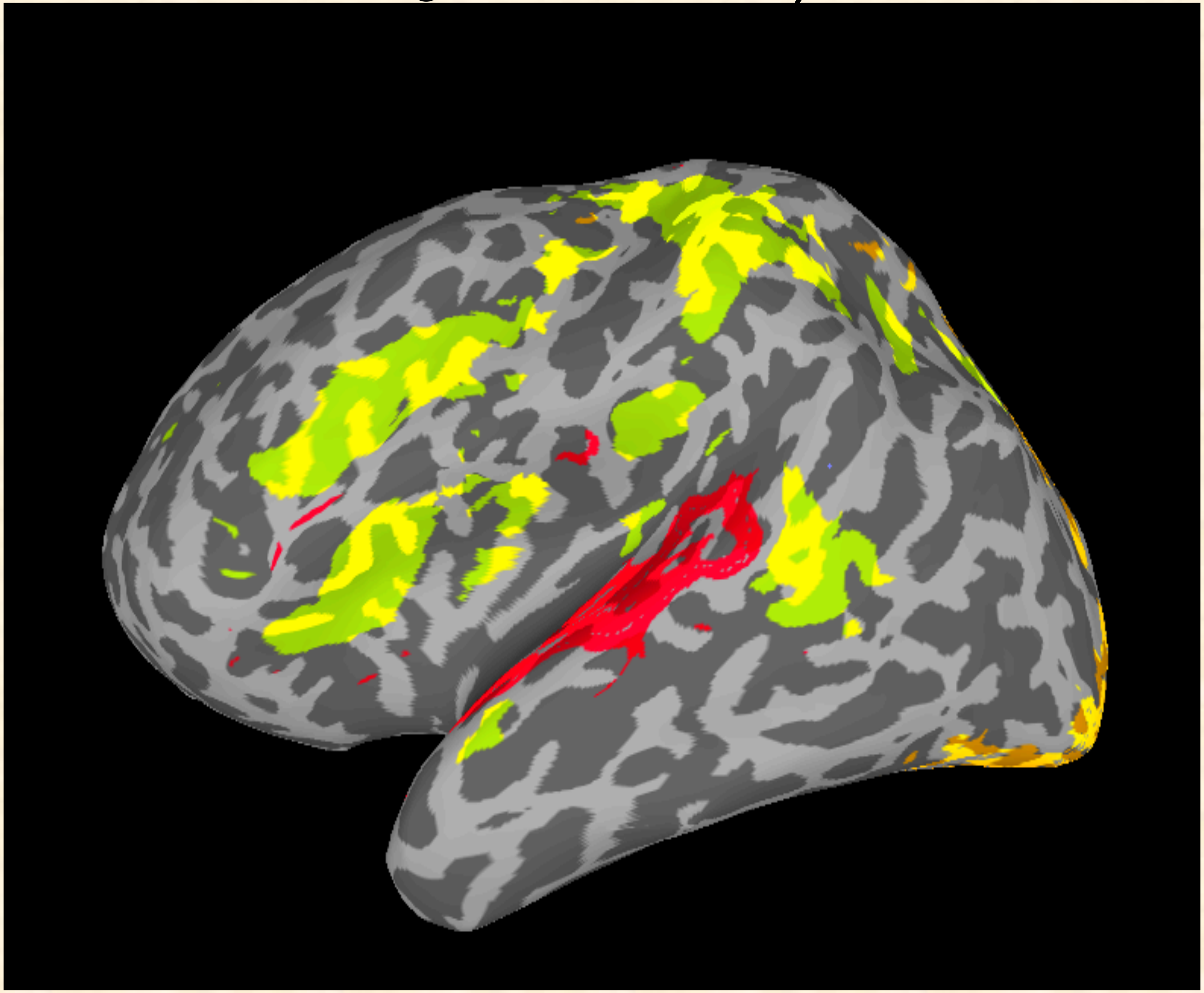
In-vivo brain research: Mapping spoken and written language with neuroimaging

- Functional brain imaging:
- two major classes of techniques:
- electrophysiological (EEG; MEG)
- hemodynamic (fMRI, PET).
- The former give information on timing of brain activity while the latter provide information on localization.
- Structural brain imaging:
- MRI yields detailed measures of both grey matter volume and white matter tracts

Acquisition techniques

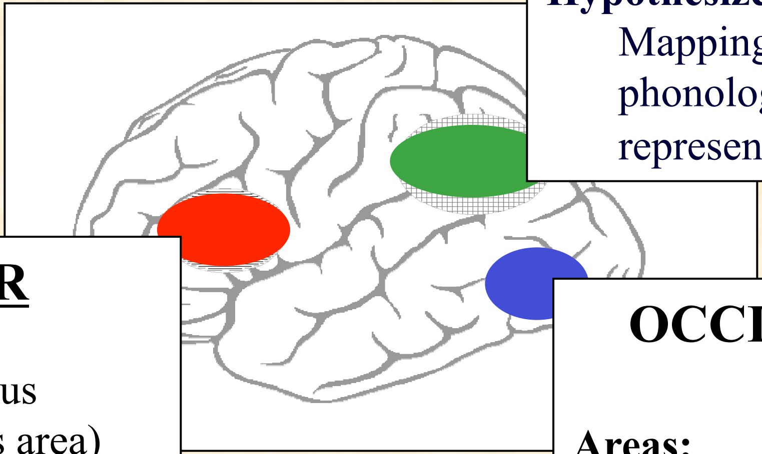


Word recognition: Print vs. speech (Frost, Pugh, et al., 2013)



A model of the reading circuitry

(Pugh et al. 2000;2010)



TEMPOROPARIETAL
<u>(DORSAL)</u>

Areas:
supramarginal, angular, superior temporal (Wernicke's) gyri

Hypothesized Function:
Mapping of orthographic to phonological and semantic representations

ANTERIOR

Areas:
inferior frontal gyrus (including Broca's area)

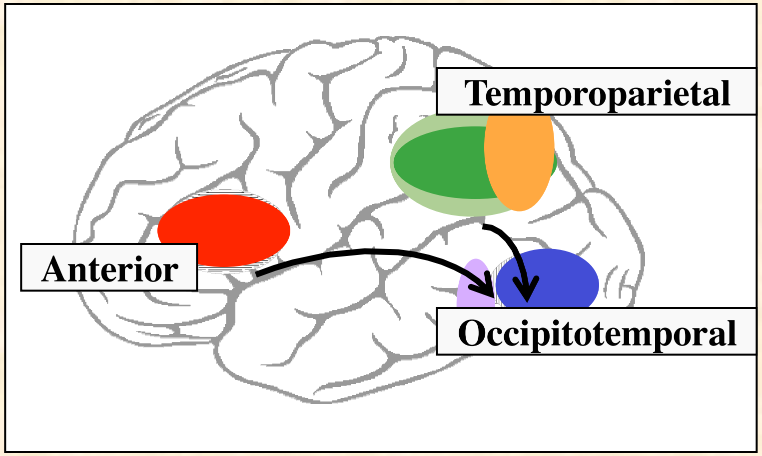
Hypothesized Function:
Articulatory recoding

OCCIPITOTEMPORAL
(VENTRAL)

Areas:
occipitotemporal juncture, middle and inferior temporal gyri

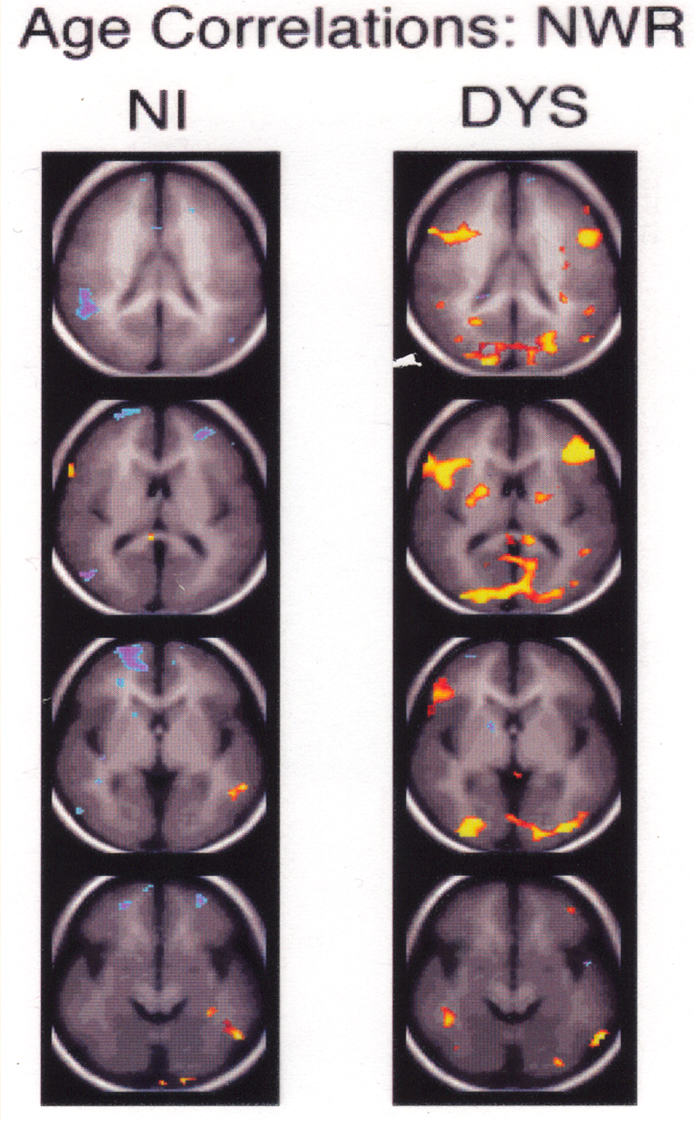
Hypothesized Function:
Linguistically structured memory-based word identification system (posterior aspect = "word-form" area)

Developing a “VWFA”

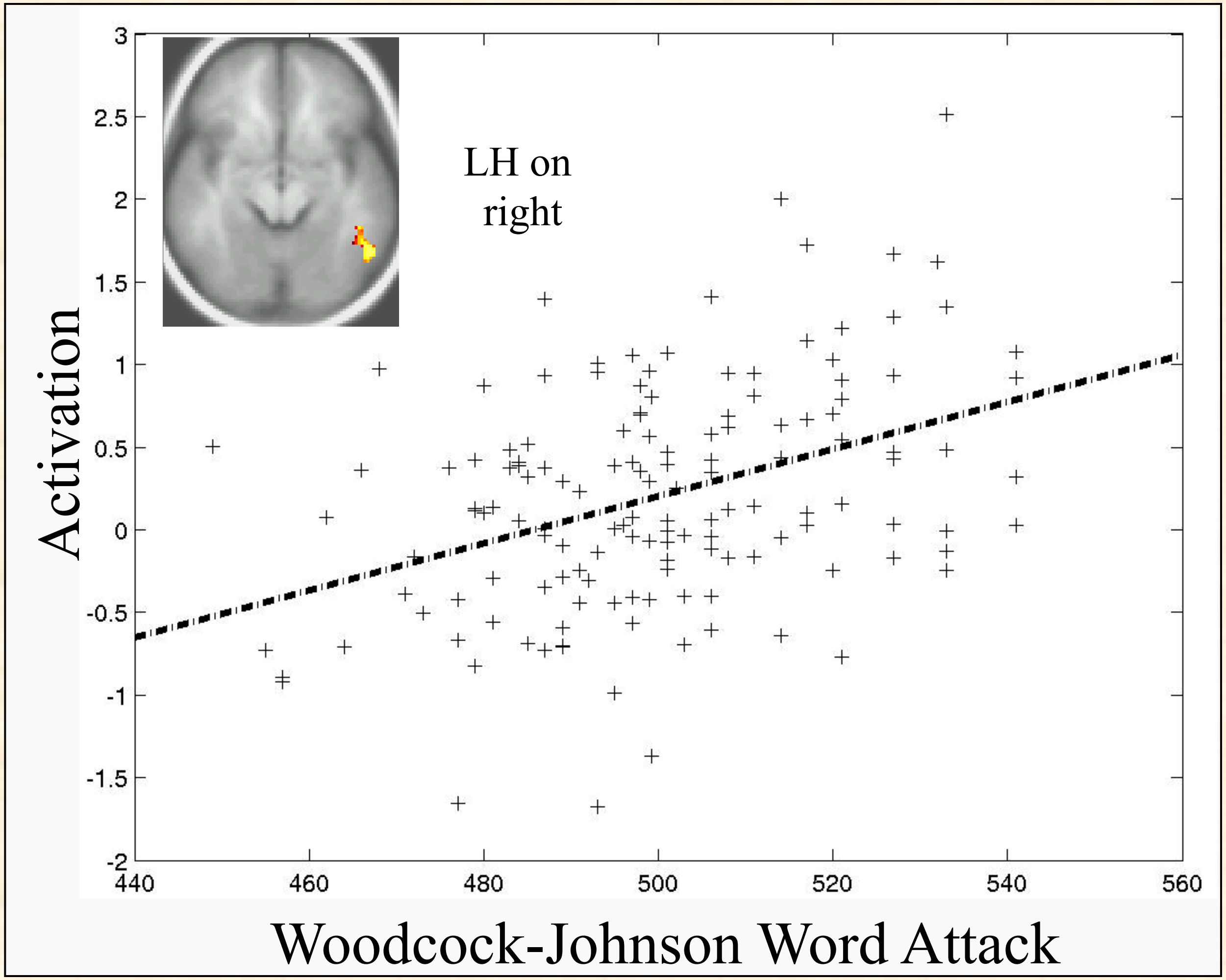


- Increases in reading skill are associated with increased specialization of ventral LH areas for print.

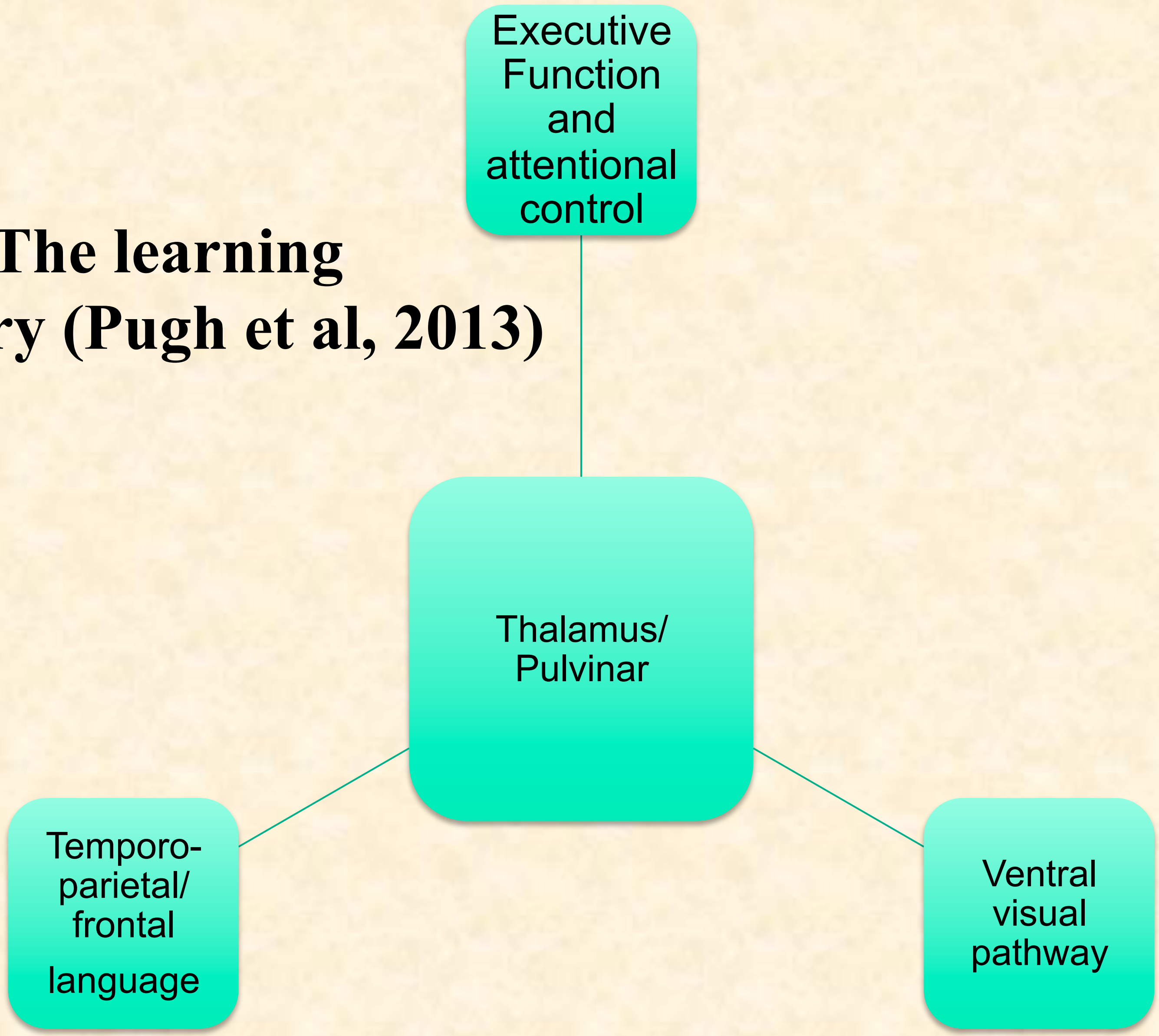
VWFA AND Reading Development
(Shaywitz, Shaywitz, Pugh et al., 2002)



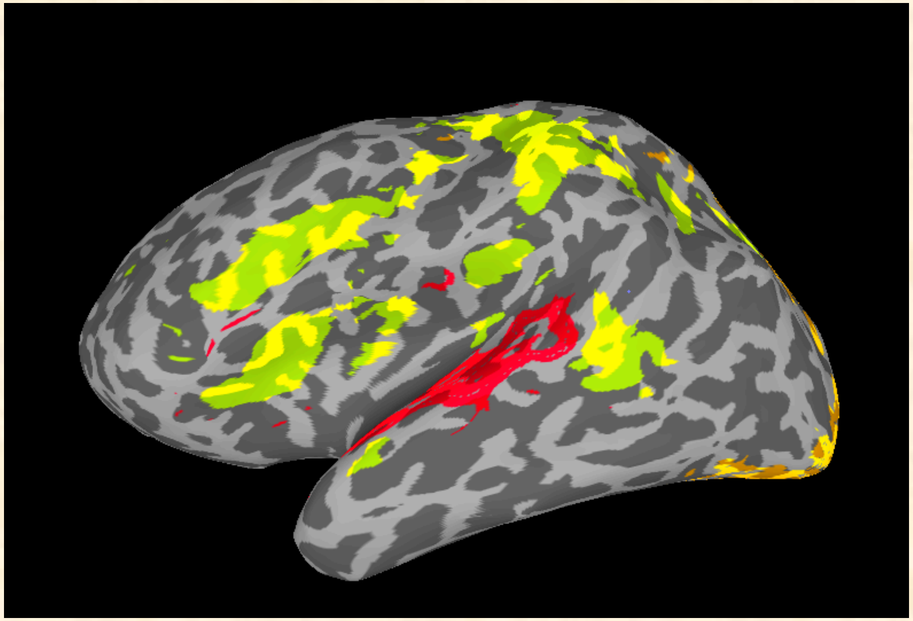
VWFA AND Reading Development (Shaywitz, Shaywitz, Pugh et al., 2002)



The learning circuitry (Pugh et al, 2013)

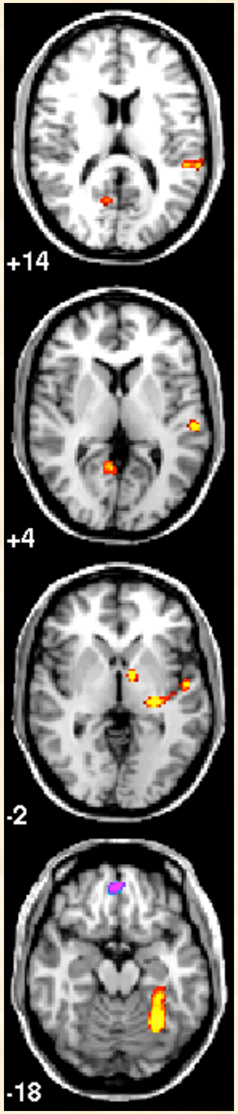


Speech/print integration is crucial in building an efficient reading circuitry



Links between phonological skills and speech/print integration in beginning readers (Frost…Pugh, 2009)

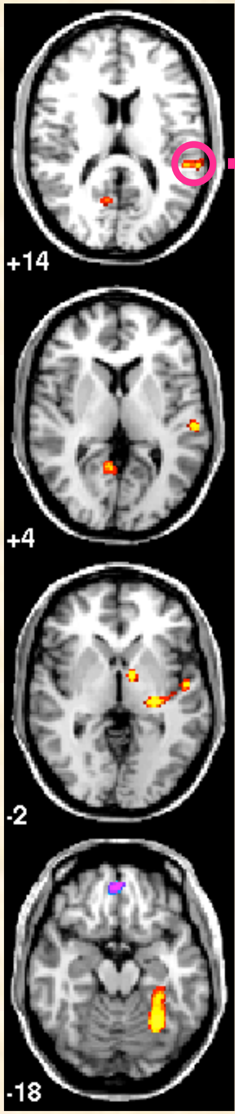
PA x Modality

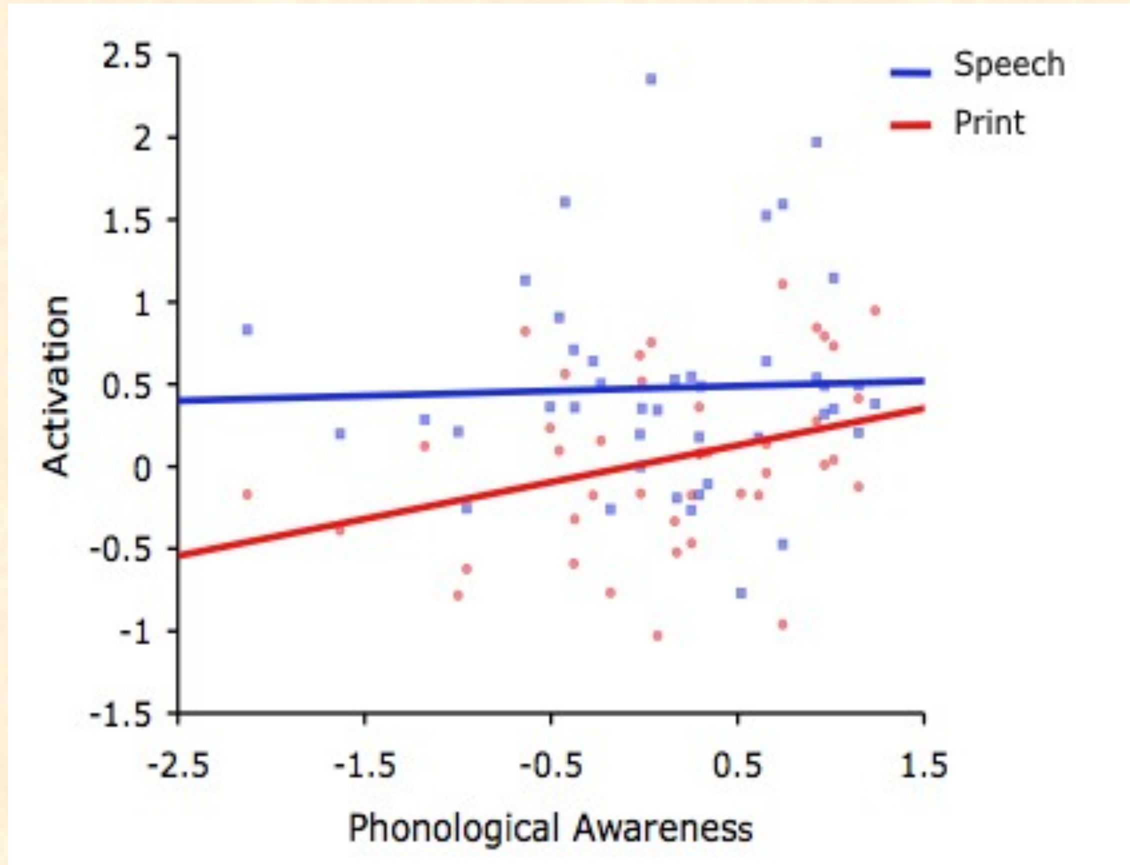


LH on right side

$p < .01$

PA x Modality





r = 0.44

$p < .01$

Speech/print integration: follow-up data on reading outcomes two years later at age 9

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ASSOCIATION FOR PSYCHOLOGICAL SCIENCE

Research Article

Psychological Science
1–10

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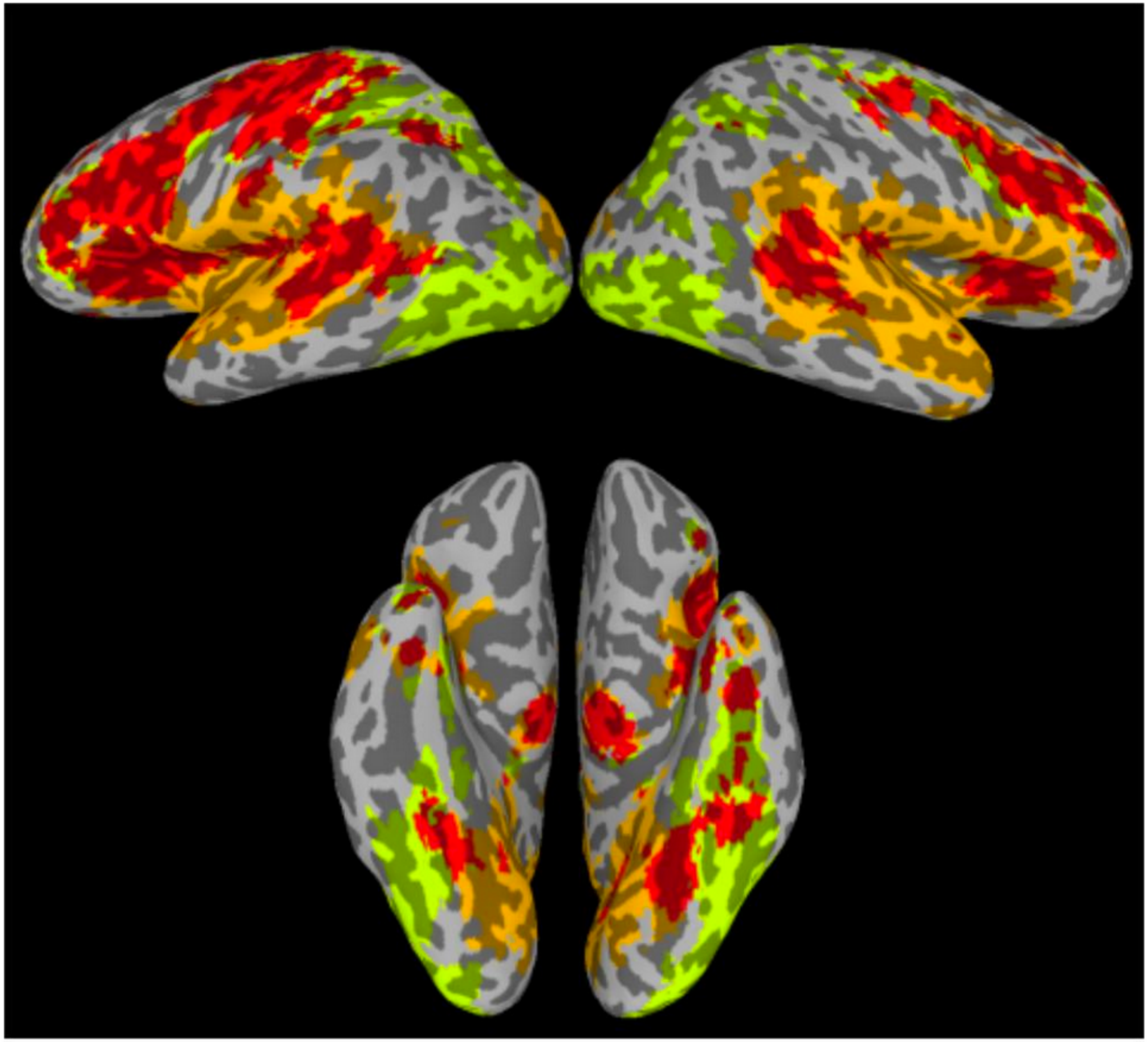
Print-Speech Convergence Predicts Future Reading Outcomes in Early Readers

Jonathan L. Preston[1,2], Peter J. Molfese[2,3], Stephen J. Frost[2], W. Einar Mencl[2], Robert K. Fulbright[4], Fumiko Hoeft[2,5], Nicole Landi[2,3], Donald Shankweiler[2,3], and Kenneth R. Pugh[2,3]

[1]Department of Communication Sciences & Disorders, Syracuse University; [2]Haskins Laboratories, Yale University; [3]Department of Psychology, University of Connecticut; [4]Diagnostic Radiology, Yale University School of Medicine; and [5]Department of Psychiatry, University of California, San Francisco

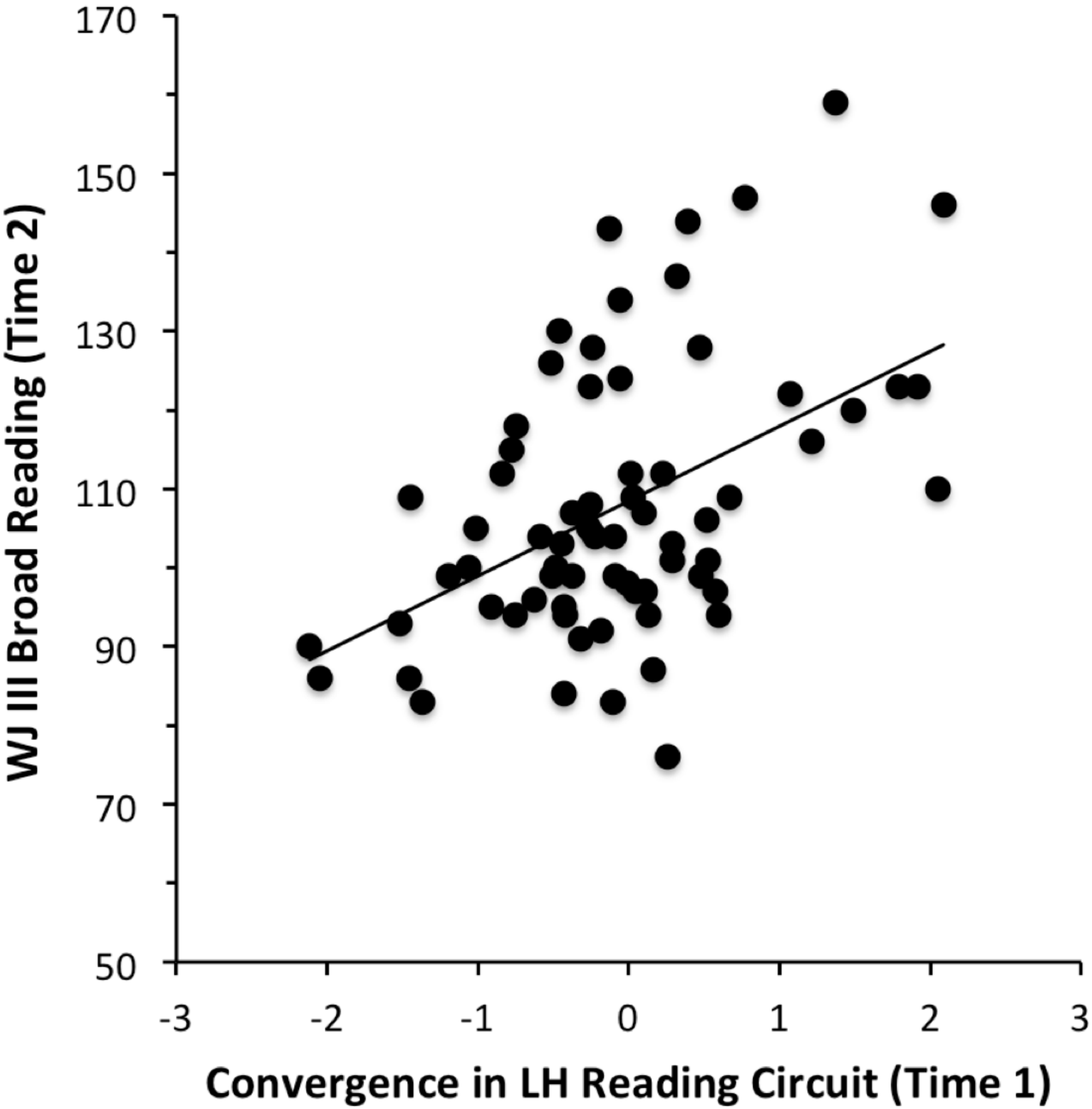
Abstract

Becoming a skilled reader requires building a functional neurocircuitry for printed-language processing that integrates with spoken-language-processing networks. In this longitudinal study, functional MRI (fMRI) was used to examine convergent activation for printed and spoken language (print-speech coactivation) in selected regions implicated in printed-language processing (the reading network). We found that print-speech coactivation across the left-hemisphere reading network in beginning readers predicted reading achievement 2 years later beyond the effects of brain activity for either modality alone; moreover, coactivation effects accounted for variance in later reading after controlling for initial reading performance. Within the reading network, effects of coactivation were significant in bilateral inferior frontal gyrus (IFG) and left inferior parietal cortex and fusiform gyrus. The contribution of left and right IFG differed, with more coactivation in left IFG predicting better achievement but more coactivation in right IFG predicting poorer



Variable	Function	*β*	*t*	*p*
Age T1	Control	-.16	-1.41	.163
WB Print activation	Control	-.60	-1.65	.103
WB Speech activation	Control	-.12	-1.77	.083
LH Reading Network Co-A	**ROI**	**1.59**	**4.32**	**<.001**
RH Reading Network Co-A	ROI	-.28	-1.00	.323

Outcome: Time 2 Woodcock Johnson Broad Reading
Model $R^2 = .30$



WJ III Broad Reading (Time 2)
170
150
130
110
90
70
50
-3
-2
-1
0
1
2
3
Convergence in LH Reading Circuit (Time 1)

Summary: Cross modal integration and reading skill

- Our recent studies in indicate that a critical factor discriminating skilled from less skilled readers is the degree of print/speech integration in relevant LH circuits.

- Educational implication: All of these findings reinforce the importance of focus on phonological processing in emergent readers.

- **Q) Is this the same in other written languages including non-alphabetic languages?**

PNAS PNAS PNAS

CrossMark click for updates

Universal brain signature of proficient reading: Evidence from four contrasting languages

Jay G. Rueckl[a,b], Pedro M. Paz-Alonso[c], Peter J. Molfese[a,b], Wen-Jui Kuo[d], Atira Bick[e], Stephen J. Frost[a,1], Roeland Hancock[f], Denise H. Wu[g], William Einar Mencl[a], Jon Andoni Duñabeitia[c], Jun-Ren Lee[h], Myriam Oliver[c], Jason D. Zevin[a,i,j], Fumiko Hoeft[a,f], Manuel Carreiras[c,k], Ovid J. L. Tzeng[l,m,n], Kenneth R. Pugh[a,b,o], and Ram Frost[a,c,e]

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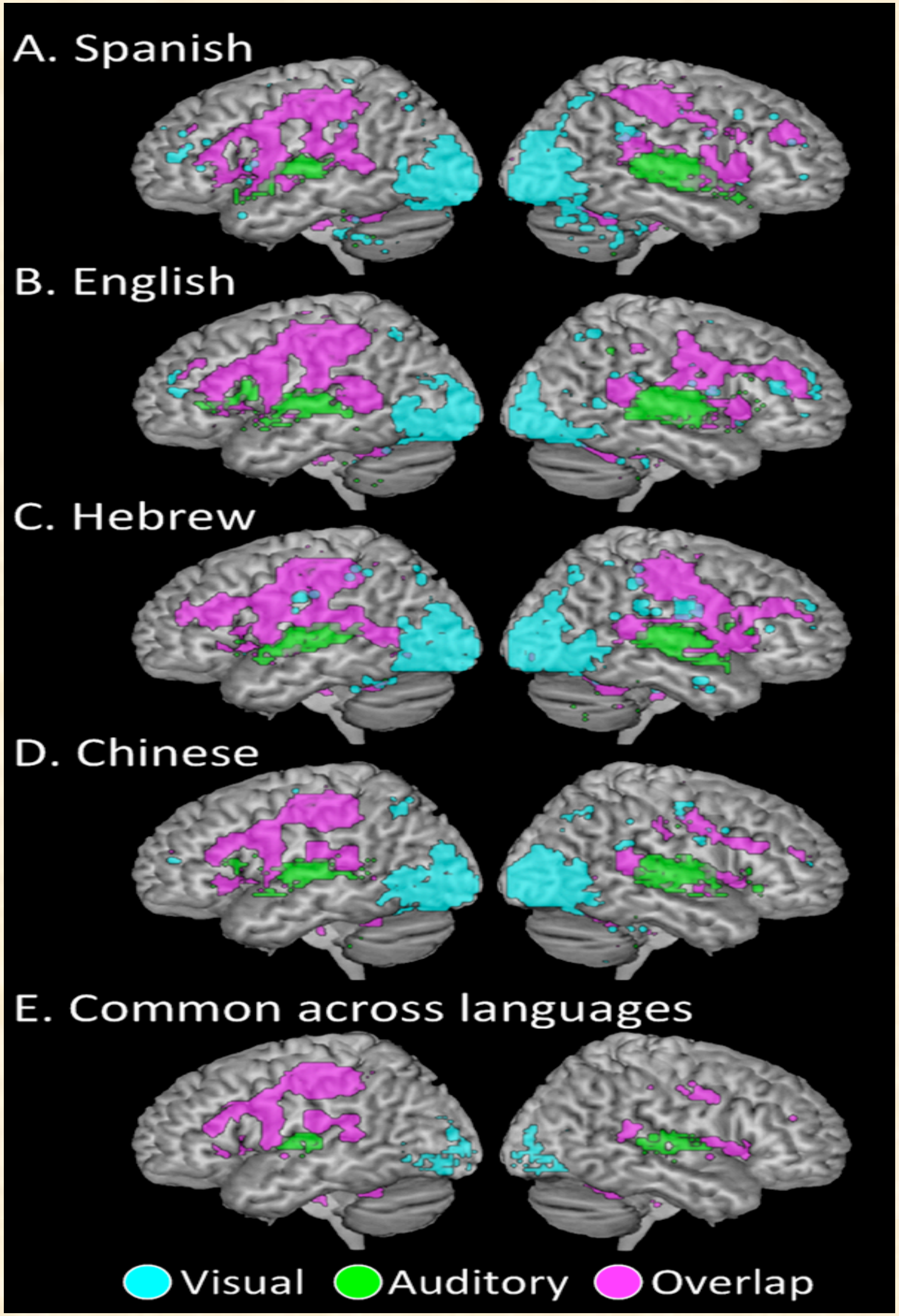
Edited by Michael I. Posner, University of Oregon, Eugene, OR, and approved November 2, 2015 (received for review May 12, 2015)

We propose and test a theoretical perspective in which a universal hallmark of successful literacy acquisition is the convergence of the speech and orthographic processing systems onto a common network of neural structures, regardless of how spoken words are represented orthographically in a writing system. During functional MRI, skilled adult readers of four distinct and highly contrasting languages, Spanish, English, Hebrew, and Chinese, performed an identical semantic categorization task to spoken and written

reading would not only recruit the neural circuits best suited for processing its orthographic symbols (which could show some front-end variation due to visuospatial differences) but would fundamentally depend on access to existing neurocircuits implicated in processing meaningful spoken words (16). By this view, a universal hallmark of successful literacy acquisition would be the emergence of a reading network that is strongly constrained by the brain network underlying the processing of spoken words (a network itself

LOGICAL AND IVE SCIENCES


A. Spanish
B. English
C. Hebrew
D. Chinese
E. Common across languages
Visual
Auditory
Overlap

Reading Disability “Consensus” Definition

- Dyslexia primarily affects the skills involved in accurate and fluent word reading and spelling.

Characteristic features of dyslexia are difficulties in phonological awareness, verbal memory and verbal processing speed.

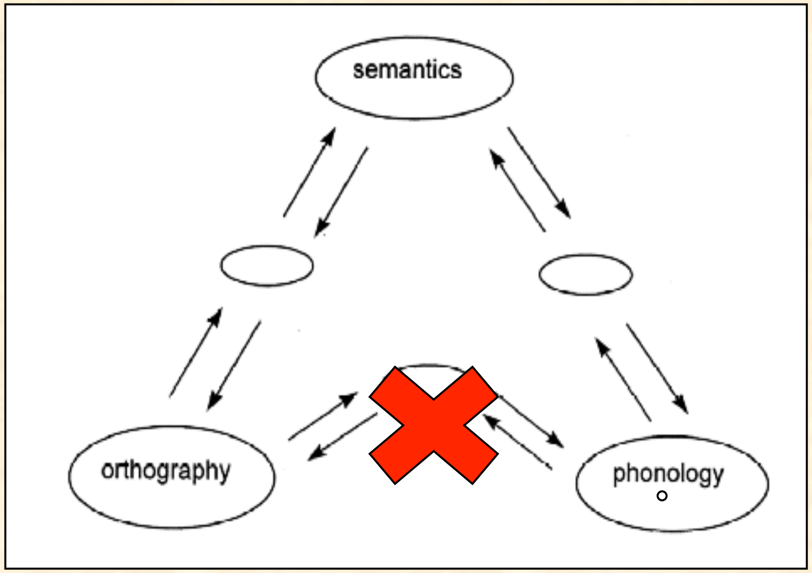
Dyslexia occurs across the range of intellectual abilities.

It is best thought of as a continuum, not a distinct category, and there are no clear cut-off points.

- Co-occurring difficulties may be seen in aspects of language, motor co-ordination, mental calculation, concentration and personal organisation, but these are not, by themselves, markers of dyslexia.
- A good indication of the severity and persistence of dyslexic difficulties can be gained by examining how the individual responds or has responded to well founded intervention.

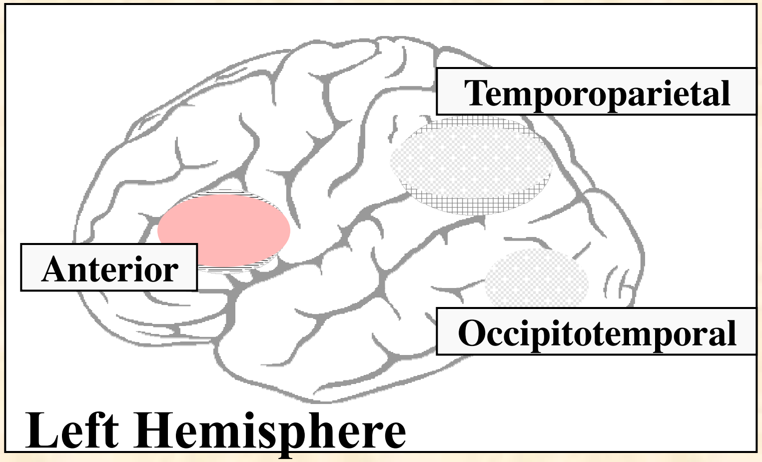
Reading Disability: Behavioral phenotype

- Word identification is slow, labored, and error prone in RD (bottleneck for comprehension).
- Early deficits in developing fine-grained **phonemic awareness** predict word reading difficulties later on.
- These deficits in **phonological awareness** impede the development of efficient **phonological assembly** routines (grapheme to phoneme mapping) which, in turn, places severe limits on word (and pseudoword) reading fluency.



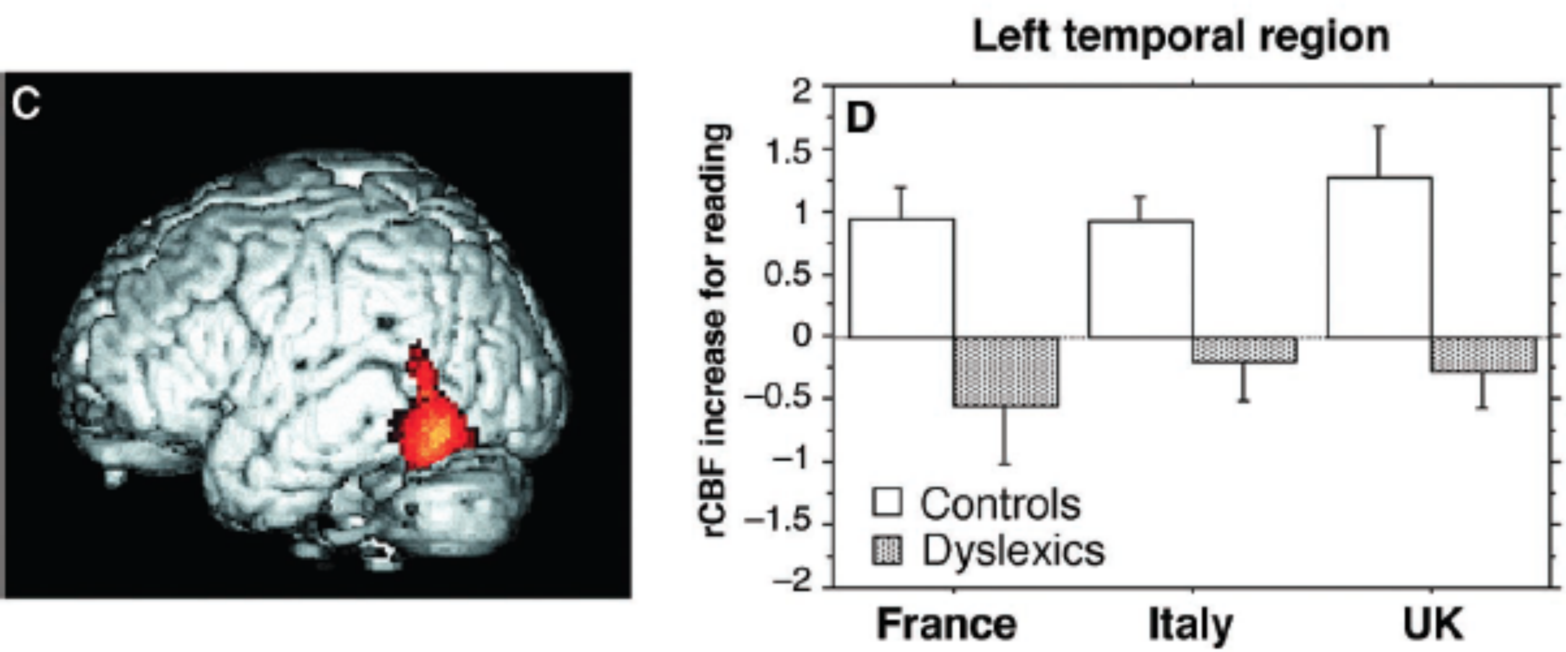
Brain circuits and Reading Disability

- Frequent finding: A large number of studies indicate that RD readers show anomalous patterns in **LH temporoparietal and LH ventral (occipitotemporal)** regions during reading and language tasks; this has been seen in several languages to date (Paulesu et al., 2001;Wu et al. 2010).
- **RH and frontal "compensatory" shift in RD often reported**



Dyslexia: Cultural Diversity and Biological Unity

E. Paulesu,[1,2]* J.-F. Démonet,[3] F. Fazio,[2,4] E. McCrory,[5]
V. Chanoine,[3] N. Brunswick,[6] S. F. Cappa,[7] G. Cossu,[8] M. Habib,[9]
C. D. Frith,[6] U. Frith[5]


C
Left temporal region
D
rCBF increase for reading
2
1.5
1
0.5
0
−0.5
−1
−1.5
−2
Controls
Dyslexics
France
Italy
UK

TD/RD differences: Insights from functional / structural neuroimaging to date

- Functional/structural neuroimaging indicate reading disabled (RD) children, adolescents, and adults fail to organize left hemisphere (LH) temporoparietal (TP) and occipitotemporal (OT) cortical regions into a coherent reading circuit (Pugh et al., 2000, 2010):

1) Unstable and reduced activation

2) Reduced functional connectivity (Pugh et al., 2000)

3) problems in learning, and consolidation of new learning **(Pugh et al., 2008, *JOCN*)**

4) Reduced grey matter volume

5) white matter tract anomalies

Value-added…

- * Identification of biomarkers provides clear neural targets for intervention.

- Big question: Does treatment result in normalization vs. compensation at the neural level?

But

- * Not-single-subject diagnostic…
- And we do not know if these markers are "causes or consequences of RD".
- …

Next steps in neurobiological research..

- It is critical that we move beyond mere identification of structural and functional biomarkers and toward brain-based causal models focused on how and why these structural and functional differences impede **the development of LH ventral specialization for print**.

Tools: Animal models; Neurochemistry; dynamic learning and plasticity experiments

Haskins/Yale longitudinal studies

- We have recently completed a large scale NIH-funded longitudinal study asking:

- What are gene-brain-cognitive preconditions necessary for successful reading acquisition?

- We tracked low and high risk children over 2 years years (ages 7-9) at multiple levels of analysis (genetics, neuroanatomy, neurochemistry, neurofunction, cognition).

Neurochemistry and RD: A initial look at MRS and behavioral relationships

4082 • The Journal of Neuroscience, March 12, 2014 • 34(11):4082–4089

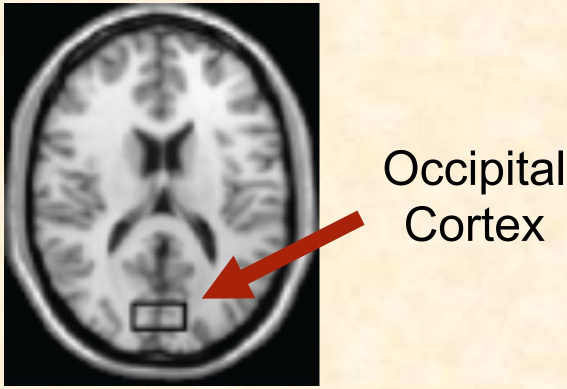
Behavioral/Cognitive

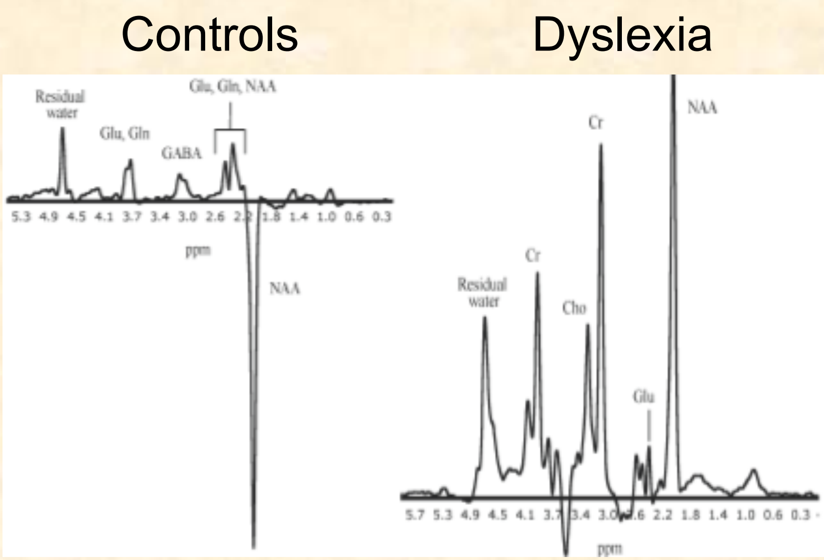
Glutamate and Choline Levels Predict Individual Differences in Reading Ability in Emergent Readers

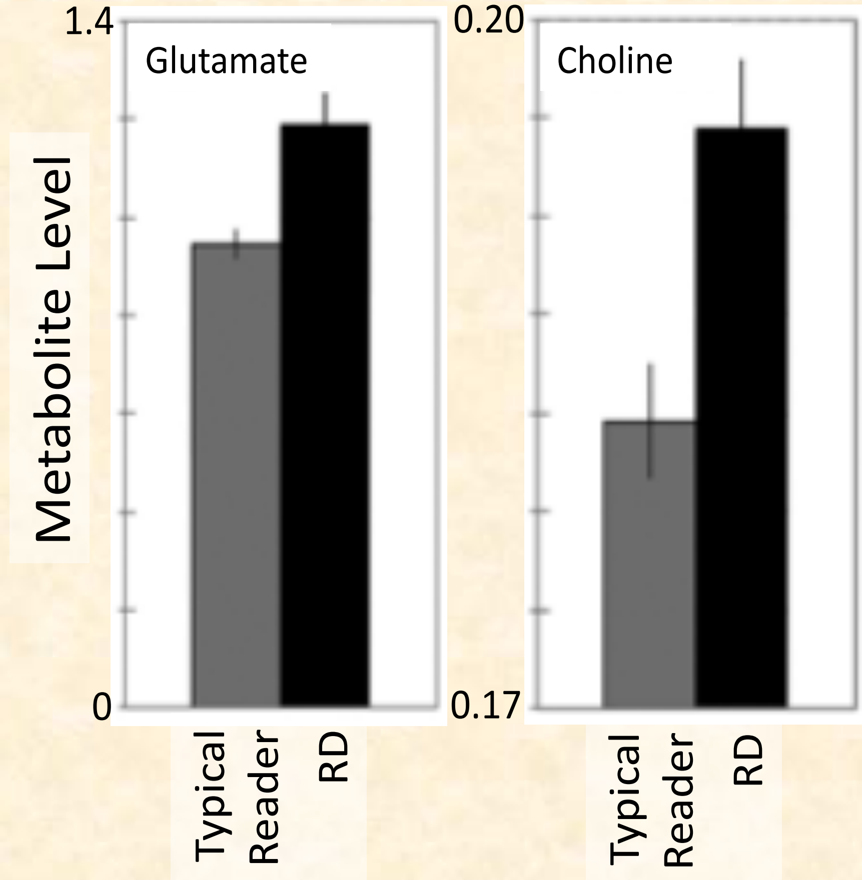
Kenneth R. Pugh,[1,2,3] Stephen J. Frost,[1] Douglas L. Rothman,[2] Fumiko Hoeft,[1,4] Stephanie N. Del Tufo,[1,3] Graeme F. Mason,[2] Peter J. Molfese,[1] W. Einar Mencl,[1] Elena L. Grigorenko,[1,5] Nicole Landi,[1,3,5] Jonathan L. Preston,[1,6] Leslie Jacobsen,[1] Mark S. Seidenberg,[1,7] and Robert K. Fulbright[1,2]

[1]Haskins Laboratories, New Haven, Connecticut 06511, [2]Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut 06520-8042, [3]Department of Psychology, University of Connecticut, Storrs, Connecticut 06269-1020, [4]Department of Psychiatry, University of California San Francisco, San Francisco, California 94143-0984, [5]Yale University Child Study Center, New Haven, Connecticut 06520, [6]Department of Communication Disorders, Southern Connecticut State University, New Haven, Connecticut 06515, and [7]Department of Psychology, University of Wisconsin Madison, Madison, Wisconsin 53706-1611

Reading disability: glutamate & choline links (Pugh et al., J Neuroscience 2014)







Longitudinal outcome data (Glutamate)

The inverse relationship between glutamate and reading scores is stable at multiple time points

Thus elevated glutamate levels at age 7 predict poor reading two years later.

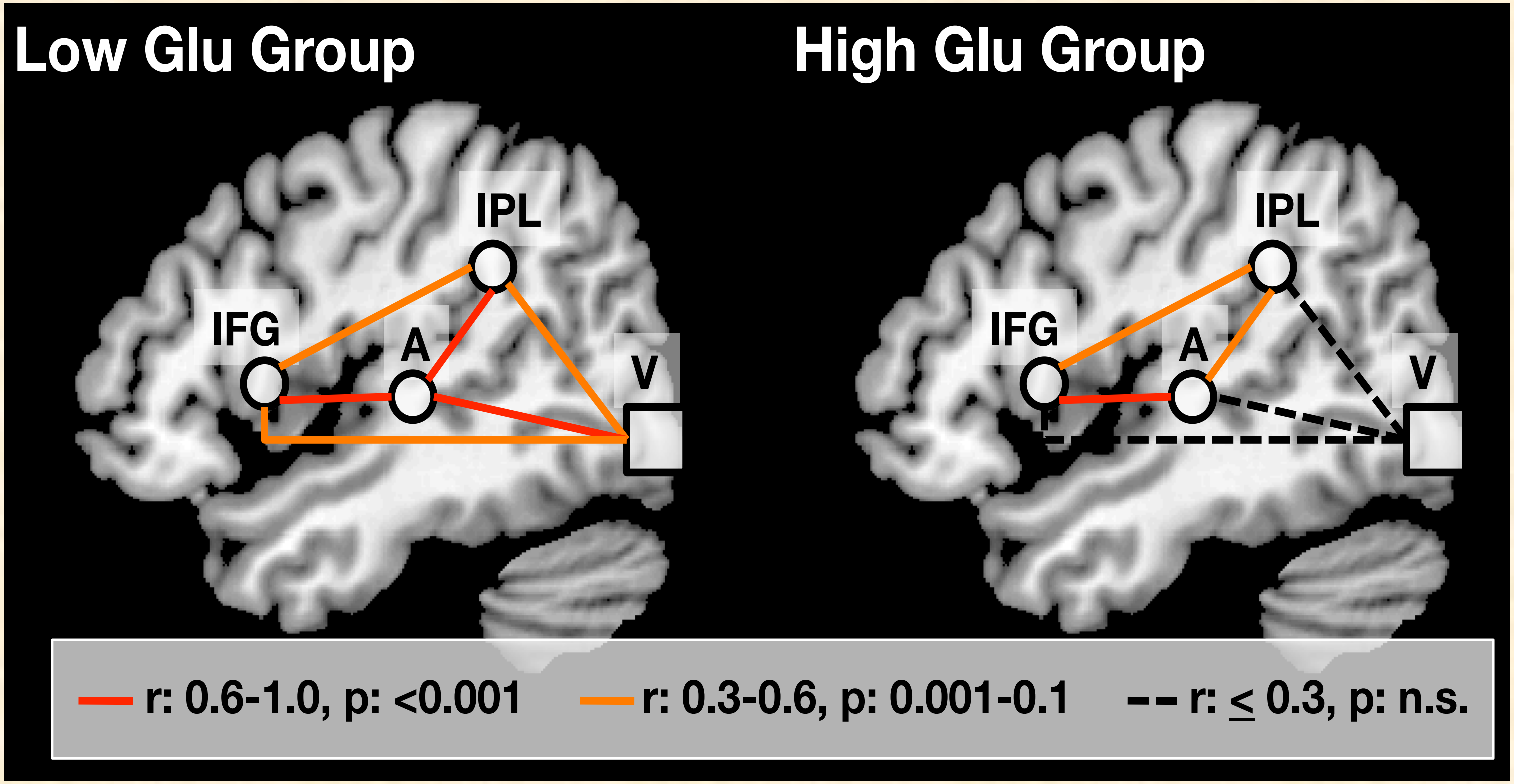
Elevated glutamate, neural noise, and RD

We are the first to study to examine Glu and GABA in RD children:

But elevated Glutamate has been **seen** in neurodevelopmental populations (e.g., autism and ADHD) and has been associated with hyper-excitability and "noisy" processing accounts for these populations.

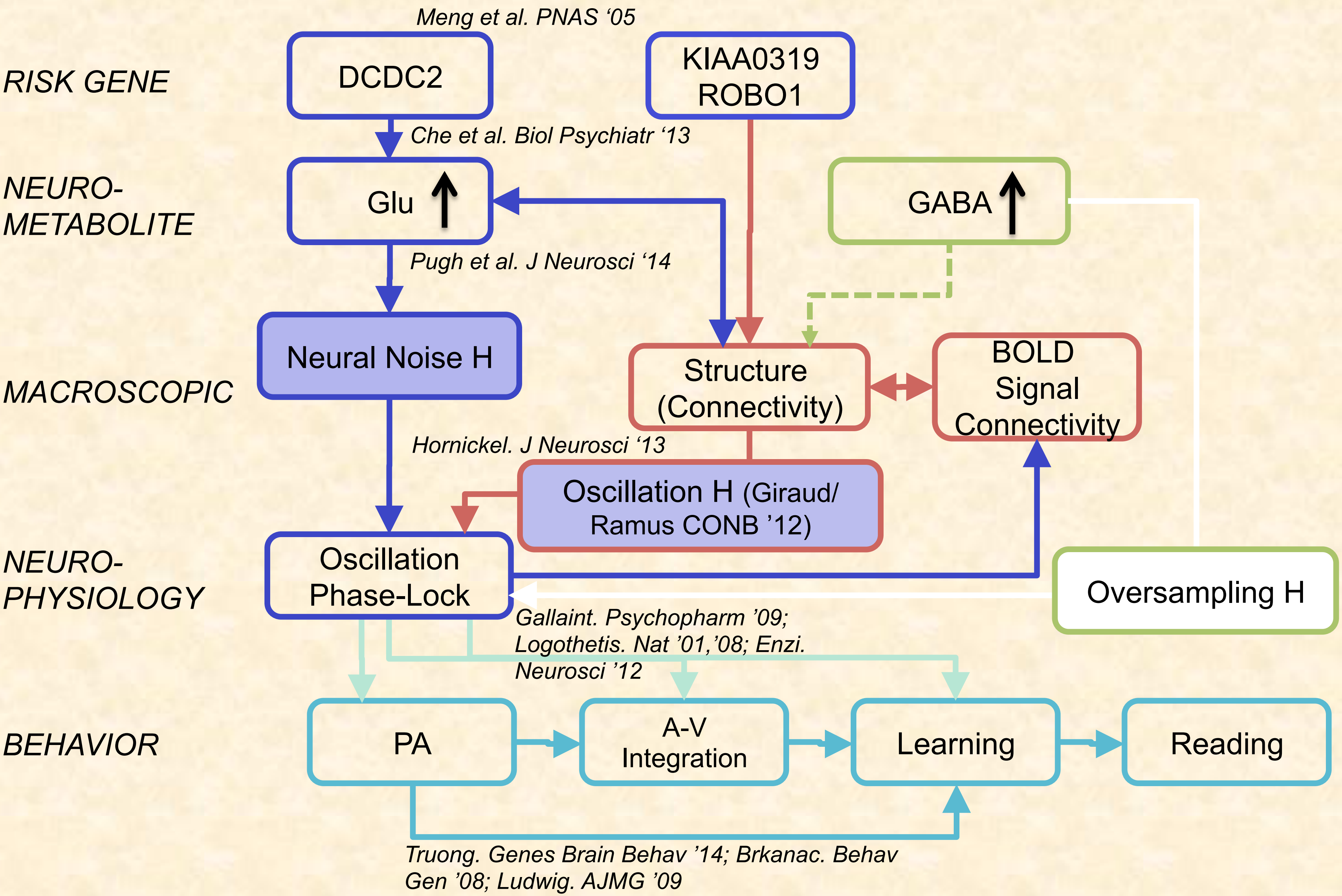
Is a "neural noise" account of RD a viable theory? These accounts have been gaining popularity recently but we need a <u>mechanistic account.</u>

MRS vs. fMRI connectivity on 58 subjects



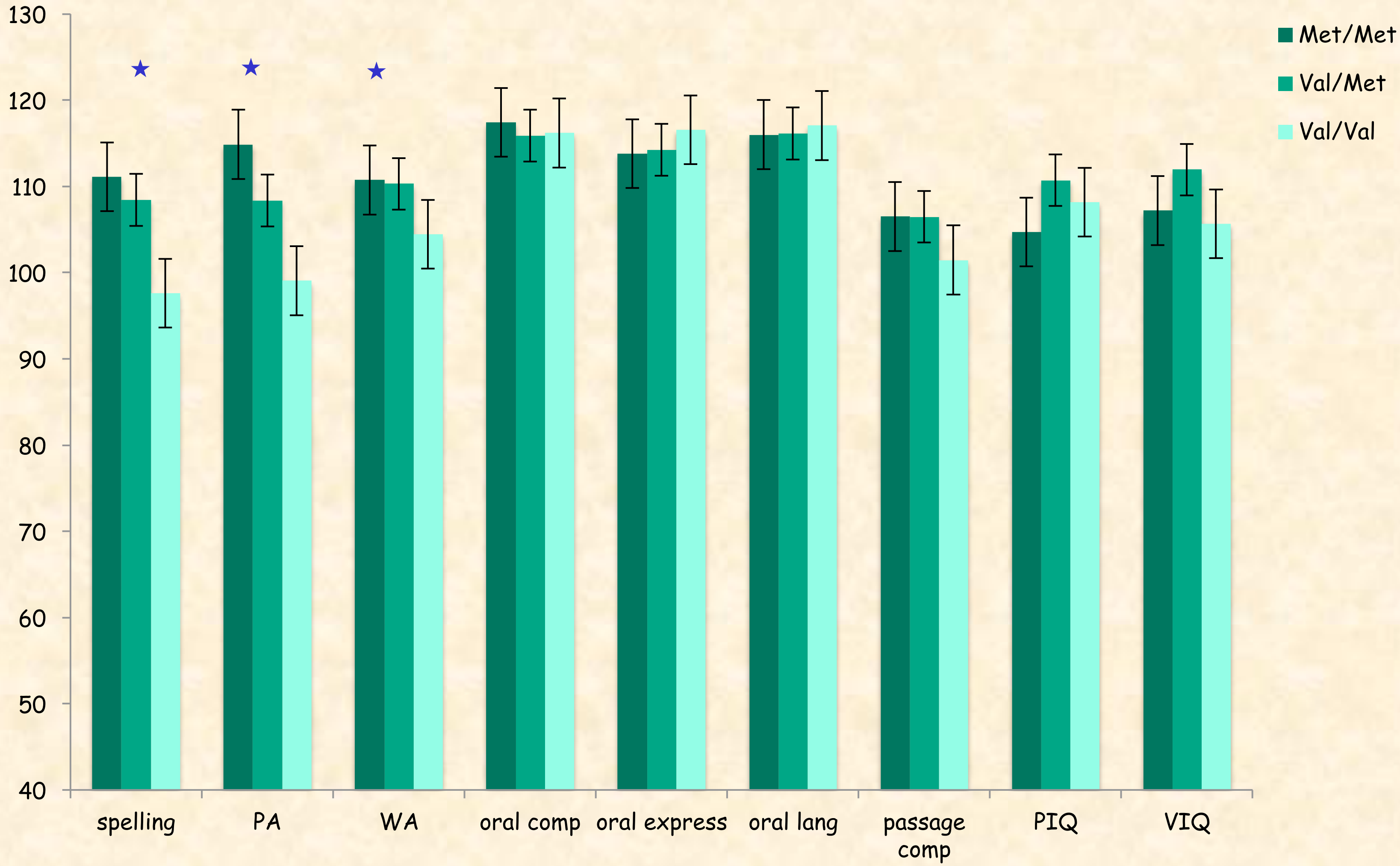
Eunice Kennedy Shriver NICHD National Institute of Child Health & Human Development

R01HD086168 (Multi-PIs: Pugh/Hoeft)



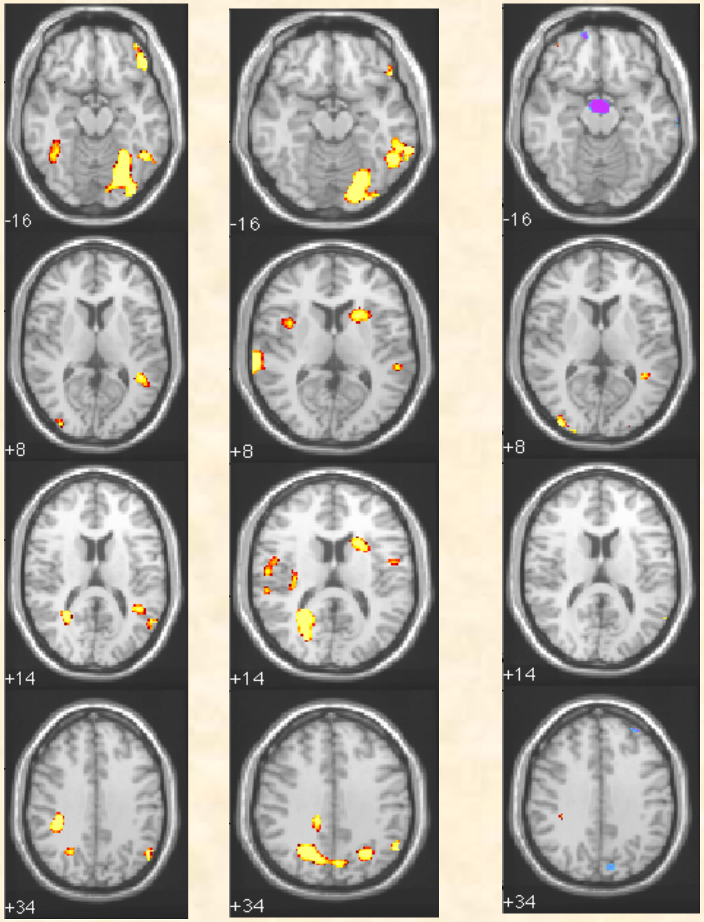
Genetics: Relations between *COMT* genotype, behavioral phenotype and fMRI activation (Landi et al., 2013 *Dev. Science*)

COMT Val/Met: Behavioral data



Landi et al. 2013

COMT Val/Met: fMRI findings



Met/Met > Val/Val | Met/Met > Val/Met | Val/Met > Val/Val

Met carriers look like better readers.

Developmental Science

Developmental Science 16:1 (2013), pp 13–23 DOI: 10.1111/j.1467-7687.2012.01180.x

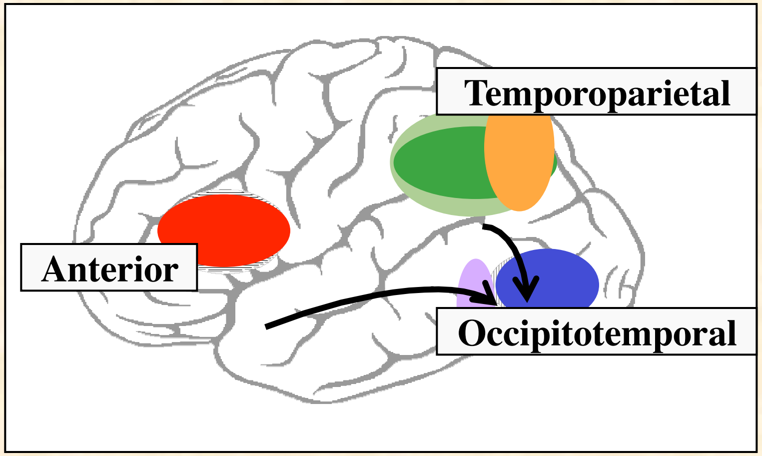
PAPER

The *COMT* Val/Met polymorphism is associated with reading-related skills and consistent patterns of functional neural activation

Nicole Landi, Stephen J. Frost, W. Einar Mencl, Jonathan L. Preston, Leslie K. Jacobsen, Maria Lee, Carolyn Yrigollen, Kenneth R. Pugh and Elena L. Grigorenko

$p<.01$, FDR corrected

A brief look at remediation and plasticity in RD



- RD readers do not tend to show the typical neurodevelopmental trend.

- **Question: Does remediation normalize this trajectory?**

Remediation of RD (Shaywitz, Shaywitz, Pugh et al., 2004, *Biological Psychiatry*)

- Q) Are under-engaged LH systems fundamentally disrupted, or does observed de-activation reflect an unstable but potentially “trainable” state?

- First grade cohorts: TD, RD-treat, RD-control

- fMRI: pre, post and (for RD-treat) at **one year follow up**

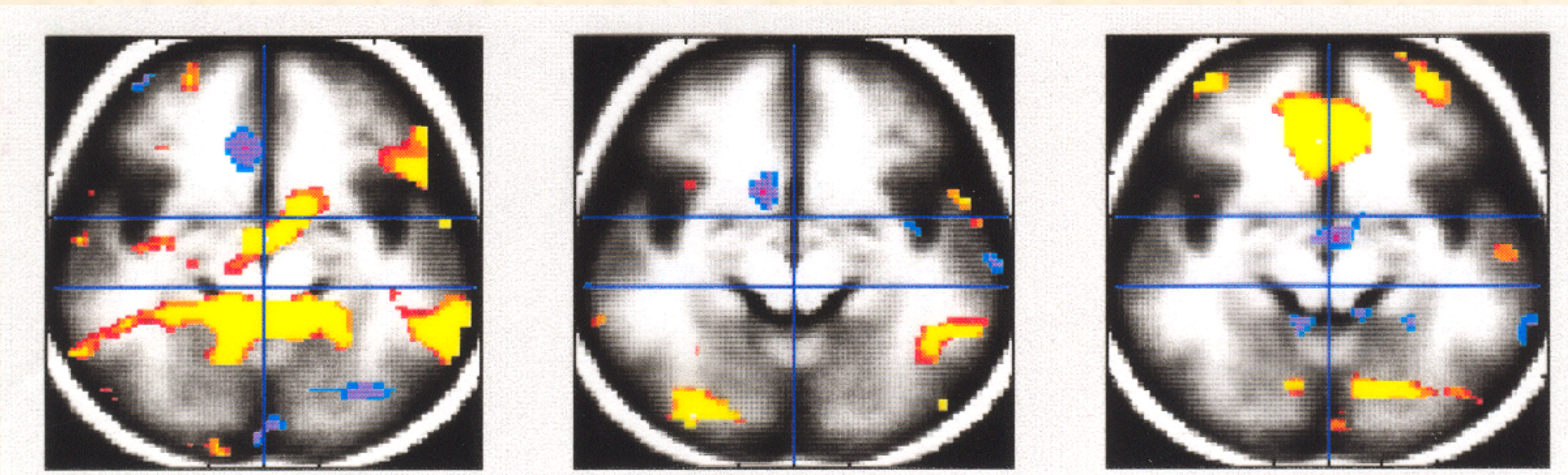
Treatment Protocol (from B. Blachman)

- 50 min tutoring, 5 days per week, 9 months (105 hours total)
- 5 step plan (unscripted) & individualized
  - Letter-sound associations
  - Phoneme manipulation
  - Reading words
  - Reading text
  - Assessment

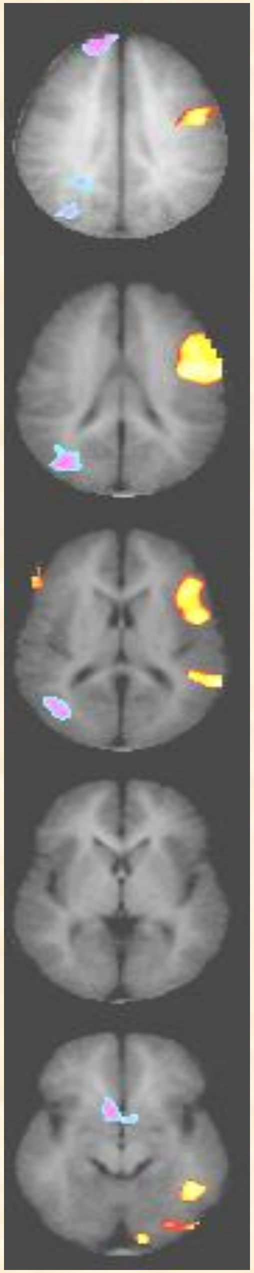
Treatment Year 2
Vs
RD Control Year 2

Treatment Year 2
Vs
Treatment Year 1

RD Control Year 2
Vs
RD Control Year 1



Year 3 (follow-up) vs. Year 1 (Pre-Treatment)



LH on right

A consistent story on treatment effects is emerging

- A growing number of treatment studies have shown modulation of LH reading circuits with effective treatment:
- **functional changes (Shaywitz et al., 2004;** Simos et al.,2002 Temple et al.,2003; Eden et al., 2004; Meyler et al, 2009**)**

  and

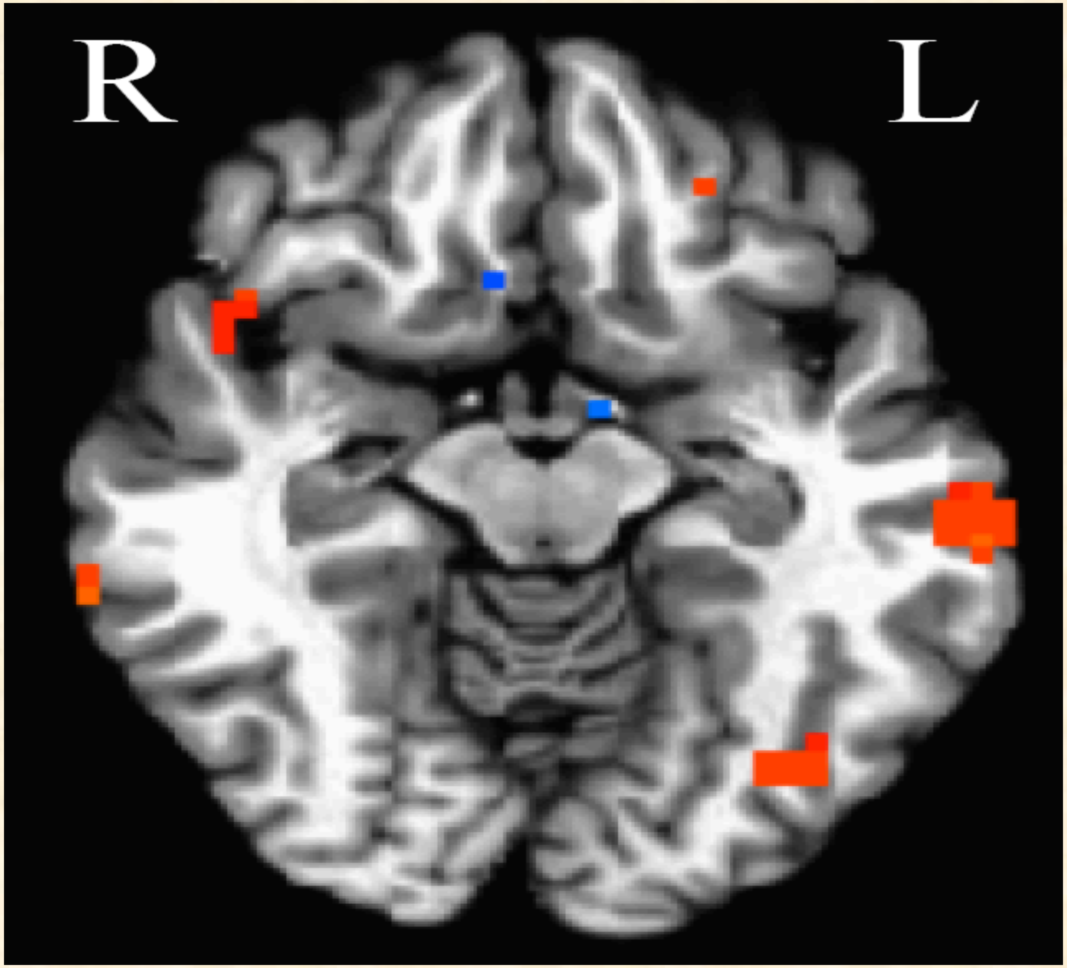
- **Grey and white matter changes (**Keller et al., 2009; Flowers et al., 2011**)**

- **BUT: we must better understand why some children do not respond to treatment…**

Treatment Resistor/Responder Project (2013-2018)

- A new NIH-funded P01 project involves a collaboration between Haskins Labs, Georgia State University, and Hospital for Sick Children.
- We employ:
- An evidence based phonological treatment (90 hours)
- pre and post fMRI,
- cognitive experiments,
- computational modeling
- To:
- discriminate treatment resistors from treatment responders

Brain regions showing strong predictive relationship to treatment responsiveness



A challenge to current theories: visuospatial "strengths" in RD might represent a neural tradeoff

- A good deal of anecdotal support for the claim that RD individuals might have better skills at visuospatial processing than controls.

- But: Limited controlled studies to date.

- One particularly compelling research study suggesting a possible tradeoff found that children with RD appear to have advantages in configural, or "global" processing (seeing the whole) over feature-based, or "local" processing (von Károlyi et al., 2003; von Károlyi, 2001).

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Neural correlates of a language and non-language visuospatial processing in adolescents with reading disability

Joshua J. Diehl [a,b,*], Stephen J. Frost [b], Gordon Sherman [c], W. Einar Mencl [b], Anish Kurian [b,d], Peter Molfese [b], Nicole Landi [b], Jonathan Preston [b], Anja Soldan [e], Robert K. Fulbright [b,f], Jay G. Rueckl [b,d], Mark S. Seidenberg [b,g], Fumiko Hoeft [b,h], Kenneth R. Pugh [b,d]

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ABSTRACT

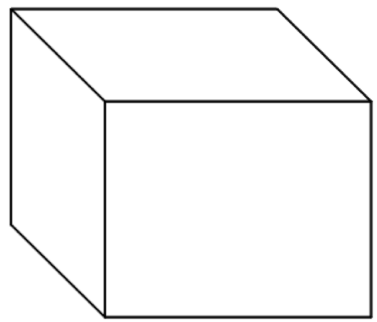
Despite anecdotal evidence of relative visuospatial processing strengths in individuals with reading disability (RD), only a few studies have assessed the presence or the extent of these putative strengths. The current study examined the cognitive and neural bases of visuospatial processing abilities in adolescents with RD relative to typically developing (TD) peers. Using both cognitive tasks and functional magnetic resonance imaging (fMRI) we contrasted printed word recognition with non-language visuospatial processing tasks. Behaviorally, lower reading skill was related to a visuospatial processing advantage (shorter latencies and equivalent accuracy) on a geometric figure processing task, similar to findings shown in two published studies. FMRI analyses revealed key group by task interactions in patterns of cortical and subcortical activation, particularly in frontostriatal networks, and in the distributions of right and left hemisphere activation on the two tasks. The results are discussed in terms of a possible neural tradeoff in visuospatial processing in RD.

fMRI: reading tasks vs. configural tasks

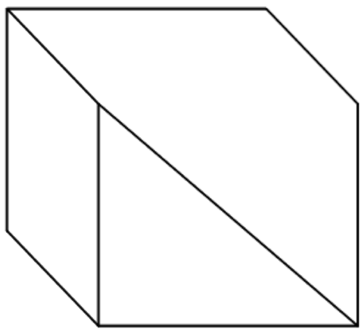
- In this study with both cognitive tests and functional Magnetic Resonance Imaging (fMRI) scans we examined:

- 1) word/nonword reading (a print lexical decision task)
- 2) a non-linguistic visuospatial processing task (the Possible-Impossible Figure Task) that had previously shown processing advantages for individuals with RD (von Károlyi et al., 2001; 2003).
- 3) A control one-back tasks with both print and figures.

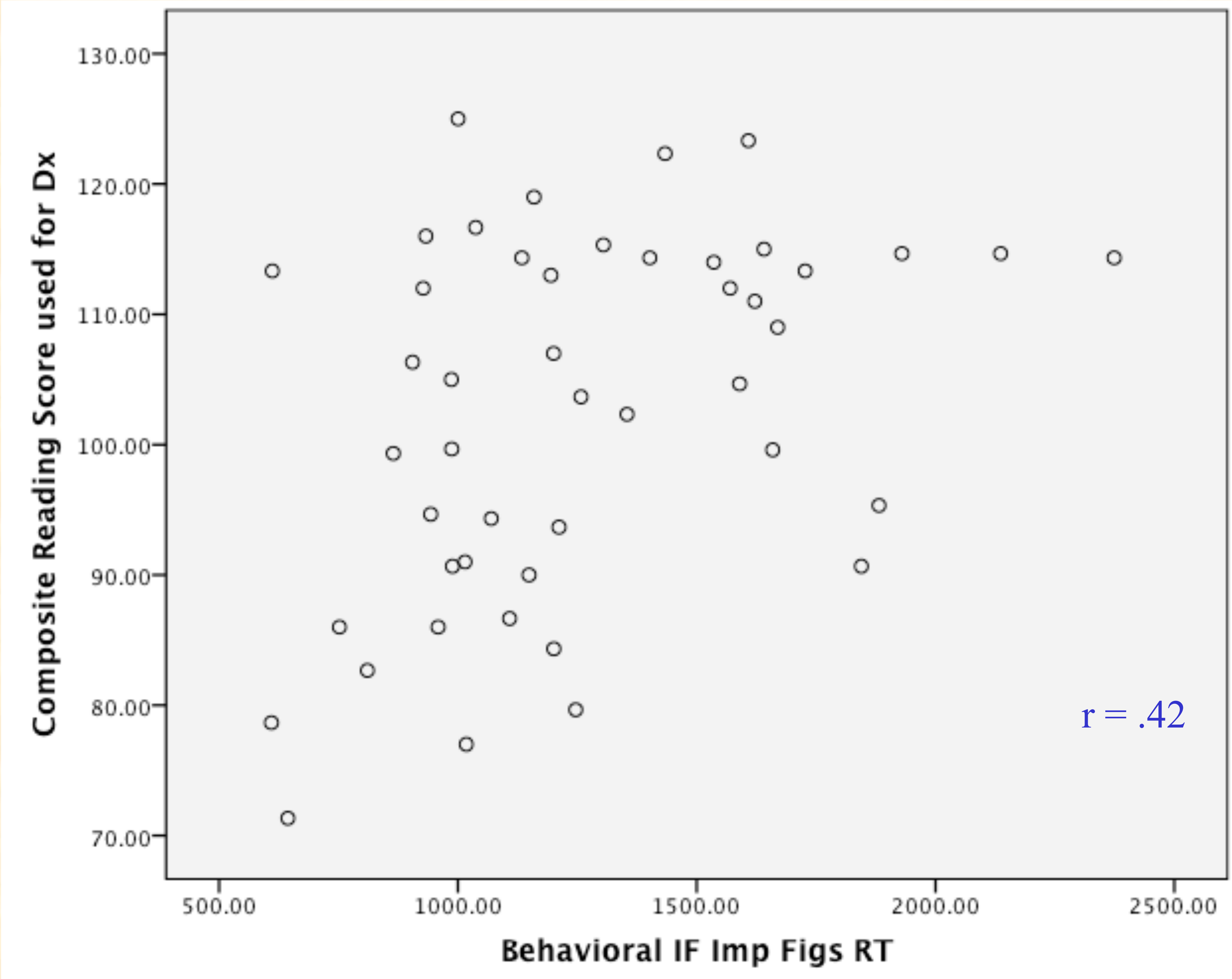
Figure 1. Examples of possible and impossible figures.



(a)



(b)


130.00
120.00
110.00
100.00
90.00
80.00
70.00
Composite Reading Score used for Dx
500.00
1000.00
1500.00
2000.00
2500.00
Behavioral IF Imp Figs RT
r = .42

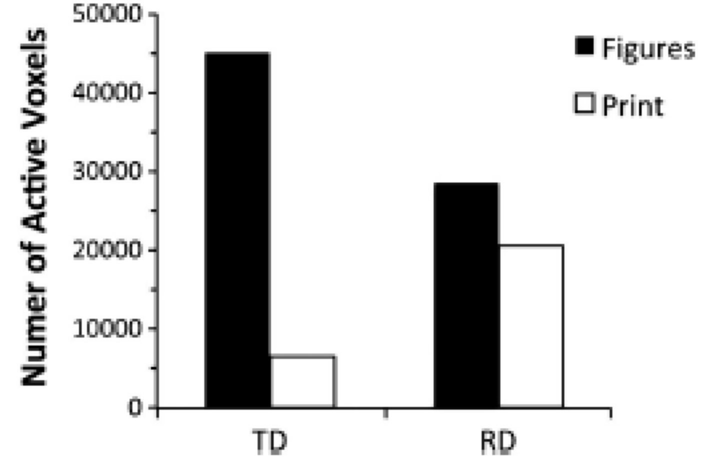


Fig. 3. Reader group differences during the one-back task in voxels significantly activated ($p < .001$, FDR corrected) for figures and print across the entire cortex.

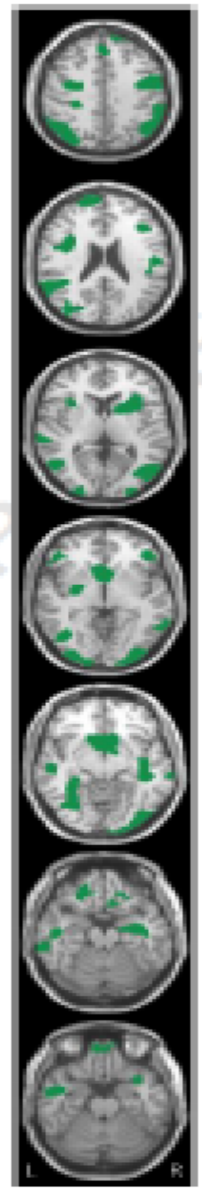


Fig. 2. Regions showing a reader group by task (impossible figures, lexical decision) effect ($p < .01$, corrected for FDR). Images from top to bottom correspond to the following position along the z-axis in MNI space: +40 + 22, + 4, −4, −10, −20, and −24, respectively, with the LH on the right side of the images.

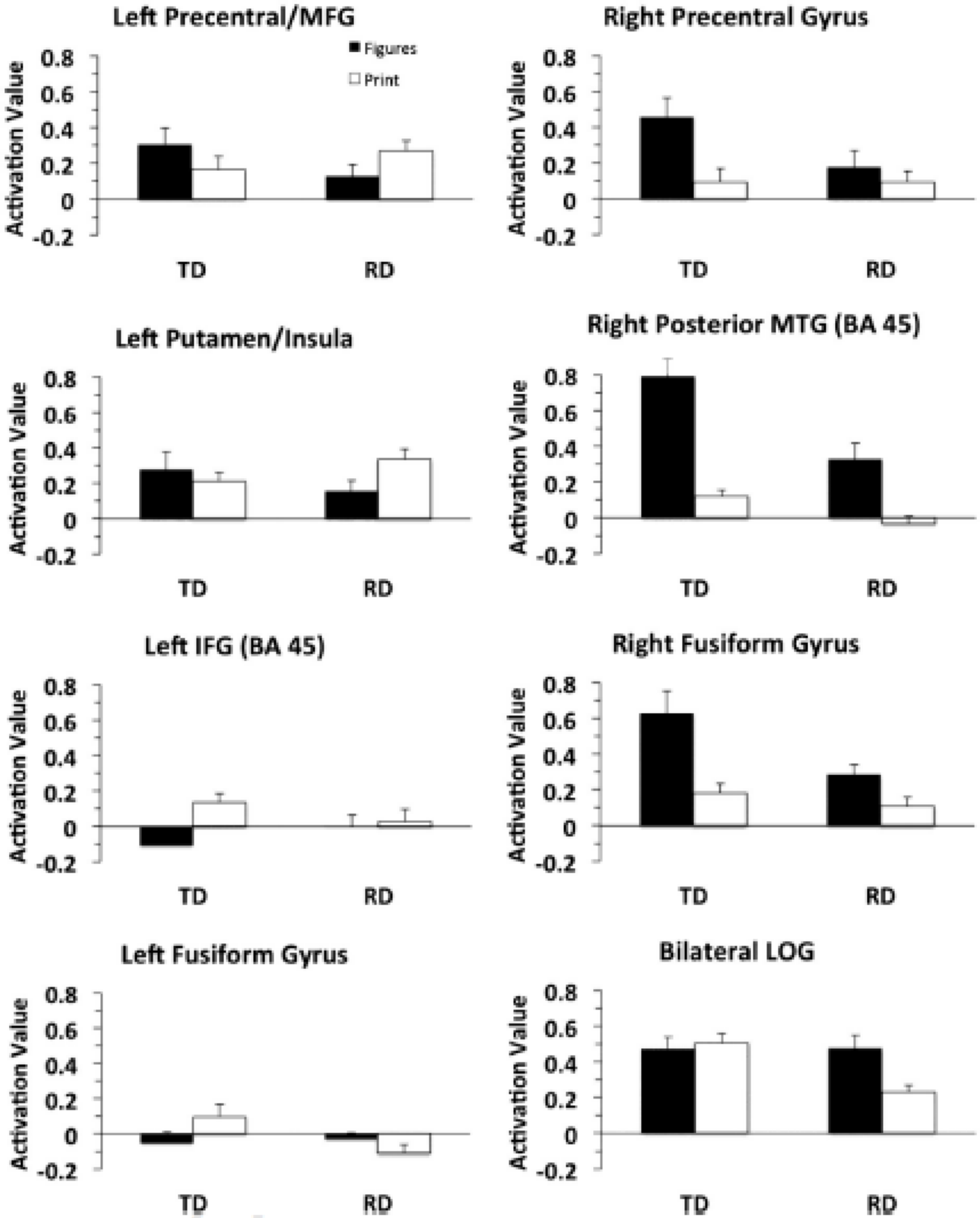


Fig. 4. Functionally defined regions of interest from the reader group by task (impossible figures, lexical decision) pattern interaction.

Implications

These results indicate that figures are processed with greater expertise in RD while a print advantage is obtained in typically developing peers.

This study provides the first neurobiological evidence for a possible hemsipheric tradeoff between reading and visuo-spatial processing in RD.

Next question: Is this hemispheric tradeoff a consequence of reading experience or a predisposition in RD children?

Collaborators

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