The Typical and Atypical Reading Brain

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www.childrenshospital.org/research-and-innovation/research-labs/gaab-laboratory
www.babymri.org
Overview

- Overview about the Brain
- The typical and atypical reading brain
- Remediating the reading brain
- Can brain measures enhance the accurate identification of children at risk for DD?
  - The Boston Longitudinal Dyslexia Study (BOLD).
  - Project READ (Research on the Early Attributes of Dyslexia)
- Detecting children at risk for DD in infancy?
- Educational and Clinical Implications
Lobes & Directions

Superior

Anterior

Left

Inferior

Posterior
Brain Size: Is bigger better?
Figure 7. Differences in gray-matter density between subjects with three neurodevelopmental disorders. The percentage differences in gray-matter density between subjects with Williams syndrome (WS) (a), attention-deficit-hyperactivity disorder (ADHD) (b), fetal alcohol syndrome (FAS) (c) and their respective normally developing control groups are color-coded. In all maps, warmer colors represent positive differences, indicating an increase in the patient group (arbitrarily coded as 1) relative to the control group (arbitrarily coded as 0), with red representing the largest group difference. Note that the maximum value varies on the three color bars, depending on the maximum group difference from each comparison. Adapted, with permission, from [36,41,46].
Anatomical differences between musicians and non-musicians

Brain regions with gray matter differences between professional musicians, amateur musicians and nonmusicians.

Gaser, Schlaug; 2003. The Journal of Neuroscience
Plasticity in taxi drivers

Maguire et al., (2000)
Morphological changes induced by a short intervention

Increased density of the grey matter in the jugglers compared to the non-juggler controls.

3 months training in juggling

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What is Developmental Dyslexia?

- Affects 5-17% of children.

- Specific learning disability characterized by
  - difficulties with accurate and/or fluent word/text recognition.
  - poor spelling and poor decoding performance.

- Cannot be explained by poor vision or hearing, lack of motivation or educational opportunities.

- Familial occurrences as well as twin studies strongly support a genetic basis for DD.

- Currently up to seven theories that try to explain DD.

- No medications available.

- Strong psychological and clinical implications which start long before reading failure.
Genetics

- Studies of families with DD suggest that DD is strongly heritable, occurring in up to 68% of identical twins and up to 50% of individuals who have a first degree relative with DD [Finucci et al., 1984; Volger et al., 1985).

- The genetic foundation of developmental disorders may be formed not by isolated genes, but rather by a combination of genes and the pathways that these genes regulate [Grigorenko, 2009].

- Several genes (e.g.; ROBO1, DCDC2, DYX1C1, KIAA0319) have been reported to be candidates for dyslexia susceptibility and it has been suggested that the majority of these genes plays a role in brain development. [e.g.; Galaburda et al., 2006; Hannula-Jouppi et al., 2005; Meng et al., 2005; Paracchini et al., 2006; Skiba et al., 2011].

- It has been hypothesized that DD may be the result of abnormal migration and maturation of neurons during early development [e.g.; Galaburda et al., 2006].
Psychological and Clinical Implications of DD

- Children with DD are often perceived by others as being ‘lazy’ or as those who ‘do not try enough.’

- Teachers, parents and peers often misinterpret the ‘dyslexic’ child’s struggle to learn as negative attitude or poor behavior and decreased self-esteem is often a result [Saracoglu et al., 1989; Riddick et al., 1999].

- These negative experiences leave children with DD vulnerable to feelings of shame failure, inadequacy, helplessness, depression and loneliness [e.g.; Valas et al., 1999].

- Possible anti-social behavior with long-standing consequences [Baker et al., 2007].

- Less likely that these children will complete high school [Marder et al., 1992] or join programs of higher education [Quinn et al., 2001], and increased probability that they will enter the juvenile justice system [Wagner et al., 1993].
The typical reading network with its key components

Mature reading is performed by a left hemispheric network. It maps visual (orthographical) information onto ‘auditory’ (phonological) and conceptual (semantic) representations.

Some of these functional areas seem to be fully developed in elementary school and some develop through adolescence [e.g.; Turkeltaub, et al., 2003].
Several theories try to explain dyslexia:

- Impaired perceptual deficit
- Deficient phonological representations
- Grapheme-phoneme mapping
- Impaired reading
- Poor phonological skills

[after Ramus, 2003]
Typical reading network with its key components:

Temporo-parietal/Temporo-occipital dysfunction in dyslexia:

[Temple, 2002]

[Meta-analysis: 17 studies; Richlan et al., 2009]
Structural brain differences (gray matter): Typical and atypical readers

[Silani et al., 2005]

[Hoeft et al., 2006]

[Pernet et al., 2009]

[Meta-analysis: Linkersdoerfer et al., 2012]

[Steinbrink et al., 2008]
DD has been associated with structural differences in left-hemispheric white matter organization as measured by Diffusion tensor imaging tractography [e.g., Klingberg et al., 2000; Rimrodt et al., 2010; Steinbrink et al., 2008].

Most studies report alterations of the Arcuate Fasciculus, a neural pathway connecting the posterior part of the temporoparietal junction with the frontal cortex.

Differences may reflect weakened white-matter connectivity among left-hemispheric areas that support reading. Measures (e.g.; fractional anisotropy) in left temporoparietal regions corelate positively with reading skills [e.g., Deutsch et al., 2005].
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Midway through the exam, Allen pulls out a bigger brain.
n = 45

Intervention:
Fast ForWord (8 weeks)

<table>
<thead>
<tr>
<th></th>
<th>Dyslexic-reading children</th>
<th>Normal-reading children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretraining</td>
<td>Posttraining</td>
</tr>
<tr>
<td>Reading: WJ-RMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word ID</td>
<td>78.2 (56–95)</td>
<td>86.0 (72–99)</td>
</tr>
<tr>
<td>Word Attack</td>
<td>85.5 (72–102)</td>
<td>93.7 (82–109)</td>
</tr>
<tr>
<td>Passage Comp</td>
<td>83.3 (51–103)</td>
<td>88.9 (77–107)</td>
</tr>
<tr>
<td>Language: CELF-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receptive</td>
<td>92.5 (69–120)</td>
<td>101.3 (75–122)</td>
</tr>
<tr>
<td>Expressive</td>
<td>95.0 (61–125)</td>
<td>102.2 (80–150)</td>
</tr>
<tr>
<td>Rapid Naming</td>
<td>79.1 (35–97)</td>
<td>86.5 (67–103)</td>
</tr>
</tbody>
</table>
Neural deficits in children with dyslexia ameliorated by behavioral remediation: Evidence from functional MRI

Elise Temple, Gayle K. Deutsch, Russell A. Poldrack, Steven L. Miller, Paula Tallal, Michael M. Merzenich, and John D. E. Gabrieli

Control

Example:
- B  D = Rhyme
- B  K = Do Not Rhyme

Dyslexia

Frontal AND Temporo-parietal

Frontal but NOT Temporo-parietal

n= 45
8 weeks intervention

[Temple et al. (2003) PNAS, 100]
Neural effect of intervention

Pre-Intervention

Frontal but NOT Temporoparietal

Post-Intervention

Increased activity in Frontal AND Temporoparietal

After training, metabolic brain activity in dyslexics more closely resembles that of typical readers.

[Temple et al. (2003) PNAS, 100]
Neural Changes following Remediation in Adult Developmental Dyslexia

Guinevere F. Eden, Karen M. Jones, Katherine Cappell, Lynn Gareau, Frank B. Wood, Thomas A. Zeffiro, Nicole A.E. Dietz, John A. Agnew, and D. Lynn Flowers

n=38
Intervention: Lindamood-Bell (8 weeks)

Sound deletion > word repetition

Post remediation > Pre-remediation
Who compensates? Brain measures predicted with 92% accuracy which individual children improved and which individual children did not improve 2.5 years later (Hoeft et al., 2011)
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To date, the earliest that DD can be reliably diagnosed is in second/third grade and most children exhibit enduring reading impairments throughout adolescence and into adulthood [e.g.; Francis & Shaywitz, 1996; Juel et al., 1988; Torgesen & Buress, 1998].

Intervention studies are most effective in kindergarten and first grade. When “at risk” beginning readers receive intensive instruction, 56% to 92% of at-risk children across six studies reached the range of average reading ability [Vellutino et al., 2004].
The Boston Longitudinal Dyslexia Study (BOLD)

Diagnosis Dyslexia
- Functional MRI
- Structural MRI
- Behavioral tests
- Psychophysics
- Questionnaires
- DNA

Early Identification children at-risk
Preschool
Kindergarten
3rd grade
Middle School

Follow up:
- prior to first grade
- prior to second grade
- prior to third grade

To date 114 children enrolled longitudinally (64 FHD+/50 FHD-).

Pre-readers (Word ID <5), reading instruction within next year.
Tasks within MRI scanner:
- Phonological Processing
- Rapid auditory processing
- Executive functioning
- Reading Fluency

Psychometric Measures:
- Clinical Evaluation Language Fundamentals – Preschool 2
- Comprehensive Test Of Phonological Processing
- Grammar And Phonology Screening Test
- York Assessment for Reading for Comprehension
- Rapid Automatized Naming and Rapid Alternating Stimulus Test
- Kaufman Brief Intelligence Test 2
- Year 2: Word reading (timed/untimed), passage comprehension, fluency, spelling, letter knowledge

Psychophysics Measures:
- RAP (tones and environmental sounds)
- Rise Time perception

Questionnaires:
- Development
- Home literacy
- SES

Structural brain differences
- (gray matter, DTI)
Control task:
Voice matching
[Raschle et al., 2009; Raschle et al., 2012]
<table>
<thead>
<tr>
<th>YEAR 1 (prereading status)</th>
<th>YEAR 2 (beginning readers)</th>
<th>YEAR 3/4 (readers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant differences in:</td>
<td>Significant differences in:</td>
<td>Significant differences in:</td>
</tr>
<tr>
<td>Expressive and receptive language/content</td>
<td>Expressive language/ Language content</td>
<td>Core and receptive Language</td>
</tr>
<tr>
<td>Phonological processing</td>
<td>Phonological processing</td>
<td>Rapid automatized naming</td>
</tr>
<tr>
<td>Rapid automatized naming</td>
<td>Rapid automatized naming</td>
<td>Rapid automatized naming</td>
</tr>
<tr>
<td>Rapid auditory Processing</td>
<td>Letter knowledge</td>
<td>Single word reading (timed/untimed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Passage comprehension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spelling</td>
</tr>
<tr>
<td>all p&lt;0.05</td>
<td>all p&lt;0.05</td>
<td>all p&lt;0.05</td>
</tr>
</tbody>
</table>

No differences in IQ, age, Home Literacy, SES

33
All left-hemispheric ROIs (Year 1) strongly correlate with reading skills in Year 2

[Raschle et al., 2010]
Examining Genotype vs. Phenotype

**Genotype**
Based on familial risk

- **FHD+**
  - one 1st degree relative with a clinical diagnosis of DD

- **FHD-**
  - no relative with reading problems

**Phenotype**
Based on reading scores after 1 year of reading instruction

- **PR**
  - TOWRE SWE average \([SS]= 82.55\)

- **GR**
  - TOWRE SWE average \([SS] = 109.83\)
Structural brain differences at the end of preschool based on reading scores (phenotype) one year later (VBM)

Good readers > Poor readers  p<0.001unc

[Raschle et al., in prep]
Bilateral atypical parietal sulcal pattern in pre-readers with familial risk of developmental dyslexia and young readers with developmental dyslexia

Im, K., Raschle, N., Smith, S., Grant, P.E. & Gaab, N. (under review)

- Sulcal pattern, meaning the global pattern of arrangement, number and size of sulcal segments, has been hypothesized to relate to optimal organization of cortical function and white matter connectivity (Van Essen, 1997; Klyachko and Stevens, 2003; O’Leary et al., 2007; Fischl et al., 2008), which cannot be examined with volumetric techniques.

- Individuals with DD may undergo atypical sulcal development originating from altered function and white matter organization. Moreover, global sulcal pattern is determined during prenatal development and may therefore better reflect genetic brain development (Rakic, 2004; Kostovic and Vasung, 2009).
Four groups:

- n = 16 Beginning readers FHD-
- n = 15 Beginning readers FHD+
- n = 13 Developmental Dyslexia
- n = 14 Typical developing

Bilateral parietal sulcal patterns atypical in pre-readers/beginning readers with a familial risk of DD compared to controls.

Significantly atypical bilateral parietal sulcal patterns were confirmed in children diagnosed with DD compared to controls, as well as its relationship with phonological processing and single word reading.
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The READ Study
(Researching Early Attributes of Dyslexia)

- Screening over 1,000 kindergartners in New England with assessments known to predict reading outcomes and dyslexia in the fall of the 2011, 2012, and 2013 school years.


- Inviting children with and without risk for dyslexia to participate in a follow-up study including brain imaging with MRI and EEG (to date n =180 for EEG and n=150 for MRI).

- Following these children to see which measures from kindergarten best predict reading ability at the end of 1st and 2nd grade.
READ at a Glance

- 21 schools: inner-city charter schools, private, suburban district-run schools, and Archdiocese schools
- Free/reduced lunch eligibility from 0% to 80%
- Ethnically diverse student population (49% minority)
- Teacher professional developments and parent presentations conducted in all schools
- Brain awareness days conducted in various schools

“We very much enjoyed everything you and your staff provided. You are warm and professional and certainly put your subjects at ease...It’s exciting to see such cutting-edge research from the inside out!” (Parent, Wheeler School)

“...They were excellent presenters. The students had a wonderful time and were very engaged in the activities.” (Teacher, Lowell Elementary)

“Your whole team was terrific in making the afternoons lots of fun and educational” (Parent, Hosmer Elementary)
Assessments

- Deficits in the following most consistently predict reading failures: phonological processing/awareness, rapid automatized naming abilities, and letter-name knowledge.

- We will assess these with a 45 minute, individualized assessment.

- Measures to be used include:
  - Comprehensive Test of Phonological Processing (CTOPP)
    - Elision
    - Blending
    - Nonword repetition
  - Woodcock Reading Mastery Tests (WRMT-III)
    - Letter ID
    - Word ID
  - Rapid Automatized Naming (RAN)
    - Objects, Colors, Letters
  - KBIT Matrices
Subtypes of DD Risk: 25th Percentile Cutoff Based on Screening Sample

- **PA**: 15.3%
- **RAN**: 8.4%
- **LK**: 5.3%

- **No Risk**: 43.1%

Subtypes of DD Risk: 25th Percentile Cutoff Based on Screening Sample
EEG: Electroencephalography

- We study the mismatch negativity (MMN)

→ a component of the event-related potential (ERP) to an odd stimulus in a sequence of stimuli. The MMN can be elicited regardless of whether the subject is paying attention to the sequence.

- Auditory “oddball” – passive listening with no task
ERP MMN Data

Grand average MMN waveform (standard-deviant) at site Fz;

n=94

Norton et al., in prep
Can kindergartners’ MMN predict reading at the end of 1st grade?

MMN Difference Waves: (n=8 per group)
---Lowest TOWRE scores
---Highest TOWRE scores

Mean amplitude 300-500ms differs between groups $p = .002$

[Norton et al.; in preparation]
White matter in pre-readers

- The left arcuate fasciculus (AF) is a major white matter pathway connecting the brain’s language areas.

- Are smaller volume and weaker organization of the AF in adults with dyslexia a cause or a consequence of poor reading?
Saygin, Norton et al., J Neurosci 2013
In the present study, we demonstrate that previously described white matter alterations in DD already exist in preschoolers/kindergarteners with behavioral risk for DD.

Patterns of hypoactivation/attenuated MMNs in key brain regions seem to differ depending on risk subtype suggesting differences in the underlying mechanisms.

Children at risk in RAN have attenuated MMN relative to children not at risk or at risk in PA or LK suggesting that MMN may be an index of the automaticity shared with the processes that underlie efficient naming and reading tapped by RAN.
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### Demographics

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<thead>
<tr>
<th></th>
<th>FHD-</th>
<th>FHD+</th>
<th>T-test 2-tailed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Age (days)</td>
<td>$316.57 \pm 100.55$</td>
<td>$289.14 \pm 115.95$</td>
<td>$p &gt; .100$</td>
</tr>
<tr>
<td>Expressive Mullen T-score</td>
<td>$48.67 \pm 4.77$</td>
<td>$47.90 \pm 10.87$</td>
<td>$p &gt; .100$</td>
</tr>
</tbody>
</table>
Tract Profiles of White Matter Properties: Automating Fiber-Tract Quantification

Jason D. Yeatman¹,²*, Robert F. Dougherty², Nathaniel J. Myall³, Brian A. Wandell¹,², Heidi M. Feldman³,⁴

¹ Department of Psychology, Stanford University, Stanford, California, United States of America, ² Stanford Center for Cognitive and Neurobiological Imaging, Stanford University, Stanford, California, United States of America, ³ Stanford University School of Medicine, Stanford, California, United States of America, ⁴ Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, California, United States of America

Tract Diffusion Profile
AFQ
LH Arcuate FA Comparison ($p$-values range from 0.05 to 0.0004)

LH Arcuate FA Comparison age-corrected ($p$-values range from 0.05 to 0.0002)

Langer et al., in prep
FA values correlate with Expressive Language Scores

\[ R = 0.481 \]

\[ p = 0.037 \]
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Educational and Clinical Implications

- Early identification may reduce the clinical, psychological and social implications of DD.

- Development and implementation of early and customized remediation programs

- Changes in educational policies (early IEPs; design and implementation of customized curriculums for children at-risk).

- Evaluation and improvement of existing remediation programs will likely prove cost-efficient as programs are made more effective.

- Improved psycho-social development (reduced child stress, parental stress, improved overall family dynamic).

- Maximizing use of ‘intellectual potential’.

- Most importantly, maximizing the joy to learn to read.
Other projects in the GaabLab

- Examining the comorbid brain (DD/ADHD): two distinct disorders?
- Time- and cost-efficiency analyses for psychometric/fMRI data
- Neural correlates of reading fluency in typical and atypical readers
- Examining the link between musical training and cognitive/language development
- Music as a diagnostic or intervention tool? [Brazil Project]
- Dyslexia in Fetal Alcohol Syndrome (with Joseph/Sandra Jacobson: Cape Town)
- Autism (BCH site investigator for NIH Autism Center Excellence Program)
- The delayed development of implicatures: inferences from fMRI (with Gennaro Chierchia, Harvard University)
Collaborators:
John Gabrieli, MIT
Ellen Grant, CHB
Paula Tallal, Rutgers University
April Benasich, Rutgers University
Sandra/Joseph Jacobson, Wayne State
Gennaro Chierchia, Harvard University
Autism Excellence Center
Maryanne Wolf, Tufts University
Paulo Andrade, São Paulo
Georgio Sideridis, BCH

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Nicolas Langer (Postdoc)
Einat Shetreet (Postdoc)
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Danielle Sliva (RA, BOLD + Infants)
Michelle Lee (Psychometric Assessments)
Sarah Beach (RA, READ)
Abby Cyr (RA, READ)
Zeynep Saygin (READ)
MIRI Team, Children’s Hospital Boston & MIT

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- Charles H. Hood Foundation (BOLD)
- Grammy Foundation
- William Randolph Hearst Foundation (Infants)
- Children’s Hospital Boston Pilot Award (BOLD)
- Developmental Medicine Center Young investigator Award
- Victory Foundation

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