Brain Connections: Neuroimaging studies of language development reading and reading disabilities

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Outline of the presentation

• 1) An overview of findings on brain organization for language and reading in typically and atypically developing readers.
• 2) An update on longitudinal findings on emergent readers: Early language skills and the developing reading circuitry
• 3) Remediation, learning, and plasticity in reading
• 4) Consideration of the role of Executive function (EF) in reading and learning to read

Reading Disability: Behavioral phenotype

• Phonological processing deficits are 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)
• ** 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
**Language Reading and Brain**

- Spoken language is a **biological specialization** but written language is largely a cultural invention. Moreover, 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.
- **Implication**: Literacy acquisition is a challenge of brain plasticity. Learning to read is a cognitive challenge and EF plays a crucial role in this reorganization of language and visual networks.

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**Executive function**

- The term executive function describes a set of cognitive abilities that control and regulate other abilities and behaviors. Executive functions are necessary for goal-directed behavior. They include the ability to initiate and stop actions, to monitor and change behavior as needed, and to plan future behavior when faced with novel tasks and situations.

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[Diagram of the brain with labeled areas: Broca's area, Motor cortex, Auditory cortex, Wernicke's area, Angular gyrus, Primary visual cortex]
Auditory vs Visual Sentence Task

Constable, Pugh et al. (2004)

A reading model for alphabetic languages

(Pugh et al. 2000)

Brain circuits and Reading Disability

- Frequent finding: A large number of studies indicate that RD readers tend to under-activate both 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
Functional Connectivity (Pugh, et al., 2000 Psychological Science)

• A fuller account requires focus not only on within-region group differences, but also on differences in patterns of inter-regional correlations or functional connectivity (e.g., Horwitz, Rumsey & Donahue, 1998).
• 32 adult TD readers vs. 29 adult RD readers.
• Task Hierarchy: Two alternative forced choice same/different: Line (\//, //\); Letter case (BTBT, BTBT); Single Letter Rhyme (B, T); Non-word Rhyme (LETE, JEAT); Word Category (CORN, RICE).

Longer time scale learning in typically and atypically developing readers
Developmental trajectories in TD and RD children

(Shaywitz, Shaywitz, Pugh et al., 2002, Biological Psychiatry)

N=144 (ages 7-17: 74 TD controls, 70 RD)

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Age Correlations: NWR

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Reading Development: “Skill Zone” in Putative VWFA

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Summary: Reading Development

- Increases in reading skill in English are associated with increased specialization of ventral LH areas for print.
- Frontal lobe systems and EF implicated early on
- RD readers show very different trajectory

Shorter time scale learning in typically and atypically developing readers

- To examine potential short time-scale learning related changes in activation in we examined stimulus type and repetition effects on words.
- Skill learning involves coordinated interactions of perceptual/motor, visual, language, and association networks, under the control of frontal lobe/EF networks
characterization

Repetition Study
- present 56 words in each 5-minute imaging run; judge animacy
- 6 of these are presented 6 times pseudorandomly throughout
- 20 intermixed novel words serve as controls
- repeat up to 10 runs with different words

<table>
<thead>
<tr>
<th></th>
<th>NI readers</th>
<th>RD readers</th>
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<tbody>
<tr>
<td>N</td>
<td>18</td>
<td>14</td>
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<tr>
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<td>FSIQ</td>
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Group X Rep Interaction
Theoretical characterization

Learning Curve Hypothesis:
Activation levels follow an inverted-U shaped function with respect to familiarity and/or skill in processing words.

- poor readers, repeated words
- good readers first exposure

- poor readers first exposure
- good readers, repeated words

> familiarity >

Implications

- These data suggest that relation between “skill” and activation is complex and dynamic.
- Simple > or < contrasts will not inform us much.
- We need to employ online learning and consolidation measures of learning in studying individual differences in reading skill.
Conclusions from this experiment

Repetition demonstrates latent functionality in phonologically tuned LH systems in RD readers.

But, why do these kids need a local boost from repetition to reveal the circuit?

These data suggest we must attend to learning and consolidation failure in addition to phonological processes, because while the phonologically-tuned circuitry can engage, it appears not to preserve the neural learning!

We are currently engaged in a new NIH-funded study looking at consolidation and memory problems in RD

Structural neuroimaging and Reading Disability

• 1) Recent structural MR studies reveal reduced grey matter density in reading-related temporo-parietal regions (Brambati; Keller; others).

• 2) New research examining cortico-cortico pathways with MRI/DTI suggest white matter tract anomalies (Klingberg, Niogi & McCandliss, others), between reading relevant LH regions.

• Note: Potential links with histology studies implicating neuronal migration abnormalities (ectopias) in LH language zones (Geschwind Galaburda and colleagues at MGH).

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., 2010):
  1) Unstable and reduced activation
  2) Reduced functional connectivity
  3) problems in learning, and consolidation of new learning
  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 are conducting two ongoing 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).
Timeline

<table>
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<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
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<tr>
<td>Time 1 (7.5 yrs of age)</td>
<td>Time 2 (8.5 yrs of age)</td>
<td>Time 3 (9.5 yrs of age)</td>
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<td>DNA, MRS, fMRI, Behavior</td>
<td>DNA, MRS, fMRI, Behavior</td>
<td>DNA, MRS, fMRI, Behavior</td>
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MRS scanning

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

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

Schematic of fMRI Task

Event-related fMRI: match/mismatch judgment via button press of speech and print targets to a picture

Mismatch/Match ratio (80-20)

Only mismatch trials included in analyses
• Examining the effects of early language history on reading outcomes:
  • Behavioral research shows that both early receptive and expressive language development predicts reading outcomes.
  • Q) what are the neurobiological markers of early language problems?

Effects of Early Language delays on reading at age 7 Preston et al., (2010 Brain)

• Several studies of “late talkers” have suggested residual deficits in reading in young school-age children (Rescorla 2002, 2005, 2009; Scarborough & Dobrich, 1990)

• Parents complete questionnaire on child/family background and child’s development
  • Asked to report on when child began to “Speak 2-3 word sentences.”
  • Parent rated child as Early, On Time or Late

Talker Group Comparisons on Reading Measures: Woodcock-Johnson Tests of Achievement
Late versus early talkers: Brain activation in reading and speech at 7.5 years of age. Brain regions of interest include the thalamus, putamen, and superior temporal gyrus.

Significance:
p < .025, FDR corrected
Implications

These data suggest that late talking, along with its negative impact on reading scores, is associated with failure to develop subcortical (basal Ganglia and thalamus) and cortical circuits relevant to both reading and listening.

Implies an important, but still poorly understood, role for motor learning in the emergence of reading circuits.

May suggest an early “biomarker” for risk for language and reading difficulties.

Q) Are children with early speech motor problems a subtype of RD or just a more overt manifestation of a general problem in most RD children?

The influence of phonological and sensorimotor skills on the learning circuitry (Pugh et al., in press, 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.

As we shift our focus from older children and adults to beginning readers:

Our expectation is that better “reading-readiness” will be associated not only with increased activation at those LH cortical regions known to support skilled word identification in older children and adults (IFG, TP and especially OT VWFA), but will involve additional cortical and subcortical pathways critical in learning to adequately bind orthographic, phonological, and semantic information.
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

### Behavioral Inter-correlations

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<tr>
<th></th>
<th>TOWRE</th>
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<th>TOWRE</th>
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<td>.824*</td>
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*p<.05; **p<.01

### Brain-behavior analytic approach

- **Shared and unshared influences:**

  Given these correlations, we used PCA and partial correlation scores to determine whether these highly distinct tasks influence reading, and the neural pathways that support reading, via shared or unshared neurocognitive pathways.
• For both PA and TOJ no unique influences of residual scores on behavior (or brain) were found.
• Thus the impact of these very different non-print tasks on print skills appears to be via common pathways.
Print: Summary and discussion

The initial learning circuitry: For printed word and pseudoword processing, this 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), frontal lobe and RH regions including MTG and IPL.

Thalamus (pulvinar) Involvement: These data suggest a strong link between reading problems and thalamo-cortical pathways. Extrapolating from human and animal models of pulvinar function and connectivity (e.g., Serences & Yantis, 2006), we speculate that, in the context of learning to read, pulvinar mediates visual selective attention to those features that will shape emergent print specialization along the ventral visual pathway (especially the occipito-temporal cortex).

**Importantly, this brain/behavior analysis suggests that “training up” of ventral visual pathway is influenced by a distributed set of cortical regions sensitive to phonological form, including LH STG and IFG.

Summary and Conclusions from this study

1) Relative to findings from studies of older cohorts of good and poor readers, where brain-behavior analyses implicate LH TP, OT, and IFG, the skill-correlated circuitry in beginning readers appears to be more broadly distributed, including additional frontal, visual, RH, and subcortical networks. EF circuitry is seen as skill correlated early on.

2) The influence of varied skill measures of “reading-readiness”, on word reading, and on the neural pathways that support word reading, is largely through shared neurocognitive mechanisms (at least in this age range).
The pulvinar and reading development: Predicting Word reading at Time 3 from Time 1

- Dataset with N = 70 children as of March 28

Brain behavior regression

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

\[ R^2 = .426 \]

Elision (Time 1) \( \beta = .489, p < .001 \)

age (Time 1) \( \beta = .207, p < .05 \)

LH Pulvinar \( \beta = .201, p < .05 \)

Cortical/subcortical pathways and skill learning
Summary of 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) sensory and cognitive indices map onto pulvinar activation differences for printed words (Pugh et al., in press)
• 4) indices of neurochemistry (particularly Glutamate and NAA) appear to be sensitive to reading difficulties in young children (Fulbright et al. in prep)
• 5) Genetics: initial links with COMT (Landi et al. in press)

Implications

• These findings on 7 year old children suggest that children who are developing normally in reading modify cortical/subcortical systems (including motor learning and language areas) for speech print integration.
• RD risk presents as failure develop multi-modal integration early on. Early expressive and receptive language milestones, along with metaplanological skills, constrain initial development of the LH reading circuitry.
• *we need a next wave of birth-to-five studies that target cortical/subcortical development in high risk infants and toddlers

A brief look at remediation and plasticity in RD

• Increases in reading skill are associated with increased specialization of ventral LH areas for print
RD readers do not tend to show this neurodevelopmental trend.

Trajectory is rightward and frontward.

Question: Does remediation normalize this trajectory?

Key questions:

- Are these under-engaged LH systems fundamentally disrupted, or does observed deactivation 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.

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).
- 3 Groups: TD (N = 28); RD control (N = 12), RD Treatment (N = 32). Each group scanned at baseline (average age = 6.9), 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

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.

Treatment Group:
Year 3 (follow-up) minus Year 1 (Pre-Treatment)
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.

A final word on Executive function and reading

- Skill learning in literacy acquisition early on involves re-organization of cortical and subcortical networks (fronto-striatal pathways) to support efficient fast mapping between visual and language representations.
- As shown by recent work from Morrison, Blair, and others early development of frontal lobe EF systems is crucial in setting the stage for this skill learning.
- Greater focus on early EF development will be key in developing more holistic understanding of reading as cognitive learning.
Collaborators

- Haskins Laboratories: Einar Menc, Rebecca Sandak, Stephen Frost, Nicole Landi, Jon Pragias, Leonard Kotz, Jay Rasch, Tim Moorman, David Shopkeeler, Jim Ren Lee, David Brodie, Daragh Sibley, Allison Austin, Peter Wellese, Mark Seidenberg

- Yale Reading Center: Ken Pugh (Director), Gina Della Porta, Eleanor Tajada, Kelley Delaney, Ashley Zenns, Annish Karan, Heatherly Carlsen, Priya Pugh, Beth Estah, Ann Shatman

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

- Yale University/Diagnostic Radiology: John Gore, Todd Castiglione, Robert Fulbright, Doug Rothman, brooke Mason, Pawel Skudarski, Cheryl Lacadie

- Yale University/Psychiatry: Leslie Jacobsen

- Yale Child Study Center: Elena Grigorenko