Neuroscience applications to pediatric speech and language disorders

Martha S. Burns, Ph.D.
May 12, 2011

Selected New References


Newer references (continued)

Agenda

• Neuroscience update
• New applications to childhood speech sound disorders (perceptual/phonological vs. apraxia)
  – Evidence-based interventions
• New applications to ASD
  – Evidence-based interventions

DeHaene, 2009
Early fMRI studies of networks: Neurons that fire together wire together in networks.

Neurological Development

• Critical "optimal" Periods – Huttenlocher, 2002

• Four major divisions:
  – Neuron formation (neurogenesis) –between post-ovulatory day (POD) 52-140
    • Supported by increased sensitivity to ionizing radiation
      – reduced neuronal number in cerebral forebrain causes microcephaly and mental retardation
  – Neuronal Migration – Second trimester
  – Dendritic and Synaptic development –third trimester and first two postnatal years
  – Myelination

Protein domains and possible functions

Migration and Axon Growth (Galaburda et al., 2006)

Synaptogenesis (Huttenlocher, 2002)

• The onset of function in the human cortex occurs when synapses are formed
  – Form largely during first year of life – but varies by part of brain
  – At the end of the first year – total no. of synapses is 2 times that of the adult
    • Environmental factors are essential in synaptogenesis (earlier developmental steps are genetically driven)
    • Functioning circuits are stabilized and persist, those that are not used are resorbed – synaptic pruning

Brain Morphometry
Mapping of Cortical Thinning with Longitudinal MRI Data
Gogtay et al., PNAS, 2004

Longitudinal Mapping of Cortical Thickness and Brain Growth in Normal Children
(Sowell et al., J. Neurosci., 2004)

Widespread cortical thinning, and focal areas of cortical thickening observed longitudinally in children over 2 years, from 7 to 9.

Plots of grey-matter density are based on data by Gogtay et al. 2004 and illustrate the local grey-matter density in the mid-dorsolateral prefrontal cortex in red, in the angular gyrus of the parietal cortex in blue, in the posterior superior temporal sulcus of the temporal cortex in purple, and in the occipital pole in green.
The role of fiber tract connections

Diffusion Tensor Imaging

- Measures diffusion (motion) of protons in water molecules.
- Direction of proton motion within a voxel can be described by a "tensor".
- Proton diffusion tends to be relatively isotropic in gray matter.
- The linear structure of fiber tracts constrains proton diffusion and produces anisotropy.
Fiber Tract Development
Observable with DTI
(from Hermoye et al., 2006)
Inferior Longitudinal Fasciculus – links vision to sound

Intermediate Tracts

Slowly Developing Tracts
Implications for Childhood Speech Sound Disorders

COGNITIVE PROCESSING SPEED AND THE STRUCTURE OF WHITE MATTER PATHWAYS: CONVERGENT EVIDENCE FROM NORMAL VARIATION AND LESION STUDIES

Turken, Whitfield-Gabrieli, Bammer, Baldo, Dronkers, Gabrieli


Figure 1: White matter regions showing a positive correlation between FA and processing speed. Axial cross sections, overlaid on the average normalized FA image for the group, run along the superior to inferior direction in steps of 5 mm (i.e., 5 mm to 12 mm). Pointed regions of significance are shown at the top row; left frontal region in second row, and temporal regions at the third row. Caudate indicates the nucleus for the expansion. In this and the following figures, the anatomical orientation is followed (left side of the brain is shown on the left side of the figure).

Turken, et al.

In conclusion, we have found evidence for which white matter pathways might be essential for processing speed, often treated as a key property of the cognitive architecture (Kail and Salthouse, 1994). Voxel-based analysis of diffusion tensor images and fiber tractography findings indicated that variations in the microstructure of white matter tracks interconnected brain regions that subserve high-level cognition can account for variations in a psychometric measure of processing speed among healthy young adults. Assessment of the effects of lesion lesions on performance on the same task provided results consistent with a critical role for left posterior parietal lobe and its white matter.
CAS References


CAS References (continued)


CAS References (continued)

CAS References (continued)


CAS References (continued)


What we know from perceptual studies and fMRI research

- Kuhl’s landmark infant perception studies
- Hickock and Poeppel – neurolinguistic perspectives
- Genetic causes – Fox P2
Language Learning Timetable

Newer research from Kuhl, Language Magnet Theory, 2008

Kuhl, 2008 Phases in early perceptual/production

- **Phase 1** - infants begin life with a capacity to discriminate the acoustic cues that code differences among phonetic units. The ability to discriminate the sounds, albeit crudely, assists development in phase 2.

- **Phase 2** – two aspects of environmental input—**exaggerated acoustics (motherese) and distributional properties**—interact to support infants’ perception of categories infants’ sensitivity to categories
  - Learning occurs earlier for vowels than consonants which could reflect the availability of exaggerated cues in ID speech (consonants are not as easily exaggerated as vowels, because exaggeration can change the category, e.g. stretching the formant transitions of /b/ produces /w/).
  - Alternatively, there may be differences in the availability and/or prominence of distributional differences for consonants (e.g. consonants like /th/ occur in function words, which are lower in energy and do not capture infant attention, see Sundara et al. 2006).

- By the end of phase 2, infant perception is
Organization of cortical responses to spoken language in 3 m old infants.

Kuhl, 2008 (continued)

- By the end of phase 2, infant perception is altered. The detection of native language phonetic cues is enhanced in the process, while detection of non-native phonetic patterns is reduced.

- Phase 3 - enhanced speech perception abilities improve three independent skills that propel infants towards word acquisition (and predict future language skills):
  - the detection of phonotactic patterns (Friederici & Wessels 1993; Mattys et al. 1999);
  - the detection of transitional probabilities between segments and syllables (Goodall et al. 1993; Saffran et al. 1996; Newport & Aslin 2004); and
  - The association between sound patterns and objects (Swingley & Aslin 2002; Werker et al. 2002; Ballem & Plunkett 2005).

Kuhl, 2008 continued

Phase 4 -- analysis of incoming language has produced relatively stable neural representations—new utterances do not cause shifts in the distributional properties coded neurally.
- In infancy, neural networks are not completely formed and do not restrict learning.
- Infants are thus capable of learning from multiple languages, as shown in everyday life, and also as shown by experimental interventions (Maye et al. 2002; Kuhl et al. 2003).
Intracranial electrophysiology (ICE) (Sahin, et al., 2009)

- Recorded local field potentials from populations of neurons using electrodes implanted in language-related brain regions while people read words verbatim or grammatically inflected them (present/past or singular/plural)
- Neighboring probes within Broca’s area revealed distinct neuronal activity for lexical (~200 milliseconds), grammatical (~320 milliseconds), and phonological (~450 milliseconds) processing, identically for nouns and verbs, in a region activated in the same patients and task in functional magnetic resonance imaging.
Fig. 2 (A) Main results: sequential processing of lexical, grammatical, and phonological information in overlapping circuits

Fig. 4 Additional features of the triphasic waveform support the lexical-inflectional-phonological progression

Categorical speech representation in human superior temporal gyrus

Edward F Chang, Jochem W Rieger, Keith Johnson, Mitchel S Berger, Nicholas M Barbaro & Robert T Knight
Nature Neuroscience
VOLUME 13 | NUMBER 11 | NOVEMBER 2010
What is Childhood Apraxia of Speech?

• Diagnostic criteria are all over the place
  – ASHA website and position papers essentially include all problems with speech production saying more research is necessary
• Shriberg et al have been studying CAS from production characteristics to genetics (FOX P2)

But Turken and Dronkers, in press take it further to processing tracts

• Differentiating
  – Speech, Grammar and Fluency pathways
  – Differentiating underlying auditory speech processing
  – With semantics overlying everything
Turken and Dronkers (2010 in press) speech, fluency and grammar pathways

Turken and Dronkers (2010 in press) White Matter tracts underlying auditory speech processing

Turken and Dronkers, 2011 (in press) semantic processing network revisions
So – we should be able to distinguish:

- Children with perceptual problems
- Children with motor speech, grammar, fluency problems (CAS)
- Children with broader problems that effect semantics

13 Characteristics used characterize children with severe speech disorders

2. Stopping - Substitution of glottal stops for final tip-alveolar or velar consonants or plosives for fricatives. (Canter, Trost and Burns, 1984)
3. Backing - Substitution of blade alveolar or velar placed productions for tip alveolar consonants (Canter, Trost and Burns, 1984)
4. Absent Frication - Absence of frication or affrication in spontaneous speech productions (Trost and Canter, 1974)
5. Simplification - Simplifies words by replacing difficult sounds with easier ones or by deleting difficult sounds (ASHA 2007)
6. Final Consonant deletion - Imploding or deletion of final consonants (ASHA 2007)
7. Reduced Oral Motor - Problems with oral motor posture imitation (Trost and Canter, 1974)
8. Reduced Fluency - problems combining sounds: may show long pauses between sounds (ASHA 2007; Shriberg, 1993)
Characteristics (3)

9. Reduced phonemic repertoire - spontaneous speech limited to a few different consonant and vowel sounds (ASHA 2007)
10. Low tone - seated slouched in chair, little upper body postural support (Darley, Aronson and Brown, 1975; literature on motor skills maturation, NDT)
11. Reduced bilabial tone - Chronic open-mouth posture and/or excessive drooling (ASHA 2007)
12. Single syllable - Spontaneous speech limited to single-syllable productions (viewed as an extreme form of simplification – ASHA 2007)
13. Reduced Word Repetition - Phonemic repertoire remains reduced on real word and/or non-word repetition on the Kaufman Speech Praxis Test (see also, Shriberg et al, 2009) – divided into simple and complex constructions depending on syllable structure complexity

Table 1. Children determined to exhibit marked Motor-Speech (+CAS) problems [five or more characteristics], and those with possible Motor Speech (?CAS) problems who exhibited four characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MAC</th>
<th>CCH</th>
<th>GAR</th>
<th>JAM</th>
<th>LAN</th>
<th>CAR</th>
<th>CAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronological AGE</td>
<td>2-11</td>
<td>3-0</td>
<td>4-0</td>
<td>3-5</td>
<td>3-3</td>
<td>3-5</td>
<td>3-5</td>
</tr>
<tr>
<td>MSU</td>
<td>1.22</td>
<td>1.95</td>
<td>1.10</td>
<td>1.3</td>
<td>1.3</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>G &amp; F</td>
<td>58</td>
<td>71</td>
<td>72</td>
<td>84</td>
<td>95</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Nasalization</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Glottal Stops</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Final con vel</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Backing</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Low postural tone</td>
<td></td>
<td></td>
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<tr>
<td>Low bilabial tone</td>
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<tr>
<td>Single syllable</td>
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<tr>
<td>- Oral Motor imitation</td>
<td>+</td>
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<td></td>
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<tr>
<td>- Phonemic repertoire</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td></td>
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<tr>
<td>Simplification</td>
<td>+</td>
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<td></td>
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<tr>
<td>- Phonemic</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>- Word repetition</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<td>Total</td>
<td>8</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Children who did not exhibit evidence of motor speech problems per se, with one phonological process (stopping or backing) that might be associated with phonological delay; simplification of phoneme use and/or reduced phoneme repertoire, and/or language production reduced to single syllables with phonemic repertoire consistent with language age.
Summary – children with motor speech disorders:

- Can be distinguished from other severe speech problems by seven characteristics
- Do appear to have auditory processing disorders as well as motor speech signs
  - Supported by newer research
  - Lack of self-monitoring
- Are not necessarily more severe to start with but do not show as much improvement with intensive speech/language therapy
- Do benefit from FFWD Language (Literacy) along with speech therapy
- Should receive RAEE as well
Autism Spectrum Disorders

• Autism spectrum disorders (ASDs) are a group of developmental disorders characterized by impairments in:
  – social interaction;
  – varying degrees of verbal and nonverbal communication deficits; and
  – restricted, repetitive, and stereotyped patterns of behavior and interests.

• ASD’s are neurodevelopmental disorders

ASD’s

• The term includes:
  – autistic disorder,
  – Asperger disorder, and
  – Pervasive developmental disorder, not otherwise specified (PDD-NOS)

• The incidence of ASD’s is now 1 in every 110 children
  – 1 in 70 males

• autism is a polygenic disorder with a heritability index of 0.90.

Autism Spectrum Disorder is Partially Genetic

• Autism spectrum disorders have a strong genetic bases
  – autism susceptibility genes
  – Copy number variations (insertion or deletion of large DNA fragments) – both inherited and idiosyncratic – and other mutations
  – Genetic syndromes

• But linking genes to specific language, social skill and repetitive behaviors will help drive interventions
Abrahams and Geschwind (2008) 
Advances in autism genetics: on the threshold of a new neurobiology

- Figure 1 | Loci implicated in ASD etiology.
- Green bars correspond to genes that are observed to modulate autism spectrum disorder
  - light green and dark green bars represent promising or probable candidate genes, respectively
- Red and yellow bars correspond to de novo losses and gains, respectively, that are observed in cases but not in controls

Some of the genes regulate brain development

- For example - CDH9 and CDH10
  - Are very important for the development of the obito-frontal cortex
EPIGENETICS

Environmental factors that change genes in the first and second generation

Epigenetic factors revealed so far include:
- Nutrition during pregnancy and early postnatal months
- Xenobiotic chemicals
- Behavioral cues
- Reproductive factors
- Low-dose radiation

But what other factors exist?

- Epigenetics
  - Literally means “above the genome”
  - If the genome is the hardware of the body
  - Epigenetics is the software that tells the gene when and how to work
  - Looks at genetic actions that turn genes on and off
  - Video
  - Factors that may be causing genetic mutations and/or turn genes on that we do not want turned on
UC Davis M.I.N.D. Institute

- M.I.N.D. (Medical Investigation of Neurodevelopmental Disorders)
- Study Shows California Autism Increase Not Due to Better Counting, Diagnosis - By UC Davis Health System, January 06, 2009
  - The incidence of autism by age six in California has increased from fewer than nine in 10,000 for children born in 1990 to more than 44 in 10,000 for children born in 2000.
  - Some have argued that this change could have been due to migration into California, inclusion of children with milder forms of autism and earlier ages of diagnosis.
  - Hertz-Picciotto and her colleagues two large studies aimed at discovering the causes of autism. Hertz-Picciotto is the principal investigator on the CHARGE (Childhood Autism Risk from Genetics and the Environment) and MARBLES (Markers of Autism Risk in Babies Learning Early Signs) studies.

M.I.N.D. Institute (U.C. Davis)
C.H.A.R.G.E

- CHARGE is the largest epidemiologic study of reliably confirmed cases of autism to date.
  - the first major investigation of environmental factors and gene-environment interactions in the disorder.

- In October, 2009 a symposium was organized in conjunction with the International Neurotoxicology Conference Meeting which included:
  - Autism Speaks
  - M.I.N.D. Institute
  - Vanderbilt University
  - Wadsworth Center, New York State Department of Health, Albany, NY
  - Robert Wood Johnson Medical School
  - Golisano Children’s Hospital at University of Rochester School of Medicine and Dentistry, Rochester, NY
  - Lab of Developmental Neuroscience, Università Campus Bio-Medico, Roma, Italy
  - Department of Neurobiology, University of Arizona
  - Department of Genetics, North Carolina State University, Raleigh, NC,
Neurotoxicology in autism (Halladay et al., 2011 continued)

• Amaral - Evidence has been accumulating for over 20 years suggesting that immune factors may play a role in the etiology of some forms of autism (Warren et al., 1986, 1996; Ashwood and Vandewater, 2004).
• Judy Van de Water, Paul Ashwood and colleagues at the M.I.N.D. Institute have conducted comprehensive evaluations of children with autism and their parents to determine what, if any, perturbations of immune function are characteristic of the disorder.
• Part of this effort has been to evaluate these individuals for evidence of autoimmunity.

Pamela Yein, U.C. Davis

• Have identified three different classes of environmental factors that modulate neuronal connectivity in primary cultures of hippocampal neurons
  – identify non-coplanar PCBs as candidate environmental risk factors in ASD and suggest the possibility that exposure even to very low PCB levels could amplify adverse effects in genetically susceptible individuals
  • May be a factor in perceptual problems (see next section) and birth order findings (see Newschaffer, 2008)

Autism increases with maternal and paternal age (Newschaffer, 2008)

• The results of this study provide the most compelling evidence to date that ASD risk increases with both maternal and paternal age and decreases with birth order
• The observation in this and at least 2 previous studies (2, 4) that the risk of developing ASD was highest for firstborn children and declined with increasing birth order is a pattern also observed for other childhood disorders, including type I diabetes and atopy, and is cited as support for the “hygiene hypothesis.”
Hygiene Hypothesis

• First born children are exposed to fewer infections from other children early in childhood and, because of delayed immunologic challenge, may be more likely to develop autoimmune responses including those that may adversely affect neurodevelopment.

Incidence in first born children

• Another possible factor that could lead to the observed birth order effect is exposure to potentially neurotoxic, fat-soluble chemicals accumulated in maternal tissue that have been passed to offspring transplacentally or through breast milk.
• Because of accumulation over a lifetime, the load of such neurotoxins transmitted might be expected to be highest for firstborn children, particularly when combined with advanced maternal age.

Pamela Yein, U.C. Davis

– the second class of environmental factors we are studying, the pro-inflammatory cytokines, interferon-γ and interleukin (IL)-6 decrease dendritic arborization and synapse formation in cultured hippocampal neurons (Kim et al., 2002).
• Our preliminary data suggest that at least interferon-γ modulates dendritic growth and synaptic density similarly in situ. Interestingly, these cytokines are elevated in the serum and cerebrospinal fluid of ASD patients (Ciaranello and Ciaranello, 1995).
M.A.R.B.L.E.S

- MARBLES is a prospective investigation that follows women who already have had one child with autism, beginning early in or even before a subsequent pregnancy, to search for early markers that predict autism in the younger sibling.

M.I.N.D. biomarker research

- Patent number: 7604948
  Filing date: May 5, 2006
  Issue date: Oct 20, 2009
  Application number: 11/381,976

- A method for diagnosing an autism spectrum disorder in an individual, said method comprising:
  - a) determining the level of complement factor H-related protein (FHR1) in a blood or serum sample from a first individual exhibiting symptoms of an autism spectrum disorder; and
  - b) comparing the level of the FHR1 determined in step a) with the level of the FHR1 in a control sample from a second individual or a population of individuals who do not have an autism spectrum disorder;

- wherein levels of increased complement factor H-related protein (FHR1) in the sample from the first individual in comparison to the control sample from the second individual or population of individuals is indicative of an autism spectrum disorder.

Amaral, D. 2009 U.S. Patent

Autism has been associated with autoimmune disorders in the proband’s relatives. Comi et al. compared families of patients with autism (81 families) and healthy controls (40 families) and reported that 48% of the autism group reported having relatives with rheumatoid arthritis (RA) (Comi et al., 1999) / Child Neurol 14(8)). Table 20 shows frequency data of family history of rheumatoid arthritis (RA), multiple sclerosis (MS) and autism among typically developing normal children (TYP), children with low functioning autism (LFA) and children with high functioning autism (HFA). In the current investigation 29% of the children with autism (HFA and LFA) and only 6% of the typically developing, normal children had relatives with rheumatoid arthritis (Table 20). The data suggest previous reports of abnormalities of various immune-regulated molecules in the blood of children and adults with autism.

<table>
<thead>
<tr>
<th>TABLE 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History</td>
</tr>
<tr>
<td>RA</td>
</tr>
<tr>
<td>TYP</td>
</tr>
<tr>
<td>LFA</td>
</tr>
<tr>
<td>HFA</td>
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### TABLE 17

<table>
<thead>
<tr>
<th>Association Number</th>
<th>Peptide Description</th>
<th>Peptide (SEQ ID NO)</th>
<th>P-value</th>
<th>Fold Change</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>N9_000217.1</td>
<td>Fibronectin 1 isoform A</td>
<td>FN1F1 (5)</td>
<td>0.004</td>
<td>1.19</td>
<td>1.29</td>
</tr>
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<td>N9_000217.1</td>
<td>Fibronectin 1 isoform A</td>
<td>FN1F2 (14)</td>
<td>0.002</td>
<td>1.25</td>
<td>1.03</td>
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<td>N9_000503.3</td>
<td>Complement component 4b</td>
<td>HP15600199.1 (8)</td>
<td>0.012</td>
<td>1.38</td>
<td>1.07</td>
</tr>
</tbody>
</table>


### TABLE 18

<table>
<thead>
<tr>
<th>Protein Description</th>
<th>Peptide (SEQ ID NO)</th>
<th>P-value</th>
<th>Fold Change</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAD1-like 1; MAD1</td>
<td>VLIEMSNLATWVQRR (9)</td>
<td>0.042</td>
<td>-1.34</td>
<td>-1.34</td>
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<tr>
<td>apo-Lipoprotein A-IV precursor</td>
<td>LPLAEWR (11)</td>
<td>0.014</td>
<td>-1.16</td>
<td>-1.12</td>
</tr>
<tr>
<td>apo-Lipoprotein C-III precursor</td>
<td>TNLQFQ (13)</td>
<td>0.016</td>
<td>-1.45</td>
<td>-1.01</td>
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<tr>
<td>Wnt-9a protein precursor (Wnt-14)</td>
<td>WMTLIGR (14)</td>
<td>0.026</td>
<td>-1.38</td>
<td>-0.99</td>
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<tr>
<td>WD repeat domain 17 isoform 1</td>
<td>NELLECYTOYGALLAIR (15)</td>
<td>0.001</td>
<td>-1.31</td>
<td>-0.99</td>
</tr>
</tbody>
</table>

# Peptide with p < 0.05
Pamela Yein, continued

Third, we are investigating organophosphorus pesticides (OPs), which we have shown inhibit axonal growth in developing neurons by interfering with the morphogenic activity of acetylcholinesterase (Yang et al., 2008).

Status of research on other potential causes of autism?

“Leaky Gut” theory of autism —

Belief, based on a paper he wrote about 12 children, is that the three vaccines, given together, can alter a child’s immune system, allowing the measles virus in the vaccine to infiltrate the intestines; certain proteins, escaping from the intestines, could then reach and harm neurons in the brain.

Gave parents a hope that autism is caused by a real medical issue and can be “treated” and perhaps cured through dietary changes.

Repercussions

Evidence that Wakefield fabricated some research, with no other evidence that MMR leads to autism and physicians worry that separating vaccines will result in many children under-immunized — but... Parents need to be taken seriously and gastrointestinal problems studied.

• Statement 12
  – Available research data do not support the use of a casein-free diet, a gluten-free diet, or combined gluten-free, casein-free (GFCF) diet as a primary treatment for individuals with ASDs.
  – only 1 double-blind placebo controlled study has been published to date (Elder JH, Shanker M, Shuster J, Thérique S, Blum S, Sherrill L. The gluten-free casein-free diet in autism: results of a preliminary double blind clinical trial. J Autism Dev Disord. 2006;36(2):413–420)
    • In this double-blind crossover trial of GFCF or typical diet in 15 children with ASDs, there were no differences in measures of severity of ASD symptoms, communication, social responsiveness, and urinary peptide levels after 12 weeks.
• Nevertheless, after being informed of the results 9/15 parents wanted to continue the diet and reported positive subjective clinical changes while their child was on the GFCF diet.

Buie, et al 2010 -- GFCF diet (continued)

• Parents need information to help plan a balanced diet within the restrictions imposed by any chosen diet
• Given the real hardships associated with implementation of a strict GFCF diet, additional studies are needed to assess risk factors and possible markers that identify individuals who might benefit from these diets.

Localization of White Matter Volume Increase in Autism and Developmental Language Disorder

[Further text regarding a study on white matter volume increase in autism and developmental language disorder]
Figure 1. Graphical representation of somatotopic growth patterns in motor cortex. Yellow area indicates the outer motor cortex; white zone, which are larger in volume in this study of children with autism than in the controls. The white area represents bridging and sagittal components, which did not differ in volume from controls. The volumes of areas in blue were absolutely but not relatively different. Image courtesy of Marta Herbst, MD, PhD. 14

Mirror neuron system (MNS) (red) and its main visual input (yellow) in the human brain, anterior area located in the inferior frontal cortex, A posterior area in the rostral part of the inferior parietal lobule (IPL). Together, these three areas form a core circuit for imitation.

Children with and w/o autism on fMRI while they observed or imitated facial emotional expressions (a), children with autism show reduced activity in (MNS) in the pars opercularis of the inferior frontal gyrus. This correlates with the severity of disorder.
Figure 4.
A, Brain activation of autism and control groups during sentence comprehension (sentence vs. fixation contrast). Participants with autism show less activation in the left inferior frontal gyrus (LIFG) than the control group, but more activation in the left posterior superior temporal gyrus (LSTG) than the control group.
B, Functional connectivity for autism and control participants in the 10 region of interest (ROI) pairs with a reliable (<.05) difference between autism and control participants (presented in descending order of mean connectivity). The pattern of functional connectivities across these 10 ROI pairs is very similar for the 2 groups (r=.98). Error bars represent the standard error of the mean.

CALC indicates calcarine fissure; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye field; IES, inferior extrastriate; IFG, inferior frontal gyrus; IPL, inferior parietal lobe; IPS, intraparietal sulcus; IT, inferior temporal; OP, occipital pole; SMFP, superior medial frontal paracingulate; and TRIA, triangularis. Image courtesy of Oxford University Press.

Decreased Interhemispheric Functional Connectivity in Autism

- Jeffrey S. Anderson, T. Jason Druzgal, Alyson Froehlich, Molly B. DuBay, Nicholas Lange, Andree L. Alexander, Tracy Abboud, Jared A. Nelson, Annahir N. Cariello, Jason R. Cooperider, Erin D. Bigler and Janet E. Lainhart
- Cerebral Cortex Advance Access published October 12, 2010

• Examined resting-state blood oxygen level–dependent interhemispheric correlation in 53 males with high functioning autism and 39 typically developing males from late childhood through early adulthood
Anderson, et al., 2010

- found significantly reduced interhemispheric correlation specific to regions with functional relevance to autism:
  - sensorimotor cortex,
  - anterior insula,
  - fusiform gyrus,
  - superior temporal gyrus, and
  - superior parietal lobule
- Observed interhemispheric connectivity differences were better explained by diagnosis of autism than by potentially confounding neuropsychological metrics of language, IQ, or handedness.

Distortions and disconnections: disrupted brain connectivity in autism (Wass, 2011)

- Point to evidence that there is local over-connectivity
  - Perhaps leading to repetitive behaviors and savant characteristics
- Long Distance underconnectivity
  - Leading to problems with long fiber track networks for:
    - Language and problem solving
    - MNS and TOM (see tomorrow’s discussion)

Wass, 2011

- Review DTI studies that reveal inter-hemispheric structural under-connectivity in mature subjects with ASD
  - With younger subjects the results are more mixed
- Also evidence showing disruptions to and from frontal and temporal cortices may be most heavily disrupted in ASD
  - This is consistent with early relatively intact development becoming progressively more disrupted during the first two years of life
Wass, 2011

- fMRI and EEG studies show evidence of functional over-connectivity but with this regard DTI is more mixed
  - Strongest evidence of local over-connectivity comes from the micro-level from a small number of post-mortem studies
- Tantalizing evidence that increased short-range connectivity and decreased long-range may resemble that found in immature vs. mature typically developing children
- ASD may be partially due to failure to undergo typical developmental process
- SO – is this the primary pathogenesis or does it develop over time?

N.Y. Times November 1, 2010

A camera operator observed Carmen and Saul Aguilar during a therapy session with their son Emilio at 7 months old. Emilio showed signs of autism, and his older brother, Diego, received a diagnosis at age 2.

By APRIL DEMBOSKY
Published: November 1, 2010
SACRAMENTO — In the three years since her son Diego was given a diagnosis of autism at age 2, Carmen Aguilar has made countless contributions to research on this perplexing disorder.

Mindblind Eyes: An Absence of Spontaneous Theory of Mind in Asperger Syndrome

- Atsushi Senju, Victoria Southgate, Sarah White, Uta Frith
- SCIENCE VOL 325 14 AUGUST 2009
Eye-tracking task that has revealed the spontaneous ability to mentalize in typically developing infants

In familiarization trials, participants were familiarized to an event in which (A) the puppet placed a ball in one of two boxes, (B) both windows were illuminated and chime sounded, and (C) an actor reached through the window above the box in which the ball was placed and retrieved the ball. The participants were familiarized to the contingency between (B) and (C). In (D), the puppet moves the ball while the actor is looking away. This operation induces a false belief in the actor about the location of the ball.

Peça, J. et al. *Shank3* mutant mice display autistic-like behaviours and striatal dysfunction. 20 Mar 2011 *Nature*

- *Shank3* knockout mice (*Shank3B−/−* mice)
- found that mutant mice spent much less time engaging in social interaction than wild-type animals.
- In addition, mutant mice exhibited excessive repetitive grooming — a potential correlate of the repetitive behaviour observed in ASDs
- Altered basal ganglia function
PCB poisoning radically alters cortical map development

Exactly the same bizarre typography seen in autism
PCB exposure in pregnant mothers .87 correlation with % of autism – some regions of Texas – Merzenich, 2006

There are also perceptual deficits

- That interfere with ability to perceive pitch variations in voice that signal emotion, Russo and Kraus, 2008
- And perceive facial cues, Dalton et al
- And perceive human bodily movement

Methods

- 12 children diagnosed with an Autism Spectrum Disorder
  - 6 trained, 6 control
  - Age matched (Trained=9.17 ± 1.47 years; Control= 9.0 ± 1.47 years, n.s.)
- Brainstem neurophysiology tests
  - /da/ in quiet and background noise
  - rising and falling /ya/ in quiet
Pitch tracking and phase locking of F0 improved

Pitch tracking to the harmonics improved
Two-year-olds with autism orient to non-social contingencies rather than biological motion

- Ami Klin, David J. Lin, Phillip Gorrindo, Gordon Ramsay & Warren Jones
- Video demonstration

### Conclusions

- Autism is genetic – new research will point to:
  - What each of the genes does
  - What causes the genes to be expressed and/or corrupted (epigenetics – eg. environmental factors)
- In general the genes affect brain development of:
  - Prefrontal lobe functions – TOM and Mirror neuron system
  - Perceptual functions related to preferences for human faces, biological motion and human vocal intonation


- 3% and 25% of children reportedly lose their ASD diagnosis and enter the normal range of cognitive, adaptive and social skills
  - Predictors of recovery include
    - Relatively high intelligence, receptive language, verbal and motor imitation, and motor development, but not overall symptom severity.
    - Earlier age of diagnosis and treatment, and a diagnosis of Pervasive Developmental Disorder- Not Otherwise Specified are also favorable signs

- The presence of seizures, mental retardation and genetic syndromes are unfavorable signs,
- whereas head growth does not predict outcome.
- Residual vulnerabilities affect higher-order communication and attention.
- Tics, depression and phobias are frequent residual co-morbidities after recovery.

Possible mechanisms of recovery include:
- normalizing input by forcing attention outward or enriching the environment;
- promoting the reinforcement value of social stimuli;
- preventing interfering behaviors;
- mass practice of weak skills;
- reducing stress and stabilizing arousal.

Improving nutrition and sleep quality is non-specifically beneficial.

So, what can we do?

- Right now the research evidence points to value of ABA approaches and promising new areas for intervention:
- perceptual training and the mirror neuron system in young children
  - Interactive play
  - Imitation
- mentalizing and other prefrontal lobe functions as the children mature
  - TOM
  - Working memory
Karen Pierce, U.C. San Diego

- Published April 28, Journal of Pediatrics
- 5 minute checklist for pediatricians
- 10,479 babies screened at one year checkups
- 24 questions
- Accurately predicted problems in 75% of children (184)
- False alarms for 25%
  - Lack of shared attention (babies should try to pull your attention to their world)

Pierce, continued

- Lack of shared enjoyment – may smile at mom but not engage if other people play peek-a-boo
- Repetitive behaviors like spinning a car wheel rather than play with the car
- Language problems seen with any of the above