Neurobehavioral Outcomes in Spina Bifida: Learning and the Brain

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SPINA BIFIDA

- A common birth defect affecting 0.5-1.0/1000 live births
- Defect in neural tube closure in early embryogenesis resulting in malformation of the CNS at the level of the brain and spine
- Most common congenital birth defect in North America
Several Specific Types of Spina Bifida

- Meningocele, Lipoma, SB Occulta
- Spina bifida meningomyelocele – most common and most severe form
- Spinal lesion- nerve impairment may occur several levels above and below the lesion
- Characteristic brain malformations and hydrocephalus
- Problems with motor functions, bladder/bowel regulation, and learning
Neural Tube Defect Sequence

- Failure of the neural tube to close leads to
  - interrupted spinal cord
  - hydrocephalus
  - neurogenic bladder
  - club feet
Spina Bifida: Cognitive and Neurobiological Variability (SANDI Project: Supported by NICHD)

Project 1 (Genetics) – Hope Northrup, M.D. – UTH
Project 2 (Development) – Susan Landry, Ph.D.- UTH
Project 3 (Cerebellum) - Maureen Dennis, Ph.D.- HSC
Project 4 (Corpus Callosum) - Julia Hannay, Ph.D.- UH
Project 5 (Academics) – Marcia Barnes, Ph.D.- HSC
Core A (Administrative) - Jack Fletcher, Ph.D. – UTH
Core B (Recruit/Assess) - Jack Fletcher, Ph.D. – UTH
Core C (Quantitative) – David Francis, Ph.D. – UH

(Michael Brandt, Jon Frederick, Larry Kramer, Susan Blaser, Jim Drake, John Laurent, Grace Villareal, Richard Haynes, Irene Townsend, Susan Inwood, Kim Edleston, Laura Lomax)
Interdisciplinary Team

- Cognitive Neuroscience
- Computational Biomedicine
- Developmental Psychology
- Genetics
- Neurology
- Neuropsychology
- Neurosurgery
- Ophthalmology
- Quantitative Psychology (Statistics)
Central Theme

• Spina bifida has distinct dysmorphologies and modal cognitive characteristics, but outcomes vary. What are the mechanisms underlying this variability?
Sources of Variability

- Complex pattern of gene-environment interactions
- CNS manifestations - spinal lesion level, Chiari malformation, corpus callosum anomalies
- Treatment - hydrocephalus and its treatment, early development
- Environmental factors: diet, familial, cultural

*Genetic, neuroimaging, and cognitive neuroscience investigations of a common, representative sample*
Four Primary Samples (Houston and Toronto)

- Genetic sample: >1800 blood samples from children (>600) and one or more parents
- Infant sample followed from birth to 36 months (91 SBM, 71 controls)
- School-age sample (309 SBM, 62 controls)
- Cognitive neuroscience studies (cerebellum, corpus callosum, math and discourse) (130 SBM, 40 controls)

Diverse, multi-ethnic sample with good representation of economically disadvantaged and minority participants
Sources of Variability

Figure 1.
Sources of Variability

Figure 1. Central organizing framework for the research program. Complex gene-environment interactions produce variability in physical, neural, and cognitive phenotypes.
Genetic Factors

• Family history
  – Parents with one child with SBM have an increased risk for having an additional child with SB

• Variation in incidence by ethnicity
  – Hispanic > Caucasian > African-American > Asian-American (physical phenotype varies with ethnicity)

• Animal models
  – NTD malformations detected in several mouse models
Accounting for Heterogeneity

• Simplex Families
  – Patients, Mothers, Fathers

• Ethnicity (An important aspect of our study is that we have subdivided our subject pop’n according to ethnicity)
  – Hispanics of Mexican-American Descent
  – North American Caucasians (Non-Hispanic Whites)

• Level of Spinal Defect
  – Upper
  – Lower
Level of Defect

“Multi-Site Closure Model”

Closure Site 1: Upper Level Defect (T1 and above)

Closure Site 5: Lower Level Defect (L1 and below)

(Van Allen et al. 1993)
MTHFR Results

- Maternal C677T homozygous genotype significant risk factor for upper level SB defects in Hispanics [OR=2.3, P=0.02]
  - Hispanic mothers of children with upper level defects have the highest frequency of the 677T variant allele [f(T)=0.592]

- Maternal combined C677T/A1298C heterozygous genotype significant risk factor for upper level SB defects in non-Hispanic whites [OR=3.6, P=0.03]
MTHFR 677TT: Upper Defects
Hispanics vs. Controls

Patients/Controls: 30% SB Family, 22% Control
Mothers/Controls: 38% SB Family, 21% Control
Fathers/Controls: 25% SB Family, 24% Control

OR=2.3, P=0.02
MTHFR 677CT/1298AC: Upper Defects Non-Hispanic Whites vs. Controls

Combined CT/AC Heterozygous Genotypes

OR=3.6, P=0.03
MTHFR Results

• Maternal MTHFR variant genotypes confer risk for upper level SB defects
  – Limiting transfer of folate from maternal circulation to neuroepithelial cells of embryonic neural tube
  – Supplying inadequate folate to facilitate growth required to produce neural folds large enough to elevate, overarch and fuse
Physical Phenotype

- Variation in type of lesion: Few children with any form of SB spared ambulation and bladder/bowel difficulties
- Meningomyelocele most likely associated with adverse neuropsychological outcomes
- Varies with level of lesion: Lesions above L1(30%) associated with more brain dysmorphology and poorer neuropsychological outcomes than L1 and below (70%)
- Lesion level varies with ethnicity (Nonhispanics: 28% > L1; Hispanics: 44%)
- *Lesion level accounts for genetic and cognitive variability*
Neural Phenotype

- Dysmorphology of cerebellum, midbrain, corpus callosum, and posterior cortex (latter due to hydrocephalus)
- Cerebellum: Arnold Chiari II (93%), AC I/Other (3%), Normal (3%); No variation with lesion level
- Midbrain: Tectum (65% Upper, 53% Lower)
Neural Phenotype

- Posterior fossa, pons, medulla abnormal in 2/3 or more, but more frequent in upper lesions
- Corpus callosum: 52% partial dysgenesis, 44% hypoplastic, 4% normal
  24 different patterns
- Upper level lesions: 47% with dysgenesis of splenium (26% lower)
Neural Phenotype

Cortex: Quantitative analysis of brain volumes

• Precallosal not different in tissue composition
• Pericallosal and retrocallosal: twice as much CSF with proportional reductions in gray and white matter
• Cerebellum is smaller, especially in upper level lesions
Cognitive Phenotype: Questions

- Do children with spina bifida have a “signature” phenotype with regard to neuropsychological outcomes?
- Are there core processing deficits associated with neuropsychological outcomes?
- What factors account for the variability of neuropsychological outcomes?
- What happens across the life span?
Preliminary Answers

• There is a modal phenotype, but there is also substantial variability around this modal phenotype.
• The phenotype can be accounted for by impairments in a few core processes that cut across domains.
• Variability due to variability in physical and neural phenotypes as well as environmental factors (SES, caretaking).
• Core deficits emerge early in development and persist into adulthood.
Clinical Outcomes (Research Criteria)

- No problems (in the areas assessed): 22%
- Mental deficiency: 23% with IQ and adaptive behavior below 70 (59%: 20/34 upper level lesions of Hispanic origin)
- Attention: 34% elevated parent ratings (26% inattentive, 2% hyper-impulsive, 6% both)
- Academics: 58% with difficulties in reading (3%), math (29%), or both (26%)
Intelligence

- Children with SBM have lower nonverbal than verbal IQ scores; verbal IQ often in average range
- Cannot estimate average IQ of SB as studies almost always employ varying selection criteria
- Why would we want to know IQ as it explains little about SB and is an outcome, not a determinant?
- Nonetheless....
Intelligence

- Related to numerous clinical markers: lesion level, corpus callosum dysmorphism, degree of posterior thinning, but not shunt revisions or infections (in our studies)
- Patterns apparent across the life span
Bayley Mental

Figure 5.
Figure 5. Growth curves for the Bayley mental scale for children with spina bifida meningomyelocele (shunted and unshunted) from 6-36 months.
Bayley Motor

Chronological Age (months)

Raw scores

NC
SBMM - No shunt
SBMM - Shunted
Bayley Motor

Figure 6. Growth curves for the Bayley motor scale for children with spina bifida meningomyelocele (shunted and unshunted) from 6-36 months.
## School Age: SB IQ X Ethnicity

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Comparisons of Lower (<T12) and Upper Level (> L1) Spinal Lesions on Stanford- Binet IQ

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<tr>
<td>Verbal IQ</td>
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<td>Visual IQ</td>
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Comparisons of Lower (<T12) and Upper Level (> L1) Spinal Lesions: NonHispanics

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<tr>
<td>Verbal IQ</td>
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<tr>
<td>Visual IQ</td>
<td>87(19)</td>
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Comparisons of Lower (<T12) and Upper Level (>L1) Spinal Lesions: Hispanics

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<tr>
<td>N</td>
<td>52</td>
<td>31</td>
<td>.0001</td>
</tr>
<tr>
<td>Verbal IQ</td>
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<td>Visual IQ</td>
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Neuropsychological Outcomes

• Modal pattern: VIQ > PIQ
• Impairment of fine motor, upper limb, and visual perceptual skills
• Lexical and syntactic > meaning construction
• Memory, attention, executive function vary
• Word Recognition stronger than math and reading comprehension

Also variability within these domains
Motor

- Upper limb dysfunction and motor performance related to cerebellar volumes and midbrain
- Timing emerges independently of motor demands and related to cerebellar volumes
- Emerge early in development and persist
- *Motor control and learning, as well as timing, are core deficits*
Attention

- Children with SB have difficulties orienting, initiating, engaging, and shifting attention
- Can be detected as early as 6 months of age
- Related to quantitative posterior volumes and midbrain
- Difficulties sustaining attention less apparent
- *Attention orientation is a core deficit*
Figure 3
Visual Perception

- Perceptual deficits well established, but not all perceptual skills comparably impaired
- Object-based perception (face recognition, fragmented objects) better than action-based perception (figure-ground, visually guided perceptual-motor)
- Not explained by motor deficits
- Emerge early and stable across the life span
- Related to posterior volumes and asymmetric thinning
Language

**SPEECH**
- Dysfluency
- Ataxic dysarthria
- Slowed speech rate

**LANGUAGE**

**SYNTAX**
- Using word forms
- Understanding sentence syntax

**LEXICON**
- Using single words
- Understanding single words
- Vocabulary

**MEANING CONSTRUCTION**
- Linking old and new knowledge
- Making inferences for coherence or for elaboration
- Understanding non-literal language

**PRAGMATIC COMMUNICATION**
- Verbose language
- Stereotyped phrases poorly matched to context
- Poor grasp of gist and core information
- Text cohesion and coherence problems
Memory and Executive Functions

- Children with SBM do poorly on many tests of memory and executive functions
- Difficulties not obviously specific to this domain: reflect demands of tests on core processes
- In adults, evidence of emerging clinical disorders of memory (related to lifetime history of shunt revisions)
Mathematics

- Problems often involve learning procedures (multi-digit problems, algorithms), not facts-similar to LD involving only math
- Some with SB have profound math deficits that hamper quality of life and independence
- Best single predictor of adult independence (in one study) was functional math
- Deficits emerge in preschool
# Reading and Discourse Skills in Hydrocephalic Children With Average to Above-Average Verbal IQs

<table>
<thead>
<tr>
<th>Skill</th>
<th>Same as Normally Developing Children?</th>
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<tr>
<td><strong>Reading</strong></td>
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<tr>
<td>Word recognition accuracy</td>
<td>Yes</td>
</tr>
<tr>
<td>Phonological analysis</td>
<td>Yes</td>
</tr>
<tr>
<td>Written vocabulary knowledge</td>
<td>Yes</td>
</tr>
<tr>
<td>Reading comprehension</td>
<td>No</td>
</tr>
<tr>
<td><strong>Narrative production</strong></td>
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<tr>
<td>Quantity produced</td>
<td>Yes</td>
</tr>
<tr>
<td>Syntactic complexity</td>
<td>Yes</td>
</tr>
<tr>
<td>Core semantic content</td>
<td>No</td>
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<tr>
<td><strong>Oral discourse elements</strong></td>
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<tr>
<td>Idiomatic expressions</td>
<td>Yes</td>
</tr>
<tr>
<td>Novel figurative expressions</td>
<td>No</td>
</tr>
<tr>
<td>Inferences</td>
<td>No</td>
</tr>
</tbody>
</table>
Cerebellum and Corpus Callosum

• Cerebellar functions involving timing and rhythmicity impaired; nonrhythmic not impaired
• Cerebellar functions involving motor acquisition not impaired despite significant problems with perceptual aspects of task
• Corpus Callosum: Interhemispheric transfer disrupted, especial in non-righthanders, those missing the splenium, and upper level lesions
Why worry about cognition and the brain?

Most with SBM have cognitive difficulties related to the neural phenotype that can make SBM disabling beyond effects of orthopedics and hydrocephalus

• When do core process deficits emerge and how are they modified by the environment? Why do they persist?

• How do core processes contribute to social difficulties: manifestation of cognitive problems? (e.g., pragmatic language)
Why worry about cognition and the brain?

- How can the environment be modified to enhance outcomes?
- What are the neural correlates of core process deficits?

SBM is an incredible example of neural plasticity
MSI in SBM: Word Recognition
Conclusions: Future Research Directions

1. Cognitive, physical, and neural phenotypes are variable
2. Variability related to genetic and environmental factors
3. Must go beyond traditional domains: Core processes
4. Variability is the key
5. Need large, representatives samples to model relationships and an interdisciplinary perspective across the life span
Conclusions: Future Research Directions

6. Research has to move beyond clinical samples of convenience, must deal with classification issues, and assess brain integrity.
7. Use new technologies.
8. Intervention research is needed.

WE NEED MORE RESEARCH OF ALL KINDS!