Neuroimaging studies of language development reading and reading disabilities

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Language Reading and Brain

• Spoken language is a biological specialization but written language is largely a cultural invention.
• Spoken language 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

How do skilled readers recognize words

• 1) Skilled readers can read words fast (approx. 200 msec.)
• 2) Pseudoword reading is nearly as fast!
• 3) Reading disabled (RD) readers are slow, non-automatic, and error prone at the level of decoding words.
• Key concept: The development of skilled reading depends upon establishing efficient connections between graphemes and phonemes and even skilled adult readers continue to engage phonological codes.

Reading Disability: Behavioral phenotype

• Phonological processing deficits are nearly universal, but what is the underlying cause?
• Proposals include:
  1) poorly specified phonological representations/language-specific deficits (Fowler/Elbro)
  2) visual (Stein; Eden) and/or auditory (Tallal; Goswami)sensorimotor deficits
  3) access/retrieval deficits (Ramus)
  3) noisy processing/attentional deficits (Sperling; Ziegler)
  4) Procedural learning (Fawcett and Nicolson)
  5) Cumulative risk markers (Snowling and Hulme)
Reading Disability: Behavioral phenotype

- It is possible that there are multiple sub-types, with different pathways but a common end-state (phonological processing deficit).

- Neurobiological research can be discriminative in contrasting these theories.

What is the brain basis of typical vs. atypical reading development?

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

In vivo brain studies: Mapping the reading circuitry 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.

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

A tentative model of skilled reading

(Pugh et al. 2000; 2010)
**Effects of phonological skill on speech/print integration (Frost et al., 2009)**

- Phonemic awareness (PA) is the metalinguistic understanding that spoken words are made of smaller segments and this ability discriminates children at high or low risk for RD and scores on PA tasks reflect "reading readiness" in emergent readers.

- How do beginning readers with higher or lower reading readiness as indexed by PA differ in early brain organization for spoken and written stimuli?

**Correlation of PA with BOLD Modality Effect**

- $r = 0.44$
- $p < .01$

**fMRI Sentence processing study (Shankweiler et al., 2008).**

Does print/speech integration vary as a function of reading comprehension scores?

**Illustrating high and low values of the Convergence Index**
Correlation of convergence and skill at dorsal IFG

Summary: Cross modal integration and reading skill

- These studies indicate that both at the level of word recognition and at the level of sentence processing a critical factor discriminating skilled from less skilled readers is the degree of print/speech integration in relevant LH circuits. Some questions:
  1) What are the implications for instruction?
  2) Is there a parallel relation in non-alphabetic orthographies?
  3) What are the relevant gene-brain-behavior factors that make integration problematic in many children?

Reading Development

- Increases in reading skill in English are associated with increased specialization of ventral LH areas for print.
- RD readers show very different trajectory

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

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

TD/RD differences: Insights from functional /structural neuroimaging

- 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
But

- These findings of brain differences in RD are simply **describing** the condition at the level of brain systems.
- They do not explain it.

**Going beyond descriptive 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.
- Prospective longitudinal studies, focused on gene-brain-behavior pathways in emergent readers, are at a premium at this stage (Pugh & McCardle, 2009).

**Haskins/Yale longitudinal studies**

- We have recently completed two NICHD-funded longitudinal studies asking:
  - What are the behavioral and neurobiological preconditions for successful reading acquisition?
- Study 1) From 7-9 years examines at risk children with multiple levels of analysis (genetics, neuroanatomy, neurochemistry, neurocircuitry, behavior).
- Study 2) From 5-11 years examines brain/behavior trajectories in three languages that vary in orthographic depth (English, Finnish, Mandarin Chinese).

Some key longitudinal findings to date

- 1) late onset of talking is linked to subcortical anomalies in basal ganglia and thalamus (Preston et al., 2010)
- 2) problems with early reading-readiness skills such as phonological awareness limit print/speech integration in temporal lobe regions (Frost et al., 2009)
- 3) High risk emergent readers differ in cortical and subcortical activation printed words (Pugh et al., 2013)
- 4) indices of neurochemistry (particularly Glutamate and NAA) appear to be sensitive to reading difficulties in young children (Pugh et al., submitted)
- 5) Genetics: initial links with COMT (Landi et al. 2013)

The learning circuit in emergent readers (Pugh et al., 2013, Brain and Language)

- Our major goal in this study is to identify brain pathways that are most strongly associated with individual differences on multiple indices of reading-relevant skills (phonological awareness, decoding, and auditory sensory processing) at a point in time when the mature circuitry that will eventually come to support fluent reading is, to a large extent, still coming online.
62 beginning readers (ages 5-8, mean = 7.7) ranging along a continuum from conventionally RD to superior readers.

- **Predictor tasks:**
  - 1) Phonemic Awareness (Elision; CTOPP)
  - 2) rapid auditory processing (TOJ Task)
  - 3) timed pseudoword reading (PDE; TOWRE)

- **Dependent measures:**
  - 1) Timed word reading (SWE; TOWRE)
  - 2) brain activation for print stimuli during fMRI

Summary and discussion

**The initial learning circuitry:** For printed word and pseudoword processing, our brain-behavior analysis revealed links between variation in reading-relevant skills and neural responses in:

1) well-established cortical components of the LH circuit (TP, IFG and OT)

and

2) visual cortex including V1 and extrastriate areas, precuneus, thalamus (pulvinar), and RH regions including MTG and IPL

**Correlation map of correlation between component scores and print activation**

\[ p < .01, \text{FDR corrected} \]
Brain behavior regression

Two step regression model, predicting sight word reading efficiency at time 3:

\[ R^2 = 0.426 \]

- Elision (Time 1) \( \beta = 0.489, p < 0.001 \)
- age(Time 1) \( \beta = 0.207, p < 0.05 \)
- LH Pulvinar \( \beta = 0.201, p < 0.05 \)

MRS scanning

Metabolites examined in a region of interest centered on medial occipital cortex:

- N-acetyl aspartate (NAA)
- GABA
- Glutamate
- Choline

Neurochemistry and RD: A initial look at MRS and behavioral relationships (Pugh et al, submitted)

Context: A recent study from a USC group used MRS to examine relations between choline and reading: Bruno et al., in press Neuroimage

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<thead>
<tr>
<th>Reading Composite</th>
<th>Pa Composite</th>
<th>Vocabulary</th>
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<tr>
<td>Chol: -25(-20)(-15)(-10)(-5), p = 0.008</td>
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Significance indicated for non-order correlations only.
Elevated choline has been reported in many clinical populations and is associated with abnormal white matter and/or cell membrane turnover.

Elevated Glutamate is also frequently reported in neurodevelopmental populations and is associated with hyper-excitability and "noisy" processing circuits.

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.

A brief look at remediation and plasticity in RD

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

Key questions:

- Are these under-engaged LH systems fundamentally disrupted, or does observed de-activation reflect an unstable but potentially "trainable" state?
- Can remediation focused on training up phonemic awareness (PA) skills modulate the neurocognitive risk profile in beginning reading.

· RD readers do not tend to show this neurodevelopmental trend.

· Trajectory is rightward and frontward.

· Question: Does remediation normalize this trajectory?
Testing effects of intensive phonological remediation in RD in emergent readers

• Overview: In collaboration with Dr. Benita Blachman (Syracuse University) we examined neurobiological changes associated with a nine month intervention emphasizing phonemic awareness, alphabet principle, and vocabulary development in young children (Shaywitz et al., 2004).

• Groups: TD (N = 28); RD control (N = 12); RD Treatment (N = 32). Each group scanned at baseline (average age = 6.5), one year later (post-treatment), and for the RD Treatment Group at one year follow up.

Treatment Protocol

• 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

A consistent story on treatment effects in brain 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)

• We thus have evidence that appropriate training has a normalizing effect on the neurobiological trajectory in emergent “at risk” readers.
• LH posterior system appears to be unstable but trainable in young at risk readers.
• But some kids don’t respond:
  • Who are these kids and what works for them?
  • Does optimal treatment differ in kids with ADHD or math disability?
• We need designs that contrast multiple approaches and ask what works for whom.

Key behavioral result: Reliable improvement on a battery of reading-related tests for the treatment relative to the control RD group (Blachman et al., 2005) after nine months of intensive evidence based training.

Effects stable at one year follow up.
Do reported visuospatial advantages in RD 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).

Impossible figures vs. reading (Diehl, Sherman…Pugh submitted) 

- In this new experiment with both cognitive tests and functional Magnetic Resonance Imaging (fMRI) scans we contrasted:
  1) word 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).
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 hemispheric 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?

Current focus of neuroimaging projects at Haskins

1) Examining the neural pathways associated with individual differences in learning and consolidation for spoken and written language materials.

2) Extending our neurobiological studies to multiple languages and to bilingual populations.

3) Linking individual differences in early brain organization for speech motor learning with later reading development in contrastive languages.

4) Extending Haskins neuroimaging research to comprehension and its disorders.

5) Examining differences between treatment responders and non-responders (Morris, Lovett, Haskins NIH-funded collaboration)

6) Better links between computational modeling, and neurobiological data; emphasis on dynamics

Collaborators

- Haskins Laboratories: Einar Mencl, Rebecca Sengok, Stephen Frost, Nicole Landi, Jon Frost, Leonard Kert, Joey Raciki, Jim Magnell, Donald Shopkewiler, Jun-Ren Lee, David Braze, Darragh Sibley, Allison Austin, Peter Malfe, Mark Seidenberg

- Yale Reading Center: Ken Pugh (Director), Gina Della Porta, Eleanor Tejada, Kelley Deloney, Ashley Zemis, Anah Kurani, Heather Carlin, Priya Pugh, Beth Estok, Ann Stutman

- Yale Center for the Study of Learning and Attention: Bennett Shaywitz, Sally Shaywitz (Directors), Karen Marchione, John, Holahan, Jack Fletcher

- Yale University/Diagnostic Radiology: John Gori, Todd Constable, Robert Fulkbright, Doug Reifman, Brianne Misan, Pawel Studinski, Cheryl Lac:rde

- Yale University/Psychiatry: Leslie Jacobson

- Yale Child Study Center: Elena Grigorenko