Neuropsicología de Espina Bífida e Hidrocefalia: mecanismos genéticos,neuronales y cognitivos

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What is Spina Bifida

Neural Tube Defect Sequence

- Failure of the neural tube to close leads to
  - interrupted spinal cord
  - hydrocephalus
  - neurogenic bladder
  - club feet

-Second most prevalent birth defect in the world

-.3-.5-10 per 1,000 live births

-Failed embryogenesis: Neural tube does not close around 26-28 days gestation

-Myelomeningocele (80%): neural groove does not separate from ectoderm, remains exposed on back

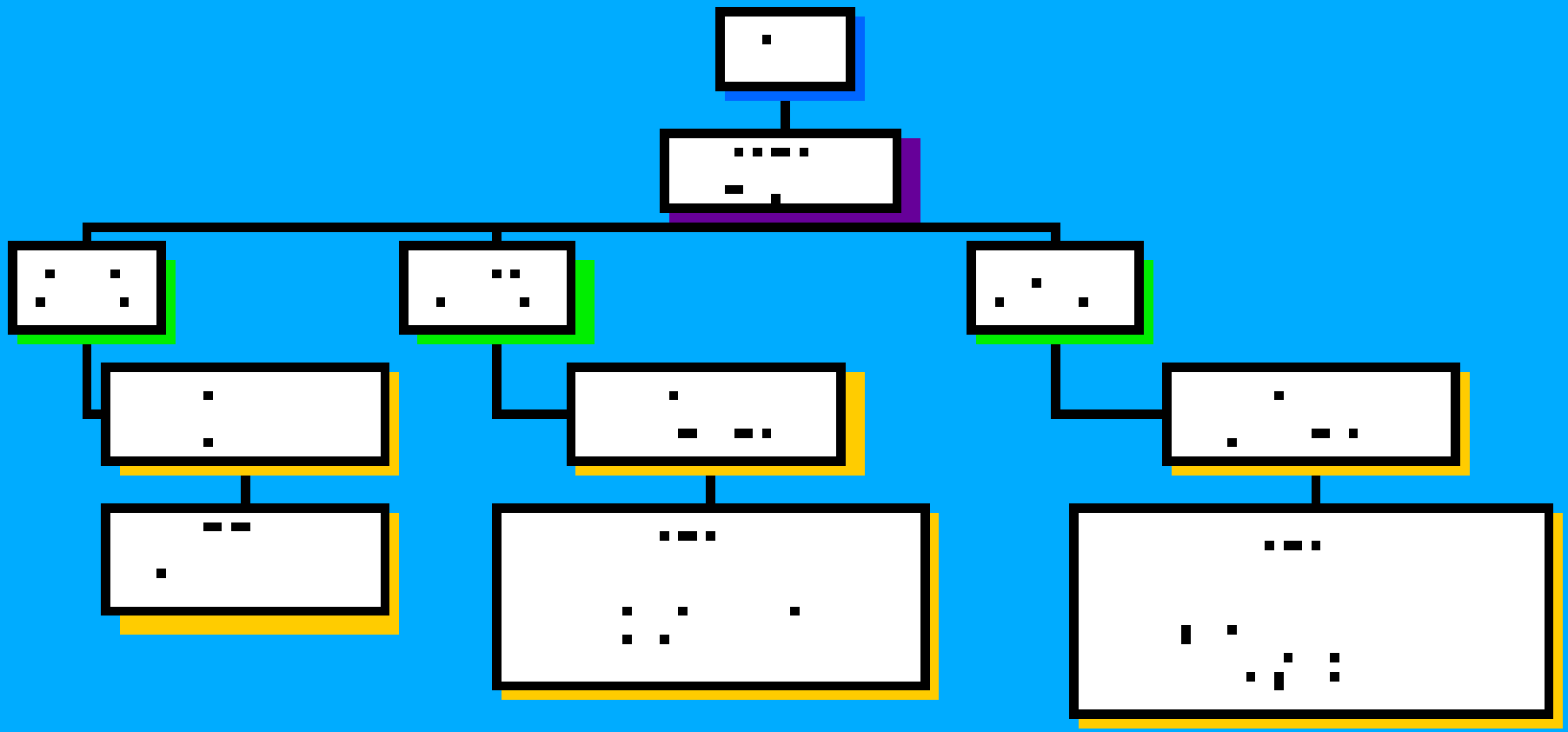
-Lesion anywhere on spine

-Characteristic brain malformations

SPINA BIFIDA

- Understudied relative to prevalence and long term consequences
- Public perception: spinal disorder that affects ambulation and bladder/bowel control
- Reality: SB has 3 sources of phenotypic variability: physical, neural, cognitive that interact with genes and environment to produce variable outcomes

Sources of Variability



Central Theme

- Spina bifida has distinct physical features and neural dysmorphologies and modal cognitive characteristics, but outcomes vary. What are the mechanisms underlying this variability?

Sources of Variability

Complex pattern of gene- environment interactions

- Physical: Level of spinal lesion
- Neural: CNS manifestations- Chiari malformation, corpus callosum anomalies, hydrocephalus
- Environmental factors: diet, familial, cultural, treatment

Genetic, neuroimaging, and neuropsychological investigations of a common, representative sample

Genes

Hope Northrup, Paul Au

SB is a Neurogenetic Disorder

About 60- 70% of variability explained by genetic factors

- Family history
  - Parents with one child with SB 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)

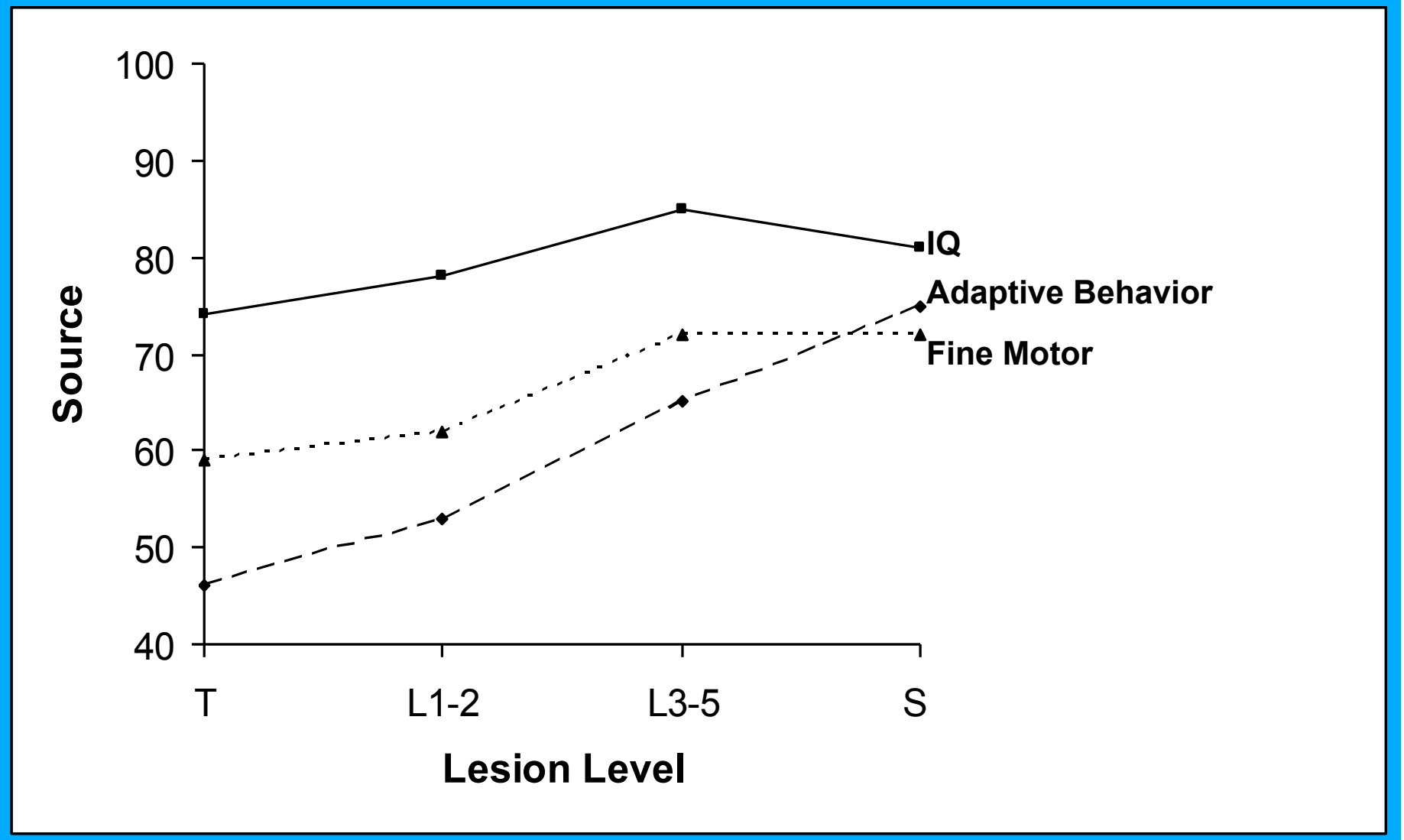
  Folate supplementation will not make SB disappear

Genetic Factors

- Genetic alterations in folate metabolism are associated with increased risk for neural tube defects
- Women with a child affected with a neural tube defect have elevated blood homocysteine levels that have been related to problems with the metabolism of folate acid.
- The frequency of the C677T mutation in certain ethnic groups roughly corresponds to incidence of neural tube defects: common among Hispanics, less frequent among whites, and rare in blacks; more apparent in upper level lesions

Physical Phenotype

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

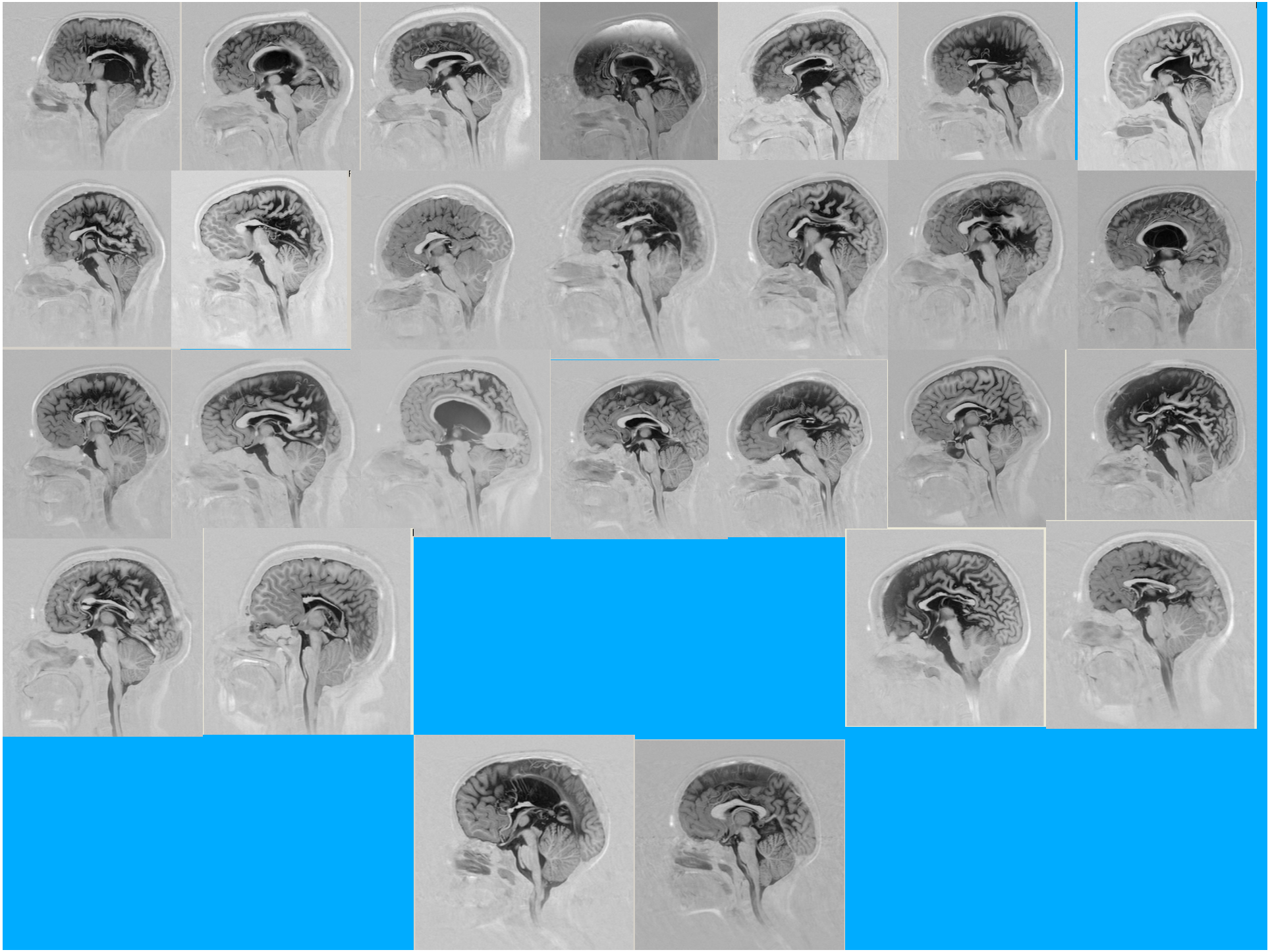

100
90
80
70
60
50
40
Source
IQ
Adaptive Behavior
Fine Motor
T
L1-2
L3-5
S
Lesion Level

Brain

Susan Blaser (Radiology), Khader Hasan (MRI Physics, DTI), Larry Kramer (Radiology), Jenifer Juranek (MRI), Andrew Papanicolaou (MSI)

Brain Regions Affected In Spina Bifida

- Cerebellum
- Midbrain and tectum
- Corpus callosum
- Posterior cortex



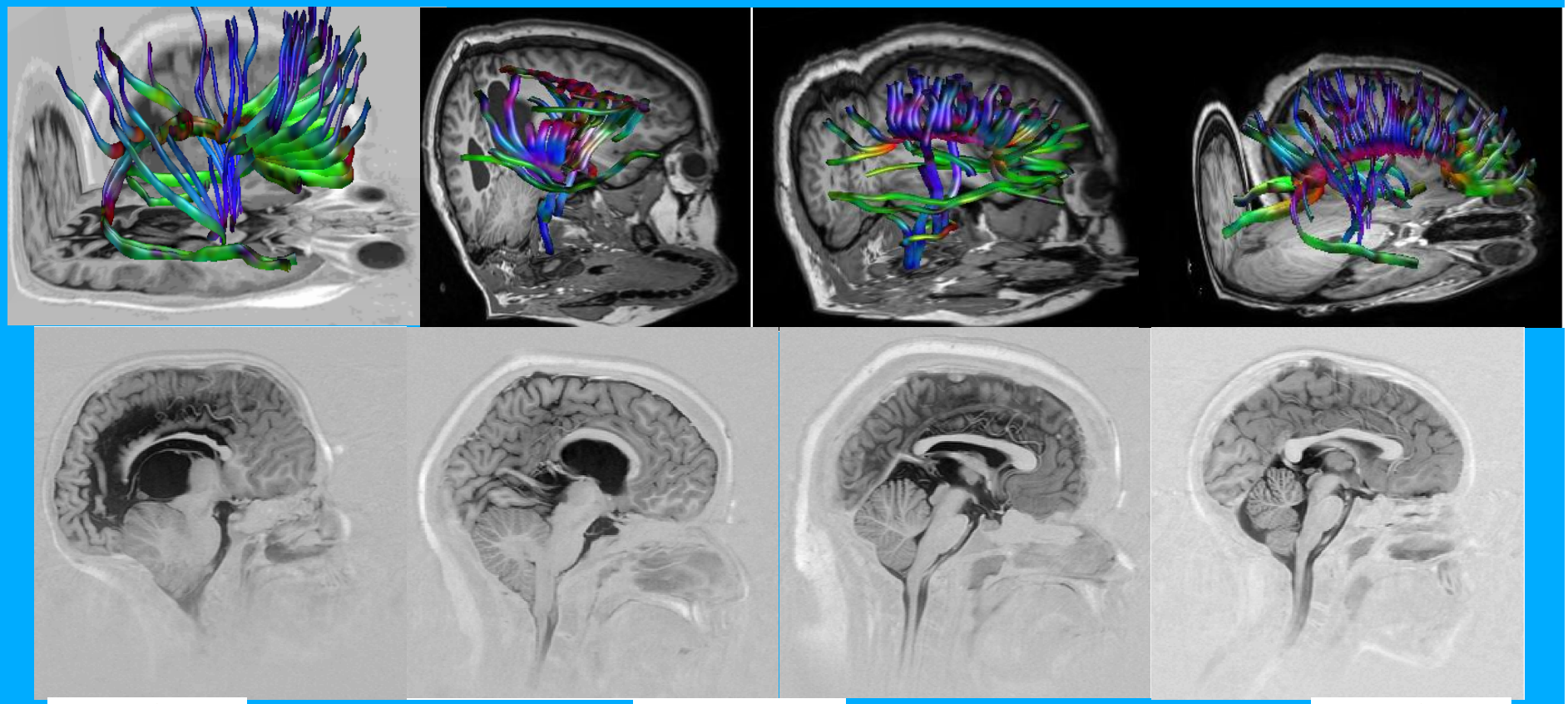
Cerebellum and Neuropsychological Outcomes (Juranek)

- Cerebellum smaller in volume, especially in upper level spinal lesions
- Qualitatively reorganized: the posterior lobe was significantly reduced in SBM, the corpus medullare was not different, and the anterior lobe was significantly enlarged
- SBM represents a reconfiguration involving anterior lobe enlargement and posterior lobe reduction

Cerebellum and Neuropsychological Outcomes

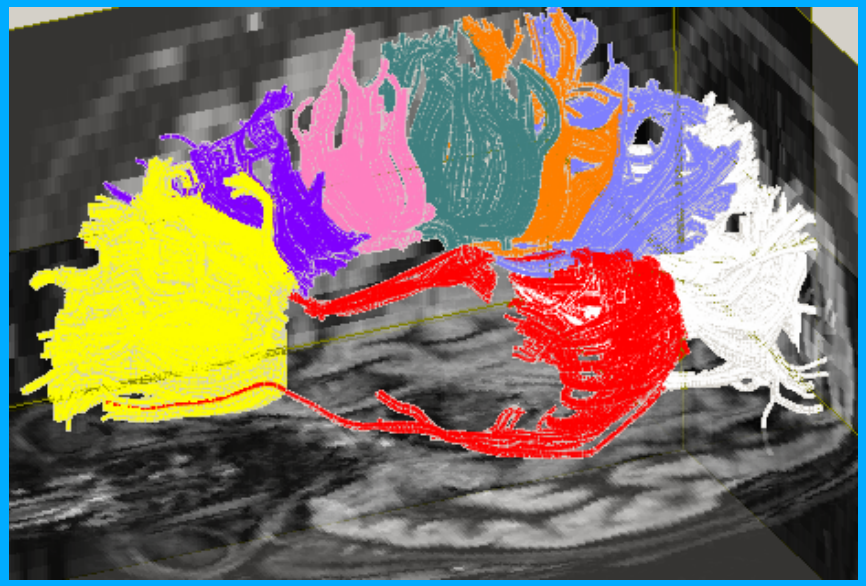
- Marked impairment of upper limb coordination
- Preservation of procedural motor learning, but impaired at baseline and poor online adaptation
- Impaired rhythmicity and timing
- Correlated with cerebellar volume

DTI CC Connectivity
Hasan, JNS: Pediatrics, 2008)

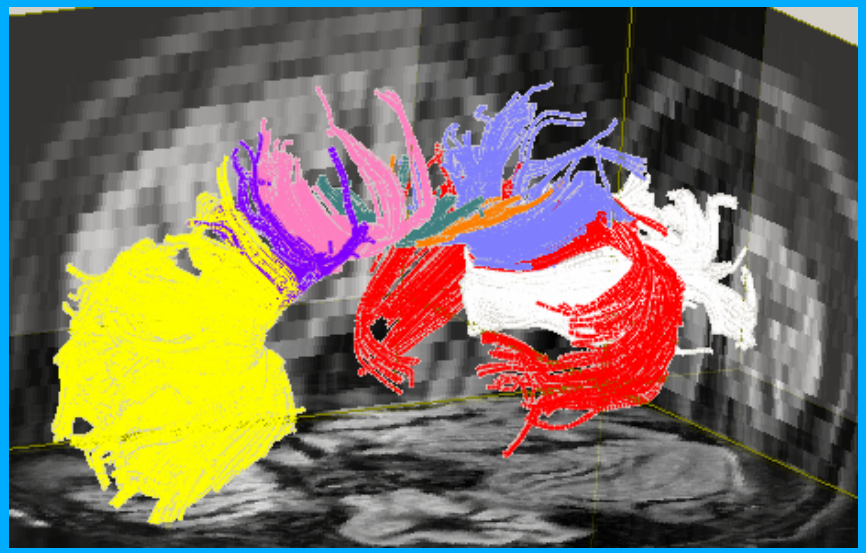


DTI Tractography of the Corpus Callosum

Typically Developing



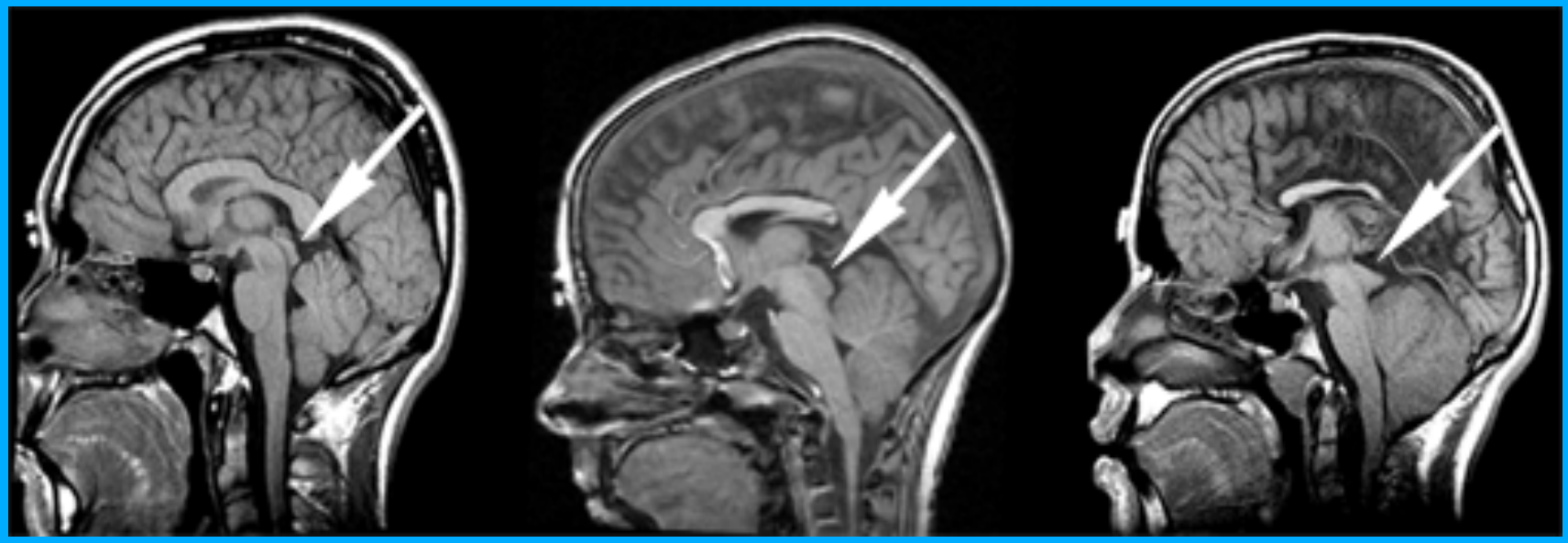
SB with hypoplasia



CC and Neuropsychological Outcomes (Hannay)

- Hypogenesis maximally affects splenium and posterior body
- Interhemispheric communication reduced on visual transfer tasks, with no right ear advantage on verbal dichotic listening tasks
- Hypoplastic (thinned) CC are not normal, but children show expected right ear advantage for words

Midbrain: Tectal Beaking (Fletcher et al., JNS:PEDS, 2005)



Midbrain Anomalies and Neuropsychological Outcomes

- Connectivity from midbrain very abnormal if tectum beaked
- Tectal beaking associated with more severe attention problems reflective of posterior attention system

Attention Strengths and Weaknesses

- The attention strengths of children with spina bifida concern THE (ANTERIOR) DIRECTED ATTENTION SYSTEM (e.g., they can detect interesting events when given an "cognitive" signal such as a word or arrow to directs their attention).

- The attention weaknesses of children with spina bifida concern THE (POSTERIOR) ATTENTION ORIENTING SYSTEM (e.g., have difficulty disengaging from no-longer-relevant things and are slow to move attention to new things, especially if they have brain anomalies in the orienting system.

What Do Posterior Attention Orienting System Deficits Look Like?

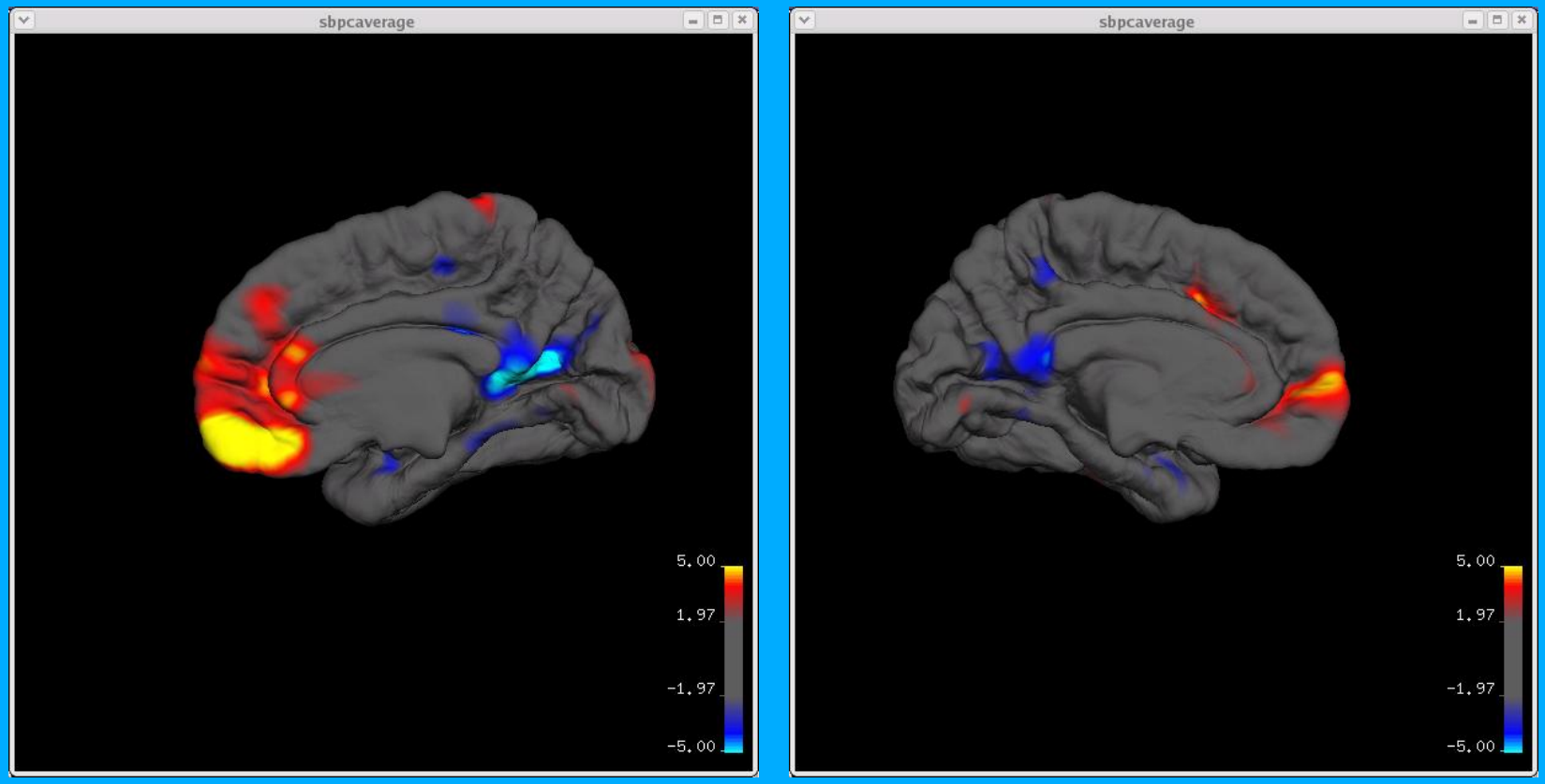
- Individuals who have impairments in the posterior attention system
  - Can voluntarily control “top-down” attention
  - Can orient to interesting information
  - Are not hyperactive
  - Cannot disengage appropriately and so get “glued” to material or information
  - Cannot orient flexibly to salient information and do not easily shift their attention between different tasks or materials.

Children With Spina Bifida vs. Children With AD/HD

- Problems directing attention
  - Children with spina bifida can direct their attention
  - Children with AD/HD have trouble sustaining attention
  - Children with spina bifida can sustain attention
- Problems with attention orienting
  - Children with spina bifida are slow to disengage from what they have oriented to
  - Children with spina bifida repetitively explore the same location or information
  - Children with AD/HD generally do not have these problems.

SUSTAINED ATTENTION OVER TIME (Brewer et al., Neuropsychology, 2001)

Cortical Thickness- Medial View (Juranek et al., NeuroImage, 2008)

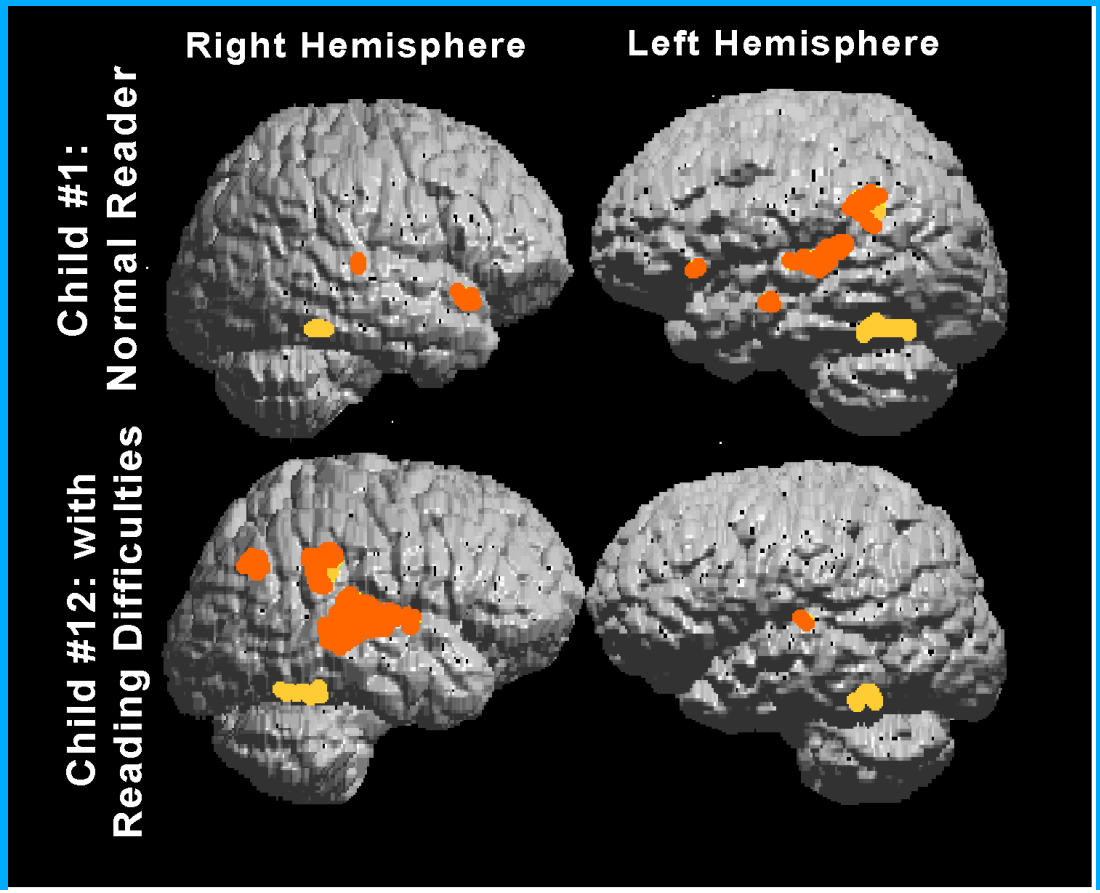


Cortical Thickness and Neuropsychological Outcomes

- Posterior cortex thinned, but anterior cortex enlarged
- Goldilocks principle: too big or too small is not “just right.”
- Trebel et al. (Cerebral Cortex, in press): cortical thickness that deviates from normative values in either direction associate with lower IQ and fine motor dexterity

Cortical Plasticity?

- Little evidence of age-based functional plasticity in subcortical and subtentorial regions, brain regions with highly conserved functions (timing, reflex orienting)
- BUT: Function of cortex is to learn and adapt, at any age. Do children show cortical plasticity?

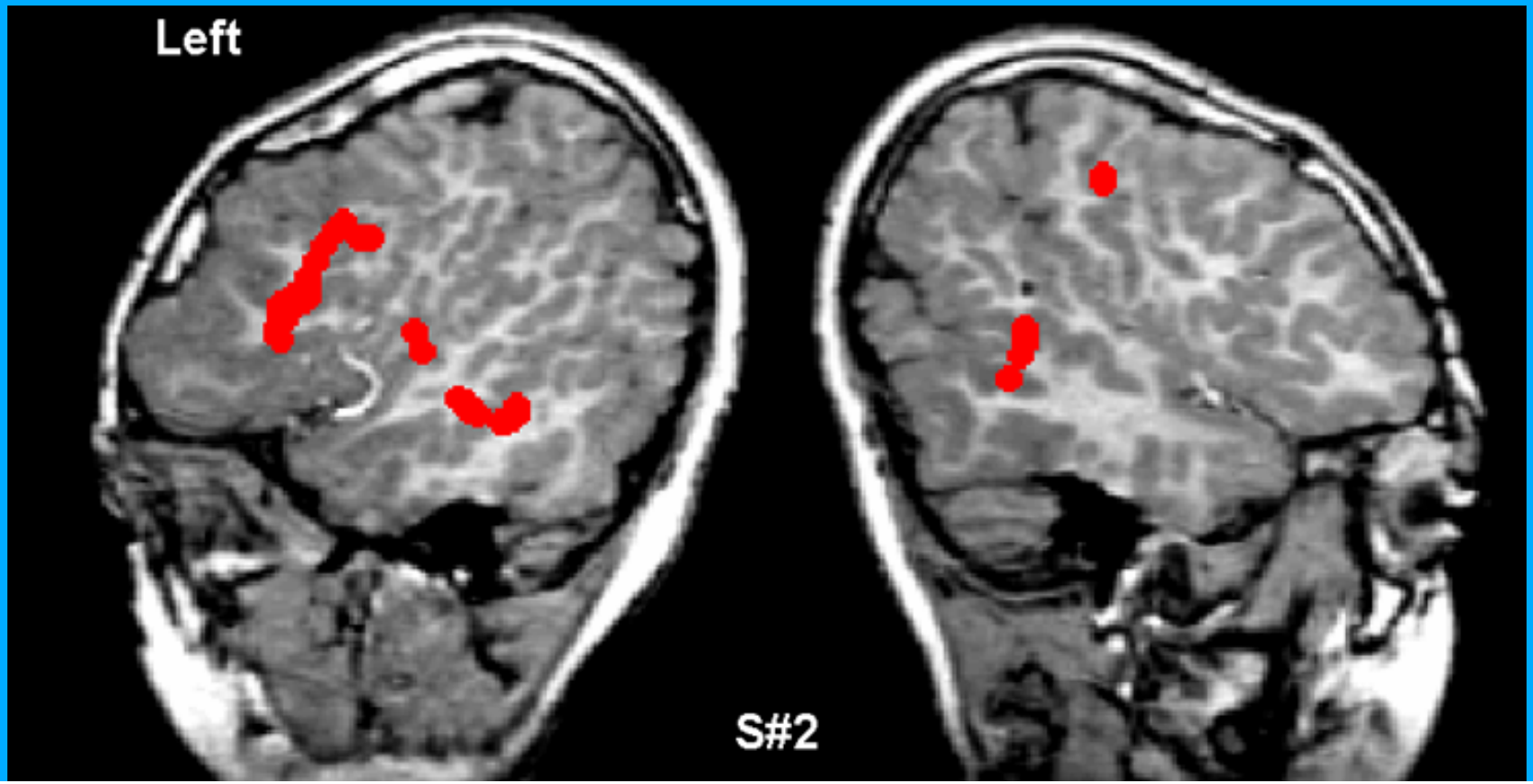


MSI, word recognition

- Normal reader activates left hemisphere network (Broca-angular gyrus-Wernicke)
- Poor reader activates right posterior brain

Cortical Plasticity In SB

- MSI in child with SB, good word recognition
- Activating only frontal part of network bilaterally, not using thin posterior cortex
- Effecting same task with different brain systems, so cortex shows age-based functional plasticity



Behavior

Marcia Barnes, Maureen Dennis, Julia Hannay, Susan Landry, Heather Taylor

Clinical Outcomes (Research Criteria)

- No problems (in the areas assessed): 22%
- Intellectual 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%)

Three Behavioral Issues

- *Modal cognitive-behavioral profile*
  - Typical pattern of stronger and weaker skills
  - Observed in many individuals with spina bifida
  - Apparent over the lifespan
    - infants
    - young adults
    - middle aged
- *Variability*
  - Differences between individuals is principled, not error variance
  - Related to moderators in genetic, brain, medical history; poverty, parenting, and perhaps teaching
- *Core processing deficits*
  - *Assembled vs. Associative processes*

Core Processing Deficits

- emerge in infancy
- persist throughout childhood and into adult life
- can be demonstrated over a range of cognitive ability levels
- are weakly related to other core deficits
- are strongly correlated with specific congenital brain dysmorphologies
- show little plasticity

Interfere with Assembled Processing

- Timing: Synchronizing behavior with the environment (Cerebellum)
- Attention Orientation: Automatic direction and disengagement of attention to the environment (Midbrain)
- Movement: Learning and controlling coordinated movements (Spinal lesion, Cerebellum)
- Operate across and within domains

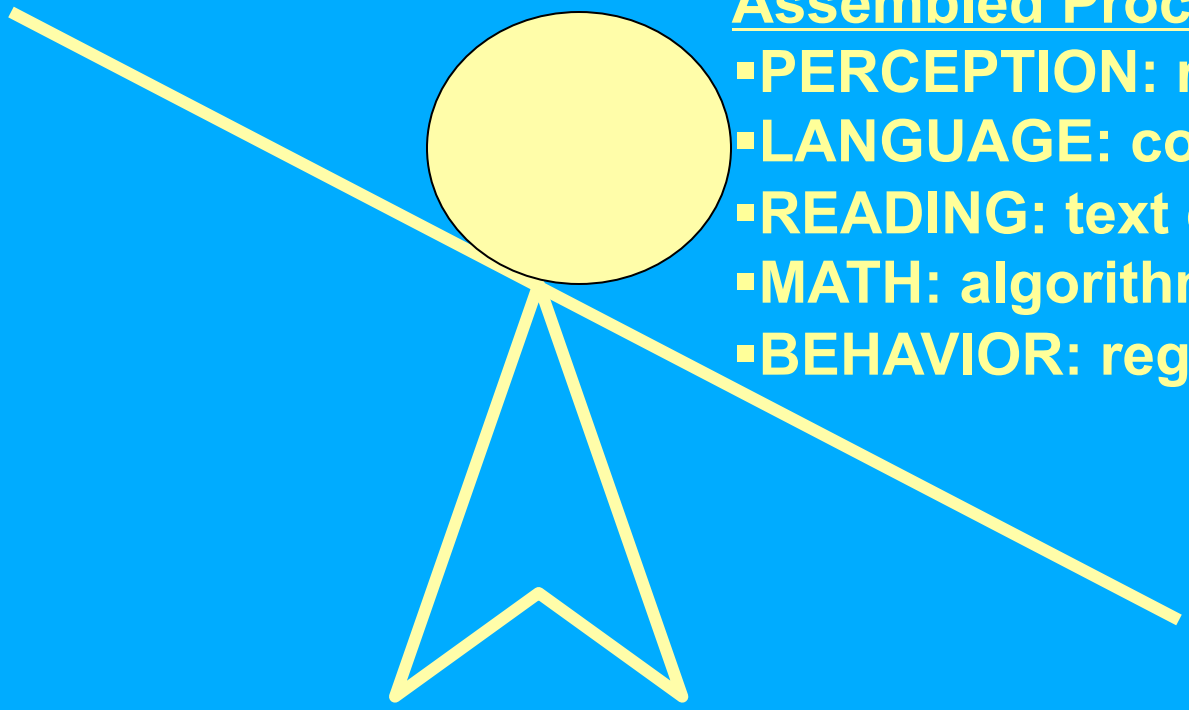
Affect Broad Outcome Domains

- Associative Processing is data-driven and based on the formation of associations, enhancement, engagement, and categorization: recognizing faces, decoding words, using vocabulary, carrying out routines
- Assembled Processing, is based on dissociation, suppression, disengagement, and contingent relations. It requires the assembling of models of input across various content domains: inferring, constructing meaning, integrating knowledge, problem solving, learning routines

Modal Cognitive Profile: Assets & Deficits

Associative Processing: Strengths

- PERCEPTION: categories
- LANGUAGE: stipulated meaning
- READING: word decoding
- MATH: numbers
- BEHAVIOUR: activation



Assembled Processing: Weakness

- PERCEPTION: representations
- LANGUAGE: constructing meanir
- READING: text comprehension
- MATH: algorithms
- BEHAVIOR: regulation

Future Directions

- How do genes directly influence the cognitive and neural phenotype? MTHFR_1 associated with lower lesion and ADHD
- What are the neural correlates (structural and functional) of core process deficits?
- Relation of movement and attention
- How can the environment be modified to enhance outcomes?

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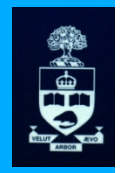

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