Using Genetics and Neuropsychology to Understand Comorbidity

Bruce F. Pennington

Supported by grants from NIH (HD-2780 and HD 049027)
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   C. ADHD
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Why is Comorbidity Important?

**Clinical:** One disorder may influence course and treatment of the other.

**Taxonomic:** Comorbidities may lead to remapping diagnostic categories.

**Basic Science:** Comorbidities can provide insight into neurobiology and development.
Explanations of Comorbidity
(from Caron & Rutter, 1991; Neale & Kendler, 1995)

I. **Chance** - two disorders co-occur but not more frequently than chance would predict (chance = rate 1 x rate 2)

II. **Artifactual**
   A. Referral bias (e.g. Berkson’s bias)
   B. Rater biases
   C. Definitional overlap
   D. Population stratification, e.g. non-random mating

III. **Causal Relation**
    A. Same etiology with severity continuum: A or A+B
    B. Partly shared etiology: A, B, A+B
    C. Etiological subtype: 3 distinct etiologies
    D. One disorder causes the other: A → B
Dyslexia is a specific learning disability that is neurobiological in origin. It is characterized by difficulties with accurate and/or fluent word recognition and by poor spelling and decoding abilities. These difficulties typically result from a deficit in the phonological component of language that is often unexpected in relation to other cognitive abilities and the provision of effective classroom instruction. Secondary consequences may include problems in reading comprehension and reduced reading experience that can impede growth of vocabulary and background knowledge.
WORD ATTACK

ift  fit
bim  bim
ut   ut
rayed  rate
kak  cake
maft  mat
nen  any or en
ab   add
tash  trash/tash
wip’s  wippies
beb  bid
Reading Comprehension

Components
- Fluent Printed Word Recognition Skills (WR)
  - Phonological Coding (PC)
- Orthographic Coding (OC)
- Listening Comprehension (LC)
- Discourse-Specific Comprehension Skills

Precursors
- Phoneme Awareness (PA)
- Rapid Serial Naming (RSN)
- Phonological Memory (PM)
- Oral Vocabulary (OV)
- Syntax (S)
Definition of Speech Sound Disorder (SSD)

A delay in the acquisition of developmentally appropriate speech sounds, resulting in reduced intelligibility. Not due to peripheral problems (e.g. hearing loss or cleft palate) or a known syndrome (e.g. autism or mental retardation). Distinct from stuttering or mutism. Formerly called articulation disorder and phonological disorder (DSM-IV-TR).
Classic Errors in Speech Sound Disorder

Omissions:
- bathtub → “batub”
- blue → “bue”
- Christmas tree → “Christmas tee”

Substitutions:
- cup → “tup”
- shovel → “sobel”
- bathtub → “baftub”

Omissions and substitutions can co-occur:
- sleeping → “feeping”
- brush → “bus”
Definition of (specific) language Impairment

• There is less agreement on the definition of SLI, but most researchers agree that it represents an impairment in one or more domains of language (e.g., semantics, morphology and syntax), that is not due to mental retardation, autism, neurologic impairment or disease, or hearing loss. The language impairment is disproportionately greater than the impairment in non-linguistic domains. Deficits can be receptive and/or expressive, with impairment in both not atypical. Operationalization of what constitutes a deficit often differs by study, but most researchers place the cutoff between 1.25 and 2 standard deviations below the mean on a language composite (e.g., Tomblin et al, Leonard).
Summary of Definitions

Speech Sound Disorder and Dyslexia are both idiopathic (unexplained) problems with a particular aspect of linguistic development: speech sounds in SSD and printed word recognition in dyslexia. Phonological development is implicated in both. Language impairment, by definition, implies a broader set of deficiencies, but phonological memory is considered to be a potential core aspect of the disorder.
Phenotypic Overlap Among SD, LI, & RD
Connectionist Models

**Speech Development** (from Joanisse, 2000)

![Diagram of Speech Development]

**Reading Development** (from Harm & Seidenberg, 1999)

![Diagram of Reading Development]
DSM IV (1994) Criteria for
Attention-Deficit/Hyperactivity Disorder

Inattention (6 for subtype)

1. Poor attention to details
2. Cannot sustain attention in tasks or play
3. Does not seem to listen
4. Fails to finish tasks
5. Difficulty organizing
6. Avoids sustained mental effort
7. Loses things
8. Easily distracted
9. Forgets to do things
DSM IV (1994) Criteria for Attention-Deficit/Hyperactivity Disorder (cont’d)

Hyperactivity
1. Fidgets or squirms
2. Leaves seat
3. Runs or climbs inappropriately
4. Lack of quiet play
5. On the go, “driven by a motor”
6. Talks excessively

Impulsivity
1. Blurts out answers
2. Can’t wait for turn
3. Interrupts or intrudes

Total of 6 for H-I subtype
Evidence for Comorbidity

Dyslexia + ADHD – 25-40% overlap

- August & Garfinkel, 1990
- Semrud-Clikeman, et al., 1992
- Willcutt & Pennington, 2000

Dyslexia + SSD

A) SSD leads to later Dyslexia

- Lewis & Freebairn, 1992
- Felsenfeld et al., 1992
- Bird, Bishop & Freeman, 1995
- Larrivee & Catts, 1999

B) Speech problems in young children at risk for Dyslexia

- Scarborough, 1990
- Elbro et al., 1998
- Gallagher, et al., 2000
- Pennington & Lefly, 2001

SSD + ADHD

Higher rates of ADHD in SSD + LI, not SSD only

- Beitchman et al., 1989
## Steps in a Genetic Analysis

<table>
<thead>
<tr>
<th>Question</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is it familial?</td>
<td>Familial Risk Studies</td>
</tr>
<tr>
<td>2. Is familiality genetic?</td>
<td>Twin Studies, Adoption Studies</td>
</tr>
<tr>
<td>3. What is the mode of transmission?</td>
<td>Segregation Analysis</td>
</tr>
<tr>
<td>4. Where are the gene(s)?</td>
<td>Linkage and Association Analyses</td>
</tr>
</tbody>
</table>
Family and Twin Studies of Normal and Abnormal Reading

1. Normal and abnormal reading runs in families:
   A. In general population, first degree relatives correlated at .40
   B. First degree relatives of RD proband 4-14 times more likely to have RD (Hallgren, 1950; Finucci et al, 1976; Vogler et al, 1985; Gilger et al, 1991)

2. Normal ($h^2 = .56 - .73$) and abnormal ($h^2g = .50 \pm .11$) variations in reading are moderately heritable (e.g. DeFries & Gillis, 1993)
Linkage Analysis

Two genes are said to be linked when they are positioned close together on the same chromosome, such that recombination between them is significantly decreased.

If a trait is found to be linked to a marker with known position, the position of the gene for the trait is then known.
Possible Locations of Genes Influencing Reading Disability

1p1p
6p6p
15q15q
2p2p
3q3q
21q
Xq
18p
Figure 3. Replicated regions of chromosomes 2, 3, 6, 15 and 18 implicated by linkage studies of dyslexia. Ideograms of each chromosome are shown with the cytogenetic bands of interest indicated. Each chromosome has a short (p) arm and a long (q) arm, which are separated by a centromere. Red bars indicate approximate positions of positive regions of linkage, with the misc. citation number of the study shown above. All included two independent genome scans (using samples from the United Kingdom and the United States) and a further replication set (45). Further details of each study are given in TABLES 2-4 and in the main text.
Gene broken in translocation

Expressed in brain

Homologous to mouse Ekn1, a ubiquitin protein ligase for degradation of misfolded proteins

No mutations found in coding regions

Association found in Finnish families and Canadian families, but not found in US and Italian families
Novel gene with unknown function

PKD transmembrane domain suggests cell-cell adhesion properties

Knockdown with RNAi blocks neuronal migration
(reported by Silvia Paracchini, 10/28/05, ASHG, Salt Lake City)
DCX, XL doublecortin gene is involved in neural migration to cortex
Lissencephaly in hemizygous males and subcortical laminar
Heterotopia in heterozygous females
Involved in microtubule formation
Pathologic mutations occur in conserved (doublecortin) regions

DCDC2 expression in brain and thalamus confirmed by screen of fetal library

Knockdown of DCDC2 with RNAi slows neuronal migration
DYX5: Chromosome 3

The Axon Guidance Receptor Gene ROBO1 Is a Candidate Gene for Developmental Dyslexia

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Dyslexia, or specific reading disability, is the most common learning disorder with a complex, partially genetic basis, but its biochemical mechanisms remain poorly understood. A locus on Chromosome 3, DYX5, has been linked to dyslexia in one large family and speech-sound disorder in a subset of small families. We found that the axon guidance receptor gene ROBO1, orthologous to the Drosophila roundabout gene, is disrupted by a chromosome translocation in a dyslexic individual. In a large pedigree with 21 dyslexic individuals genetically linked to a specific haplotype of ROBO1 (not found in any other chromosomes in our samples), the expression of ROBO1 from this haplotype was absent or attenuated in affected individuals. Sequencing of ROBO1 in apes revealed multiple coding differences, and the selection pressure was significantly different between the human, chimpanzee, and gorilla branch as compared to orangutan. We also identified novel exons and splice variants of ROBO1 that may explain the apparent phenotypic differences between human and mouse in heterozygous loss of ROBO1. We conclude that dyslexia may be caused by partial haplo-insufficiency for ROBO1 in rare families. Thus, our data suggest that a slight disturbance in neuronal axon crossing across the midline between brain hemispheres, dendrite guidance, or another function of ROBO1 may manifest as a specific reading disability in humans.


Hannula-Jouppi et al., PLOS-Genetics, Oct. 1 (4) e50, 2005
DYX3: Chromosome 2p12
MRPL19 and C20RF3
(Anthoni et al, 2007)

A risk haplotype between these two genes was found in two RD samples.

These two genes are widely expressed in fetal and adult human brain, including reading centers in the brain.

These two genes are co-regulated and their expression is correlated with other dyslexia candidate genes.
Ectopias and Microgyri in Dyslexia

G.D. Rosen et al., 2002:
Summary: RD Loci

Reading disability is genetically heterogeneous, with at least 6 well-confirmed loci.

The locus for which there is the greatest phenotypic information, 6p22, affects all component phenotypes.

The six proposed candidate genes involve neuronal and axonal migration and their expression is correlated.
SSD and RD Share Etiologies

SSD & RD are co-familial (Lewis et al, 1989; 1990; 1992) and coheritable (Tunick & Pennington, 2002)

So, the comorbidity between SSD and dyslexia is caused by a partly shared genetic etiology. Therefore, we predict some of the risk loci already identified for RD will also be risk loci for SSD. This genetic overlap may vary by subtypes of SSD.
### Dyslexia Genes Influence SSD

*(Smith, et al., 2003)*

<table>
<thead>
<tr>
<th>Region</th>
<th>Marker</th>
<th>Phenotype</th>
<th>Analysis</th>
<th>Peak p/LOD</th>
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<tbody>
<tr>
<td><strong>1p36</strong></td>
<td>D1S199</td>
<td>NW</td>
<td>NHES</td>
<td>p=0.06344</td>
</tr>
<tr>
<td></td>
<td>D1S199</td>
<td>NW</td>
<td>GH2</td>
<td>LOD=1.0719</td>
</tr>
<tr>
<td></td>
<td>D1S2843</td>
<td>NW</td>
<td>NHES</td>
<td>p=0.06178</td>
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<tr>
<td><strong>6p21.3</strong></td>
<td>D6S1605</td>
<td>DX</td>
<td>GH2</td>
<td>p=0.04411</td>
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<tr>
<td></td>
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<td>PA</td>
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<td>LOD=1.0059</td>
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<td>GF</td>
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<tr>
<td></td>
<td>D6S1588</td>
<td>GF</td>
<td>NHEM</td>
<td>p=0.00382</td>
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<tr>
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<td>D6S1567-D6S1588</td>
<td>PA</td>
<td>GH2</td>
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<td>DX</td>
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<td><strong>15q21</strong></td>
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<td>GF</td>
<td>NHEM</td>
<td>p=0.03457</td>
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<tr>
<td></td>
<td>D15S994-D15S1028</td>
<td>GF</td>
<td>GH2</td>
<td>LOD=1.30186</td>
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<tr>
<td></td>
<td>D15S978-D15S1029</td>
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<td>NHEM</td>
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<tr>
<td></td>
<td>D15S1029</td>
<td>GF</td>
<td>NHES</td>
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<tr>
<td></td>
<td>D15S117</td>
<td>GF</td>
<td>NHES</td>
<td>p=0.004673</td>
</tr>
<tr>
<td></td>
<td>D15S1017-D15S117</td>
<td>GF</td>
<td>GH2</td>
<td>LOD=1.92563</td>
</tr>
</tbody>
</table>

*(maximum significance; all other markers except D6S258 showed p<0.05)*
Y Chromosome Map

- Testis determining factor (TDF)
- Channel Flipping (FLP)
- Catching & Throwing (BLZ-1)
- Self-confidence (BLZ-2)
- Ability to remember & tell jokes (GOT-1)
- Air Guitar (RIF)
- Ability to identify aircraft (DC-10)
- Facination with Reptilia & Arachnoidia (MOM-4U)
- Spitting (P2-E)
- Lack of recall for dates (OOPS)
Mean Heritability of ADHD = .76

Slide Courtesy of S. Faraone, March 2004
Molecular Genetics of ADHD  
(Faraone, 2004)

Linkage: Genome Scans

- Bakker et al. 2003: 7p13, 15q15
- Arcos-Burgos et al. 2003: 17p11, 11q22, 5q33

Association: Meta-Analyses

Dopamine receptors

- DAT1 (14 studies, OR = 1.13)
- DRD4 (15 studies, OR = 1.44)
- DRD5 (14 sites, OR = 1.25)
- DBH Taq 1 (6 studies, OR = 1.33)

Serotonin receptors

- 5HTT (5 studies, OR = 1.31)
- 5HT1B (5 studies, OR = 1.44)
- SNAP-25 T1069C T-allele (5 studies, OR = 1.18)

Null results: NET1, COMT, MAOA, DRD2, DRD3, TH, 5HT2A
RD and ADHD are Comorbid: Why?

Rejected Hypotheses

• Not a selection artifact: Comorbidity found in population samples (eg Willcutt & Pennington, 2000)

• Not a secondary phenocopy: Comorbid subjects have both EF and PA deficits (Willcutt et al, 2001), contrary to Pennington et al (1993)

• Not cross-assortment (Friedman et al, 2003)

Supported Hypothesis: Shared Etiological Influences

• Bivariate $h^2g$ for RD and ADHD (Stevenson et al, 1993; Light et al, 1995)

• Bivariate $h^2g$ for RD and Inatt is about .40, whereas NS for RD and HI (Willcutt et al, 2000)

• QTL for RD on 6p21.3 is also linked to ADHD and shows bivariate linkage with RD phenotypes (Willcutt et al, 2002)
Linkage of ADHD to markers on chromosome 6

![Graph showing linkage of ADHD to markers on chromosome 6 with markers D6S291, D6S439, D6S461, D6S276, D6S105, D6S306, D6S258, D6S1019, and D6S291. The graph indicates a peak at D6S105 with a t-value of 3.5 and a P-value of .001. Linkage is marked by distances 6pter, 5 cM, and 6cen.](image-url)
Bivariate linkage of RD and ADHD to markers on chromosome 6p

P = .01
Genome Scans for Shared Risk Loci For RD and ADHD

Start with ADHD Sample, Test Linkage to RD
Lou et al. (2004)

Start with RD Sample, Test Linkage to ADHD
Gayan et al. (submitted)
Possible Locations of Genes That Influence
RD, ADHD, or both RD and ADHD
SSD and RD Project

- SSD (N=107), Siblings (N=69), Controls (N = 41)
- SSD probands and controls tested at ages 5 and 8 y; sibs only at age 5.
- Measures of speech, language, and literacy given at both ages.
- Determination of SSD status
  Persistent vs. Resolved
- Determination of LI status
  LI or not, based on composite scores from TOLD-P:3
1.) Entire SSD group worse than controls on PA and letter knowledge (LK), but not Rapid Serial Naming (RSN). Normalized SSD + LI group worst on RSN.

2.) Within the SSD group, main effects of persistence and LI status on PA, with non-verbal IQ covaried. Main effect of LI on Letter Knowledge.

3.) Even the normalized SSD without LI subgroup was worse than Controls on PA.
Conclusions from Time 1 Studies

1) Deficits in both explicit and implicit phonology are pervasive in SSD, but their severity varies as a function of LI & persistence.

Predictions:
   a) If phonological deficits are a sufficient cause of literacy problems, then the entire SSD group, including the normalized no LI subgroup, will have worse literacy outcome than controls.
   b) Both LI status and persistence will contribute additively to literacy outcome.

2) Contrary to the severity hypothesis, SSD and RD have a similar deficit in PA, but differ on RSN. The SSD+LI subgroup, however, has a deficit in RSN.

Prediction:
   Intact RSN may be a protective factor in SSD without LI.
Literacy Outcome of children with SSD – Time 2 Questions

1) Is SSD in general a risk factor for RD?

2) Does SSD + LI pose a greater risk for RD than SSD alone?

3) Does persistent SSD pose a greater risk for RD than resolved SSD?

4) What predicts RD in SSD?
Is SSD status in general a risk factor for categorical RD? Yes.

<table>
<thead>
<tr>
<th></th>
<th>SSD (n=92)</th>
<th>Control (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RD</td>
<td>27.2 % (n = 25)</td>
<td>7.9 % (n = 3)</td>
</tr>
<tr>
<td>Not RD</td>
<td>72.8% (n = 67)</td>
<td>92.1 % (n = 35)</td>
</tr>
</tbody>
</table>

χ²(1) = 5.92, p = 0.015

(If you select SS<85 on all four literacy tests, rates are 9-11% in SSD and 0% in controls.)
2) Does SSD + LI pose a greater risk RD than SSD alone? YES!

In fact, children with SSD alone do not appear to be at greater risk than controls for categorical literacy problems. But children with SSD + LI are at highly elevated risk.

<table>
<thead>
<tr>
<th></th>
<th>SSD alone (n=72)</th>
<th>SSD + LI (n=20)</th>
<th>Control (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RD</td>
<td>13.9% (n=10)</td>
<td>75.0% (n=15)</td>
<td>7.9% (n=3)</td>
</tr>
<tr>
<td>Not RD</td>
<td>86.1% (n=62)</td>
<td>25.0% (n=5)</td>
<td>92.1% (n=35)</td>
</tr>
</tbody>
</table>

- All three groups: \( \chi^2(2) = 40.50, p < 0.001 \)
- SSD alone vs. control: \( \chi^2(1) = 0.86, p > 0.3 \)
- SSD + LI vs. control: \( \chi^2(1) = 27.57, p < 0.001 \)
- SSD alone vs. SSD + LI: \( \chi^2(1) = 29.54, p < 0.001 \)

<table>
<thead>
<tr>
<th></th>
<th>Resolved SSD (n=61)</th>
<th>SD (persistent) (n=30)</th>
<th>Control (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RD</td>
<td>24.6% (n=15)</td>
<td>30.0% (n=9)</td>
<td>7.9% (n=3)</td>
</tr>
<tr>
<td>Not RD</td>
<td>75.4% (n=46)</td>
<td>70.0% (n=21)</td>
<td>92.1% (n=35)</td>
</tr>
</tbody>
</table>

All three groups: $\chi^2(2) = 5.89$, $p = 0.053$
Resolved SSD vs. control: $\chi^2(1) = 4.39$, $p = 0.036$
SD vs. control: $\chi^2(1) = 5.64$, $p = 0.018$
Resolved SSD vs. SD: $\chi^2(1) = 0.30$, $p > 0.5$
<table>
<thead>
<tr>
<th></th>
<th>Model 1 (Exploratory; all predictors)</th>
<th>Model 2 (Core phonological deficit model)</th>
<th>Model 3 (Final multiple deficit model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\beta) (T1 NIQ)</td>
<td>.22*</td>
<td>--</td>
<td>.26**</td>
</tr>
<tr>
<td>(\beta) (T1 PA)</td>
<td>.40**</td>
<td>.60***</td>
<td>.36***</td>
</tr>
<tr>
<td>(\beta) (T1 RSN)</td>
<td>.01</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>(\beta) (T1 Syntax)</td>
<td>.35**</td>
<td>--</td>
<td>.29**</td>
</tr>
<tr>
<td>(\beta) (T1 Semantics)</td>
<td>-.05</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>(\beta) (T1 Speech)</td>
<td>.02</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Total R(^2)</td>
<td>.61</td>
<td>.36</td>
<td>.52</td>
</tr>
</tbody>
</table>

* p<.05, **p<.01, ***p<.001
### Table 48  Comorbidity rates among SSD, LI, and RD (relative risks)

<table>
<thead>
<tr>
<th>Sample sizes</th>
<th>SSD in LI</th>
<th>LI in SSD</th>
<th>RD in LI</th>
<th>RD in SSD</th>
<th>RD in SSD+LI</th>
<th>RD in SSD–LI</th>
<th>RD in LI–SSD</th>
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</thead>
<tbody>
<tr>
<td>Epidemiological</td>
<td>1328</td>
<td>1a*</td>
<td>5.3</td>
<td>4.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>570*</td>
<td>1b*</td>
<td>-</td>
<td>-</td>
<td>6.2 (second), 6.9 (fourth)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>527</td>
<td>1c*</td>
<td>-</td>
<td>-</td>
<td>1.9–2.2 (second, fourth, eighth)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>604</td>
<td>1d*</td>
<td>-</td>
<td>-</td>
<td>2.8 (second), 3.1 (eighth)</td>
<td>-</td>
<td>3.9 (second), 4.9 (eighth)</td>
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<td>453</td>
<td>2*</td>
<td>2.2</td>
<td>2.3</td>
<td>1.9</td>
<td>2.6</td>
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<td></td>
<td>925--955</td>
<td>3*</td>
<td>-</td>
<td>-</td>
<td>4.4 (7y), 4.9 (9y), 5.1(11y)</td>
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<td>-</td>
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<td>4*</td>
<td>6.1</td>
<td>6.1</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Referred</td>
<td>277</td>
<td>5*</td>
<td>-</td>
<td>4.2</td>
<td>3.0</td>
<td>4.6</td>
<td>0.9+</td>
</tr>
<tr>
<td></td>
<td>936</td>
<td>6*</td>
<td>4.0</td>
<td>4.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>7*</td>
<td>-</td>
<td>2.6</td>
<td>-</td>
<td>3.2</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>8*</td>
<td>-</td>
<td>-</td>
<td>3.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>9*</td>
<td>-</td>
<td>-</td>
<td>1.6+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* = NS  
* = defined RD as 1 SD below weighted mean on reading comprehension composite.

Key: relative risk = rate in risk group/population rate (p) or rate in risk + group/rate in risk – group (r)  
1 = Iowa sample, 1a = Shriberg et al. (1999); 1b = Catts et al. (2002)[AU: 2002a or 2002b?]; 1c = Catts et al. (2005), 1d = Tomblin (unpublished)  
2 = Colorado LTS sample = B.F. Pennington, L.D. Shriberg, & R. Boada, manuscript under review  
3 = Silva, Williams, & McGee (1987) [AU: Not list in Literature Cited. Please add.]  
4 = Beitchman et al. (1986) [AU: Not list in Literature Cited. Please add.]  
5 = Cleveland SSD sample = Lewis et al. (unpublished) [AU: Please add initials and names of all authors for unpublished study.]  
6 = Brownfield & Dodd (2004)  
7 = Denver SSD sample = (Raitano et al. 2004), 7a = Peterson, B.F. Pennington, L.D. Shriberg, & R. Boada, manuscript under review  
8 = McArthur et al. (2000)  
9 = Bishop & Adams (1990)
Executive Inhibition Theory
(e.g. Pennington & Ozonoff, 1996; Barkley, 1997; Nigg, 2000)

• **Key Idea**: The PFC-mediated process of voluntary motor inhibition is impaired in AD/HD

• **Marker Task**: Stop Signal task (Logan, Cowan, & Davis, 1984)
  – More specifically, longer SSRT in AD/HD vs. controls is thought to reflect a deficit in behavioral inhibition

• **Issues**:
  – Can SSRT be reduced to slow RT?
  – If so, are there impulsive errors that cannot be reduced to slow RT?
  – Inhibition deficits are found in other disorders
  – If someone fails to inhibit, is it because top-down control is too weak, or because bottom-up impulses are too strong, or both?
State Regulation Theory
(e.g. Sergeant & van der Meere, 1990; Douglas, 1989)

- **Key Idea**: In contrast to executive inhibition, holds that core problem is in maintaining optimal state for task. For instance, manipulation of event rate can lessen inhibition deficits.

- **Markers**: Reaction time (RT) and RT variability (SDRT)

- **Issues**:
  - **Is greater SDRT just a by-product of slower RT?**
  - Slower and more variable RTs are pervasive in developmental disorders
  - Neuroimaging studies of RT and SDRT implicate PFC
Delay Aversion Theory
(e.g. Sonuga-Barke, 2005; Sagvolden et al., 2004)

• **Key Idea**: Prefer immediate small rewards to delayed larger rewards. Fall-off in reinforcement gradient is steep.

• **Related Constructs**:
  – Delay discounting (Green & Myerson, 2004)

• **Issues**:
  – DA deficits do not replicate in all samples, including the CLDRC twin sample
  – Is DA more related to CD than AD/HD?
  – Stronger effects in younger age groups?
## Delay Aversion Results in CLDRC

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean (SD)</th>
<th>Controls (n = 142)</th>
<th>AD/HD (n = 88)</th>
<th>p</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-11 years</td>
<td>Mean (SD)</td>
<td>31.82 (5.30)</td>
<td>31.45 (5.30)</td>
<td>.61</td>
<td>.07</td>
</tr>
<tr>
<td>12-18 years</td>
<td>Mean (SD)</td>
<td>32.78 (5.74)</td>
<td>33.64 (6.10)</td>
<td>.39</td>
<td>-0.15</td>
</tr>
</tbody>
</table>
## Predicting AD/HD Ratings
(n=671)

<table>
<thead>
<tr>
<th></th>
<th>Adjusted $R^2$</th>
<th>$R^2$ Change</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS Motor</td>
<td>.235</td>
<td>.236</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inhibition</td>
<td>.291</td>
<td>.057</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SDRT</td>
<td>.296</td>
<td>.006</td>
<td>.022</td>
</tr>
<tr>
<td>Vigilance</td>
<td>.302</td>
<td>.007</td>
<td>.011</td>
</tr>
<tr>
<td>PS Verbal</td>
<td>.305</td>
<td>.004</td>
<td>.040</td>
</tr>
<tr>
<td>Working Memory</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Latent Variable</td>
<td>Indicators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading Ability</td>
<td><em>Time limited word recognition task &amp; PIAT Reading Recognition,</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention Symptoms</td>
<td><em>Mother, Father &amp; Teacher Ratings,</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactive/Impulsive Symptoms</td>
<td><em>Mother, Father &amp; Teacher Ratings,</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phoneme Awareness</td>
<td><em>Phoneme Deletion (% correct, blocks 1 &amp; 2), Pig Latin test, &amp; the</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Lindamood Auditory Conceptualization task</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal Reasoning</td>
<td><em>Information, Similarities, Vocabulary, &amp; Comprehension from</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>the WISC-R</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working Memory</td>
<td><em>Nonword Repetition, Digit Span (Forward &amp; Backward), Sentence Span &amp;</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Counting Span</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibition</td>
<td><em>Gordon Diagnostic System commission errors (Vigilance &amp;</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Distractibility), &amp; Stop Signal Reaction Time from the Stop Task</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing Speed Motor</td>
<td><em>WISC-R Coding, WISC-III Symbol Search, Colorado Perceptual Speed</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Task, Identical Pictures, Trailmaking Test,</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing Speed Verbal</td>
<td><em>Rapid Automatized Naming Task (Colors, Numbers, Letters, &amp; Pictures) &amp;</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Stroop Task (Word Naming &amp; Color Naming)</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note.* For ADHD, mean severity ratings from each rater were used as the indicators. This strategy allows for more variance than the more typical strategy of defining ADHD using symptom counts.

*Note.* Errors from the same instrument (e.g., WISC Coding and Symbol Search) were allowed to correlate in both measurement models.
**Results**

**Measurement Models**

The best fitting DV measurement model was one which created separate latent variables for the continuous symptoms of inattention and symptoms of hyperactivity/impulsivity: $\chi^2 (14, N=624) = 14.90$, $ns$, $\chi^2/df = 1.06$, CFI = 1.00, RMSEA = .01.

The best fitting IV measurement model was one which split Processing Speed into Verbal and Motor components: $\chi^2 (344, N=624) = 926.02$, $p<.001$, $\chi^2/df = 2.70$, CFI = .93, RMSEA = .05.

**Full SEM Model**

The full SEM model was also a good fit, $\chi^2 (580, N=624) = 1678.41$, $p<.001$, $\chi^2/df = 2.89$, CFI = .91, RMSEA = .055.
Summary of Results and Discussion

✓ This model accounted for 83% of the variance in RD, 35% of the variance in symptoms of inattention, and 18% of the variance in symptoms of hyperactivity/impulsivity.

✓ Furthermore, the model reduced the relationship between RD and inattention symptoms from a zero-order correlation of 0.425 to a non-significant partial correlation of .06. The model also reduced the relationship between RD and hyperactivity/impulsivity from a zero-order correlation of .215 to a non-significant partial correlation of .08. The reduction in these correlations implies that PS explains a significant amount of the overlap between RD and ADHD symptoms.

✓ Contrary to prediction, WM did not contribute uniquely to either RD or ADHD symptoms.

✓ These results indicate that PS is a shared cognitive risk factor for RD and ADHD.

✓ Moreover, by using latent traits of symptoms of inattention and hyperactivity/impulsivity and their neuropsychological predictors, we were able to explain a much greater amount of the variance (18% - 35%) in the symptoms of ADHD than is typically found in the literature (10-12%).
Accounting for the cognitive overlap between reading and attention: A genetic investigation of processing speed

Rebecca S. Betjemann,
Erik G. Willcutt,
Lauren McGrath,
Richard K. Olson,
Sally J. Wadsworth,
Janice M. Keenan,
John C. DeFries, &
Bruce F. Pennington
Results: Multivariate Cholesky

- A1
  - F1: PS-Motor
    - C1: .49
  - A2: PS-Verbal
    - F2: .30
  - A3: Word Reading
    - F3: .65
  - A4: Inattention
    - F4: .17
  - A5: Hyp/Imp
    - F5: .52

- C1
  - F1: .77
  - F2: .50
  - F3: .52
  - F4: .51
  - F5: .00

- A2
  - F2: .65
  - A3: .17
  - A4: .03
  - A5: .05

- A3
  - A1: .77
  - A2: .50
  - A4: .10
  - A5: .05

- A4
  - A1: .50
  - A2: .77
  - A3: .79
  - A5: .50
Results: Multivariate Cholesky

F1: PS-Motor
F2: PS-Verbal
F3: Word Reading
F4: Inattention
F5: Hyp/Imp

A1
A2
A3
A4
A5

C1
E1
E2
E4
Figure 1. Multiple Deficit Model

Level of Analysis

Etiologic Risk and Protective Factors

G₁ E₁ G₂ E₂ G₃ ... G x E interaction & G-E Correlation

Cognitive Causes

Phon Sem RSN

Interactive Development

Complex Behavioral Disorders

RD SSD SLI

Comorbidity

KEY

G = genetic risk or protective factor, E = environmental risk or protective factor, Phon = Implicit phonological representations, Sem = Semantics, RSN = Rapid serial naming, RD = Reading disability, SSD = Speech sound disorders, SLI = Specific language impairment
Conclusions

1. Dyslexia (RD) is comorbid with SSD and ADHD.

2. Genetic studies demonstrate that RD shares genetic risk factors with SSD and ADHD.

3. Multiple cognitive deficits are needed to explain RD, SSD, and ADHD.

4. Shared cognitive deficits help explain the comorbidity between RD and SSD (phoneme awareness) and between RD and ADHD (processing speed).

5. More work is needed to understand how LI relates to SSD and RD genetically and how LI and SSD interact to increase risk for later RD.