DYSEXIA: NEUROBIOLOGICAL AND GENETIC ASPECTS

Gerd Schulte-Körne
NEUROBIOLOGY
DYSLEXIA: CAUSAL MODEL

- Genetic predisposition
- Perception and processing of letters and words
- Perception and processing of sounds and phonemes
- Environmental factors: school, family and psychosocial environment
- Intelligence, memory, attention, emotion and motivation
- Dyslexia

Genetic predisposition influences perception and processing of letters and words, which in turn affect the perception and processing of sounds and phonemes. Environmental factors can also impact these processes. Intelligence, memory, attention, emotion and motivation interconnect with these factors and contribute to the development of dyslexia.
DEVELOPMENTAL PATHWAYS TO WORD READING

Genetic predisposition-candidate genes

Speech perception

Letter perception

Phoneme awareness

Letter single, bi- and trigram processing

Grapheme-phoneme association

Orthographic word lexicon

Phonological word decoding

Phonological word lexicon
NEUROBIOLOGICAL CORRELATES: STRUCTURAL AND FUNCTIONAL ANALYSES
METAANALYSE OF STRUCTURAL BRAIN-ABNORMALTIES IN ADOLESCENTS AND ADULTS WITH DYSLEXIA (RICHLAN ET AL. 2013)

GM reduction left superior temporal sulcus between Superior and middle temporal gyri

GM reduction right superior temporal cortex (posterior dorsal bank)

Corresponding underactivation in fMRI adult studies (blue) and children (red)
FMRI AND PET STUDIES – METAANALYSES (PAULESU ET AL. 2013 FRONTIERS IN HUMAN NEUROSCIENCE)
LETTER - SOUND ASSOCIATION (ATTEVELDTC ET AL. 2004, NEURON)

letter a: gyrus fusiforme, visual word form area

Letter-sound-association a-/a/
gyrus supratemporalis

sound /a/: auditory cortex

Auditory Visual
LETTER-SOUND INTEGRATION IN DYSLEXIC ADULTS
(BLAU ET AL. 2009, CURRENT BIOLOGY)

Lower activation in supratemporal cortex
FUNCTIONAL BRAIN-ABNORMALITIES IN DYSLEXIA (RICHLAN ET AL. 2013, NEUROIMAGE)

- Overactivation in precentral gyrus
- Underactivation in children left and right parietal lobule
- Underactivation in IFG in adults
- Underactivation in STG in adults
- Underactivation in children and adults in fusiforme gyrus
CONNECTIVITY WHITE MATTER ANALYSES (VANDERMOSTEN ET AL. 2013, NEUROSCIENCE AND BIOBEHAVIOURAL REVIEWS)
CONNECTIVITY WHITE MATTER ANALYSES (VANDERMASTEN ET AL. 2013, NEUROSCIENCE AND BIOBEHAVIOURAL REVIEWS)

- AF connects Wernicke’s area (STG) with Broca’s area (IFG)
- AF direct: phonological processing
- Posterior part AF: speech perception, anterior part: articulation

Sagittal view of left corona radiata (CR, depicted in blue) and left superior longitudinal fasciculus (AF, depicted in green).
SUMMARY OF NEUROBIOLOGICAL FINDINGS

- Neurobiological reading networks
  - **Left dorsal temporoparietal (TP) reading circuit:** superior temporal gyrus (STG), the supramarginal and angular gyri of the inferior parietal lobule (IPL): dorsal phonological pathway
  - **Left ventral occipito-temporal (OT) reading circuit:** lateral extrastriate, gyrus fusiforme, and inferior temporal regions: ventral orthographic pathway
  - **Single regions:**
    - Left STS: less GM, lower activation in fMRI: underactivation correlates with phonological processing and grapheme-phoneme association
    - Left ventral occipito-temporal cortical region (including VWFA) lower activation in fMRI: correlates with word and letter decoding
WORD PROCESSING:
NEUROPHYSIOLOGY OF TEMPORAL PROCESSES
TIME COURSE OF WORD PROCESSING IN CHILDREN WITH AND WITHOUT DYSLEXIA (HASKO ET AL. 2013) FRONTIERS IN HUMAN NEUROSCIENCE

(A) Print sensitivity

Letter and word identification

Orthographic lexicon

Phonological processing

Phonological lexicon

Late positive component
WORD PROCESSING AT OCCIPITO-TEMPORAL ELECTRODES AT 220MS: LESS PRINT SENSITIVITY DYSLEXICS (HASKO ET AL. 2013)
PHONOLOGICAL PROCESSING AT 400MSEC
GENETICS
PEDIGREE OF A FAMILY WITH DYSLEXIA

Female

Male
Recurrence risk ratio for spelling and reading (Ziegler, et al.; Human Heredity 2005)

<table>
<thead>
<tr>
<th>Criterion for affection</th>
<th>Spelling</th>
<th>Reading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>λ</td>
</tr>
<tr>
<td>( \leq 15.0 )</td>
<td>277</td>
<td>3.032</td>
</tr>
<tr>
<td>( \leq 10.0 )</td>
<td>257</td>
<td>3.813</td>
</tr>
<tr>
<td>( \leq 5.0 )</td>
<td>209</td>
<td>4.880</td>
</tr>
<tr>
<td>( \leq 2.5 )</td>
<td>145</td>
<td>6.621</td>
</tr>
</tbody>
</table>

**Discrepancy**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SD</td>
<td>287</td>
<td>4.516</td>
</tr>
<tr>
<td>1.5 SD</td>
<td>270</td>
<td>7.644</td>
</tr>
</tbody>
</table>
HERITABILITY ESTIMATES

- Stevenson et al. 1997
- Light et al. 1998
- Hohnen and Stevenson 1999
- Davies et al. 2001
- Gajewski and Olson 2001
- Harlaar et al. 2005
- Petrill et al. 2006

Word reading vs. Spelling
CANDIDATE GENES

- **DYX1C1** - dyslexia susceptibility 1 candidate 1) (Chromosom 15)
  - Regulation of transcription
- **KIAA0319** (Chromosom 6)
  - rs4504469 (coding SNP) found associated with dyslexia in several independent studies, reduction of expression of KIAA0319
- **DCDC2** (chromosome 6)
- **ROBO1** (chromosome 3)
- **MRPL19** und **C2ORF3** (chromosome 2)
NORTHERN-BLOT ANALYSIS OF THE DCDC2 TRANSCRIPT OF HUMAN BRAIN TISSUES, WHICH INDICATE AN EXPRESSION OF AN 2-KB TRANSCRIPT IN MOST BRAIN TISSUES; AJHG: SCHUMACHER ET AL. 2005
Expression of candidate genes in the brain

- Prefrontal cortex
- Frontal cortex
- Superior temporal cortex
- Superior parietal cortex
- Medial temporal cortex
- Inferior temporal cortex
- Occipital cortex
- Primary visual cortex
- Hypothalamus
- Amygdala
- Hippocampus

Relative gene expression

Thalamus

Whole brain

Midsagittal section
Candidate gene – neuronal migration

THE GENETIC LEXICON OF DYSLEXIA: PARACCHINI S, SCERRI T, MONACO AP. ANNU REV GENOMICS HUM GENET. 2007;8:57-79

control  Kiaa319  Dcdc2  Dyx1c1
ASSOCIATION BETWEEN DCDC2 POLYMORPHISM WITH GRAY MATTER CORTICAL THICKNESS (DARKI ET AL. 2014, THE JOURNAL OF NEUROSCIENCE)
ASSOCIATION BETWEEN DCDC2, DYX1C1 AND KIAA0319 WITH WHITE MATTER VOLUME (DARKI ET AL. 2014, THE JOURNAL OF NEUROSCIENCE)
SPEECH PROCESSING:
A MODEL FOR GENE-NEUROBIOLOGY-
BEHAVIOR INTERACTION
Speech perception - endophenotype for dyslexia

- Quantitative phenotype
- High heritability
- Familial aggregation
Speech perception – in children and adults with dyslexia and controls

- **Control group**
- **dyslexia**

**Speech perception deficit in dyslexic adults as measured by mismatch negativity (MMN)**

**Auditory processing and dyslexia: evidence for a specific speech processing deficit**
Speech perception – in siblings and controls (Neuhoff et al. 2012, PloS ONE)
Significance of speech environment (Bruder et al. 2011, Psychophysiology)
Significance of speech environment (Bruder et al. 2011, Psychophysiology)

Table 3. Pearson (r) Correlations (Two-Tailed) between MMN Amplitudes to Both Vowel Stimuli and Spelling and Reading Measures

<table>
<thead>
<tr>
<th></th>
<th>MMN native vowel</th>
<th>MMN atypical vowel</th>
<th>Spelling</th>
<th>Reading fluency</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMN native vowel</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMN atypical vowel</td>
<td>.009</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spelling</td>
<td>− .522**</td>
<td>.232</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Reading fluency</td>
<td>− .471*</td>
<td>.168</td>
<td>.844**</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: Correlations conducted over all subjects (N = 26).
*p < .05; **p < .01.
PREDICTION OF DYSELSXIA BY EARLY SPEECH PERCEPTION (HÄMÄLÄINEN ET AL. 2013, DEVELOPMENTAL NEUROPSYCHOLOGY)

- **Stimuli:** short /ata/ and a long /at:a/ (300msec each)

- Typically reading control children ($n=27$, bold black line),

- Typically reading children with familial risk for dyslexia ($n=27$, bold gray line)
Figure 1  MMN curves. Grand average of (a) the standard /da/ (dotted line) and deviant /ba/ (dashed line) curves and (b) the MMN demonstrating the MMNa (time window 188–300 ms) and the MMNb (time window 300–710 ms).
## SPEECH PERCEPTION: CANDIDATE GENE SLC2A3 FOR DYSLEXIA (ROESKE ET AL. 2012, MOLECULAR PSYCHIATRY)

<table>
<thead>
<tr>
<th>SNP</th>
<th>Phenotype</th>
<th>Model¹</th>
<th>initial sample²</th>
<th>replication sample²</th>
<th>combined sample²</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2487742</td>
<td>MMNa</td>
<td>carrier T</td>
<td>2.77e-06</td>
<td>3.02e-01</td>
<td>1.09e-04</td>
</tr>
<tr>
<td>rs11300</td>
<td>MMNb</td>
<td>allelic</td>
<td>8.47e-06</td>
<td>7.61e-02</td>
<td>1.11e-05</td>
</tr>
<tr>
<td>rs1365152</td>
<td>MMNa</td>
<td>allelic carrier A</td>
<td>4.27e-08</td>
<td>8.30e-01</td>
<td>1.44e-04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9.02e-07</td>
<td>9.86e-01</td>
<td>1.14e-03</td>
</tr>
<tr>
<td>rs2114167</td>
<td>MMNa</td>
<td>allelic carrier G</td>
<td>1.17e-07</td>
<td>8.68e-01</td>
<td>6.82e-04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9.02e-07</td>
<td>9.86e-01</td>
<td>5.41e-03</td>
</tr>
<tr>
<td>rs7683638</td>
<td>MMNa</td>
<td>carrier G</td>
<td>4.60e-06</td>
<td>n.a.⁴</td>
<td>n.a.⁴</td>
</tr>
<tr>
<td>rs4234898</td>
<td>MMNb</td>
<td>allelic carrier T</td>
<td>3.29e-06</td>
<td>4.97e-03</td>
<td>1.44e-07</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.20e-06</td>
<td>1.46e-03</td>
<td>5.14e-08</td>
</tr>
<tr>
<td>rs4704133</td>
<td>MMNb</td>
<td>carrier C</td>
<td>7.56e-06</td>
<td>n.a.⁴</td>
<td>n.a.⁴</td>
</tr>
<tr>
<td>rs9390586</td>
<td>MMNb</td>
<td>genotypic carrier T</td>
<td>2.24e-06</td>
<td>4.89e-01</td>
<td>3.73e-02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.79e-07</td>
<td>4.89e-01</td>
<td>1.05e-02</td>
</tr>
<tr>
<td>rs7793973</td>
<td>MMNa</td>
<td>genotypic</td>
<td>9.78e-06</td>
<td>3.54e-01</td>
<td>4.12e-04</td>
</tr>
<tr>
<td>rs1607924</td>
<td>MMNb</td>
<td>carrier A</td>
<td>9.91e-06</td>
<td>9.10e-01</td>
<td>1.55e-03</td>
</tr>
<tr>
<td>rs965670</td>
<td>MMNb</td>
<td>allelic</td>
<td>1.53e-06</td>
<td>8.95e-01</td>
<td>1.55e-03</td>
</tr>
<tr>
<td>rs10996111</td>
<td>MMNa</td>
<td>carrier G</td>
<td>9.54e-06</td>
<td>n.a.³</td>
<td>n.a.³</td>
</tr>
<tr>
<td>rs4751178</td>
<td>MMNb</td>
<td>genotypic carrier G</td>
<td>7.25e-06</td>
<td>8.61e-02</td>
<td>1.04e-05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.30e-06</td>
<td>1.08e-01</td>
<td>6.55e-06</td>
</tr>
<tr>
<td>rs1777697</td>
<td>MMNa</td>
<td>genotypic</td>
<td>9.83e-07</td>
<td>5.71e-01</td>
<td>1.28e-03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.16e-06</td>
<td>5.41e-01</td>
<td>6.05e-03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.36e-06</td>
<td>6.95e-01</td>
<td>3.69e-04</td>
</tr>
<tr>
<td>rs4238922</td>
<td>MMNa</td>
<td>genotypic</td>
<td>7.48e-06</td>
<td>8.44e-01</td>
<td>2.12e-03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.20e-06</td>
<td>5.67e-01</td>
<td>4.50e-04</td>
</tr>
<tr>
<td>rs11871364</td>
<td>MMNa</td>
<td>carrier C</td>
<td>9.69e-06</td>
<td>7.84e-01</td>
<td>2.84e-02</td>
</tr>
<tr>
<td>rs7217223</td>
<td>MMNb</td>
<td>carrier C</td>
<td>4.57e-06</td>
<td>n.a.³</td>
<td>n.a.³</td>
</tr>
<tr>
<td>rs2612570</td>
<td>MMNb</td>
<td>carrier C</td>
<td>4.42e-06</td>
<td>7.72e-01</td>
<td>4.87e-04</td>
</tr>
<tr>
<td>rs1736148</td>
<td>MMNa</td>
<td>allelic</td>
<td>1.93e-06</td>
<td>9.85e-02</td>
<td>5.05e-02</td>
</tr>
</tbody>
</table>
SPEECH PERCEPTION: CANDIDATE GENE SLC2A3 FOR DYSEXIA (ROESKE ET AL. 2012, MOLECULAR PSYCHIATRY)

• *SLC2A3* (also called *GLUT3*) belongs to the family of facilitative glucose transporters strongly expressed in brain,
• provides energy for synaptic transmission and
• plays a role in axonal and/or dendritic transport regulatory impact of rs4234898 on *SLC2A3* only in children.
NEUROBIOLOGY OF TREATMENT RESPONSE
INTERVENTION METHODS

**Symptom oriented methods:** focussing on the child's individual achievement level in word reading or spelling

**Intervention aimed to alter causes of dyslexia:** training visual and/or auditory perception

**Interventions combining symptom oriented and causally related methods**

**Psychopharmacology:** nootropica, like piracetam to increase performance on a variety of cognitive tasks.
INTERVENTION METHODS

phonemic awareness instruction
- foster the ability to recognize and manipulate phonemes in words,
- blending phonemes to words,
- segmenting a word into its phonemes,
- eliminating a phoneme from a word, or adding a phoneme to a word.
- All tasks are presented and performed orally.

phonics instruction
- letter-sound-correspondences and decoding strategies
- blending or segmenting individual letters or phonemes
- dividing a spoken or written word into syllables or onset and rimes.
- These interventions comprise reading and writing activities.

reading fluency training
- repeated oral word reading practice or
- Guided repeated word reading.
- These interventions aim to improve word recognition.
# Table 1. Efficacy of treatment approaches on reading performance.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>N</th>
<th>$g'$</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment approach</td>
<td>Phonemic awareness instruction</td>
<td>3</td>
<td>0.279</td>
<td>-0.244</td>
<td>0.802</td>
</tr>
<tr>
<td></td>
<td>Phonics instruction</td>
<td>29</td>
<td>0.322</td>
<td>0.177</td>
<td>0.467</td>
</tr>
<tr>
<td></td>
<td>Reading fluency training</td>
<td>5</td>
<td>0.301</td>
<td>-0.105</td>
<td>0.707</td>
</tr>
<tr>
<td></td>
<td>Reading comprehension training</td>
<td>3</td>
<td>0.177</td>
<td>-0.181</td>
<td>0.535</td>
</tr>
<tr>
<td></td>
<td>Auditory training</td>
<td>3</td>
<td>0.387</td>
<td>-0.065</td>
<td>0.838</td>
</tr>
<tr>
<td></td>
<td>Medical treatment</td>
<td>2</td>
<td>0.125</td>
<td>-0.072</td>
<td>0.322</td>
</tr>
<tr>
<td></td>
<td>Coloured overlays</td>
<td>4</td>
<td>0.316</td>
<td>-0.012</td>
<td>0.644</td>
</tr>
</tbody>
</table>

95% CI
ERp-CORRELATES OF TREATMENT RESPONSE (HASKO ET AL. 2014, FRONTIERS IN HUMAN NEUROSCIENCE)

**Intervention**

Twice a week, lasting 45min for 6 months, individual treatment

<table>
<thead>
<tr>
<th>Kieler Leseaufbau</th>
<th>Marburger Rechtschreibtraining</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Phonics training</td>
<td>• Phoneme discrimination, orthographic knowledge, rule based</td>
</tr>
<tr>
<td>• Word reading</td>
<td>Schulte-Körne &amp; Mathwig (2001-2009)</td>
</tr>
<tr>
<td>Dummer-Smoch &amp; Hackethal (2007)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CON (n = 25)</th>
<th>IMP (n = 11)</th>
<th>NIMP (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>8.18 (0.32)</td>
<td>8.28 (0.39)</td>
<td>8.27 (0.35)</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>13:12</td>
<td>8:3</td>
<td>10:7</td>
</tr>
<tr>
<td>Handedness (right:left)</td>
<td>24:1</td>
<td>10:1</td>
<td>13:4</td>
</tr>
<tr>
<td>IQa</td>
<td>112.04 (10.78)</td>
<td>101.55 (6.33)</td>
<td>104.94 (7.57)</td>
</tr>
<tr>
<td>Attentionb</td>
<td>2.88 (1.83)</td>
<td>4.82 (2.23)</td>
<td>4.35 (2.06)</td>
</tr>
</tbody>
</table>
ERP-CORRELATES OF TREATMENT RESPONSE (HASKO ET AL. 2014, FRONTIERS IN HUMAN NEUROSCIENCE)

FIGURE 1 | Phonological lexical decision task. Words (W; e.g., Mund /mʊnt/, engl.: mouth), pseudohomophones (PH; e.g., Munt /mʊŋt/), pseudowords (PW; e.g., Munk /mʊŋk/) and false fonts (FF; e.g., Χιπλ) were presented individually in white on black background in the center of a 17" screen. Participants were instructed to decide via button press whether a presented stimulus sounded like a real word or not.

FIGURE 2 | Illustration of the 128-channel-system and electrode position taken from Electrical Geodesics Inc. (2007). Filled blue circles depict electrodes included in the ROI of the N400. Filled green circles depict electrodes included in the LH and RH ROIs of the N300.
ERP-CORRELATES OF TREATMENT RESPONSE (HASKO ET AL. 2014, FRONTIERS IN HUMAN NEUROSCIENCE)
ERP-CORRELATES OF TREATMENT RESPONSE (HASKO ET AL. 2014, FRONTIERS IN HUMAN NEUROSCIENCE)
ERP-CORRELATES OF TREATMENT PREDICTION (HASKO ET AL. 2014, FRONTIERS IN HUMAN NEUROSCIENCE)
THANK YOU FOR YOUR ATTENTION

Prof. Dr. Gerd Schulte-Körne

Chair of Child and Adolescent Psychiatry and Psychotherapy
Director of the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy University of Munich Nußbaumstr. 5a
80997 Munich / Germany

Tel 0049 89440055901
www.kjp.med.uni-muenchen.de