PLASTICITY AND RE-ORGANIZATION IN THE DEVELOPING AUDITORY BRAIN: EVIDENCE FROM CHILDREN WITH HEARING IMPAIRMENT AND AUDITORY NEUROPATHY

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<thead>
<tr>
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<tbody>
<tr>
<td>Leif Hergils and Hans Lindehammer</td>
<td>Linkoping Hospital, Sweden</td>
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CHILDREN WITH COCHLEAR IMPLANTS

AUDITORY NEUROPATHY SPECTRUM DISORDER (ANSD)
AIM

To examine plasticity in the developing central auditory nervous system.

To explore implications for clinical intervention.
Plasticity

The brain’s ability to change in structure and function in response to input from the environment.

Early in life, neurons begin to form connections or synapses. Proper connections are essential for learning.
Plasticity begins before birth and continues into adulthood
P1 generated in primary and secondary auditory cortex
Normal Hearing Children (N=190)

\[ y = -34.56 \ln(x) + 161.49 \]

\[ R^2 = 0.846 \quad p < 0.0001 \]

Sharma et al., 2002
Cochlear Implanted Children (N = 245)

Sharma et al., (2002; 2006)
There is a sensitive period of 3.5 years during which implantation takes place into a highly plastic auditory cortex.
Synaptic Density in Auditory Cortex

Huttenlocher and Dhabolkar (1997)
Current Density Reconstructions

Normal Hearing
n=10

Early Implanted
n=8*

Late Implanted
n=8*

Right ITG
Bilateral STS

Right ITG
Contralateral STS

Contralateral Parieto Temporal

Gilley, Sharma, Dorman, 2008

* Corrected for ear of stimulation
Age-matched groups of children (n=26)
Partial or Complete Decoupling between Primary & Higher Order Cortex

Kral, 2007
If proper auditory stimulation is not provided then there may be a disconnection between areas of the brain which connect sound with meaning. These children will have difficulty learning oral language.
Compensatory or Maladaptive plasticity: Cross Modal Re-organization
CROSS-MODAL PLASTICITY: SOMATOSENSORY-AUDITORY

MEG Dipole Reconstructions - Somatosensory

Normal hearing adult

Deaf adult

Sharma et al., 2007
CROSS-MODAL PLASTICITY: VISUAL-AUDITORY

fMRI activity in deaf adults in response to visual stimuli

Visual activity in temporal cortex at STS  

Finney et al., 2001
If auditory stimulation is not delivered in a timely fashion, then areas of the auditory cortex will re-organize to process stimuli from other sensory modalities.
Does cross-modal plasticity affect outcome?
<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Age at onset of deafness (years)</th>
<th>Cause of deafness</th>
<th>Degree of loss (dB threshold)</th>
<th>Deaf. duration (years)</th>
<th>CI duration (years)</th>
<th>Side of CI</th>
<th>Speech recognition with the CI (%)</th>
<th>Communication</th>
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<tbody>
<tr>
<td>S1</td>
<td>M</td>
<td>21</td>
<td>3</td>
<td>Unknown</td>
<td>Left = 118, Right = 105</td>
<td>16</td>
<td>2</td>
<td>L</td>
<td>73</td>
<td>Oral + lip-reading</td>
</tr>
<tr>
<td>S2</td>
<td>F</td>
<td>52</td>
<td>47</td>
<td>G.-Sjogren syndrome</td>
<td>Left = 110, Right = 105</td>
<td>2</td>
<td>3</td>
<td>R</td>
<td>98</td>
<td>Oral + lip-reading</td>
</tr>
<tr>
<td>S3</td>
<td>M</td>
<td>37</td>
<td>12–25 (progressive)</td>
<td>Hereditary</td>
<td>Left = 113, Right = 113</td>
<td>11–24</td>
<td>1</td>
<td>L</td>
<td>80</td>
<td>Oral + lip-reading</td>
</tr>
<tr>
<td>S4</td>
<td>F</td>
<td>42</td>
<td>27</td>
<td>Unknown</td>
<td>Left = 110, Right = 87</td>
<td>13.5</td>
<td>1.5</td>
<td>L</td>
<td>92</td>
<td>Oral + lip-reading</td>
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<tr>
<td>S5</td>
<td>F</td>
<td>18</td>
<td>0–15 (progressive)</td>
<td>Hereditary</td>
<td>Left = 93, Right = 93</td>
<td>1–16</td>
<td>2</td>
<td>R</td>
<td>85</td>
<td>Oral + lip-reading</td>
</tr>
<tr>
<td>S6</td>
<td>M</td>
<td>54</td>
<td>30–50 (progressive)</td>
<td>Hereditary</td>
<td>Left = 108, Right = 105</td>
<td>2–22</td>
<td>2</td>
<td>R</td>
<td>82</td>
<td>Oral + lip-reading</td>
</tr>
<tr>
<td>S7</td>
<td>F</td>
<td>25</td>
<td>0</td>
<td>Hereditary</td>
<td>Left = 107, Right = 107</td>
<td>23</td>
<td>2</td>
<td>R</td>
<td>92</td>
<td>Oral + lip-reading</td>
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<tr>
<td>S8</td>
<td>F</td>
<td>23</td>
<td>2</td>
<td>Meningitis</td>
<td>Left = 100, Right = 100</td>
<td>18</td>
<td>3</td>
<td>R</td>
<td>0</td>
<td>Sign language + lip-reading</td>
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<tr>
<td>S9</td>
<td>F</td>
<td>50</td>
<td>5</td>
<td>Chronic otitis media</td>
<td>Left = 118, Right = 118</td>
<td>44</td>
<td>1</td>
<td>R</td>
<td>0</td>
<td>Sign language + lip-reading</td>
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<tr>
<td>S10</td>
<td>F</td>
<td>41</td>
<td>2–12 (progressive)</td>
<td>Meningitis</td>
<td>Left = 117, Right = 117</td>
<td>28–38</td>
<td>1</td>
<td>R</td>
<td>0</td>
<td>Sign language + lip-reading</td>
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<tr>
<td>S11</td>
<td>M</td>
<td>18</td>
<td>0</td>
<td>Hereditary</td>
<td>Left = 97, Right = 93</td>
<td>16</td>
<td>2</td>
<td>L</td>
<td>0</td>
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<tr>
<td>S12</td>
<td>M</td>
<td>62</td>
<td>10</td>
<td>Meningitis</td>
<td>Left = 113, Right = 115</td>
<td>52</td>
<td>1</td>
<td>L</td>
<td>0</td>
<td>Sign language + lip-reading</td>
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<tr>
<td>S13</td>
<td>M</td>
<td>49</td>
<td>0</td>
<td>Hereditary</td>
<td>Left = 105, Right = 110</td>
<td>47</td>
<td>2</td>
<td>L</td>
<td>0</td>
<td>Sign language + lip-reading</td>
</tr>
</tbody>
</table>
Fig. 1 High contrast sinusoidal concentric grating (0.8 c/deg), subtending 10 deg², followed, 500 ms after onset, by a similar grating radially modulated in frequency.
Fig. 3  Top: Waveforms for five electrodes (Fz, Cz, Oz, T5, T6) next to topographical maps of the mean voltage amplitudes (μV—see middle colour bar) in good performers (left), controls (middle) and poor performers (right) groups, at the maximum amplitude of the Oz P2 component (see blue vertical line on the curves at left side of each map). Bottom: Subtraction waves next to topographical maps representing t-statistics of the differences between the good performers and controls (left) as well as the poor performers and controls (right).
Cross-modal plasticity appears to be correlated to outcome.
128 channel high density EEG net
Clinically feasible high-density EEG testing

Photo courtesy EGI
Due to proprietary information contained on this slide, you will not be able to view it. Thank you for your understanding.
How does cross modal re-organization affect integration across auditory and visual modalities?
McGurk Effect

Auditory-Visual Fusion

e.g., hear /pa/, see /ka/

perceive /ta/
Responses of individual subjects to the incongruent auditory-visual/pa/ka/stimulus (McGurk test). “ta” responses indicate audiovisual fusion, “pa” responses indicate auditory dominance, and “ka” responses indicate visual dominance.
Late-implanted children show deficits in auditory-visual integration.
Conclusions

There is a sensitive period for optimal performance with the cochlear implant in congenitally deaf children.

Deafness that continues beyond these sensitive periods results in cortical re-organization.

Cortical re-organization typically results in poor outcomes for oral language learning.
AUDITORY NEUROPATHY/DYS-SYNCHRONY (AN/AD)

AUDITORY NEUROPATHY SPECTRUM DISORDER (ANSD)
DEMOGRAPHICS

**INCIDENCE** - 10% - 15% of children with sensorineural hearing loss.

Sininger, Hood, Berlin, Uus. (Talaat et al., 2009, Kirkhim et al., 2008)
Characteristics of ANSD: Summary

Evidence of outer hair cell function in the cochlea
- Present OAE’s
- Cochlear microphonic present in ABR

Evidence of neural impairment
- ABR is absent/abnormal
- Acoustic Stapedial reflexes are absent/abnormal
- Audiogram ranges from normal to profound, can fluctuate
- No correlation between speech perception skills and audiogram

- High inter and intrasubject variability
Lack of neural synchrony is a hallmark of children with ANSD
Auditory Brainstem

Auditory Thalamocortical pathways

Auditory Cortex

ABR
No Response/Abnormal resulting in degraded acoustic signal

Cochlea
CAEP in ANSD

CAEP can be measured in many patients with ANSD

Aim

To explore development and plasticity of the central auditory pathway in ANSD.
Cortical Maturation in Children with ANSD

- Existing data base of 115 children with ANSD on whom we have cortical maturation data.

- Majority have congenital disorder

- Initial analysis on subset of children

<table>
<thead>
<tr>
<th>Participant</th>
<th>Etiology</th>
<th>ABR</th>
<th>OAE - R</th>
<th>OAE - L</th>
<th>PTA unaided R</th>
<th>PTA unaided L</th>
<th>HA Fit Age</th>
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<tbody>
<tr>
<td>1</td>
<td>Jaundiced - no trmt, CM present Au - 92 dBnHL</td>
<td>DP TEOAEs present DPOAEs present</td>
<td>118</td>
<td>108</td>
<td></td>
<td></td>
<td>1.08</td>
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<tr>
<td>2</td>
<td>no risk factors, CM present Au; Wave V component developed over time down to 50 dBnHL (prolonged interpeak latencies)</td>
<td>TEOAEs present DPOAEs present</td>
<td>63</td>
<td>31</td>
<td></td>
<td></td>
<td>1.19</td>
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<tr>
<td>3</td>
<td>oxygen deprivation @ birth, prematurity (27 week), low birth weight, hyperbilirubinemia, chronic lung disease, ototoxic meds</td>
<td>DPOAEs present</td>
<td>95</td>
<td></td>
<td></td>
<td></td>
<td>1.68</td>
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<tr>
<td>4</td>
<td>prematurity (36 weeks), mech vent, diaphragmatic hernia, ototoxic meds</td>
<td>TEOAEs present</td>
<td>62</td>
<td>70</td>
<td></td>
<td></td>
<td>0.77</td>
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<tr>
<td>5</td>
<td>prematurity (31 week), NICU stay, jaundice (blood transfusion), mech. Vent</td>
<td>TE and DPOAEs present</td>
<td>72</td>
<td>75</td>
<td></td>
<td></td>
<td>0.27</td>
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<tr>
<td>6</td>
<td>premature, 62 - 93, 0.72</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>premature (down to 65) Au</td>
<td>82</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>premature, failure to thrive, kidney problems, blood transfusion</td>
<td></td>
<td>95</td>
<td></td>
<td></td>
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<td>9</td>
<td>premature (24 week), low birth weight, hyperbilirubinemia, 3 blood transfusions</td>
<td>DPOAEs present</td>
<td>90</td>
<td>80</td>
<td></td>
<td></td>
<td>0.16</td>
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<td>10</td>
<td>prematurity (36 week), acute hepatitis and kidney failure, ototoxic meds, NICU stay, mech ventilation</td>
<td>TE and DPOAEs present</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td>1.29</td>
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<td>11</td>
<td>premature (36 week), acute hepatitis and kidney failure, ototoxic meds, NICU stay, mech ventilation</td>
<td>TEOAEs present</td>
<td>70</td>
<td>67</td>
<td></td>
<td></td>
<td>2.62</td>
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<td>12</td>
<td>family history - no known risk factors, CM present, (90, 21.1) Au, reversal down to 11.1</td>
<td>TE and DPOAEs present</td>
<td>82</td>
<td>85</td>
<td></td>
<td></td>
<td>2.38</td>
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<td>13</td>
<td>premature (28 week), jaundiced, mech vent, chronic lung disease, hypothyroidism</td>
<td>TEOAEs absent</td>
<td>80</td>
<td>82</td>
<td></td>
<td></td>
<td>0.59</td>
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<td>14</td>
<td>maternal tuberculosis + medication, radiation exposure (X-Ray in utero), hernia on umbilical cord</td>
<td>CM Present Au (90) DPOAEs partially present reported absent</td>
<td>93</td>
<td>68</td>
<td></td>
<td></td>
<td>6.72</td>
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<td>15</td>
<td>jaundiced, CM present Au (90dBnHL)</td>
<td>TE and DPOAEs present</td>
<td>98</td>
<td>93</td>
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<td>2.4</td>
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<td>prematurity (gest. Age 6 mo), transfusions, extended NICU stay, ototoxic meds</td>
<td>DPOAEs present</td>
<td>83</td>
<td>85</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>17</td>
<td>seizures, family history of hearing loss</td>
<td>TEOAEs absent/DPOAEs present</td>
<td>93</td>
<td>98</td>
<td></td>
<td></td>
<td>6.12</td>
</tr>
<tr>
<td>18</td>
<td>epilepsy, other developmental delays</td>
<td>TEOAEs absent/DPOAEs present</td>
<td>111</td>
<td>80</td>
<td></td>
<td></td>
<td>1.82</td>
</tr>
<tr>
<td>19</td>
<td>premature (32 week), NICU stay, mech vent, blood transfusions, ototoxic meds</td>
<td>TE and DPOAEs present</td>
<td>62</td>
<td>93</td>
<td></td>
<td></td>
<td>0.72</td>
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</table>
Cortical response (P1) latencies

ANSD CHILDREN FELL INTO 3 DISTINCT GROUPS REFLECTING THE EXTENT OF DISRUPTION IN NEURAL DYS-SYNCHRONY AND ITS EFFECT IN CORTICAL DEVELOPMENT.

Due to proprietary information contained on this slide, you will not be able to view it. Thank you for your understanding.
We correlated the P1 against the IT-MAIS test of auditory skill development.
P1 vs auditory development


p<0.05
Relationship between cortical maturation and behavioral auditory skill development.

$r=0.8 \ p<0.05$

$R^2=0.6$

Cortical maturation may be an important predictor of speech/language outcomes in children with ANSD.
Hearing aid fit age

• There are likely sensitive periods for cortical maturation in children with congenital ANSD.

• Appropriate treatment options provided within these time frames may increase likelihood of successful outcomes for children with ANSD.
Summary

• 38% of children showed normal cortical development and good behavioral outcomes.
• Normal cortical development is suggestive of mild synchrony problem which may benefit from hearing aids consistent with Rance et al., (2002).

• 33% showed delayed and 29% showed abnormal cortical development and poor behavioral outcomes.
• Delayed and abnormal cortical development likely reflect more severe synchrony problems.

Sharma, Cardon et al., International Journal of Audiology 2011; 50: 98–106
We are exploring the use of cortical potentials to assist in management of children with ANSD.
Benefit From Hearing Aid Use

- IT-MAIS Score: 32
- IT-MAIS Age: 1.08
- PTA Unaided: 62
- PTA Aided: 40
- HA Fit Age: .77
- Etiology: prematurity (27 week), low birth weight, hyperbilirubinemia, chronic lung disease, ototoxic meds
No Benefit From Hearing Aid Use

- **IT-MAIS Score**: 4
- **IT-MAIS Age**: 1.08
- **PTA Unaided**: 83
- **PTA Aided**: 57
- **HA Fit Age**: 2.38
- **Etiology**: family history, no known risk factors
Benefit From CI Use

- **IT-MAIS Score:**
- **IT-MAIS Age:**
- **PTA Unaided:** 105
- **PTA Aided:** 85
- **HA Fit Age:** .90
- **CI Fit Age:** 1.27
- **Etiology:** twin - no other known risk factors
Persistently Delayed Post-implant

- IT-MAIS Score: 9
- IT-MAIS Age: 6.83
- PTA Unaided: 95
- PTA Aided: 65
- HA Fit Age: 6.12
- CI Fit Age: 6.62
- Etiology: seizures, family history of hearing loss
High Intra-individual variability in some patients with ANSD
Case Study

• 9 year old child with congenital unilateral AN in left ear.

• **AN ear**: Normal OAE, Abnormal ABR; mild hearing loss, speech discrimination 20%, poor speech perception in noise.

• **Non AN ear**: Normal OAE, ABR, normal pure tone thresholds, speech discrimination 92%, good speech perception in noise.
9 yr. old with unilateral ANSD
9 yr. old with unilateral ANSD
High Density EEG study
Cortical Auditory Evoked Potentials
from 64 scalp electrodes
Due to proprietary information contained on this slide, you will not be able to view it. Thank you for your understanding.
CONCLUSIONS

Children with ANSD show different patterns of cortical maturation.

Normal cortical maturation appears to reflect better synchrony and is a good predictor of acquisition of oral speech and language.

On the other hand, delayed, abnormal and variable cortical potentials reflect poor dys-synchrony and correlates with poor speech outcomes.
Cortical potentials are powerful objective bio-markers of central auditory system plasticity and maturation.

Biomarkers of plasticity are useful to guide clinical intervention via hearing aids and/or cochlear implants for children with hearing loss and ANSD.
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